NCC-WCH

V1.0

Bronchiolitis: diagnosis and management of bronchiolitis in children - Appendices A – I & K

Appendices A- I & K

Clinical Guideline <…>

Appendices

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Draft for Consultation

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Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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A.1 Treatment of Bronchiolitis

A.1.1 Review question

What is the efficacy of inhaled bronchodilator therapy?

What is the efficacy of systemic corticosteroid therapy?

What is the efficacy of combined bronchodilator and corticosteroid therapy?

A.1.2 Introduction

A.1.2.1 Review of published evaluations

One cost-effectiveness analysis was identified for this question (Sumner et al. 2010). This analysis was based on the RCT by Plint et al. 2009. This was a Canadian study comparing nebulized epinephrine plus oral dexamethasone, nebulized epinephrine alone, oral dexamethasone alone, and no active treatment. The trial included infants between 6 weeks and 12 months of age. The effectiveness was measured as a combined outcome of days without symptoms and this included; difficulties in infant feeding, sleeping, coughing, and noisy breathing. The results of the clinical evaluations did not show statistical significance for all differences in outcomes. The perspective for the analysis was societal, including costs to the health care system and costs borne by the families of children with bronchiolitis. The analysis was also run from the health care perspective. All costs were presented in 2009 Canadian dollars. The time horizon of the model was 22 days after enrolment into the trial.

The results showed that the combination of epinephrine and dexamethasone was both less expensive than all other treatments including no active treatment, and also more effective, with the lowest average time to relief of all symptoms (12.17 days compared to 12.69 for no active treatment, 12.62 for oral dexamethasone, and 13.02 for nebulized epinephrine). The length of hospital stay and re-admissions were not reported separately and so it is not possible to adapt this model to the UK setting.

A.1.2.2 New economic evaluation

A network meta-analysis (Hartling et al. 2011) was published comparing bronchodilators and corticorsteroids, alone and in combination, with no treatment. This clinical evidence was used to develop a model to consider the cost-effectiveness of various treatment strategies.

A.1.2.3 Methods

A decision tree model was developed in Excel based on the outcomes of the network meta-analysis (Figure 1).

The following comparisons were considered in the model:

- No treatment
- Adrenaline
- Adrenaline plus steroid
- Steroid

- Steroid plus salbutamol
- Salbutamol

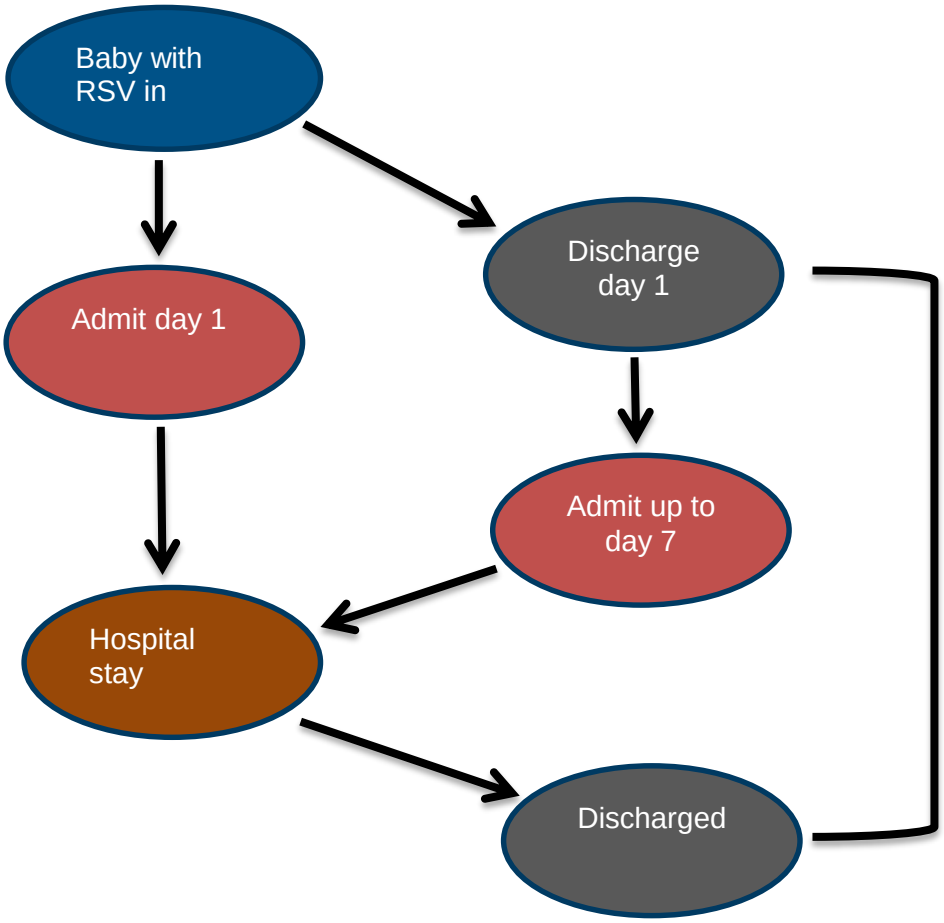


Figure 1: Decision tree model

The model was developed from the perspective of the UK NHS, using 2013/14 costs. The time horizon for the model was less than a year and so no discount rate was applied.

The clinical evidence was presented as odds ratios. Using the baseline risk of admission from all studies of 20% as reported in Hartling et al. 2011, the relative risks for each treatment strategy were calculated.

(OR admission x OR treatment) / (1-(OR admission x OR treatment) = risk of admission given treatment

Risk of admission given treatment / baseline risk of admission = relative risk of admission given treatment.

Table 1: Risk of admission

Treatment strategy	OR	Lower 95% CI	Upper 95% CI	Calculated RR
Admissions at day 1				
Adrenaline	0.48	0.18	1.01	0.54
Adrenaline plus steroid	0.52	0.15	1.57	0.58

Treatment strategy	OR	Lower 95% CI	Upper 95% CI	Calculated RR
Steroid	0.84[a)]	0.33	2.05	0.87
Steroid plus salbutamol	0.92	0.28	3.4	0.93
Salbutamol	1.04	0.46	2.35	1.03
Admissions at day 7				
Adrenaline	0.85	0.18	3.85	0.88
Adrenaline plus steroid	0.56	0.12	2.6	0.61
Steroid	0.93	0.29	2.95	0.94
Steroid plus salbutamol	0.53	0.07	4.57	0.58
Salbutamol	1.02	0.2	5.12	1.02
Length of stay	**Mean difference**	**Lower 95% CI**	**Upper 95% CI**	
Adrenaline	-0.28	-0.7	0.12	
Adrenaline plus steroid	-1.01	-5.3	3.01	
Steroid	-0.35	-0.8	0.08	
Steroid plus salbutamol	0.41	-0.6	1.38	
Salbutamol	0.04	-0.3	0.41	

(a) correction from the authors

A.1.2.4 Outcomes

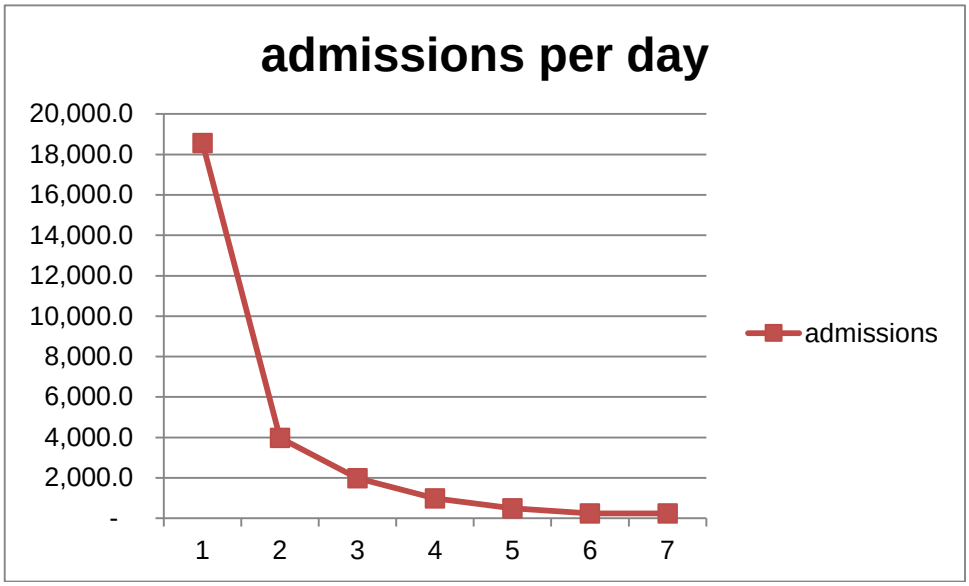
The main outcomes in the model were hospital admissions and length of stay. Re-admissions to hospital, further treatments, and admissions to intensive care were not reported in the clinical trials.

Quality of life scores were not identified for bronchiolitis. A systematic review of all published evidence reporting the use of EQ-5D in an asthma population was carried out by the Decision Support Unit in 2010 (Wailoo et al. 2010[a]). In this review the quality of life scores reported for children (aged 7 to 18 years) at 12 months were 0.97 (sd 0.05) in the control group and 0.98 (0.04) in the intervention group. Given that this model looks at first admissions only, this small change in quality of life would be applied to a few days of hospital stay. As the differences would be very small and unlikely to give meaningful results for a change in quality of life between treatment strategies it was decided not to include these in the model.

The network meta-analysis (Harling et al. 2011) reports admissions on day 1, and up to day 7. For the model it was assumed that the majority of admissions would be on day 1, and the number of admissions would decrease towards day 7 (Figure 2). The population of children being treated for bronchiolitis in the NHS was estimated using the NHS reference cost data. This data reports the number of finished consultant episodes due to bronchiolitis for paediatric care, N=33,154. As this figure includes re-admissions it has been assumed that approximately 80% of these episodes will be initial admissions, N=26,523. The admissions have been distributed over 7days, with 70% of admissions occurring on day 1.

a Wailoo et al. The incorporation of health benefits in cost utility analysis using the EQ-5D. November 2010. Report by the Decision Support Unit, University of Sheffield

Figure 2: Paediatric admissions due to bronchiolitis per day after diagnosis in the emergency department



The network meta-analysis (Harling et al. 2011) baseline risk of admission from all studies was 20%. Therefore, if N=26,523 infants are admitted for bronchiolitis, then N=132,616 will have been diagnosed with bronchiolitis.

A.1.2.5 Costs

All infants are diagnosed by a physician (in the emergency department) and so the costs of an initial diagnosis have not been included in the model. After the initial diagnosis infants may be admitted on that day, or subsequent days up to day 7. The mean difference in length of stay is reported, but it is unclear what further treatments were given once an infant is admitted. However, these costs will be incorporated into the cost of a bed day for bronchiolitis. It is assumed that the treatments being compared relate only to the initial treatment given in the emergency department.

Table 2: Drug costs taken from the Prescriptions Pricing Authority Drug Tariff (April 2014) for initial treatment in the accident and emergency department

	Pack size	Unit cost	Pack costs
Adrenaline (epinephrine)	500micrograms/0.5ml amp	£4.72 per amp	£47.18 for 10 amps 2 amps per use (GDG)
Steroid (dexamethasone)	Oral solution 2mg/5ml	£1.41 per 5ml	£42.30 for 150ml
Salbutamol	100micrograms 200 dose inhaler	£1.50	CFC free

The mean difference in length of stay was calculated by weighting the average length of stay, and this approach was used to calculate a weighted mean cost per bed day of £516 for bronchiolitis paediatric admissions taken from the NHS reference costs (Table 3).

Table 3: Paediatric admissions due to bronchiolitis, hospital costs and length of stay (NHS reference costs 2012/13)

		Finished consultant episodes (FCE)	Average length of stay - days	FCE cost	Average cost bed day
	Non-elective long stay				
PA15B	Acute Bronchiolitis with CC Score 0	9,040	3.23	£1,847	£424
PA15A	Acute Bronchiolitis with CC Score 1+	3,857	4.64	£2,669	£423
	Non-elective short stay				
PA15B	Acute Bronchiolitis with CC Score 0	17,740	≤1	£526	£526
PA15A	Acute Bronchiolitis with CC Score 1+	2,517	≤1	£603	£603
	Total number of paediatric admissions for acute bronchiolitis	33,154			
	Weighted mean length of stay		2.03		
	Weighted cost per bed day				£516

A.1.2.6 Results

Using the mean inputs from the Hartling et al. 2011 network meta-analysis the base case results show that using adrenaline and steroids could lead to reduced admissions, up to 10,958 when compared to no treatment (Table 4).

Table 4: Results – number of admissions compared to no treatment when 132,616 infants are diagnosed with bronchiolitis

	N admission at day 1	N admission day 2 - day 7	Total N admissions	Difference in admissions
No treatment	18,566	7,957	26,523	
Adrenaline + steroid (dexamethasone)	10,680	4,886	15,566	- 10,958
Adrenaline	9,946	6,973	16,919	1,353
Steroid	16,111	7,505	23,616	6,697
Steroid + salbutamol	17,359	4,655	22,013	- 1,603
Salbutamol	19,156	8,084	27,239	5,226

The reduction in admissions leads to cost savings compared to no treatment, approximately £18million savings are made due to fewer admissions when adrenaline and steroids are given in the emergency department. These savings are seen when compared to no treatment which may not reflect current care.

Table 5: Results – treatment costs, hospital stay costs, total costs and cost differences

	Treatment cost	Total cost of hospital stay	Total costs	Incremental costs
Adrenaline + steroid (dexamethasone)	£1,438,353	£8,211,233	£9,649,586	
Adrenaline	£1,251,365	£15,296,031	£16,547,396	£6,897,809
Steroid	£186,989	£20,498,351	£20,685,340	£4,137,944
No treatment		£27,810,074	£27,810,074	£7,124,735
Steroid + salbutamol	£878,615	£27,737,141	£28,615,756	£805,682
Salbutamol	£691,627	£29,123,074	£29,814,700	£198,944

A.1.2.7 Sensitivity analyses

The model was run with the lower 95% credible intervals to show the best case results for treatment compared to no treatment (Table 6). This shows that all treatments compared to no treatment would result in fewer hospital admissions and therefore reduced costs.

Table 6: Best case results

	Total N admissions	Total costs	Incremental costs
Adrenaline + steroid (dexamethasone)	4,514	£3,819,672	
Adrenaline	5,711	£5,147,666	£1,327,994
Steroid + salbutamol	6,757	£5,976,974	£829,308
Steroid	9,764	£6,597,109	£620,135
Salbutamol	11,469	£10,764,803	£4,167,694
No treatment	26,523	£27,810,074	£17,045,271

The lower 95% credible interval was a difference in length of stay of -5.29days which gives a negative length of stay and so the mean was used for this calculation

However, all the inputs crossed unity and running the model with the upper 95% credible intervals to show the worst case results for treatment compared to no treatment (Table 7) shows all treatments would results in more admissions and therefore a cost increase when compared to no treatment.

Table 7: Worst case results

	Total N admissions	Total costs	Incremental costs
No treatment	26,523	£27,810,074	
Adrenaline	38,227	£43,699,087	£15,889,013
Steroid	48,342	£52,869,701	£9,170,613
Salbutamol	56,690	£72,121,872	£19,252,171
Adrenaline + steroid (dexamethasone)	41,839	£110,268,783	£38,146,911
Steroid + salbutamol	63,868	£113,309,304	£3,040,521

A study was identified by the GDG which considered hospital admission rates among infants in England (Murray et al. 2012[b]). They reported 24.2 admissions per 1000 infants under 1 year. This was applied to the England and Wales birth cohort for 2012, N=729,674 (ONS 2013[c]). The number of admissions would be estimated as N=17,658. The direction of the results does not changes, the total costs and therefore potential cost savings are reduced (Table 8).

Table 8: Admissions rate from Murray et al. 2012, 24.2 admissions per 1000 infants under 1 year

	Total N admissions	Total costs	Incremental costs
Adrenaline + steroid (dexamethasone)	10,363	£6,424,318	
Adrenaline	11,264	£11,016,610	£4,592,292
Steroid	15,723	£13,771,492	£2,754,882
No treatment	17,658	£18,514,862	£4,743,370
Steroid + salbutamol	14,656	£19,051,253	£536,391
salbutamol	18,135	£19,849,463	£798,210

A.1.2.8 Probabilistic sensitivity analysis

To consider the variability in the inputs to the model a probabilistic sensitivity analysis (PSA) was developed. Distributions could be described for the clinical inputs, and the cost of a bed day. As parameters to describe the distributions were not available for the drug costs or mean length of stay, these remained deterministic.

Table 9: Probabilistic inputs

	Distribution	parameters	
Admissions day 1		Log odds ratio	Standard error
Adrenaline	Lognormal	-0.73397	0.500423
Adrenaline plus steroid	Lognormal	-0.65393	0.634282
Steroid	Lognormal	-0.17435	0.476688
Steroid plus salbutamol	Lognormal	-0.08338	0.606931
Salbutamol	Lognormal	0.039221	0.416199
Admissions day 7		Log odds ratio	Standard error
Adrenaline	Lognormal	-0.16252	0.791979
Adrenaline plus steroid	Lognormal	-0.57982	0.785941
Steroid	Lognormal	-0.07257	0.594543
Steroid plus salbutamol	Lognormal	-0.63488	1.032848
Salbutamol	Lognormal	0.019803	0.831245

b Murray J, et al. 2012. Creating a birth cohort to examine RSV bronchiolitis hospital admission rates among term and preterm infants in England. Arch Dis Child 2012; 97: A23

c ONS 2013. Statistical bulletin: Births in England and Wales 2012, July 2013

	Distribution	parameters	
Mean difference in length of stay		Mean	Standard error
Adrenaline	Normal	-0.28	0.219388
Adrenaline plus steroid	Normal	-1.01	2.183673
Steroid	Normal	-0.35	0.209184
Steroid plus salbutamol	Normal	0.41	0.5
Salbutamol	Normal	0.04	0.188776
		Mean	Standard error
Cost per bed day	Normal	516	176
Mean length of stay	deterministic		
Drug costs	deterministic		

When 1,000 simulations were run with the PSA, the mean cost differences followed the same trend as the deterministic results (Table 10). Using adrenaline plus steroid gave the greatest cost savings when compared to no treatment, and in resulted in cost savings in 81% of the simulations. Using only salbutamol would result in increased costs when compared to no treatment, and was cost saving in only 35% of the simulations.

Table 10: Probabilistic sensitivity analysis results – mean of 1,000 simulations

	Total cost	Cost difference compared to no treatment	Proportion of simulations where treatment is cost saving compared to no treatment
No treatment	£25,556,555		
Adrenaline + steroid (dexamethasone)	£9,320,408	£16,791,481	81%
Adrenaline	£21,166,199	£9,526,822	90%
Steroid	£21,630,360	£5,809,863	82%
Steroid + salbutamol	£14,111,962	-£4,088,016	44%
salbutamol	£22,109,207	-£4,054,557	35%

A.1.2.9 Discussion

The results of this analysis point towards adrenaline plus steroid having the potential to reduce costs in the NHS due to fewer admissions and shorter hospital stays. However, the clinical evidence used in the analysis compare all treatments to no treatment (placebo arm), and this does not reflect current practice.

Also, the credible intervals for difference in length of stay when using adrenaline plus steroid were -5.3 days for the lower 95% credible interval, and plus 3.01 days for the upper credible interval. This data is likely to be out-of-date as when the GDG discussed the clinical evidence for this question the current length of stay was reported as approximately 3 days. Therefore, the adrenaline plus steroid data may be overestimating the benefit of reduced length of stay.

The GDG noted that the patients included in the only study for adrenaline plus steroids in the NMA were less severe than would normally be admitted in the UK. When adrenaline is given in the UK it is for the sicker infants, and these infants would always be admitted.

A.1.2.10 Conclusion

The results of this analysis show treatment in the emergency department with adrenaline plus steroid, adrenaline or steroid, may reduce admissions and length of hospital stay. However, the clinical evidence may not reflect current practise and further research would be needed based on current care, which includes re-admissions and treatment once admitted, in order to develop a more useful cost effectiveness analysis.

A.2 Costs of CPAP and high flow oxygen

A.2.1 Costing analysis

No clinical evidence was identified comparing CPAP and high flow oxygen and so an economic evaluation was not developed. However, the GDG requested costing information for these two interventions.

Costs for CPAP and high flow oxygen equipment and consumables were provided by medical suppliers (Solus Medical Ltd. Email 28/4/14, Carefusion email 25/6/14).

Purchasing the equipment for CPAP or high flow oxygen is a capital cost, requiring an up-front payment. It was assumed that the equipment can be used for approximately 7 years before it needs to be replaced. There are two facets to capital costs:

- Opportunity cost – this is the money spent on equipment that could have been invested in another venture. This cost is calculated by applying an interest rate on the sum invested in the capital.
- Depreciation cost – the monitor has a certain lifespan and depreciates over time, and will eventually need to be replaced.

The usual practice for economic evaluation is to calculate an 'annual equivalent cost'. This is calculated by annuitizing the initial capital outlay over the expected life of the equipment. A unit cost can be calculated based on the typical use of the equipment pro rata. Calculating the equivalent annual cost means making allowance for the differential timing of costs by discounting.

The formula for calculating the equivalent annual cost is:

$E = K – [S / (1+r)n] / A(n,r)$

Where:

E = equivalent annual cost

K = Purchase price of the CPAP or high flow oxygen device

S = resale value

r = discount (interest) rate

n = equipment lifespan

A(n,r) = annuity factor (n years at interest rate r)

Using this formula a cost per day for use of a CPAP or high flow oxygen device was calculated to allow for comparison.

As the mean length of stay has been estimated as two days, the cost per use for each device has been calculated for a two day length of stay. Table 11,Table 12 and Table 13, report the cost per use for equipment plus consumables for high flow oxygen, and two CPAP devices. The EME CPAP was identified by the GDG as in use in the NHS (Table 13).

Table 11: Equipment and consumables costs for high flow oxygen

		Unit cost	notes
Precision flow heat and humidification device (with stand and hoses)		£4,550	Unit costs included training
Cost per day of use of vapotherm device		£1.65	assuming lifespan of 7years
Disposable patient circuits	£375 box of 5	£75	high or low flow
Standard infant nasal cannula	£130 box of 25	£5.20	
Cost per use of high flow oxygen		£84.28	Assuming mean length of use for high flow oxygen is 2 days

Table 12: Equipment and consumables costs for CPAP

		Unit cost	notes
CPAP unit and charger, harness, mask, flowmeter BSI, quick start IFU, attachment cord		£2,978	
Cost per one day of use		£1.08	Assuming a lifespan of 7years
Kit with harness; extension tube, ringer tube, device for generating the pressure, FiO2 regulator device, trigger for detection of inspiration and expiration, 1 facial mask, 1 head strap	£125 box of 5	£25	
Cost per use of CPAP		£27.67	Assuming mean length of use for CPAP is 2 days

Table 13: Equipment and consumables costs for SiPAP

		Unit cost	notes
SiPAP includes interface transducer, abdominal sensor, stand, bracket for stand, air hose, oxygen hose, humidifier, dual temp probe, electrical adaptor		£8,336.39	
Cost per one day of use		£3.74	Assuming a lifespan of 7years
Infant flow LP generator and neonatal singlelimb heated circuit	£676.11 box of 20	£33.81	
Nasal prong	£41.11 box of 10	£4.11	
Headgear	£71.61 box of 10	£7.16	
Bonnet	£63.30 box of 10	£6.33	
Silencer/bacteria filter	£143.11 for box of 20	£7.16	
Cost per use of SiPAP		£66.03	Assuming mean length of use for SiPAP is 2 days

In addition to the cost per use of the equipment and associated consumables there may be increased nursing requirements. The GDG identified a nursing ratio of two per infant when

using CPAP, whereas only one nurse is needed for high flow oxygen. Currently CPAP is given in intensive care and high flow oxygen is given on a normal ward. The potential additional costs per day of CPAP are shown in Table 14.

Table 14: Nursing costs

		Unit cost	notes
Nurse per hour 24 hour ward		£41	Curtis 2013
10 minute checks every hour for 24hours		£164	

The weighted cost per day for acute bronchiolitis taken from the NHS reference costs (2012/13) is £516. Neonatal critical care, special care, without an external carer (NHS reference cost for neonatal critical care with the greatest activity) has an average unit cost of £505. High dependency care and intensive care is more expensive (£791 and £1,118 respectively). If using CPAP requires this high cost care, then this would add £275 to £601 per day in hospital.

Although CPAP equipment is less expensive per use than high flow oxygen equipment, the additional costs of extra staffing make this a more expensive intervention. More evidence on staffing requirements for each device, and potential reductions in length of stay are needed in order to properly assess the cost-effectiveness of these interventions.

A.3 Costs of giving intravenous fluids or nasogastric hydration

A.3.1 Costing analysis

There was limited clinical evidence available to compare intravenous fluids with gastric tube feeding, or nasogastric hydration. The evidence was of low quality and few of the outcomes of interest were reported. The GDG requested a costing analysis for this area. A costing analysis was developed for the NICE guideline on diarrhoea and vomiting in children under 5 years (CG84) and this has been updated for this guideline.

A description of the process for giving IV fluids was reported in the diarrhoea and vomiting guideline. A patient is cannulised in the emergency department. They are reviewed hourly for the 4 hours they spend in the emergency department; this takes approximately 5 minutes per hour (total of 20 minutes) and is done by a nurse (band 5). Baseline observations, equipment adjustments and site checks are carried out hourly for the first 4 hours, these are all carried out by a band 5 nurse.

Table 15: Staff costs

Task	Staff	Time (minutes)	Unit cost (per hour)	Cost	source
Patient education	Band 5 nurse	10	£41	£6.83	Curtis 2013
Patient review	Band 5 nurse	20	£41	£13.67	Curtis 2013
Clinical examination	Registrar	10	£59	£9.82	Curtis 2013
Ametop application for IV only	Band 5 nurse	5	£41	£3.42	Curtis 2013
Cannulation	Band 5 nurse	35	£41	£23.92	Curtis 2013
	Registrar	17.5	£59	£17.21	Curtis 2013
Fluid preparation and attaching	Band 5 nurse	15	£41	£10.25	Curtis 2013
Equipment adjustment	Band 5 nurse	4 (4 times)	£41	£10.93	Curtis 2013
Baseline observations	Band 5 nurse	10 (4 times)	£41	£27.33	Curtis 2013

Table 16: Consumable costs for 24hours of nasogastric feeding

	quantity	Unit costs	Cost	source
formula milk	6 per 24hours	£0.48 per 200ml	£2.88	Ready-made formula www.tesco.co.uk
giving set	1	£1.95	£1.95	www.dsmedical.co.uk
colloid dressing	1	£70.46	£4.40	www.dsmedical.co.uk
endotrachael tube	1	£19.50 Box of 10	£1.95	www.dsmedical.co.uk
transparent film dressing 6x7cm	1	£38.15 Pack of 100	£0.38	www.dsmedical.co.uk
sterile exam gloves	1	£13.50 Pack of 50	£0.27	www.oncallmedicalsupplies.co.uk
pH paper	1	£28.00 Pack of 100	£0.28	www.oncallmedicalsupplies.co.uk

	quantity	Unit costs	Cost	source
syringe	1	£15.50 Box of 30	£0.52	www.oncallmedicalsupplies.co.uk

Table 17: Consumable costs for 24 hours of IV hydration

	quantity	Unit costs	Cost	source
IV solution - sodium chloride (0.9% saline)	500ml	£2.75	£2.75	www.spservices.co.uk
giving set with burette	1	£16.65 10 sets	£1.67	www.dsmedical.co.uk
cannula	2	£1.10	£2.20	www.midmeds.co.uk costs for an extension piece and a one-way valve needle free port were not identified
swabs	1 pack of 5	£1.99 100 swabs	£0.10	www.midmeds.co.uk
alcohol skin prep	2	£2.60 Pack of 100	£0.05	www.spservices.co.uk
0.9% saline flush syringe	1 x 5ml	£1.10	£1.10	www.spservices.co.uk
transparent film dressing 6x7cm	1	£38.15 Pack of 100	£0.38	www.oncallmedical.co.uk
sterile exam gloves	1	£13.50 Pack of 50	£0.27	www.oncallmedical.co.uk
pH paper	1	£28.00 Pack of 100	£0.28	www.oncallmedical.co.uk

Purchasing the equipment is a capital cost, requiring an up-front payment. An infusion pump and stand are required for IV fluids. It was assumed that the infusion pump can be used for approximately 10 years before it needs to be replaced and the drip stand lasts for approximately 5 years.

There are two facets to capital costs:

- Opportunity cost – this is the money spent on equipment that could have been invested in another venture. This cost is calculated by applying an interest rate on the sum invested in the capital.
- Depreciation cost – the monitor has a certain lifespan and depreciates over time, and will eventually need to be replaced.

The usual practice for economic evaluation is to calculate an 'annual equivalent cost'. This is calculated by annuitizing the initial capital outlay over the expected life of the equipment. A unit cost can be calculated based on the typical use of the equipment pro rata. Calculating the equivalent annual cost means making allowance for the differential timing of costs by discounting.

The formula for calculating the equivalent annual cost is:

$E = K – [S / (1+r)n] / A(n,r)$

Where:

E = equivalent annual cost

K = Purchase price of the CPAP or high flow oxygen device

S = resale value

r = discount (interest) rate

n = equipment lifespan

A(n,r) = annuity factor (n years at interest rate r)

Using this formula a cost per day for use of an infusion pump and drip stand was calculated to allow for comparison.

Table 18: Capital costs for IV fluids

	Duration of use	Life span of equipment	Unit cost	Cost per use	source
Infusion pump	24 hours	10years	£450 £1,200	£0.29	www.gb-medical.co.uk
Drip stand	24 hours	5years	£89.95	£0.05	www.spservices.co.uk

Table 19: Total costs for nasogastric feeding or IV fluids for 24hours

	Staff costs	Consumable costs	Capital costs	TOTAL
Nasogastric feeding	£133.64	£12.63	£0	£146.20
IV fluids	£137.06	£8.80	£0.34	£146.27

A.4 Treatment of Bronchiolitis

A.4.1 Review question

What is the efficacy of nebulised hypertonic saline?

A.4.2 Introduction

A.4.3 The use of nebulised hypertonic saline was identified as a priority area for economic evaluation as hypertonic saline is more expensive than normal saline. The clinical evidence demonstrated that hypertonic saline was potentially more effective than normal saline, in reducing admissions, length of stay and need for mechanical ventilation, although some results were equivocal.

A.4.4 Review of published evaluations

No published economic evaluations were identified for this question.

A.4.5 New economic evaluation

A.4.6 The clinical evidence for hypertonic saline all concentrations vs. normal saline 0.9% was used to develop a new economic evaluation. Results from all the studies were used as the base case for the model. However, there was considerable variation between the older and newer studies (will define in line with clinical review), with the newer studies being larger and with a better study design. Therefore, the model has been run with inputs from the older studies and again with inputs from the newer studies.

A.4.7 Methods

A decision tree model was developed in Excel based on the outcomes of the clinical review.

Hypertonic saline was compared to the following in the model:

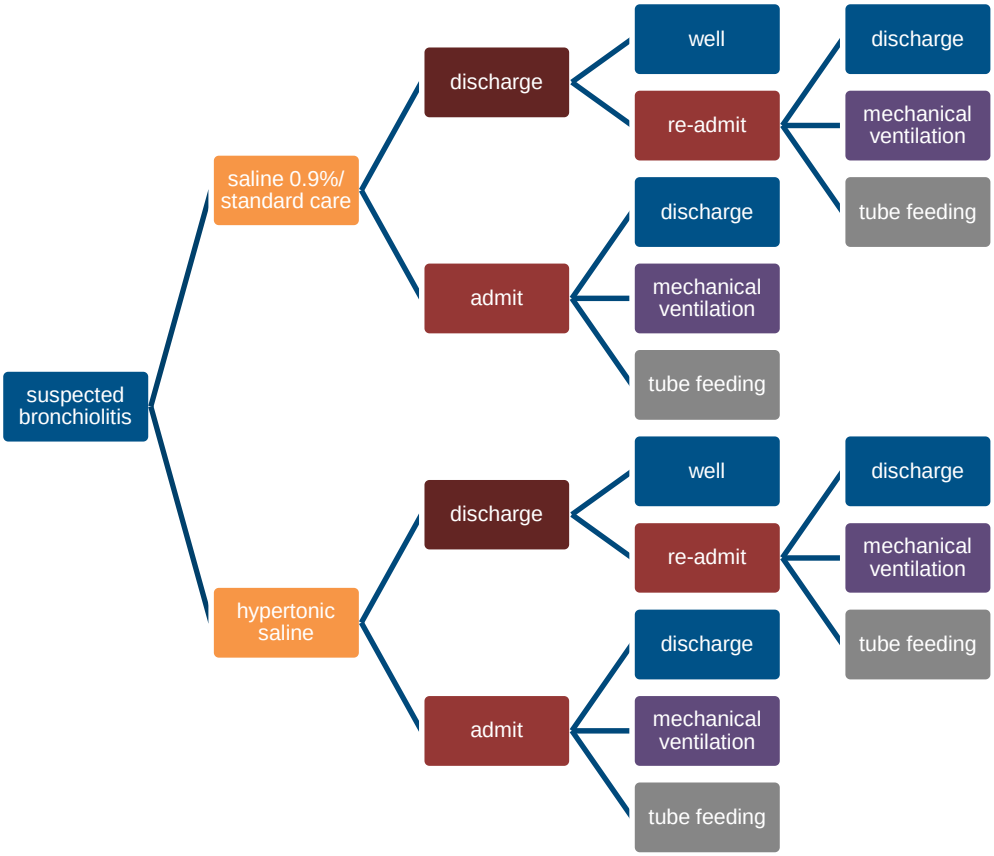
- Saline 0.9%
- Standard care (oxygen as required, minimal handling and fluid administration as appropriate)

In the studies identified patients were given other treatments, such as bronchodilators, salbutamol, and epinephrine. These treatments were given to both arms in the studies and so have not been taken into account in this model.

A schematic of the model is shown in Figure 3. Evidence was available to demonstrate the number of hospital admissions, discharge and re-admissions, use of mechanical ventilation and tube feeding, which would reflect an infant's condition worsening.

The model was developed from the perspective of the UK NHS, using 2012/13 costs. The time horizon for the model was less than a year and so no discount rate was applied.

Figure 3: Schematic diagram



A.4.8 Population

The population of children being treated for bronchiolitis in the NHS was estimated using the NHS reference cost data. This data reports the number of finished consultant episodes due to bronchiolitis for paediatric care, N=33,154. As this figure includes re-admissions it was assumed that approximately 80% of these episodes will be initial admissions, N=26,523. A network meta-analysis of bronchodilators and corticosteroids (Harling et al. 2011) reported the baseline risk of admission from all studies was 20%. Therefore, if N=26,523 infants are admitted for bronchiolitis, then N=132,616 will have been diagnosed with bronchiolitis.

The number of admissions includes non-elective short and long stays. A short stay is defined as ≤1 day. There are other reference costs for attendances to accident and emergency, however these are not defined by condition and so it is not possible to identify attendances due to bronchiolitis. So the model was also run with a population of N=26,523, assuming that this figure reflects the number of infants referred to hospital from primary care or go straight to hospital.

All infants diagnosed with bronchiolitis at hospital are assumed to be treated with either saline 0.9% or hypertonic saline for the base case analysis, or with standard treatment without saline for analysis based on the SABRE trial. Treatment will continue if an infant is admitted.

A.4.9 Outcomes

The main outcomes in the model were hospital admissions, length of stay, re-admissions, need for mechanical ventilation or tube feeding, and admission to ICU/HDU. The clinical

inputs are shown in Table 20 for saline 0.9% vs. hypertonic saline. The clinical inputs for standard care vs. hypertonic saline 3% are shown in Table 21.

As with the review for bronchodilators and corticosteroids, quality of life scores were not identified for bronchiolitis.

Table 20: Clinical inputs for saline 0.9% and hypertonic saline (all concentrations) (see evidence tables for further details

	Hypertonic saline, N	Total	Saline 0.9%, N	Total	RR
Hospital admission rate	123	486	156	460	0.79
Re-admission rate	32	213	22	153	1.04
Need for mechanical ventilation	0	27	2	26	0.19
Need for tube feeding	60	170	44	160	1.28
	Mean difference				
Length of stay	-0.45				

Table 21: Clinical inputs for standard care (oxygen as required, minimal handling and fluid administration as appropriate) and hypertonic saline 3% plus standard care (see evidence tables for further details)

	Hypertonic saline, N	Total	Standard care, N	Total	RR
Re-admission rate	4	128	7	140	0.625
Admitted to ICU/HDU	12	142	15	149	0.839
	Mean	**SD**	**Mean**	**SD**	
Time to discharge (hours)	100.6	76.9	101.3	84.4	

A.4.10 Costs

The costs of interest in this analysis are bed day costs related to the hospital stay and ICU and the cost of saline. 4ml of saline is given 3 times a day, reflecting the most common practice in the studies, and the suggested dosage in the BNF 2014. When the dosages are considered the difference in costs between normal saline and hypertonic saline are small, 4ml of 0.9% saline costs approximately 40p compared to 45p for hypertonic saline (Table 22). Currently, 3% and 6% saline costs the same amount (BNF 2014).

Table 22: Saline costs taken from the Prescriptions Pricing Authority Drug Tariff (June 2014) and BNF 2014

	Pack size	Pack cost	Unit cost
Saline 0.9% 2ml ampoules	10	£2.07	0.207
Mucoclear 3% or 6% nebuliser solution 4ml	60	£27.00	0.45

The cost of nebuliser equipment would be the same regardless of saline solution and so this has not been included in the base case analysis. For the comparison with standard care the

cost of using nebuliser equipment, associated consumables and staff time has been included (Table 23).

Table 23: Nebuliser equipment and consumables costs, staff time for giving saline

	Pack size	Pack cost	Unit cost	Source
Nebulizer		£95	£0.09	evergreen-nebulizers.co.uk
Face mask			£2.50	evergreen-nebulizers.co.uk
Filters	4	£4.50	£1.13	evergreen-nebulizers.co.uk
Tubing			£5.50	evergreen-nebulizers.co.uk
	Task time	**Cost per hour**	**Unit cost**	**Source**
Nurse time	3 x 15 mins	£41	£30.75	Curtis 2013

The mean length of stay was calculated by weighting the average length of stay for paediatric bronchiolitis admissions taken from the NHS reference costs, and this approach was used to calculate a weighted mean cost per bed day of £516 (Table 24).

Table 24: Paediatric admissions due to bronchiolitis, hospital costs and length of stay (NHS reference costs 2012/13)

		Finished consultant episodes (FCE)	Average length of stay - days	FCE cost	Average cost bed day
	Non-elective long stay				
PA15B	Acute Bronchiolitis with CC Score 0	9,040	3.23	£1,847	£424
PA15A	Acute Bronchiolitis with CC Score 1+	3,857	4.64	£2,669	£423
	Non-elective short stay				
PA15B	Acute Bronchiolitis with CC Score 0	17,740	≤1	£526	£526
PA15A	Acute Bronchiolitis with CC Score 1+	2,517	≤1	£603	£603
	Total number of paediatric admissions for acute bronchiolitis	33,154			
	Weighted mean length of stay for long stay (days)		3.65		
	Weighted cost per bed day				£516

The NHS reference costs for a FCE will include all staff time and any procedures necessary during the hospital admission. Mechanical ventilation would require the patient being in an ITU bed, and so the costs are reflected as a bed day on an ITU/HDU. As tube feeding could be done in a normal paediatric ward, an additional cost for equipment and consumables has been included to reflect differences in the need for this intervention. The costs for tube feeding are reported in the Table 25.

Table 25: Costs for tube feeding

	Unit cost	Description	Source
Intubation	£24.72	Endotracheal tube, laryngoscope blade, colloid dressing, (other equipment: laryngoscope handle, stethoscope and scissors not included as standard equipment on the ward)	Intrapartum Care guideline 2014

A cost for a day in ITU/HDU was calculated by weighting the average cost for paediatric critical care taken from the NHS reference costs (Table 26).

Table 26: Paediatric critical care admissions and hospital costs (NHS reference costs 2012/13)

		Finished consultant episodes (FCE)	FCE cost	Average cost bed day
XB04Z	Paediatric Critical Care, Intensive Care, Basic Enhanced	16,895	£2,110	
XB05Z	Paediatric Critical Care, Intensive Care, Basic	38,738	£1,743	
XB06Z	Paediatric Critical Care, High Dependency, Advanced	30,370	£1,335	
XB07Z	Paediatric Critical Care, High Dependency	47,586	£886	
XB09Z	Paediatric Critical Care, Enhanced Care	10,811	£902	
	Total number of paediatric admissions for acute bronchiolitis	144,400		
	Weighted cost per bed day			£1,355

A.4.11 Results

The models were run with a population of 132,616, where all patients were assumed to go to the emergency department and be treated initially, and 26,523 would be admitted. The model was re-run with a population of 26,523, where it was assumed only this group would be referred to the emergency department all would be admitted. Approximately 61% of paediatric admissions for bronchiolitis in the NHS reference costs were short stay which is ≤1day.

Using the mean inputs from the clinical review for hypertonic saline compared to 0.9% normal saline, the base case results show that using hypertonic saline could lead to reduced admissions and reduced need for mechanical ventilation. However, normal saline is associated with fewer re-admissions and reduced need for tube feeding (Table 27 - Table 32). Although hypertonic saline does not consistently demonstrate health benefits compared to normal saline, the results show hypertonic saline is less expensive than using normal saline. This is mainly driven by the number of admissions and re-admissions, in total 41,778 for normal saline and 37,729 for hypertonic saline with a population of 132,616. Even though patients treated initially with hypertonic saline were more likely to be re-admitted, this did not outweigh the increased likelihood of initial admission with normal saline.

Using inputs mainly from the older studies and a population of 132,616 infants diagnosed with bronchiolitis showed saline 0.9% was less expensive than hypertonic saline (Table 29). This is likely to be due to the difference in length of stay, which was greatest mean difference (-1.01days, compared to -0.45 and -0.05 for all studies and only new studies respectively) and favoured patients treated with 0.9% saline. All other runs of the model favoured hypertonic saline, although the differences in mean costs were small.

Table 27: Results – 132,616 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – ALL STUDIES

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	15,255	1,250	4,469	£203
Hypertonic saline	20,953	16,776	272	5,180	£198

Table 28: Results – 26,523 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – ALL STUDIES

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	3,814	908	3,245	£760
Hypertonic saline	20,953	3,148	174	3,309	£659

Table 29: Results – 132,616 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – OLD STUDIES (for admission rates and length of stay)

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	15,255	1,250	4,469	£169
Hypertonic saline	15,649	17,573	239	4,561	£176

Table 30: Results- 26,523 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – OLD STUDIES

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	15,255	1,250	4,469	£169

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Hypertonic saline	15,649	17,573	239	4,561	£176

Table 31: Results – 132,616 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – NEW STUDIES (for admission rates and length of stay)

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	15,255	1,250	4,469	£231
Hypertonic saline	22,545	16,537	282	5,366	£202

Table 32: Results – 26,523 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – NEW STUDIES

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	3,814	908	3,245	£839
Hypertonic saline	22,545	3,387	187	3,560	£667

Table 33: Results – infants diagnosed with bronchiolitis and initially treated with standard care or hypertonic saline 3%– SABRE, N=132,616

	N Admitted	N Re-admitted	N admitted to ICU	Mean cost per infant (probabilistic)
Saline 0.9%	26,523	5,305	3,204	£730
Hypertonic saline	26,523	3,315	2,690	£769

Table 34: Results – infants diagnosed with bronchiolitis and initially treated with standard care or hypertonic saline 3%– SABRE, N=26,523

	N Admitted	N Re-admitted	N admitted to ICU	Mean cost per infant (probabilistic)
Saline 0.9%	26,523	1,326	2,804	£1,361
Hypertonic saline	26,523	829	2,354	£1,388

A.4.12 Probabilistic sensitivity analysis

To consider the variability in the inputs to the model a probabilistic sensitivity analysis (PSA) was developed. Distributions could be described for the clinical inputs, and the cost of a bed day. As parameters to describe the distributions were not available for the drug costs or mean length of stay, these remained deterministic (Table 35 - Table 36).

Table 35: Probabilistic inputs for all studies together, and old and new separately

	Distribution	Parameters ALL		Parameters OLD		Parameters NEW	
Hospital admission rate 0.9% saline	Beta	156	460	28	183	128	297
Re-admission rate 0.9% saline	Beta	22	153	22	153	22	153
Need for mechanical ventilation 0.9% saline	Beta	2	26	2	26	2	26
Need for tube feeding 0.9% saline	Beta	44	160	44	160	44	160
Hospital admission rate hypertonic saline	Lognormal	0.79	0.102	0.59	0.283	0.85	0.102
Re-admission rate hypertonic saline	Beta	32	213	32	213	32	213
Need for mechanical ventilation hypertonic saline	Beta	0.5[a]	27	0.5[a]	27	0.5[a]	27
Need for tube feeding hypertonic saline	Beta	60	170	60	170	60	170
Length of hospital stay	Normal	-0.45	0.133	-1.01	0.189	-0.05	0.087
		Mean	**SE**				
Cost per bed day	Normal	516	176				
Mean length of stay	Deterministic						
Cost per bed day ICU/HDU	Normal	1,340	351				
Drug costs	Deterministic						

(a) the clinical input was 0, it has been made 0.5 to allow probabilistic analysis.

Table 36: Probabilistic inputs for SABRE

	Distribution	Parameters	
Re-admission rate standard care	Beta	7	140
Admission to ICU/HDU	Beta	15	149
Length of hospital stay standard care (hours)	Gamma	101.30	84.40
Re-admission rate hypertonic saline	Lognormal	0.63	0.63
Admission to ICU/HDU	Beta	12	142
Length of hospital stay hypertonic saline (hours)	Gamma	100.60	76.0
Staff costs	Deterministic		
Nebuliser equipment and equipment	Deterministic		

When 1,000 simulations were run with the PSA, there was considerable uncertainty in the results comparing hypertonic saline with normal saline. With the admission rates and length of stay from new studies, hypertonic saline was most likely to be cost-effective (Table 37). However with all studies included hypertonic saline would be cost saving in 59% of simulations.

Using inputs from the SABRE trial showed hypertonic saline would not be cost-effective compared to standard care, in only 7% of simulations hypertonic saline was cost saving compared to standard care.

Table 37: Probabilistic sensitivity analysis results

	mean cost per infant diagnosed	Proportion of simulations where hypertonic saline is cost saving compared to 0.9% or standard care
All studies		
Hypertonic saline	£203	59%
0.9% saline	£198	
Old studies		
Hypertonic saline	£176	44%
0.9% saline	£169	
New studies		
Hypertonic saline	£202	76%
0.9% saline	£231	
SABRE		
Hypertonic saline	£760	7%
Standard care	£721	

A.4.13 Discussion

The direction of the results show hypertonic saline is cost saving compared to normal saline. However there is considerable uncertainty in the results as seen in the probabilistic sensitivity analysis. When hypertonic saline is compared to standard care, standard care is cost saving.

A.5 Pulse oximetry monitoring

A.5.1 Costing analysis

The evidence available for this area was limited and of low quality. The evidence was for the emergency department setting. Costs were considered an important factor for introducing pulse oximetry monitoring to primary care. Therefore the costs for pulse oximetry monitors were identified (Table 38 and Table 39).

Table 38: Costs for pulse oximetry monitoring equipment

	Unit cost	Description	Source
Digital oximeter	£349 to over £1,000	Basic hand held digital oximeter to a device with memory, alarms and ability to monitor temperature or blood pressure as well as O_2 saturation.	Oncallmedical.co.uk
Finger probe	£65	Reusable paediatric finger probe	Oncallmedical.co.uk

Table 39: NHS reference costs for paediatric hospital admissions for bronchiolitis

		Finished consultant episodes (FCE)	FCE cost	Lower interquartile range	Upper interquartile range
	Non-elective long stay				
PA15B	Acute Bronchiolitis with CC Score 0	9,040	£1,847	£1,495	£2,064
PA15A	Acute Bronchiolitis with CC Score 1+	3,857	£2,669	£2,042	£3,135
	Non-elective short stay				
PA15B	Acute Bronchiolitis with CC Score 0	17,740	£526	£380	£606
PA15A	Acute Bronchiolitis with CC Score 1+	2,517	£603	£450	£669

Appendix B: Scope

B.1 Guideline title

Bronchiolitis: diagnosis and management of bronchiolitis in children.

B.2 Short title

Bronchiolitis in children

B.3 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on bronchiolitis: diagnosis and management of bronchiolitis'.

B.3.1 Epidemiology

a) Bronchiolitis is the most common disease of the lower respiratory tract during the first year of life.
b) Bronchiolitis usually presents with cough with increased work of breathing and it often affects a child's ability to feed. Symptoms are usually mild and might only last for a few days, but in some cases the disease can cause severe illness.
c) Infection follows a seasonal pattern, peaking during the winter months. Respiratory syncytial virus (RSV) causes the majority of cases. Other causes include influenza, parainfluenza, adenovirus and human metapneumovirus.
d) There are several individual and environmental risk factors that can put children with bronchiolitis at increased risk of severe illness. These include premature birth, passive smoke exposure, living conditions, congenital heart disease, cystic fibrosis, immunodeficiency and chronic lung disease.
e) Although bronchiolitis can usually be managed at home, approximately 3% of affected children are admitted to hospital. In 2011/2012 in England there were 30,451 secondary care admissions for the management of bronchiolitis.
f) It is uncommon for bronchiolitis to cause death. In 2009/2010 in England, there were 72 recorded deaths of children within 90 days of hospital admission for bronchiolitis.
g) Bronchiolitis is associated with an increased risk of chronic respiratory conditions, including asthma, but it is not known if it causes these conditions.

B.3.2 Current practice

a) Most children with bronchiolitis present in primary care to a GP. The diagnosis of bronchiolitis is based on clinical assessment showing the presence of various characteristic symptoms and signs.
b) In some locations children with risk factors for severe bronchiolitis may be offered immunoprophylaxis with intramuscular pavilizumab.
c) The management of bronchiolitis depends on the severity of the illness. In most children bronchiolitis can be managed at home by parents or carers.
d) Children with severe bronchiolitis are immediately referred to hospital for specialist assessment and treatment. The following indications prompt referral for specialist care:
    - moderate or severe respiratory distress
    - poor feeding
    - lethargy
    - apnoeic episodes (stop breathing)
    - reduced oxygen saturation (SpO2)
    - diagnostic uncertainty.
e) In mild or moderate cases treatments that improve feeding and reduce the work of breathing could be beneficial. A range of treatments have been trialled, including:
    - inhaled bronchodilators

- inhaled corticosteroids
- systemic corticosteroids
- antibiotics.

f) In children admitted to hospital with severe illness, treatment focuses primarily on supportive measures such as preventing dehydration (for example, using nasogastric or intravenous fluids), providing nutrition (for example, nasogastric feeds) and using oxygen supplementation if necessary.
g) Bronchiolitis is usually a self-limiting condition with no long-term treatment or follow-up needed. However, some children develop recurrent post-bronchiolitis symptoms such as a troublesome cough that can persist for months.
h) Given the very high prevalence of bronchiolitis and its potentially serious impact on a child's health, guidance on diagnosis and management is needed.

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

B.4 Population

B.4.1 Groups that will be covered

a) Children with bronchiolitis.
b) Patient subgroups will be identified based on the available evidence – for example, premature birth, congenital heart disease, cystic fibrosis, immunodeficiency and chronic lung disease.

B.4.2 Groups that will not be covered

a) Children with other respiratory conditions, such as recurrent viral induced wheeze or asthma.

B.4.3 Healthcare setting

a) All settings in which NHS care is received or commissioned (including community care and information for home management).

B.5 Clinical management

B.5.1 Key clinical issues that will be covered

a) Diagnosis and monitoring:
    - differentiating bronchiolitis from other respiratory conditions
    - criteria for referral to secondary care and for hospital admission, including consideration of heart rate, respiratory rate, respiratory distress, oxygen saturation (SpO2) and feeding difficulty.

b) Investigations:
    - Indications for oxygen saturation (SpO2) measurement using pulse oximetry
    - indications for chest radiography

- indications for capillary blood gas testing.

c) Treatments:

- chest physiotherapy
- antibiotic treatment
- inhaled therapies (including epinephrine [adrenaline], salbutamol, corticosteroids, ipratropium bromide)
- systemic corticosteroids
- nebulised hypertonic saline
- heliox (combined helium and oxygen)
- combined bronchodilator and corticosteroid therapy
- Montelukast (leukotriene receptor antagonist).

d) Supportive measures to maintain SpO2 or ventilation, including:

- oxygen supplementation (including humidified oxygen)
- humidified high-flow oxygen
- continuous positive airway pressure (CPAP).

e) Indication for fluids and nutrition support.

f) Use of nasal suction.

g) Criteria for discharge from hospital.

Note that guideline recommendations for treatments will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

B.5.2 Clinical issues that will not be covered

a) Screening for RSV in primary care.
b) Viral testing in hospital to prevent transmission.
c) Complementary and alternative treatments.
d) Ribavirin.
e) Surfactant.
f) Normal saline.
g) Prevention of bronchiolitis by the use of palivizumab for immunoprophylaxis of RSV.
h) Supportive treatments other than those specified in section 4.3.1. For example invasive ventilation will not be covered in the guideline.

B.5.3 Main outcomes

a) Patient and clinical outcomes:

- health-related quality of life (including severity scores)
- change in clinical status (including resolution of respiratory symptoms, return to adequate feeding, or need for ventilator)
- SpO2
- long-term morbidity
- Adverse events
- mortality.

b) Health service outcomes:

- need for referral to secondary care
- admission rates
- length of treatment
- readmission rate.

c) Diagnostic outcomes:
    - diagnostic accuracy (for example, sensitivity and specificity) of symptoms and signs.

B.6 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

B.6.1 Diagnosis and monitoring in bronchiolitis

a) What characteristics, symptoms, signs and clinical progression are typical of bronchiolitis, and allow differentiation from other respiratory conditions?
b) What are the risk factors for severe bronchiolitis?
c) At the time of assessment, what predicts the likelihood of deterioration?
d) What are the indications for capillary blood gas testing?
e) What are the indications for fluids and nutritional support?
f) Based on indications for investigation and treatment what are the criteria for i) referral to secondary care, ii) hospital admission for observation or treatment, and iii) discharge from hospital?
g) What are the indications for SpO2 monitoring?
h) What are the indications for chest radiography?

B.6.2 Treatment of bronchiolitis

a) What is the efficacy of chest physiotherapy in the management of bronchiolitis?
b) What is the efficacy of antibiotic treatment?
c) What is the efficacy of inhaled bronchodilators (adrenaline, salbutamol, ipratropium bromide)?
d) What is the efficacy of inhaled corticosteroids?
e) What is the efficacy of systemic corticosteroids?
f) What is the efficacy of nebulised hypertonic saline?
g) What is the efficacy of heliox?
h) What is the efficacy of combined bronchodilator and corticosteroid therapy?
i) What is the efficacy of Montelukast?

B.6.3 Supportive treatment of bronchiolitis

a) What is the efficacy of oxygen supplementation, including humidified oxygen, CPAP or humidified high-flow oxygen?
b) b) What is the efficacy of nasal suction?

B.6.4 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions., A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The

preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

B.7 Status

B.7.1 Scope

This is the final scope.

B.7.2 Timing

The development of the guideline recommendations will begin in May 2013.

B.8 Published guidance

B.8.1 Other related NICE guidance

- Antibiotics for early-onset neonatal infection. NICE clinical guideline 149 (2012).
- Infection. NICE clinical guideline 139 (2012).
- Prevention and control of healthcare-associated infections. NICE public health guidance 36 (2011).
- Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 (2010).
- Respiratory tract infections – antibiotic prescribing. NICE clinical guideline 69 (2008).
- Omalizumab for severe persistent allergic asthma. NICE technology appraisal guidance 133 (2007).
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance 131 (2007).
- Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma. NICE technology appraisal guidance 10 (2000).

B.9 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Feverish illness in children. NICE clinical guideline (update). Publication expected May 2013.
- Asthma. NICE clinical guideline. Publication expected June 2015.
- Intravenous fluid therapy in children. NICE clinical guideline. Publication expected October 2015.

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix C: Stakeholders

AbbVie

Alder Hey Children's NHS Foundation Trust

Allocate Software PLC

Association for Respiratory Technology and Physiology

Association of Ambulance Chief Executives

Association of Anaesthetists of Great Britain and Ireland

Association of Children’s Diabetes Clinicians

Association of Paediatric Chartered Physiotherapists

Barnsley Hospital NHS Foundation Trust

Barnsley Hospital NHS Foundation Trust

Barnsley Hospital NHS Foundation Trust

Belfast Health and Social Care Trust

Belfast Health and Social Care Trust

Birmingham Children's Hospital NHS Foundation Trust

Bliss

Boots

Breastfeeding Network - Scotland

British Geriatrics Society

British Infection Association

British Infection Association

British Lung Foundation

British Medical Association

British Medical Journal

British National Formulary

British Nuclear Cardiology Society

British Nuclear Cardiology Society

British Psychological Society

British Red Cross

British Society of Paediatric Radiology

British Society of Thoracic Imaging

British Thoracic Society

Calderdale and Huddersfield NHS Trust

Cambridge University Hospitals NHS Foundation Trust

Capsulation PPS

Care Quality Commission

Chartered Society of Physiotherapy

Chartered Society of Physiotherapy

College of Emergency Medicine

Countess of Chester Hospital NHS Foundation Trust

Covidien Ltd.

Croydon Clinical Commissioning Group

Croydon Health Services NHS Trust

Croydon University Hospital

Cumbria Partnership NHS Foundation Trust

CWHHE Collaborative CCGs

Department of Health

Department of Health, Social Services and Public Safety - Northern Ireland

East and North Hertfordshire NHS Trust

East Kent Hospitals University NHS Foundation Trust

Economic and Social Research Council

Ethical Medicines Industry Group

Faculty of Sport and Exercise Medicine

Faculty of Sport and Exercise Medicine

Five Boroughs Partnership NHS Trust

Gloucestershire Hospitals NHS Foundation Trust

GP update / Red Whale

Greater Manchester & Beyond Coalition of PLW & HIV

Guidelines and Audit Implementation Network

Health & Social Care Information Centre

Health and Care Professions Council

Healthcare Improvement Scotland

Healthcare Infection Society

Healthcare Infection Society

Healthcare Quality Improvement Partnership

Healthwatch East Sussex

Herts Valleys Clinical Commissioning Group

Hockley Medical Practice

HQT Diagnostics

Humber NHS Foundation Trust

Imperial College Healthcare NHS Trust

Institute of Biomedical Science

Joint Royal Colleges Ambulance Liaison Committee

Joint Royal Colleges Ambulance Liaison Committee

King Fahd Military Medical Complex

Lactation Consultants of Great Britain

Leeds North Clinical Commisioning Group

Leeds South and East Clinical Commissioning Group

Leicestershire Partnership NHS Trust

Local Government Association

Luton and Dunstable Hospital NHS Trust

Luton and Dunstable Hospital NHS Trust

Medicines and Healthcare products Regulatory Agency

Medicines and Healthcare products Regulatory Agency

Medicines and Healthcare products Regulatory Agency

Medicines and Healthcare products Regulatory Agency

Ministry of Defence (MOD)

Monash Health

National Association of Primary Care

National Childbirth Trust

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Cancer

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Mental Health

National Collaborating Centre for Mental Health

National Collaborating Centre for Mental Health

National Collaborating Centre for Mental Health

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Collaborating Centre for Women's and Children's Health

National Deaf Children's Society

National Institute for Health Research

National Institute for Health Research Health Technology Assessment Programme

National Patient Safety Agency

Neonatal & Paediatric Pharmacists Group

NHS Barnsley Clinical Commissioning Group

NHS Choices

NHS Connecting for Health

NHS County Durham and Darlington

NHS Cumbria Clinical Commissioning Group

NHS England

NHS Hardwick CCG

NHS Health at Work

NHS Improvement

NHS Medway Clinical Commissioning Group

NHS Medway Clinical Commissioning Group

NHS Plus

NHS Richmond

NHS Sheffield

NHS South Cheshire CCG

NHS Wakefield CCG

NHS Warwickshire North CCG

NICE - CPHE

NICE - CPHE

NICE - CPHE

NICE - CPHE

NICE - DAP

NICE - Evidence Services

NICE - Health and Social Care Quality Programme

NICE - Health and Social Care Quality Programme

NICE - Implementation

NICE - Implementation

NICE - Internal Clinical Guidelines Programme

NICE - Interventional Procedures

NICE - Medicines and Prescribing Centre

NICE - Medicines and Prescribing Centre

NICE - MTEP

NICE - PIP

NICE - R&D

NICE - Scientific Advice

NICE - Scientific Advice

NICE - Technology Appraisals

NICE - Topic selection

NICE - Topic selection

North of England Commissioning Support

North West London Hospitals NHS Trust

North West London Hospitals NHS Trust

North West London Perinatal Network

Northern Health and Social Care Trust

Nottingham Children's hospital

Nursing and Midwifery Council

Nutricia Advanced Medical Nutrition

Paediatric Intensive Care Society

Parenteral and Enteral Nutrition Group

Pathfinders Specialist and Complex Care

Pharmaxis Pharmaceuticals Ltd

PHE Alcohol and Drugs, Health & Wellbeing Directorate

PrescQIPP NHS Programme

Primary Care Pharmacists Association

Primary Care Respiratory Society UK

Primrose Bank Medical Centre

Professional Network for Physiotherapists in Respiratroy Care

Public Health England

Public Health England

Public Health Wales NHS Trust

Public Health Wales NHS Trust

Public Health Wales NHS Trust

Public Health Wales NHS Trust

Queen Elizabeth Hospital King's Lynn NHS Trust

Royal Brompton Hospital & Harefield NHS Trust

Royal College of Anaesthetists

Royal College of General Practitioners

Royal College of General Practitioners in Wales

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Nursing

Royal College of Obstetricians and Gynaecologists

Royal College of Obstetricians and Gynaecologists

Royal College of Paediatrics and Child Health

Royal College of Pathologists

Royal College of Physicians

Royal College of Psychiatrists

Royal College of Radiologists

Royal College of Surgeons of England

Royal College of Surgeons of England

Royal College of Surgeons of England

Royal Cornwall Hospitals NHS Trust

Royal Free Hospital NHS Foundation Trust

Salford Royal NHS Foundation Trust

Scottish Clinical Virology Consultants Group

Scottish Intercollegiate Guidelines Network

Scottish Intercollegiate Guidelines Network

Sheffield Children's NHS Trust

Sheffield Teaching Hospitals NHS Foundation Trust

Sheffield Teaching Hospitals NHS Foundation Trust

Social Care Institute for Excellence

Society and College of Radiographers

South Eastern Health and Social Care Trust

South West Yorkshire Partnership NHS Foundation Trust

Southern Health & Social Care Trust

Southport and Ormskirk Hospital NHS Trust

St John Ambulance

St Mary's Hospital

Staffordshire and Stoke on Trent Partnership NHS Trust

Stockport Clinical Commissioning Group

Suffolk County Council

Taunton & Somerset NHS Foundation Trust

The African Eye Trust

Twins and Multiple Births Association

University Hospital Birmingham NHS Foundation Trust

University Hospital Of South Manchester NHS Foundation Trust

University Hospitals Birmingham

Welsh Government

Welsh Government

Welsh Scientific Advisory Committee

Western Health and Social Care Trust

Wigan Borough Clinical Commissioning Group

York Hospitals NHS Foundation Trust

Appendix D: Declarations of interest

Table 40: GDG members' declarations of interest

GDG member	Interest
Thomas Bourke	**Personal pecuniary** • Expenses to attend a meeting from Novartis Pharmaceuticals (not related to Bronchiolitis) • Personal non-pecuniary

GDG member	Interest
	• Published a paper on Bronchiolitis (Bronchiolitis; Bourke T, Shields M.; Clin Evid, 2011, 04 (0308)).
Kate Chadwick	No interests declared
John Crimmins	No interests declared
Steve Cunningham	**Personal non-pecuniary** • Chief investigator in a project funded by HTA (BiDS) about oxygen saturation in infant with bronchiolitis at discharge from hospital. Principle Investigator for Phase 1 study of novel drug treatment for RSV bronchiolitis in infants. **Personal pecuniary** • Attends lunch meeting sponsored by Glaxo Smith Kline every 3 months • Advisory board attendance with honorarium for Gilead at which a product for cystic fibrosis was discussed, but also a brief discussion on a novel drug treatment for RSV bronchiolitis. • Consultancy work via NHS Lothian for Biotechnology company developing a novel drug treatment for RSV bronchiolitis in infants.
Julie McKnight	No interests declared
Julian Legg	**Personal non-pecuniary** • Research interest in viral bronchiolitis **Personal pecuniary** • Attended a medical meeting sponsored by Glaxo Smith Kline at which a product unrelated to the current guideline was discussed. GlaxoSmithKline provided subsistence (a meal) for the attendees. • Chaired meeting of Wessex Paediatric Respiratory Society in February 2014. This was an educational meeting sponsored by GlaxoSmithKline who arranged the venue and provided subsistence (a meal) for the attendees. No areas related to the current guideline were discussed. • Attended a Cystic Fibrosis educational meeting (March 2014) organised by Forest Laboratories who provided overnight accommodation and subsistence (meals). No areas related to the current guideline were discussed. **Non-personal pecuniary** • Expenses from Abbott Laboratories to support attendance of a meeting on Cystic Fibrosis organised by a charity (Child Health International) in Bulgaria in 2013.
Bhavee Mahesh Patel	No interests declared
Clare van Miert	**Personal pecuniary** • Clinical doctorate research fellowship funded by the National Institute for Health Research to Measuring Clinical Severity in Infants with Bronchiolitis. This is a multi-centred project which aims to develop and validate a bronchiolitis scoring instrument for infants with bronchiolitis using mixed methods; advisory panel member for the Healthtalkeonline ARCHIE study, funded by NIHR which provided expenses to attend the advisory panel meetings; meeting expenses to attend a NIHR trainee meeting; attendee to Ground Rounds meeting sponsored by Marshall Products **Personal non-pecuniary** • Speaker at a respiratory meeting where she presented her doctorate research study (this meeting was founded by NIHR which produce inhalers for asthma); co-applicant on a grant [PCORI] with aims to identify important outcomes for parents with children with acute respiratory infections; attended a preliminary meeting with

GDG member	Interest
	representatives of Fisher & Paykel to explore the possibility that they would supply equipment and consumables for a research study investigating the efficacy and safety of high flow oxygen compared to standard care; published a paper van Miert C, Abbott J, Verhoeff F, Lane S, Carter B, McNamara P (2014) Development and Validation of the Liverpool Infant Bronchiolitis Severity Score: a research protocol. Journal of Advanced Nursing; Submitted an application to HTA commission call for a feasibility study to look at the optimum thresholds for starting nCPAP and highflow oxygen in infants with bronchiolitis (£255,816.00) • Attended a ground round meeting which had a breakfast sponsored by Spectrumthea (crossiant and coffee)
Debra Quantrill	**Personal pecuniary** • Holds shares in Futura Medical plc - pharmaceutical group that develops products for the consumer healthcare market. www.futuramedical.com
Anshu Sharma	No interests declared

Table 41: NCC-WCH staff members' declarations of interest

NCC-WCH staff	Interest
Jiri Chard	No interests declared
Gemma Marseniuk	No interests declared
Nitara Prasannan	No interests declared
Hanna Rose Douglas	No interests declared
Valentina Ricci	No interests declared
Stephen Murphy	No interests declared
Vanessa Delgado Nunes	No interests declared
Cristina Visintin	No interests declared

Appendix E: Protocols

E.1 Q1 Symptoms and signs of ABI

	Details	Additional comments
Review question	What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions?	Other respiratory conditions are – recurrent wheeze, pneumonia, and early asthma.
Objectives	The aims of this review are: 1. What is the clinical course of bronchiolitis? a. What are the typical symptoms of bronchiolitis? b. At what ages does bronchiolitis typical occur?	The diagnosis of bronchiolitis is based on the clinical presentation and progress of the condition and so it is important to describe it accurately for the purpose of diagnosis. Certain features that are not typical may indicate either the presence of a complication of bronchiolitis or an alternative disorder. Certain

	Details	Additional comments
	c. What is the typical duration of symptoms? d. How due symptoms change during the course of a bronchiolitis episode? e. When do symptoms peak?	atypical features, such as a high fever might constitute red flags. A description of the 'typical' symptoms and clinical course of bronchiolitis will give parents/carers and health professionals important information on what to expect. This can be used to determine what is not 'typical' and what action is required. A second aim had been suggested. Provide information on the diagnostic usefulness of specified symptoms and signs? However, as no 'gold' standard exists for diagnosis of bronchiolitis this question cannot be taken forward.
Language	English	
Study design	Comparative and non-comparative observational studies	Comparative observational studies including cohort studies case–control studies
Status	Published papers	
Population	Children presenting in primary care setting with acute onset respiratory symptoms	It is likely that most studies will have been undertaken in a secondary care setting with a retrospective assessment of symptoms and signs. Given the expected lack of evidence, this question is likely to require consensus work amongst the GDG.
Intervention	Symptoms for identification of 'typical' bronchiolitis • Wheeze • Crackles • Rapid breathing (tachypnoea) • Increased work of breathing (breathlessness, increased respiratory effort) • Coryzal (nasal discharge) • Cough • Fever These symptoms are for identification of potentially 'problematic/severe' bronchiolitis requiring emergency management:	European definition includes crackles, whereas the North American definition does not. Many of these symptoms are very common so could not be used in isolation (cough or nasal discharge) A number of severity scores have been developed based on symptoms.

	Details	Additional comments
	• Apnoea • Recession • Retraction • Nasal flaring • Prolonged expiration • Tachycardia • Colour change (including cyanosis) • Hypoxia • Feeding difficulty (however defined) • Social responsiveness • Irritability • Drowsiness • Age at presentation • Duration of symptoms • Stridor • Grunting • Shortness of breath • Tracheal tug • Gut feeling/concerns – parental or health professional • Head movement with breathing difficulty	
Comparator or reference standard	Other respiratory conditions that bronchiolitis needs to be differentiated from: • Recurrent wheeze • Asthma • Pneumonia	
Outcomes	Description of: • At what ages does bronchiolitis typical occur? • What are the typical symptoms of bronchiolitis? • What is the typical duration of symptoms? • How due symptoms change during the course of a bronchiolitis episode? • When do symptoms peak?	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies on panbronchiolitis and bronchiolitis obliterans • Exclude studies of children on invasive ventilation	
Search strategies	See separate document	

	Details	Additional comments
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.2 Q2 Risk factors for severe ABI

	Details	Additional comments
Review question	What are the risk factors for severe bronchiolitis?	
Objectives	The aim of this review is to identify the risk factors for developing severe bronchiolitis. This question is important because some babies (such as the very young, those with a history of prematurity etc.) may be at increased risk of more severe disease. Early identification of those at risk may help to inform the management strategy. This question is related to the question on predictors of deterioration, but it focuses on characteristics inherent to the child – i.e., are present before the onset of the illness. Severe might be defined using many criteria, but the definition used in any studies included will need to be reported clearly.	
Language	English	
Study design	Observational studies comparing patients with severe bronchiolitis and those without • Cohort • Case-control	
Status	Published papers	
Population	Children with bronchiolitis	
Intervention	Prevalence of risk factors in children with severe bronchiolitis: • History of prematurity (degree of prematurity may be relevant and should be reported) • Bronchopulmonary dysplasia	Severe bronchiolitis has been defined as the need for hospitalisation. The threshold will vary between studies.

	Details	Additional comments
	• Congenital heart disease • Chronic lung disease • Cystic fibrosis • Immunodeficiency • Non-breast fed • Young infants (for example, less than 2 months old) • Sex (Male) • Previous hospitalisation • Ethnicity • Down's syndrome • Family Smoking • Multiple birth • Neurodisability	
Comparator or reference standard	Prevalence of risk factors in children without severe bronchiolitis	Children without severe bronchiolitis might have mile/moderate bronchiolitis or might not have bronchiolitis
Outcomes	• Adjusted Relative risks • Adjusted Odds ratios	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude different disorders of the bronchioles, such as pan-bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.3 Q3 Predictors of deterioration

	Details	Additional comments
Review question	At the time of assessment, what clinical features predict deterioration?	
Objectives	The aim of this review is to identify clinical features at the time of assessment that predict likely deterioration. This question is related to the question on "risk factors for severe bronchiolitis", but considers clinical features of the illness itself. Such features could be taken into consideration in deciding on appropriate management –	The reviewer will state explicitly the definition of severe bronchiolitis used in the study.

	Details	Additional comments
	such as a decision to refer to secondary care or transfer to PICU.	
Language	English	
Study design	• Observational studies comparing the clinical features at initial assessment in those who subsequently progressed to severe bronchiolitis and those who did not. • Cohort • Case-control	Severe bronchiolitis defined as hospital admission as no other
Status	Published papers	
Population	Children presenting with non-severe bronchiolitis	For this question the population entering the study should not have severe bronchiolitis because the question is looking for predictors of deterioration. If the study looks at deterioration to the point of PICU/ventilator support, then the definition of non-severe would be those who do not initially need such support (although they might be in hospital and receiving quite a lot of other support). The definitions used will need to be clearly reported
Intervention	The prevalence of clinical features at initial assessment in children who go on to develop severe bronchiolitis at a later date: • Duration of illness (days from onset) • Heart Rate (taking account of age) • Respiratory Rate (taking account of age) • Fever (height of fever) • SpO2 (e.g., <92%) • Ability to feed (e.g., <50% or <75% normal) • Subjective assessments, e.g., social responses	
Comparator or reference standard	The prevalence of clinical features listed above in those who did not go on to develop severe bronchiolitis	
Outcomes	Adjusted figures for admission to hospital or PICU	Serious bronchiolitis is defined as admission to hospital. It is realised that the threshold for this will vary and could be based on existing clinical criteria.
Other criteria for inclusion/	• Exclude non-human studies	

	Details	Additional comments
exclusion of studies	• Exclude studies of pan bronchiolitis and bronchiolitis obliterans • Exclude studies of children on invasive ventilation	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.4 Q4 Capillary blood gas testing

	Details	Additional comments
Review question	What is the indication for capillary blood gas testing?	
Objectives	The aim of this review are to: • determine what factors indicate the need for capillary blood gas testing and • the role of arterialised carbon dioxide values in guiding the use of high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation.	The GDG believe the question in the scope should be driven by information on the usefulness of the test.
Language	English	
Study design	• Randomised controlled trials • Observational studies (comparative) • Systematic reviews	Observational studies are more likely – comparisons of cohorts of children who have received capillary blood gas testing and those that have not. This may be confounded by the severity of bronchiolitis (i.e. children with more severe disease may be more likely to receive capillary blood gas testing and so the outcomes from testing may be worse, as the children were more ill to start with).
Status	Published papers	
Population	Children with bronchiolitis	
Intervention	Capillary or arterial blood gas measurement	
Comparator or reference standard	No Capillary or arterial blood gas measurement	Measurement using different frequency or duration from intervention group
Outcomes	Adjusted figures for: • Duration of admission • Readmission rates • Duration of oxygen supplementation • Change in disease severity score	The GDG was unable to specify the timing for change in disease severity.

	Details	Additional comments
	• Need for oxygen supplementation • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation. • Adverse effects (including mortality)	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.5 Q5 Fluids and nutritional support

	Details	Additional comments
Review question	What are the indications for fluids and nutritional support?	
Objectives	The aim of this review is: • to determine what factors indicate the need for fluids and nutritional support, and • role of fluids and nutritional support	The GDG believed the indications for fluid and nutritional support would be based on its effect on different groups.
Language	English	
Study design	• Randomised controlled trials • Comparative observational studies or • Systematic reviews.	If satisfactory RCTs cannot be identified we will consider comparative observational studies Observational studies are more likely – comparisons of cohorts of children who have received fluids/nutritional support and those that have not. This may be confounded by the severity of bronchiolitis (i.e. children with more severe disease may be more likely to receive support and so the outcomes from support may be worse, as the children were more ill to start with).
Status	Published papers	
Population	Children with bronchiolitis	It is important to characterise the population in which the intervention was applied.

	Details	Additional comments
		Subgroup analysis should be considered for these groups.
Intervention	Fluid and nutritional support Enteral tube feeding or Intravenous fluid administration	Nutritional support might be simple fluids or feeds
Comparator or reference standard	Continued oral feeding, or Enteral tube feeding or Intravenous fluid administration	
Outcomes	• Change in hydration (clinical hydration status /change in body weight/serum sodium concentration) • Change in O2 saturation • Change in disease severity score • Length of hospital stay • Change in Respiratory rate • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation. • Adverse effects (including mortality)	The GDG was unable to specify the timing for change in disease severity.
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.6 Q6 Criteria for referral or admission

	Details	Additional comments
Review question	What are the criteria for a) referral to secondary care, b) hospital admission for observation or treatment, c) discharge from hospital?	
Objectives	The aim of this review is to identify the criteria for a) referral to secondary care, b) admission for observation or treatment, and c) discharge from hospital?	The GDG want to know the effect of applying indicators for referral and admission on the outcome.
Language	English	
Study design	• RCT • Observational studies comparing referral/no referral and admission/no admission	This is largely a clinical consensus question. It may be helpful for the GDG to look at other guidelines to see when they suggest referral to

	Details	Additional comments
		secondary care/hospital admission, as a starting point for discussion. Alternatively they could look for studies that compare referral/no referral and admission/no admission, but I'm not sure these would be helpful (or available). Information on which symptoms and signs lead to referral to secondary care and ICU could be included.
Status	Published papers	
Population	Children with bronchiolitis	
Intervention	Referral to secondary care Admission for observation or treatment Discharge from hospital	
Comparator or reference standard	• Treatment in primary care/at home (i.e. no referral to secondary care) • Sent home (i.e. no admission for observation or treatment) • Remaining in secondary care	
Outcomes	• (Adjusted results from observational studies) • Clinical status (e.g. stable) • Oxygen status • Hydration status • Improvement in other symptoms/signs • Readmission rates	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.7 Q7 Pulse oximetry oxygen saturation monitoring indications

	Details	Additional comments
Review question	When is pulse oximetry oxygen saturation monitoring (SpO2) indicated in bronchiolitis?	

	Details	Additional comments
Objectives	The aim of this review is to establish when pulse oximetry oxygen saturation monitoring is indicated in bronchiolitis. Pulse oximetry oxygen saturation monitoring is a commonly used technique in secondary care, and although non-invasive, it may result in prolonged admission.	The question might address criteria for starting and stopping monitoring and is closely linked to starting and stopping oxygen supplementation.
Language	English	
Study design	• Randomised controlled trials or systematic reviews suitable for meta-analysis • Observational studies (comparative)	
Status	Published papers	
Population	Children with bronchiolitis	
Intervention	SpO2 monitoring(consider subgroup analysis for length of SpO2 monitoring or whether continuous or intermittent monitoring)	We are not looking at which equipment is best to use. However, the GDG needs consider the following sub questions: • Equipment used • Length of SpO2 monitoring or • Continuous or intermittent monitoring • When to do monitor • From where the sample was taken, • How long to continue monitoring • What to do with the results/what do the results show
Comparator or reference standard	No SpO2 monitoring monitoring for different duration to intervention group	
Outcomes	• (Adjusted figures for observational studies) • Admission rates • Duration of admission • Readmission rates • Duration of oxygen supplementation • Change in disease severity score • Need for oxygen supplementation • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Adverse effects (including mortality)	The GDG was unable to specify the timing for change in disease severity.
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	

	Details	Additional comments
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.8 Q8 Chest radiography

	Details	Additional comments
Review question	What are the indications for chest radiography in bronchiolitis?	Cost implications – this could be a question for health economic evaluation
Objectives	The aim of this review is to determine the clinical criteria for performing a chest radiograph in children with bronchiolitis. Performing a chest x-ray in all children presenting to secondary care with bronchiolitis has cost implications. Incorrect interpretation of x-rays can lead to unnecessary antibiotic therapy.	Routine chest x-ray reveals changes due to mucus plugging (atelectasis) in many children, and this may lead on to unnecessary antibiotic therapy if incorrectly interpreted. It may be helpful to highlight this in the guideline and perhaps give guidance on the circumstances where a chest x-ray might be indicated. Too many being undertaken or at the wrong time. What the GDG is asking is: Who should have a chest x-ray What the chest x-ray is showing How the use of chest x-ray influence the management of bronchiolitis
Language	English	
Study design	Randomised controlled trials or systematic reviews suitable for meta-analysis Observational studies	
Status	Published papers	
Population	Children with bronchiolitis	
Intervention	Chest radiograph	
Comparator or reference standard	No chest radiograph Association between severity of bronchiolitis and chest x-ray interpretation	
Outcomes	Identification of additional or alternative diagnosis Antibiotics administration Admission rates Duration of admission	The GDG needs to be quite strict about how the ‘new’ or additional diagnosis was confirmed.

	Details	Additional comments
	Change in disease severity Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation Adverse effects (including mortality)	The GDG was unable to specify the timing for change in disease severity.
Other criteria for inclusion/ exclusion of studies	Exclude non-human studies Exclude studies of children on invasive ventilation Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) A list of excluded studies will be provided following weeding Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.9 Q9 Chest physiotherapy

	Details	Additional comments
Review question	What is the efficacy of chest physiotherapy in the management of bronchiolitis?	Specify the type of physiotherapy used?
Objectives	The aim of this review is to determine whether chest physiotherapy is an effective treatment in the management of bronchiolitis.	
Language	English	
Study design	• Randomised controlled trials or systematic reviews suitable for meta-analysis • Observational studies	
Status	Published papers (see additional comments column RE unpublished studies)	
Population	Children with bronchiolitis	Consider subgroups analysis for setting of care, severity and clinical characteristics
Intervention	Chest physiotherapy	
Comparator or reference standard	No treatment/placebo	
Outcomes	• (Adjusted for observational studies) • Change in disease severity score • Change in Respiratory rate • Change in O2 saturation	The GDG was unable to specify the timing for change in disease severity.

	Details	Additional comments
	• Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Length of hospital stay • Adverse effects (including mortality)	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.10 Q10 Antibiotics

	Details	Additional comments
Review question	What is the efficacy of antibiotic treatment?	Check the 'Antibiotics for neonatal infection' NICE guideline (low priority)
Objectives	The aim of this review is to determine whether antibiotics are effective in the management of bronchiolitis	
Language	English	
Study design	Randomised controlled trials	
Status	Published papers	
Population	Children with bronchiolitis	Bronchiolitis a clinical syndrome characterised by the acute onset of symptoms including tachypnoea, increased work of breathing, and often wheeze and reduced feeding. Pulmonary crackles are also characteristic of this condition. This disorder is usually due to a viral infection, usually RSV, Some children especially after the first year of life have a tendancy to recurrent wheeze which may be difficult to distinguish, but they do not usually have respiratory crackles and this may be helpful in distinguishing these disorders. Report the definition of bronchiolitis used in the paper

	Details	Additional comments
		Report the age of children in the paper
Intervention	Antibiotic treatment	
Comparator or reference standard	No antibiotic treatment Treatment with a placebo	
Outcomes	• Hospital admission rate • Length of hospital stay • Duration of cough • Change in Respiratory rate • Change in O2 saturation • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Adverse effects (including mortality)	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation Exclude children that are on mechanical ventilator • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.11 Q11 Inhaled bronchodilators

	Details	Additional comments
Review question	What is the efficacy of inhaled bronchodilator therapy?	
Objectives	The aim of this review is to determine whether inhaled bronchodilators such as epinephrine [adrenaline], salbutamol, and ipratropium bromide are effective in the management of bronchiolitis	
Language	English	
Study design	• Randomised controlled trials • Systematic review or meta-analysis based on RCTs	
Status	Published papers	
Population	Children with bronchiolitis	Bronchiolitis a clinical syndrome characterised by the acute onset of symptoms including tachypnoea, increased work of

	Details	Additional comments
		breathing, and often wheeze and reduced feeding. Pulmonary crackles are also characteristic of this condition. This disorder is usually due to a viral infection, usually RSV, Some children especially after the first year of life have a tendency to recurrent wheeze which may be difficult to distinguish, but they do not usually have respiratory crackles and this may be helpful in distinguishing these disorders.
Intervention	An inhaled bronchodilator	Search terms can include drugs name for Bronchodilators: • Salbutamol • Albuterol (US) • Adrenaline • Ipratropium (Atrovent)
Comparator or reference standard	No treatment with an inhaled bronchodilator May or may not use a placebo	
Outcomes	• Hospital admission rate • Length of hospital stay • Change in Respiratory rate • Change in disease severity score: • at 2 to 4 hrs after treatment for salbutamol/ipratropium • at 30 min to 2 hours for adrenaline • Change in O2 saturation • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Need for/Use of feeding support (tube feeding, IV fluids) • Adverse effects(including mortality)	If more than one data for "change in disease severity" is reported, recorded the earliest after treatment
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude children that are on mechanical ventilator • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.12 Q12 Inhaled corticosteroids

	Details	Additional comments
Review question	What is the efficacy of inhaled corticosteroid therapy?	
Objectives	The aim of this review is to determine whether inhaled corticosteroids are effective in the management of bronchiolitis.	These can be used in high does to match systemic corticosteroids or low dose to treat chronic conditions.
Language	English	
Study design	• Randomised controlled trials • Systematic review or meta-analysis based on RCTs	
Status	Published papers	
Population	Children with bronchiolitis	Bronchiolitis a clinical syndrome characterised by the acute onset of symptoms including tachypnoea, increased work of breathing, and often wheeze and reduced feeding. Pulmonary crackles are also characteristic of this condition. This disorder is due to a viral infection, usually RSV, Some children especially after the first year of life have a tendency to recurrent wheeze which may be difficult to distinguish, but they do not usually have respiratory crackles and this may be helpful in distinguishing these disorders. Report the definition of bronchiolitis used in the paper. Report the age of children in the paper.
Intervention	Inhaled corticosteroid therapy	
Comparator or reference standard	• No inhaled corticosteroid therapy • May or may not include placebo	
Outcomes	• Hospital admission rate • Length of hospital stay • Change in disease severity score at 1 to 7 days after starting treatment • Change in O2 saturation • Duration of cough • Readmission • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Adverse effects (including mortality)	If more than one data for change in disease severity is reported, recorded the latest after treatment
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies	

	Details	Additional comments
	• Exclude studies of children on invasive ventilation Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.13 Q13 Systemic corticosteroids

	Details	Additional comments
Review question	What is the efficacy of systemic corticosteroid therapy?	
Objectives	The aim of this review is to determine whether systemic corticosteroids are effective in the management of bronchiolitis.	
Language	English	
Study design	• Randomised controlled trials • Systematic review or meta-analysis for RCTs	
Status	Published papers	
Population	Children with bronchiolitis	Bronchiolitis a clinical syndrome characterised by the acute onset of symptoms including tachypnoea, increased work of breathing, and often wheeze and reduced feeding. Pulmonary crackles are also characteristic of this condition. This disorder is due to a viral infection, usually RSV, Some children especially after the first year of life have a tendency to recurrent wheeze which may be difficult to distinguish, but they do not usually have respiratory crackles and this may be helpful in distinguishing these disorders. Report the definition of bronchiolitis used in the paper. Report the age of children in the paper
Intervention	Systemic corticosteroids	Oral or intravenous

	Details	Additional comments
Comparator or reference standard	No systemic corticosteroids May or may not include/placebo	
Outcomes	• Hospital admission rate • Length of hospital stay • Change in disease severity score at 1 to 7 days after starting treatment • Change in O2 saturation • Duration of cough • Readmission • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Adverse effects (including mortality)	The outcomes for inhaled and oral corticosteroids have been aligned, resulting in an additional outcome in each. Systemic steroids may be allocated in emergency departments to patient who are to be discharged or those to be admitted. Readmission to hospital in those discharged is an important outcome. Inhaled corticosteroids can be provided at a high dose (usually short term) with an intended equivalence to systemic corticosteroids, or at a lower dose over medium/longer term to reduce the longer term consequences of bronchiolitis. Outcomes for inhaled and oral corticosteroids should therefore be aligned to include need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation. If more than one data for "change in disease severity" is reported, recorded the earliest after treatment
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude children that are on mechanical ventilator • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.14 Q14 Nebulised hypertonic saline

	Details	Additional comments
Review question	What is the efficacy of nebulised hypertonic saline?	
Objectives	The aim of this review is to determine whether nebulised hypertonic saline is effective in the management of bronchiolitis.	
Language	English	
Study design	Randomised controlled trials	
Status	Published papers (Papers soon to be published – see additional comments)	UK RCTs are currently being undertaken. It is not known when these will be published.
Population	Children with bronchiolitis	Bronchiolitis a clinical syndrome characterised by the acute onset of symptoms including tachypnoea, increased work of breathing, and often wheeze and reduced feeding. Pulmonary crackles are also characteristic of this condition. This disorder is usually due to a viral infection, usually RSV, Some children especially after the first year of life have a tendancy to recurrent wheeze which may be difficult to distinguish, but they do not usually have respiratory crackles and this may be helpful in distinguishing these disorders. Report percentage of children with a particular condition (e.g CF, Down syndrome etc.) in the description of included studies (children with CF are an important subgroup and need to be recorded)
Intervention	• Nebulised hypertonic saline • Systematic review or meta-analysis based on RCTs	There are different strengths products 3%, 5% and 7% (compare)
Comparator or reference standard	• No treatment • Normal saline • Placebo	The GDG would need to know the dose, duration and frequency used in any trial.
Outcomes	• Hospital admission rate • Length of hospital stay • Change in Respiratory rate • Change in disease severity score at 2 to 4 hrs after treatment • Change in O2 saturation • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Need for/Use of feeding support (tube feeding, IV fluids)	If more than one data for “change in disease severity” is reported, recorded the earliest after treatment.

	Details	Additional comments
	• Adverse effects (including mortality)	
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude children that are on mechanical ventilator Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.15 Q15 Heliox

	Details	Additional comments
Review question	What is the efficacy of heliox?	
Objectives	The aim of this review is to determine the efficacy of heliox (a mixture of helium and oxygen) in the management of bronchiolitis.	
Language	English	
Study design	Randomised controlled trials	
Status	Published papers (See additional comments – unpublished study ongoing)	Large UK study underway at St Mary's
Population	Children with bronchiolitis	Heliox is used in secondary care settings in children who continue to deteriorate after treatment with O2 supplementation
Intervention	Heliox inhalation therapy	
Comparator or reference standard	• No use of heliox • O2 alone • These children may or may not receive a placebo	
Outcomes	• Change in CO2 after 24 hours of heliox treatment • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Time to return to oral feeding • Length of hospital stay • Change in disease severity score at 1 to 4 hrs after treatment • Change in O2 saturation • Adverse effects (including mortality)	If more than one data for "change in disease severity" is reported, recorded the earliest after treatment
Other criteria for inclusion/	• Exclude non-human studies	

	Details	Additional comments
exclusion of studies	• Exclude studies of children on invasive ventilation • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.16 Q16 Combinations of treatments

	Details	Additional comments
Review question	What is the efficacy of combined bronchodilator and corticosteroid therapy?	Terms (included drugs name)for Bronchodilators: • Salbutamol • Albuterol (US) • Adrenaline • Ipratropium (Atrovent)
Objectives	The aim of this review is to determine the efficacy of combined bronchodilator and systemic corticosteroid therapy in bronchiolitis.	In the UK a combination of inhaled bronchodilators and systemic corticosteroid therapy are sometimes used.
Language	English	
Study design	Randomised controlled trials	
Status	Published papers	
Population	Children with bronchiolitis	Bronchiolitis a clinical syndrome characterised by the acute onset of symptoms including tachypnoea, increased work of breathing, and often wheeze and reduced feeding. Pulmonary crackles are also characteristic of this condition. This disorder is usually due to a viral infection, usually RSV, Some children especially after the first year of life have a tendency to recurrent wheeze which may be difficult to distinguish, but they do not usually have respiratory crackles and this may be helpful in distinguishing these disorders.
Intervention	Corticosteroid therapy combined with an Inhaled bronchodilator	

	Details	Additional comments
Comparator or reference standard	• No corticosteroid or bronchodilator therapy • Corticosteroid therapy alone • Bronchodilator therapy alone • May or may not include placebo(s)	
Outcomes	• Hospital admission rate • Length of hospital stay • Change in disease severity score at 1 to 7 days after starting treatment • Change in O2 saturation • Duration of cough • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Need for/Use of feeding support (tube feeding, IV fluids) • Adverse effects (including mortality)	If more than one data for "change in disease severity" is reported, recorded the earliest after treatment
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude children that are on mechanical ventilator • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.17 Q17 Montelukast

	Details	Additional comments
Review question	What is the efficacy of Montelukast?	
Objectives	The aim of this review is to determine the efficacy of Montelukast in children with bronchiolitis.	
Language	English	
Study design	• Randomised controlled trials • systematic reviews or meta-analysis of RCTs	
Status	Published papers	
Population	Children with bronchiolitis	Subgroups analysis for children: • 0 to 1 year age of age • Older than 1year of age
Intervention	Montelukast administration	

	Details	Additional comments
Comparator or reference standard	No Montelukast administration With or without placebo	
Outcomes	• Change in O2 saturation • Duration of cough • Length of hospital stay • Change in Respiratory rate • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Hospital admission rate • Adverse effects (including mortality)	Duration of cough -used as approximation for time to go back to normal
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.18 Q18 O2 supplementation

	Details	Additional comments
Review question	What is the efficacy of oxygen supplementation (non humidified, humidified and high-flow) and of CPAP?	• What are the indications for O2 supplementation in Bronchiolitis? • Optimal method (efficacy)
Objectives	The aim of this review is to determine the optimal method of providing oxygen supplementation, to children with bronchiolitis comparing: • Oxygen, unhumidified • Oxygen humidified • High-flow humidified oxygen • CPAP	
Language	English	
Study design	• Randomised controlled trials • Systematic reviews or meta-analysis of RCTs	
Status	Published papers	
Population	Children with bronchiolitis	
Intervention	• Oxygen, unhumidified • Oxygen humidified • High-flow humidified oxygen	

	Details	Additional comments
	• CPAP	
Comparator or reference standard	Any comparisons between these approaches: • Oxygen, unhumidified • Oxygen humidified • High-flow humidified oxygen • CPAP	
Outcomes	• Change in O2 saturation • Change in arterial or capillary carbon dioxide levels • Change in disease severity score • Length of hospital stay • Change in Respiratory rate • Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation • Need for/Use of feeding support (tube feeding, IV fluids) • Adverse effects (including mortality)	Change in carbon dioxide as a marker of respiratory failure. The GDG was unable to specify the timing for change in disease severity.
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children in neonatal units or ICU • Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

E.19 Q19 Nasal suction

	Details	Additional comments
Review question	What is the efficacy of suction to remove secretions from the upper respiratory tract?	
Objectives	The aim of this review is to determine the efficacy nasal suction in children with bronchiolitis	
Language	English	
Study design	• Randomised controlled trials • Systematic review or meta-analysis of RCTs	.
Status	Published papers	
Population	Children with bronchiolitis	Suction may be used in variety of settings including in the home. It will be important for the

	Details	Additional comments
		reviewer to make clear the setting in which the study has taken place.
Intervention	• Upper airway suction (nasal suction) • Different techniques might be employed, including nasal,nasopharyngeal, oropharyngeal or oral suction • Devices used will vary from manual or machine • In any setting, including home	The reviewer should if possible specific what was done in each study Alternative terminology: aspiration
Comparator or reference standard	No suction	
Outcomes	• Need for O2 supplementation • Oral feed toleration • Admission to hospital • Length of hospital stay • Readmission rates • Adverse events (bleeding apnoea etc. including mortality)	Oral feed toleration- In bronchiolitis the baby may become quite bunged up and because they are often obligatory nasal breathers this may interfere with their breathing and if they are working hard with their breathing this may also affect their feeding. Once a baby has had suction, they often feed much better. Admission to hospital chosen because often giving suction in the Emergency Department is all that is needed to allow the baby to feed, and therefore get home without any further intervention. Readmission rates chosen to see if receiving suction (or not) affects natural course of bronchiolitis, and therefore has any effect on whether a child is readmitted with bronchiolitis.
Other criteria for inclusion/ exclusion of studies	• Exclude non-human studies • Exclude studies of children on invasive ventilation Exclude studies of pan bronchiolitis and bronchiolitis obliterans	
Search strategies	See separate document	
Review strategies	• Evidence will be assessed for quality according to the process described in the NICE guidelines manual (2012) • A list of excluded studies will be provided following weeding • Evidence tables and an evidence profile will be used to summarise the evidence	
Equality		

Appendix F:Collated search strategies

F.1 What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions?

Database(s): Ovid MEDLINE(R)

BRONC_signs_symptoms_RERUN1_medline_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	or/8-10
12	RESPIRATORY SOUNDS/
13	(crepit$ or crackl$ or wheez$ or stridor$ or grunt$).ti,ab.
14	RESPIRATION DISORDERS/
15	exp APNEA/
16	exp DYSPNEA/
17	TACHYPNEA/
18	(apn?ea$ or dyspn?ea$ or tachypn?ea$).ti,ab.
19	((respirat$ or breath$) adj3 (distress$ or disorder? or alter$ or short$ or difficult$ or rapid$ or fast$ or quick$)).ti,ab.
20	(increas$ adj3 (work or effort) adj3 (breath$ or respirat$)).ti,ab.
21	breathless$.ti,ab.
22	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess$ or retract$)).ti,ab.
23	(prolong$ adj3 expirat$).ti,ab.
24	(tracheal tug$ or Campbell's sign).ti,ab.
25	HEAD MOVEMENTS/
26	(head adj3 (move$ or bob$) adj3 (breath$ or respirat$)).ti,ab.
27	NOSE/
28	((nose or nasal or nostril? or alar) adj3 flar$).ti,ab.
29	MUCUS/
30	RHINITIS/
31	(mucus or coryza? or rhinitis).ti,ab.
32	(nasal adj (catarrh or discharge)).ti,ab.
33	COUGH/
34	(cough$ or tussis$).ti,ab.
35	FEVER/

#	Searches
36	(fever$ or febri$ or pyrex$).ti,ab.
37	CYANOSIS/
38	cyano$.ti,ab.
39	FLUSHING/ or PALLOR/
40	(pallor or flush$).ti,ab.
41	(skin adj3 (colo?r$ or chang$ or pale)).ti,ab.
42	exp TACHYCARDIA/
43	(tachycardi$ or tachya?rhythm$).ti,ab.
44	ANOXIA/
45	(hypox$ or anox$).ti,ab.
46	((oxygen or O2) adj deficien$).ti,ab.
47	exp BEHAVIOR/ or IRRITABLE MOOD/ or CRYING/
48	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
49	LETHARGY/
50	(letharg$ or sluggish$ or listless$ or sleep$ or drows$).ti,ab.
51	FEEDING BEHAVIOR/ or SUCKING BEHAVIOR/
52	((able or unable or abilit$ or inabilit$ or difficult$) adj3 (feed$ or breastfeed$ or fed or breastfed$ or suck$)).ti,ab.
53	AGE FACTORS/
54	AGE DISTRIBUTION/
55	TIME FACTORS/
56	TIME TO TREATMENT/
57	((age$ or time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
58	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
59	or/12-58
60	exp "SIGNS and SYMPTOMS"/
61	(sign? or symptom$ or complain$).ti,ab.
62	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.
63	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
64	presentation?.ti,ab.
65	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.
66	((ill or sick) adj3 (looking or appearance)).ti,ab.
67	unwell.ti,ab.
68	or/60-67
69	DIAGNOSIS/
70	(diagnos$ or differentia$).ti.
71	di.fs. [Diagnosis]
72	SEVERITY OF ILLNESS INDEX/
73	CLASSIFICATION/
74	(classif$ or defin$).ti.
75	or/69-74
76	DISEASE PROGRESSION/
77	RECOVERY OF FUNCTION/
78	CONVALESCENCE/
79	((bronchiol$ or disease or ill$ or sick$ or symptom?) adj3 (durat$ or onset$ or progress$ or course? or chang$ or peak$ or trajector$)).ti,ab.

#	Searches
80	or/76-79
81	7 and 11 and (59 or 68) and 75
82	and/7,11,80
83	*BRONCHIOLITIS/cl, di, ep, sn, td [Classification, Diagnosis, Epidemiology, Statistics and Numerical Data, Trends]
84	*BRONCHIOLITIS, VIRAL/cl, di, ep, sn, td [Classification, Diagnosis, Epidemiology, Statistics and Numerical Data, Trends]
85	*RESPIRATORY TRACT DISEASES/cl, di [Classification, Diagnosis]
86	(*BRONCHIOLITIS/ or *BRONCHIOLITIS, VIRAL/ or *RESPIRATORY TRACT DISEASES/) and DIAGNOSIS, DIFFERENTIAL/
87	or/83-86
88	and/7,87
89	or/81-82,88
90	limit 89 to english language
91	LETTER/
92	EDITORIAL/
93	NEWS/
94	exp HISTORICAL ARTICLE/
95	ANECDOTES AS TOPIC/
96	COMMENT/
97	(letter or comment* or abstracts).ti.
98	or/91-97
99	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
100	98 not 99
101	ANIMALS/ not HUMANS/
102	exp ANIMALS, LABORATORY/
103	exp ANIMAL EXPERIMENTATION/
104	exp MODELS, ANIMAL/
105	exp RODENTIA/
106	(rat or rats or mouse or mice).ti.
107	or/100-106
108	90 not 107

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_signs_symptoms_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(crepit$ or crackl$ or wheez$ or stridor$ or grunt$).ti,ab.
7	(apn?ea$ or dyspn?ea$ or tachypn?ea$).ti,ab.
8	((respirat$ or breath$) adj3 (distress$ or disorder? or alter$ or short$ or difficult$ or rapid$ or fast$ or quick$)).ti,ab.
9	(increas$ adj3 (work or effort) adj3 (breath$ or respirat$)).ti,ab.
10	breathless$.ti,ab.
11	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess$ or retract$)).ti,ab.
12	(prolong$ adj3 expirat$).ti,ab.
13	(tracheal tug$ or Campbell's sign).ti,ab.
14	(head adj3 (move$ or bob$) adj3 (breath$ or respirat$)).ti,ab.
15	((nose or nasal or nostril? or alar) adj3 flar$).ti,ab.
16	(mucus or coryza? or rhinitis).ti,ab.
17	(nasal adj (catarrh or discharge)).ti,ab.
18	(cough$ or tussis$).ti,ab.
19	(fever$ or febri$ or pyrex$).ti,ab.
20	cyano$.ti,ab.
21	(pallor or flush$).ti,ab.
22	(skin adj3 (colo?r$ or chang$ or pale)).ti,ab.
23	(tachycardi$ or tachya?rhythm$).ti,ab.
24	(hypox$ or anox$).ti,ab.
25	((oxygen or O2) adj deficien$).ti,ab.
26	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
27	(letharg$ or sluggish$ or listless$ or sleep$ or drows$).ti,ab.
28	((able or unable or abilit$ or inabilit$ or difficult$) adj3 (feed$ or breastfeed$ or fed or breastfed$ or suck$)).ti,ab.
29	((age$ or time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
30	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
31	or/6-30
32	(sign? or symptom$ or complain$).ti,ab.
33	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.
34	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
35	presentation?.ti,ab.
36	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.
37	((ill or sick) adj3 (looking or appearance)).ti,ab.
38	unwell.ti,ab.
39	or/32-38

#	Searches
40	(diagnos$ or differentia$).ti.
41	(classif$ or defin$).ti.
42	or/40-41
43	((bronchiol$ or disease or ill$ or sick$ or symptom?) adj3 (durat$ or onset$ or progress$ or course? or chang$ or peak$ or trajector$)).ti,ab.
44	4 and 5 and (31 or 39) and 42
45	and/4-5,43
46	or/44-45
47	limit 46 to english language

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_signs_symptoms_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	or/8-10
12	RESPIRATORY SOUNDS/
13	(crepit$ or crackl$ or wheez$ or stridor$ or grunt$).ti,ab.
14	RESPIRATION DISORDERS/
15	exp APNEA/
16	exp DYSPNEA/
17	TACHYPNEA/
18	(apn?ea$ or dyspn?ea$ or tachypn?ea$).ti,ab.
19	((respirat$ or breath$) adj3 (distress$ or disorder? or alter$ or short$ or difficult$ or rapid$ or fast$ or quick$)).ti,ab.
20	(increas$ adj3 (work or effort) adj3 (breath$ or respirat$)).ti,ab.
21	breathless$.ti,ab.
22	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess$ or retract$)).ti,ab.
23	(prolong$ adj3 expirat$).ti,ab.
24	(tracheal tug$ or Campbell's sign).ti,ab.
25	HEAD MOVEMENTS/
26	(head adj3 (move$ or bob$) adj3 (breath$ or respirat$)).ti,ab.
27	NOSE/
28	((nose or nasal or nostril? or alar) adj3 flar$).ti,ab.
29	MUCUS/
30	RHINITIS/

#	Searches
31	(mucus or coryza? or rhinitis).ti,ab.
32	(nasal adj (catarrh or discharge)).ti,ab.
33	COUGH/
34	(cough$ or tussis$).ti,ab.
35	FEVER/
36	(fever$ or febri$ or pyrex$).ti,ab.
37	CYANOSIS/
38	cyano$.ti,ab.
39	FLUSHING/ or PALLOR/
40	(pallor or flush$).ti,ab.
41	(skin adj3 (colo?r$ or chang$ or pale)).ti,ab.
42	exp TACHYCARDIA/
43	(tachycardi$ or tachya?rhythm$).ti,ab.
44	ANOXIA/
45	(hypox$ or anox$).ti,ab.
46	((oxygen or O2) adj deficien$).ti,ab.
47	exp BEHAVIOR/ or IRRITABLE MOOD/ or CRYING/
48	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
49	LETHARGY/
50	(letharg$ or sluggish$ or listless$ or sleep$ or drows$).ti,ab.
51	FEEDING BEHAVIOR/ or SUCKING BEHAVIOR/
52	((able or unable or abilit$ or inabilit$ or difficult$) adj3 (feed$ or breastfeed$ or fed or breastfed$ or suck$)).ti,ab.
53	AGE FACTORS/
54	AGE DISTRIBUTION/
55	TIME FACTORS/
56	TIME TO TREATMENT/
57	((age$ or time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
58	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
59	or/12-58
60	exp "SIGNS and SYMPTOMS"/
61	(sign? or symptom$ or complain$).ti,ab.
62	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.
63	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
64	presentation?.ti,ab.
65	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.
66	((ill or sick) adj3 (looking or appearance)).ti,ab.
67	unwell.ti,ab.
68	or/60-67
69	DIAGNOSIS/
70	(diagnos$ or differentia$).ti.
71	di.fs. [Diagnosis]
72	SEVERITY OF ILLNESS INDEX/
73	CLASSIFICATION/
74	(classif$ or defin$).ti.
75	or/69-74

#	Searches
76	DISEASE PROGRESSION/
77	RECOVERY OF FUNCTION/
78	CONVALESCENCE/
79	((bronchiol$ or disease or ill$ or sick$ or symptom?) adj3 (durat$ or onset$ or progress$ or course? or chang$ or peak$ or trajector$)).ti,ab.
80	or/76-79
81	7 and 11 and (59 or 68) and 75
82	and/7,11,80
83	BRONCHIOLITIS/cl, di, ep, sn, td [Classification, Diagnosis, Epidemiology, Statistics and Numerical Data, Trends]
84	BRONCHIOLITIS, VIRAL/cl, di, ep, sn, td [Classification, Diagnosis, Epidemiology, Statistics and Numerical Data, Trends]
85	RESPIRATORY TRACT DISEASES/cl, di [Classification, Diagnosis]
86	(BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/ or RESPIRATORY TRACT DISEASES/) and DIAGNOSIS, DIFFERENTIAL/
87	or/83-86
88	and/7,87
89	or/81-82,88

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_signs_symptoms_RERUN1_cdsrdare_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	or/8-10
12	RESPIRATORY SOUNDS/
13	(crepit$ or crackl$ or wheez$ or stridor$ or grunt$).tw.
14	RESPIRATION DISORDERS/
15	exp APNEA/
16	exp DYSPNEA/
17	TACHYPNEA/
18	(apn?ea$ or dyspn?ea$ or tachypn?ea$).tw.
19	((respirat$ or breath$) adj3 (distress$ or disorder? or alter$ or short$ or difficult$ or rapid$ or fast$ or quick$)).tw.
20	(increas$ adj3 (work or effort) adj3 (breath$ or respirat$)).tw.
21	breathless$.tw.

#	Searches
22	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess$ or retract$)).tw.
23	(prolong$ adj3 expirat$).tw.
24	(tracheal tug$ or Campbell's sign).tw.
25	HEAD MOVEMENTS/
26	(head adj3 (move$ or bob$) adj3 (breath$ or respirat$)).tw.
27	NOSE/
28	((nose or nasal or nostril? or alar) adj3 flar$).tw.
29	MUCUS/
30	RHINITIS/
31	(mucus or coryza? or rhinitis).tw.
32	(nasal adj (catarrh or discharge)).tw.
33	COUGH/
34	(cough$ or tussis$).tw.
35	FEVER/
36	(fever$ or febri$ or pyrex$).tw.
37	CYANOSIS/
38	cyano$.tw.
39	FLUSHING/ or PALLOR/
40	(pallor or flush$).tw.
41	(skin adj3 (colo?r$ or chang$ or pale)).tw.
42	exp TACHYCARDIA/
43	(tachycardi$ or tachya?rhythm$).tw.
44	ANOXIA/
45	(hypox$ or anox$).tw.
46	((oxygen or O2) adj deficien$).tw.
47	exp BEHAVIOR/ or IRRITABLE MOOD/ or CRYING/
48	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).tw.
49	LETHARGY/
50	(letharg$ or sluggish$ or listless$ or sleep$ or drows$).tw.
51	FEEDING BEHAVIOR/ or SUCKING BEHAVIOR/
52	((able or unable or abilit$ or inabilit$ or difficult$) adj3 (feed$ or breastfeed$ or fed or breastfed$ or suck$)).tw.
53	AGE FACTORS/
54	AGE DISTRIBUTION/
55	TIME FACTORS/
56	TIME TO TREATMENT/
57	((age$ or time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).tw.
58	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).tw.
59	or/12-58
60	exp "SIGNS and SYMPTOMS"/
61	(sign? or symptom$ or complain$).tw.
62	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).tw.
63	(presenting adj3 (feature? or finding? or factor?)).tw.
64	presentation?.tw.
65	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).tw.

#	Searches
66	((ill or sick) adj3 (looking or appearance)).tw.
67	unwell.tw.
68	or/60-67
69	DIAGNOSIS/
70	(diagnos$ or differentia$).ti.
71	di.fs. [Diagnosis]
72	SEVERITY OF ILLNESS INDEX/
73	CLASSIFICATION/
74	(classif$ or defin$).ti.
75	or/69-74
76	DISEASE PROGRESSION/
77	RECOVERY OF FUNCTION/
78	CONVALESCENCE/
79	((bronchiol$ or disease or ill$ or sick$ or symptom?) adj3 (durat$ or onset$ or progress$ or course? or chang$ or peak$ or trajector$)).tw.
80	or/76-79
81	7 and 11 and (59 or 68) and 75
82	and/7,11,80
83	BRONCHIOLITIS/cl, di, ep, sn, td [Classification, Diagnosis, Epidemiology, Statistics and Numerical Data, Trends]
84	BRONCHIOLITIS, VIRAL/cl, di, ep, sn, td [Classification, Diagnosis, Epidemiology, Statistics and Numerical Data, Trends]
85	RESPIRATORY TRACT DISEASES/cl, di [Classification, Diagnosis]
86	(BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/ or RESPIRATORY TRACT DISEASES/) and DIAGNOSIS, DIFFERENTIAL/
87	or/83-86
88	and/7,87
89	or/81-82,88

Database(s): Embase

BRONC_signs_symptoms_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp NEWBORN/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	bronchiol$.ti,ab.
11	or/8-10
12	exp ABNORMAL RESPIRATORY SOUND/
13	(crepit$ or crackl$ or wheez$ or stridor$ or grunt$).ti,ab.

#	Searches
14	BREATHING DISORDER/
15	exp APNEA/
16	exp DYSPNEA/
17	exp TACHYPNEA/
18	(apn?ea$ or dyspn?ea$ or tachypn?ea$).ti,ab.
19	((respirat$ or breath$) adj3 (distress$ or disorder? or alter$ or short$ or difficult$ or rapid$ or fast$ or quick$)).ti,ab.
20	(increas$ adj3 (work or effort) adj3 (breath$ or respirat$)).ti,ab.
21	breathless$.ti,ab.
22	((chest or sternal or sternum or intercostal) adj3 (in drawing or in?drawing or recess$ or retract$)).ti,ab.
23	(prolong$ adj3 expirat$).ti,ab.
24	(tracheal tug$ or Campbell's sign).ti,ab.
25	HEAD MOVEMENT/
26	(head adj3 (move$ or bob$) adj3 (breath$ or respirat$)).ti,ab.
27	NOSE/
28	((nose or nasal or nostril? or alar) adj3 flar$).ti,ab.
29	NOSE MUCUS/
30	RHINITIS/
31	(mucus or coryza? or rhinitis).ti,ab.
32	(nasal adj (catarrh or discharge)).ti,ab.
33	COUGHING/
34	(cough$ or tussis$).ti,ab.
35	FEVER/
36	(fever$ or febri$ or pyrex$).ti,ab.
37	CYANOSIS/
38	cyano$.ti,ab.
39	FLUSHING/ or PALLOR/
40	(pallor or flush$).ti,ab.
41	(skin adj3 (colo?r$ or chang$ or pale)).ti,ab.
42	exp TACHYCARDIA/
43	(tachycardi$ or tachya?rhythm$).ti,ab.
44	exp HYPOXEMIA/
45	(hypox$ or anox$).ti,ab.
46	((oxygen or O2) adj deficien$).ti,ab.
47	exp BEHAVIOR/ or IRRITABILITY/ or CRYING/
48	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
49	LETHARGY/ or DROWSINESS/
50	(letharg$ or sluggish$ or listless$ or sleep$ or drows$).ti,ab.
51	FEEDING BEHAVIOR/
52	((able or unable or abilit$ or inabilit$ or difficult$) adj3 (feed$ or breastfeed$ or fed or breastfed$ or suck$)).ti,ab.
53	AGE/
54	AGE DISTRIBUTION/
55	ONSET AGE/
56	TIME/

#	Searches
57	TIME TO TREATMENT/
58	((age$ or time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
59	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
60	or/12-59
61	exp SYMPTOMATOLOGY/
62	(sign? or symptom$ or complain$).ti,ab.
63	(clinical adj3 (manifestation? or feature? or finding? or aspect?)).ti,ab.
64	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
65	presentation?.ti,ab.
66	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.
67	((ill or sick) adj3 (looking or appearance)).ti,ab.
68	unwell.ti,ab.
69	or/61-68
70	DIAGNOSIS/
71	(diagnos$ or differentia$).ti.
72	di.fs. [Diagnosis]
73	SEVERITY OF ILLNESS INDEX/
74	DISEASE CLASSIFICATION/
75	(classif$ or defin$).ti.
76	or/70-75
77	DISEASE COURSE/
78	DISEASE DURATION/
79	DISEASE EXACERBATION/
80	ILLNESS TRAJECTORY/
81	CONVALESCENCE/
82	((bronchiol$ or disease or ill$ or sick$ or symptom?) adj3 (durat$ or onset$ or progress$ or course? or chang$ or peak$ or trajector$)).ti,ab.
83	or/77-82
84	7 and 11 and (60 or 69) and 76
85	and/7,11,83
86	*BRONCHIOLITIS/di, ep [Diagnosis, Epidemiology]
87	*VIRAL BRONCHIOLITIS/di, ep [Diagnosis, Epidemiology]
88	(*BRONCHIOLITIS/ or *VIRAL BRONCHIOLITIS/ or *RESPIRATORY TRACT DISEASE/) and DIFFERENTIAL DIAGNOSIS/
89	or/86-88
90	and/7,89
91	or/84-85,90
92	limit 91 to english language
93	conference abstract.pt.
94	letter.pt. or LETTER/
95	note.pt.
96	editorial.pt.
97	(letter or comment* or abstracts).ti.
98	or/93-97
99	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
100	98 not 99

#	Searches
101	ANIMAL/ not HUMAN/
102	NONHUMAN/
103	exp ANIMAL EXPERIMENT/
104	exp EXPERIMENTAL ANIMAL/
105	ANIMAL MODEL/
106	exp RODENT/
107	(rat or rats or mouse or mice).ti.
108	or/100-107
109	92 not 108

F.2 What are the risk factors for severe bronchiolitis?

Database(s): Ovid MEDLINE(R)

BRONC_risk_factors_RERUN1_medline_300514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.

#	Searches
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RISK FACTORS/
48	risk?.ti.
49	risk factor?.ab.
50	or/47-49
51	exp INFANT, PREMATURE/
52	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies).ti,ab.
53	BRONCHOPULMONARY DYSPLASIA/
54	((lung or bronchopulmonary) adj3 dysplasia).ti,ab.
55	exp HEART DEFECTS, CONGENITAL/
56	(congenital adj3 (heart or cardi$) adj3 (defect$ or abnormal$ or disease$ or malform$ or anomal$)).ti,ab.
57	LUNG DISEASE/
58	(chronic$ adj3 (lung disease? or pulmonary disease? or pneumopathy)).ti,ab.
59	CYSTIC FIBROSIS/
60	(cystic fibrosis or fibrocystic disease? or mucovisc??dosi$).ti,ab.
61	exp IMMUNOLOGIC DEFICIENCY SYNDROMES/
62	(immunodef$ or immunodepress$ or immunosuppress$).ti,ab.
63	(immun$ adj3 (defic$ or defect$ or depress$ or suppress$ or incompeten$)).ti,ab.
64	BREAST FEEDING/
65	breastfe$.ti,ab.
66	(breast$ adj3 (fed or feed$)).ti,ab.
67	AGE FACTORS/
68	(age or young$).ti,ab.
69	SEX FACTORS/
70	(sex or gender or male? or female?).ti,ab.
71	HOSPITALIZATION/
72	PATIENT ADMISSION/
73	CHILD, HOSPITALIZED/

#	Searches
74	hospitali$.ti,ab.
75	(hospital adj3 (admit$ or admission$)).ti,ab.
76	EPIDEMIOLOGIC FACTORS/
77	ethnic$.ti,ab.
78	DOWN SYNDROME/
79	(down$ syndrome or trisomy 21).ti,ab.
80	TOBACCO SMOKE POLLUTION/
81	SMOKING/ae [Adverse effects]
82	(smok$ or tobacco or cigar$).ti,ab.
83	exp MULTIPLE BIRTH OFFSPRING/
84	(multiple birth$ or twin$ or triplet$ or quadruplet$ or quintuplet$).ti,ab.
85	or/51-84
86	and/46,50,85
87	BRONCHIOLITIS/ep, et [Epidemiology, Etiology]
88	or/86-87
89	and/7,88
90	limit 89 to english language
91	LETTER/
92	EDITORIAL/
93	NEWS/
94	exp HISTORICAL ARTICLE/
95	ANECDOTES AS TOPIC/
96	COMMENT/
97	CASE REPORT/
98	(letter or comment* or abstracts).ti.
99	or/91-98
100	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
101	99 not 100
102	ANIMALS/ not HUMANS/
103	exp ANIMALS, LABORATORY/
104	exp ANIMAL EXPERIMENTATION/
105	exp MODELS, ANIMAL/
106	exp RODENTIA/
107	(rat or rats or mouse or mice).ti.
108	or/101-107
109	90 not 108

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_risk_factors_RERUN1_mip_300514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3

#	Searches
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	risk?.ti.
27	risk factor?.ab.
28	or/26-27
29	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies).ti,ab.
30	((lung or bronchopulmonary) adj3 dysplasia).ti,ab.
31	(congenital adj3 (heart or cardi$) adj3 (defect$ or abnormal$ or disease$ or malform$ or anomal$)).ti,ab.
32	(chronic$ adj3 (lung disease? or pulmonary disease? or pneumopathy)).ti,ab.
33	(cystic fibrosis or fibrocystic disease? or mucovisc??dosi$).ti,ab.
34	(immunodef$ or immunodepress$ or immunosuppress$).ti,ab.
35	(immun$ adj3 (defic$ or defect$ or depress$ or suppress$ or incompeten$)).ti,ab.
36	breastfe$.ti,ab.
37	(breast$ adj3 (fed or feed$)).ti,ab.
38	(age or young$).ti,ab.
39	(sex or gender or male? or female?).ti,ab.
40	hospitali$.ti,ab.
41	(hospital adj3 (admit$ or admission$)).ti,ab.
42	ethnic$.ti,ab.
43	(down$ syndrome or trisomy 21).ti,ab.
44	(smok$ or tobacco or cigar$).ti,ab.
45	(multiple birth$ or twin$ or triplet$ or quadruplet$ or quintuplet$).ti,ab.
46	or/29-45
47	and/4,25,28,46

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_risk_factors_RERUN1_cctr_300514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40

#	Searches
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RISK FACTORS/
48	risk?.ti.
49	risk factor?.ab.
50	or/47-49
51	exp INFANT, PREMATURE/
52	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies).ti,ab.
53	BRONCHOPULMONARY DYSPLASIA/
54	((lung or bronchopulmonary) adj3 dysplasia).ti,ab.
55	exp HEART DEFECTS, CONGENITAL/
56	(congenital adj3 (heart or cardi$) adj3 (defect$ or abnormal$ or disease$ or malform$ or anomal$)).ti,ab.
57	LUNG DISEASE/
58	(chronic$ adj3 (lung disease? or pulmonary disease? or pneumopathy)).ti,ab.
59	CYSTIC FIBROSIS/
60	(cystic fibrosis or fibrocystic disease? or mucovisc??dosi$).ti,ab.
61	exp IMMUNOLOGIC DEFICIENCY SYNDROMES/
62	(immunodef$ or immunodepress$ or immunosuppress$).ti,ab.
63	(immun$ adj3 (defic$ or defect$ or depress$ or suppress$ or incompeten$)).ti,ab.
64	BREAST FEEDING/
65	breastfe$.ti,ab.
66	(breast$ adj3 (fed or feed$)).ti,ab.
67	AGE FACTORS/
68	(age or young$).ti,ab.
69	SEX FACTORS/
70	(sex or gender or male? or female?).ti,ab.
71	HOSPITALIZATION/
72	PATIENT ADMISSION/
73	CHILD, HOSPITALIZED/
74	hospitali$.ti,ab.
75	(hospital adj3 (admit$ or admission$)).ti,ab.
76	EPIDEMIOLOGIC FACTORS/
77	ethnic$.ti,ab.
78	DOWN SYNDROME/
79	(down$ syndrome or trisomy 21).ti,ab.
80	TOBACCO SMOKE POLLUTION/
81	SMOKING/
82	(smok$ or tobacco or cigar$).ti,ab.
83	exp MULTIPLE BIRTH OFFSPRING/
84	(multiple birth$ or twin$ or triplet$ or quadruplet$ or quintuplet$).ti,ab.
85	or/51-84
86	and/46,50,85

#	Searches
87	and/7,86

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_risk_factors_RERUN1_cdsrdare_300514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx,kw.
6	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).tw,tx,kw.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx,kw.
14	pneumovir$.tw,tx,kw.
15	(paramyxovir$ or metapneumovir$).tw,tx,kw.
16	(adenovir$ or mastadenovir$).tw,tx,kw.
17	influenza$.tw,tx,kw.
18	enterovir$.tw,tx,kw.
19	rhinovir$.tw,tx,kw.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	risk?.ti.
27	risk factor?.tw,tx.
28	or/26-27
29	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies).tw,tx,kw.
30	((lung or bronchopulmonary) adj3 dysplasia).tw,tx,kw.
31	(congenital adj3 (heart or cardi$) adj3 (defect$ or abnormal$ or disease$ or malform$ or anomal$)).tw,tx,kw.
32	LUNG DISEASE.kw.
33	(chronic$ adj3 (lung disease? or pulmonary disease? or pneumopathy)).tw,tx,kw.
34	(cystic fibrosis or fibrocystic disease? or mucovisc??dosi$).tw,tx,kw.
35	(immunodef$ or immunodepress$ or immunosuppress$).tw,tx,kw.
36	(immun$ adj3 (defic$ or defect$ or depress$ or suppress$ or incompeten$)).tw,tx,kw.
37	breastfe$.tw,tx,kw.

#	Searches
38	(breast$ adj3 (fed or feed$)).tw,tx,kw.
39	(age or young$).tw,tx,kw.
40	(sex or gender or male? or female?).tw,tx,kw.
41	hospitali$.tw,tx,kw.
42	(hospital adj3 (admit$ or admission$)).tw,tx,kw.
43	ethnic$.tw,tx,kw.
44	(down$ syndrome or trisomy 21).tw,tx,kw.
45	(smok$ or tobacco or cigar$).tw,tx,kw.
46	(multiple birth$ or twin$ or triplet$ or quadruplet$ or quintuplet$).tw,tx,kw.
47	or/29-46
48	and/4,25,28,47
49	(2013$ or 2014$).dp,dr,up.
50	and/48-49

Database(s): EBM Reviews - Health Technology Assessment

BRONC_risk_factors_RERUN1_hta_300514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.

#	Searches
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RISK FACTORS/
48	risk?.ti.
49	risk factor?.tw.
50	or/47-49
51	exp INFANT, PREMATURE/
52	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies).tw.
53	BRONCHOPULMONARY DYSPLASIA/
54	((lung or bronchopulmonary) adj3 dysplasia).tw.
55	exp HEART DEFECTS, CONGENITAL/
56	(congenital adj3 (heart or cardi$) adj3 (defect$ or abnormal$ or disease$ or malform$ or anomal$)).tw.
57	LUNG DISEASE/
58	(chronic$ adj3 (lung disease? or pulmonary disease? or pneumopathy)).tw.
59	CYSTIC FIBROSIS/
60	(cystic fibrosis or fibrocystic disease? or mucovisc??dosi$).tw.
61	exp IMMUNOLOGIC DEFICIENCY SYNDROMES/
62	(immunodef$ or immunodepress$ or immunosuppress$).tw.
63	(immun$ adj3 (defic$ or defect$ or depress$ or suppress$ or incompeten$)).tw.
64	BREAST FEEDING/
65	breastfe$.tw.
66	(breast$ adj3 (fed or feed$)).tw.
67	AGE FACTORS/
68	(age or young$).tw.
69	SEX FACTORS/
70	(sex or gender or male? or female?).tw.
71	HOSPITALIZATION/

#	Searches
72	PATIENT ADMISSION/
73	CHILD, HOSPITALIZED/
74	hospitali$.tw.
75	(hospital adj3 (admit$ or admission$)).tw.
76	EPIDEMIOLOGIC FACTORS/
77	ethnic$.tw.
78	DOWN SYNDROME/
79	(down$ syndrome or trisomy 21).tw.
80	TOBACCO SMOKE POLLUTION/
81	SMOKING/
82	(smok$ or tobacco or cigar$).tw.
83	exp MULTIPLE BIRTH OFFSPRING/
84	(multiple birth$ or twin$ or triplet$ or quadruplet$ or quintuplet$).tw.
85	or/51-84
86	and/46,50,85
87	and/7,86

Database(s): Embase

BRONC_risk_factors_RERUN1_embase_300514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
17	RESPIRATORY TRACT INFECTION/
18	exp LOWER RESPIRATORY TRACT INFECTION/
19	BRONCHUS DISEASE/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	or/16-22
24	exp ABNORMAL RESPIRATORY SOUND/

#	Searches
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/24-25
27	exp VIRUS INFECTION/
28	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
29	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
30	pneumovir$.ti,ab.
31	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
32	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
33	(paramyxovir$ or metapneumovir$).ti,ab.
34	ADENOVIRUS/ or ADENOVIRUS INFECTION/
35	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
36	(adenovir$ or mastadenovir$).ti,ab.
37	influenza$.ti,ab,hw.
38	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
39	enterovir$.ti,ab.
40	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
41	rhinovir$.ti,ab.
42	or/27-41
43	and/23,26
44	and/23,42
45	and/26,42
46	or/43-45
47	or/15,46
48	RISK FACTOR/
49	risk?.ti.
50	risk factor?.ab.
51	or/48-50
52	PREMATURITY/
53	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies).ti,ab.
54	LUNG DYSPLASIA/
55	((lung or bronchopulmonary) adj3 dysplasia).ti,ab.
56	exp CONGENITAL HEART MALFORMATION/
57	(congenital adj3 (heart or cardi$) adj3 (defect$ or abnormal$ or disease$ or malform$ or anomal$)).ti,ab.
58	CHRONIC LUNG DISEASE/
59	LUNG DISEASE/
60	(chronic$ adj3 (lung disease? or pulmonary disease? or pneumopathy)).ti,ab.
61	CYSTIC FIBROSIS/
62	(cystic fibrosis or fibrocystic disease? or mucovisc??dosi$).ti,ab.
63	exp IMMUNE DEFICIENCY/
64	(immunodef$ or immunodepress$ or immunosuppress$).ti,ab.
65	(immun$ adj3 (defic$ or defect$ or depress$ or suppress$ or incompeten$)).ti,ab.
66	BREAST FEEDING/
67	breastfe$.ti,ab.
68	(breast$ adj3 (fed or feed$)).ti,ab.
69	AGE/

#	Searches
70	(age or young$).ti,ab.
71	SEX DIFFERENCES/
72	(sex or gender or male? or female?).ti,ab.
73	HOSPITALIZATION/
74	CHILD HOSPITALIZATION/
75	HOSPITAL ADMISSION/
76	hospitali$.ti,ab.
77	(hospital adj3 (admit$ or admission$)).ti,ab.
78	ETHNIC DIFFERENCE/
79	ethnic$.ti,ab.
80	DOWN SYNDROME/
81	(down$ syndrome or trisomy 21).ti,ab.
82	PASSIVE SMOKING/
83	exp PARENTAL SMOKING/
84	SMOKING/ae [Adverse Drug Reaction]
85	(smok$ or tobacco or cigar$).ti,ab.
86	exp MULTIPLE PREGNANCY/
87	(multiple birth$ or twin$ or triplet$ or quadruplet$ or quintuplet$).ti,ab.
88	or/52-87
89	and/47,51,88
90	exp BRONCHIOLITIS/ep, et [Epidemiology, Etiology]
91	or/89-90
92	and/7,91
93	limit 92 to english language
94	conference abstract.pt.
95	letter.pt. or LETTER/
96	note.pt.
97	editorial.pt.
98	CASE REPORT/ or CASE STUDY/
99	(letter or comment* or abstracts).ti.
100	or/94-99
101	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
102	100 not 101
103	ANIMAL/ not HUMAN/
104	NONHUMAN/
105	exp ANIMAL EXPERIMENT/
106	exp EXPERIMENTAL ANIMAL/
107	ANIMAL MODEL/
108	exp RODENT/
109	(rat or rats or mouse or mice).ti.
110	or/102-109
111	93 not 110

F.3 At the time of assessment, what clinical features predict deterioration?

Database(s): Ovid MEDLINE(R)

BRONC_deterioration_RERUN1_medline_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	or/8-10
12	TIME FACTORS/
13	TIME TO TREATMENT/
14	((time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
15	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
16	VITAL SIGNS/
17	exp BODY TEMPERATURE/ or FEVER/
18	(temperature? or fever$ or febri$ or pyrex$).ti,ab.
19	exp HEART RATE/ or PULSE/
20	BRADYCARDIA/ or exp TACHYCARDIA/
21	(heart rate? or heartrate? or heart beat? or heartbeat? or puls$ or tachycardi$ or bradycardi$).ti,ab.
22	RESPIRATORY RATE/
23	TACHYPNEA/
24	((respirat$ or breath$) adj3 rate?).ti,ab.
25	(tachypn$ or bradypn$).ti,ab.
26	exp OXIMETRY/
27	OXYGEN/bl [Blood]
28	(oximet$ or S?O2).ti,ab.
29	((oxygen$ or O2) adj3 saturat$).ti,ab.
30	FEEDING BEHAVIOR/ or SUCKING BEHAVIOR/
31	((able or abilit$) adj3 (feed$ or fed or suck$)).ti,ab.
32	exp BEHAVIOR/ or IRRITABLE MOOD/ or CRYING/
33	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
34	or/12-33
35	SEVERITY OF ILLNESS INDEX/
36	DISEASE PROGRESSION/
37	(bronchiol$ adj5 (sever$ or progress$ or deteriorat$)).ti,ab.
38	exp HOSPITALIZATION/

#	Searches
39	CHILD, HOSPITALIZED/
40	EMERGENCY SERVICE, HOSPITAL/
41	hospitali$.ti,ab.
42	((admit$ or admission?) adj3 hospital$).ti,ab.
43	or/35-42
44	predict.ti.
45	(validat* or rule*).ti,ab.
46	(predict* and (outcome* or risk* or model*)).ti,ab.
47	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
48	decision*.ti,ab. and LOGISTIC MODELS/
49	(decision* and (model* or clinical*)).ti,ab.
50	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
51	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
52	ROC CURVE/
53	or/44-52
54	PREVALENCE/
55	INCIDENCE/
56	exp COHORT STUDIES/
57	CROSS-SECTIONAL STUDIES/
58	exp MODELS, STATISTICAL/
59	LIFE TABLES/
60	exp RISK/
61	(prevalen$ or incidence? or model$ or risk$ or rate?).ti.
62	or/54-61
63	7 and 11 and 53 and (34 or 43)
64	7 and 11 and 62 and 34 and 43
65	*BRONCHIOLITIS/cl, co, ep, mo [Classification, Complications, Epidemiology, Mortality]
66	and/7,65
67	or/63-64,66
68	limit 67 to english language
69	LETTER/
70	EDITORIAL/
71	NEWS/
72	exp HISTORICAL ARTICLE/
73	ANECDOTES AS TOPIC/
74	COMMENT/
75	(letter or comment* or abstracts).ti.
76	or/69-75
77	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
78	76 not 77
79	ANIMALS/ not HUMANS/
80	exp ANIMALS, LABORATORY/
81	exp ANIMAL EXPERIMENTATION/

#	Searches
82	exp MODELS, ANIMAL/
83	exp RODENTIA/
84	(rat or rats or mouse or mice).ti.
85	or/78-84
86	68 not 85

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_deterioration_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	((time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
7	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
8	(temperature? or fever$ or febri$ or pyrex$).ti,ab.
9	(heart rate? or heartrate? or heart beat? or heartbeat? or puls$ or tachycardi$ or bradycardi$).ti,ab.
10	((respirat$ or breath$) adj3 rate?).ti,ab.
11	(tachypn$ or bradypn$).ti,ab.
12	(oximet$ or S?O2).ti,ab.
13	((oxygen$ or O2) adj3 saturat$).ti,ab.
14	((able or abilit$) adj3 (feed$ or fed or suck$)).ti,ab.
15	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
16	or/6-15
17	(bronchiol$ adj5 (sever$ or progress$ or deteriorat$)).ti,ab.
18	hospitali$.ti,ab.
19	((admit$ or admission?) adj3 hospital$).ti,ab.
20	or/17-19
21	predict.ti.
22	(validat* or rule*).ti,ab.
23	(predict* and (outcome* or risk* or model*)).ti,ab.
24	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
25	(decision* and (model* or clinical*)).ti,ab.
26	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
27	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
28	or/21-27
29	(prevalen$ or incidence? or model$ or risk$ or rate?).ti.
30	4 and 5 and 28 and (16 or 20)
31	4 and 5 and 29 and 16 and 20
32	or/30-31

#	Searches
33	limit 32 to english language

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_deterioration_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	or/8-10
12	TIME FACTORS/
13	TIME TO TREATMENT/
14	((time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
15	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
16	VITAL SIGNS/
17	exp BODY TEMPERATURE/ or FEVER/
18	(temperature? or fever$ or febri$ or pyrex$).ti,ab.
19	exp HEART RATE/ or PULSE/
20	BRADYCARDIA/ or exp TACHYCARDIA/
21	(heart rate? or heartrate? or heart beat? or heartbeat? or puls$ or tachycardi$ or bradycardi$).ti,ab.
22	RESPIRATORY RATE/
23	TACHYPNEA/
24	((respirat$ or breath$) adj3 rate?).ti,ab.
25	(tachypn$ or bradypn$).ti,ab.
26	exp OXIMETRY/
27	OXYGEN/bl [Blood]
28	(oximet$ or S?O2).ti,ab.
29	((oxygen$ or O2) adj3 saturat$).ti,ab.
30	FEEDING BEHAVIOR/ or SUCKING BEHAVIOR/
31	((able or abilit$) adj3 (feed$ or fed or suck$)).ti,ab.
32	exp BEHAVIOR/ or IRRITABLE MOOD/ or CRYING/
33	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
34	or/12-33
35	SEVERITY OF ILLNESS INDEX/
36	DISEASE PROGRESSION/
37	(bronchiol$ adj5 (sever$ or progress$ or deteriorat$)).ti,ab.
38	exp HOSPITALIZATION/

#	Searches
39	CHILD, HOSPITALIZED/
40	EMERGENCY SERVICE, HOSPITAL/
41	hospitali$.ti,ab.
42	((admit$ or admission?) adj3 hospital$).ti,ab.
43	or/35-42
44	predict.ti.
45	(validat* or rule*).ti,ab.
46	(predict* and (outcome* or risk* or model*)).ti,ab.
47	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
48	decision*.ti,ab. and LOGISTIC MODELS/
49	(decision* and (model* or clinical*)).ti,ab.
50	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
51	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
52	ROC CURVE/
53	or/44-52
54	PREVALENCE/
55	INCIDENCE/
56	exp COHORT STUDIES/
57	CROSS-SECTIONAL STUDIES/
58	exp MODELS, STATISTICAL/
59	LIFE TABLES/
60	exp RISK/
61	(prevalen$ or incidence? or model$ or risk$ or rate?).ti.
62	or/54-61
63	7 and 11 and 53 and (34 or 43)
64	7 and 11 and 62 and 34 and 43
65	BRONCHIOLITIS/cl, co, ep, mo [Classification, Complications, Epidemiology, Mortality]
66	and/7,65
67	or/63-64,66

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_deterioration_RERUN1_cdsrdare_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,kw,jw,rw.
3	p?ediatric$.ti,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	TIME.kw.

#	Searches
7	((time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).tw,tx.
8	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).tw,tx.
9	VITAL SIGN$.kw.
10	(temperature? or fever$ or febri$ or pyrex$).tw,tx,kw.
11	(heart rate? or heartrate? or heart beat? or heartbeat? or puls$ or tachycardi$ or bradycardi$).tw,tx,kw.
12	((respirat$ or breath$) adj3 rate?).tw,tx,kw.
13	(tachypn$ or bradypn$).tw,tx,kw.
14	OXYGEN.kw.
15	(oximet$ or S?O2).tw,tx,kw.
16	((oxygen$ or O2) adj3 saturat$).tw,tx,kw.
17	(FEEDING BEHAVIOR or SUCKING).kw.
18	((able or abilit$) adj3 (feed$ or fed or suck$)).ti,ab.
19	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).tw,tx,kw.
20	or/6-19
21	SEVERITY OF ILLNESS INDEX.kw.
22	(DISEASE PROGRESSION or DISEASE SEVERITY or DISEASE COURSE).kw.
23	(bronchiol$ adj5 (sever$ or progress$ or deteriorat$)).tw,tx.
24	(EMERGENCY SERVICE, HOSPITAL or EMERGENCY HEALTH SERVICE).kw.
25	hospitali$.tw,tx,kw.
26	((admit$ or admission?) adj3 hospital$).tw,tx.
27	or/21-26
28	predict.ti.
29	(validat* or rule*).tw,tx.
30	(predict* and (outcome* or risk* or model*)).tw,tx.
31	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).tw,tx.
32	decision*.tw,tx. and MODEL*.kw.
33	(decision* and (model* or clinical*)).tw,tx.
34	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).tw,tx.
35	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).tw,tx.
36	(ROC CURVE or RECEIVER OPERATING CHARACTERISTIC).kw.
37	or/28-36
38	(COHORT or CROSS-SECTIONAL or LONGITUDINAL or LIFE TABLE?).kw.
39	(prevalen$ or incidence? or model$ or risk$ or rate?).ti,kw.
40	or/38-39
41	4 and 5 and 37 and (20 or 27)
42	4 and 5 and 40 and 20 and 27
43	or/41-42

Database(s): EBM Reviews - Health Technology Assessment

BRONC_deterioration_hta_101213

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw.
5	exp PEDIATRICS/
6	p?ediatric$.tw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	or/8-10
12	TIME FACTORS/
13	TIME TO TREATMENT/
14	((time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).tw.
15	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).tw.
16	VITAL SIGNS/
17	exp BODY TEMPERATURE/ or FEVER/
18	(temperature? or fever$ or febri$ or pyrex$).tw.
19	exp HEART RATE/ or PULSE/
20	BRADYCARDIA/ or exp TACHYCARDIA/
21	(heart rate? or heartrate? or heart beat? or heartbeat? or puls$ or tachycardi$ or bradycardi$).tw.
22	RESPIRATORY RATE/
23	TACHYPNEA/
24	((respirat$ or breath$) adj3 rate?).tw.
25	(tachypn$ or bradypn$).tw.
26	exp OXIMETRY/
27	OXYGEN/bl [Blood]
28	(oximet$ or S?O2).tw.
29	((oxygen$ or O2) adj3 saturat$).tw.
30	FEEDING BEHAVIOR/ or SUCKING BEHAVIOR/
31	((able or abilit$) adj3 (feed$ or fed or suck$)).tw.
32	exp BEHAVIOR/ or IRRITABLE MOOD/ or CRYING/
33	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).tw.
34	or/12-33
35	SEVERITY OF ILLNESS INDEX/
36	DISEASE PROGRESSION/
37	(bronchiol$ adj5 (sever$ or progress$ or deteriorat$)).tw.
38	exp HOSPITALIZATION/

#	Searches
39	CHILD, HOSPITALIZED/
40	EMERGENCY SERVICE, HOSPITAL/
41	hospitali$.tw.
42	((admit$ or admission?) adj3 hospital$).tw.
43	or/35-42
44	predict.ti.
45	(validat* or rule*).tw.
46	(predict* and (outcome* or risk* or model*)).tw.
47	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).tw.
48	decision*.tw. and LOGISTIC MODELS/
49	(decision* and (model* or clinical*)).tw.
50	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).tw.
51	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).tw.
52	ROC CURVE/
53	or/44-52
54	PREVALENCE/
55	INCIDENCE/
56	exp COHORT STUDIES/
57	CROSS-SECTIONAL STUDIES/
58	exp MODELS, STATISTICAL/
59	LIFE TABLES/
60	exp RISK/
61	(prevalen$ or incidence? or model$ or risk$ or rate?).ti.
62	or/54-61
63	7 and 11 and 53 and (34 or 43)
64	7 and 11 and 62 and 34 and 43
65	BRONCHIOLITIS/cl, co, ep, mo [Classification, Complications, Epidemiology, Mortality]
66	and/7,65
67	or/63-64,66

Database(s): Embase

BRONC_deterioration_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/

#	Searches
10	bronchiol$.ti,ab.
11	or/8-10
12	TIME/
13	TIME TO TREATMENT/
14	((time or timing) adj4 (factor$ or onset or diagnos$ or treatment$ or present$)).ti,ab.
15	((ill$ or sick$ or symptom? or bronchiol$) adj3 (durat$ or onset$)).ti,ab.
16	VITAL SIGN/
17	exp BODY TEMPERATURE/ or FEVER/
18	(temperature? or fever$ or febri$ or pyrex$).ti,ab.
19	exp HEART RATE/ or exp PULSE RATE/
20	exp BRADYCARDIA/ or exp TACHYCARDIA/
21	(heart rate? or heartrate? or heart beat? or heartbeat? or puls$ or tachycardi$ or bradycardi$).ti,ab.
22	RESPIRATORY RATE/
23	BRADYPNEA/ or TACHYPNEA/
24	((respirat$ or breath$) adj3 rate?).ti,ab.
25	exp OXIMETRY/
26	OXYGEN BLOOD LEVEL/
27	OXYGEN SATURATION/
28	(oximet$ or S?O2).ti,ab.
29	((oxygen$ or O2) adj3 saturat$).ti,ab.
30	FEEDING BEHAVIOR/ or SUCKING/
31	((able or abilit$) adj3 (feed$ or fed or suck$)).ti,ab.
32	exp BEHAVIOR/ or IRRITABILITY/ or CRYING/
33	(behav$ or respon$ or non?respon$ or cry$ or cries or irritab$).ti,ab.
34	or/12-33
35	SEVERITY OF ILLNESS INDEX/
36	DISEASE SEVERITY/
37	DISEASE COURSE/
38	DETERIORATION/
39	(bronchiol$ adj5 (sever$ or progress$ or deteriorat$)).ti,ab.
40	HOSPITALIZATION/ or CHILD HOSPITALIZATION/
41	HOSPITALIZED CHILD/ or HOSPITALIZED INFANT/
42	EMERGENCY HEALTH SERVICE/
43	hospitali$.ti,ab.
44	((admit$ or admission?) adj3 hospital$).ti,ab.
45	or/35-44
46	predict.ti.
47	(validat* or rule*).ti,ab.
48	(predict* and (outcome* or risk* or model*)).ti,ab.
49	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
50	decision*.ti,ab. and STATISTICAL MODEL/
51	(decision* and (model* or clinical*)).ti,ab.
52	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.

#	Searches
53	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
54	RECEIVER OPERATING CHARACTERISTIC/
55	or/46-54
56	PREVALENCE/
57	INCIDENCE/
58	CROSS-SECTIONAL STUDY/
59	LONGITUDINAL STUDY/
60	COHORT ANALYSIS/
61	STATISTICAL MODEL/
62	LIFE TABLE/
63	exp RISK/
64	(prevalen$ or incidence? or model$ or risk$ or rate?).ti.
65	or/56-64
66	7 and 11 and 55 and (34 or 45)
67	7 and 11 and 65 and 34 and 45
68	*BRONCHIOLITIS/co, ep [Complication, Epidemiology]
69	and/7,68
70	or/66-67,69
71	limit 70 to english language
72	conference abstract.pt.
73	letter.pt. or LETTER/
74	note.pt.
75	editorial.pt.
76	(letter or comment* or abstracts).ti.
77	or/72-76
78	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
79	77 not 78
80	ANIMAL/ not HUMAN/
81	NONHUMAN/
82	exp ANIMAL EXPERIMENT/
83	exp EXPERIMENTAL ANIMAL/
84	ANIMAL MODEL/
85	exp RODENT/
86	(rat or rats or mouse or mice).ti.
87	or/79-86

F.4 What is the indication for capillary blood gas testing?

Database(s): Ovid MEDLINE(R)

BRONC_capillary_blood_gas_RERUN2_medline_190814

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw,nw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw,nw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw,nw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/

#	Searches
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	BLOOD GAS ANALYSIS/
48	OXYGEN/bl [Blood]
49	CARBON DIOXIDE/ [Blood]
50	BLOOD SPECIMEN COLLECTION/
51	((capil??ar$ or arter$) adj3 blood adj3 (gas$ or oxygen or O2 or carbon dioxide or CO2)).ti,ab.
52	(ABG or SaO2 or SaCO2 or PO2 or PCO2 or PaO2 or PaCO2 or SpO2 or SpCO2).ti,ab.
53	or/47-52
54	and/7,46,53
55	limit 54 to english language
56	LETTER/
57	EDITORIAL/
58	NEWS/
59	exp HISTORICAL ARTICLE/
60	ANECDOTES AS TOPIC/
61	COMMENT/
62	CASE REPORT/
63	(letter or comment* or abstracts).ti.
64	or/56-63
65	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
66	64 not 65
67	ANIMALS/ not HUMANS/
68	exp ANIMALS, LABORATORY/
69	exp ANIMAL EXPERIMENTATION/
70	exp MODELS, ANIMAL/
71	exp RODENTIA/
72	(rat or rats or mouse or mice).ti.
73	or/66-72
74	55 not 73

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_capillary_blood_gas_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3

#	Searches
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab,hw.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	((capil??ar$ or arter$) adj3 blood adj3 (gas$ or oxygen or O2 or carbon dioxide or CO2)).ti,ab.
27	(ABG or SaO2 or SaCO2 or PO2 or PCO2 or PaO2 or PaCO2 or SpO2 or SpCO2).ti,ab.
28	or/26-27
29	and/4,25,28
30	limit 29 to english language

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_capillary_blood_gas_RERUN1_cctr_250614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.

#	Searches
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	BLOOD GAS ANALYSIS/
48	OXYGEN/bl [Blood]
49	CARBON DIOXIDE/ [Blood]
50	BLOOD SPECIMEN COLLECTION/
51	((capil??ar$ or arter$) adj3 blood adj3 (gas$ or oxygen or O2 or carbon dioxide or CO2)).ti,ab.
52	(ABG or SaO2 or SaCO2 or PO2 or PCO2 or PaO2 or PaCO2 or SpO2 or SpCO2).ti,ab.
53	or/47-52
54	and/7,46,53

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_capillary_blood_gas_RERUN1_cdsrdare_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,jw,rw.
3	p?ediatric$.tw,tx,jw,rw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx,kw.
6	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	or/8-10
12	(RESPIRAT$ adj2 SOUND?).kw.
13	(crepit$ or crackl$ or wheez$).tw,tx,kw.
14	or/12-13
15	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx,kw.
16	pneumovir$.tw,tx,kw.
17	(paramyxovir$ or metapneumovir$).tw,tx,kw.
18	(adenovir$ or mastadenovir$).tw,tx,kw.
19	influenza$.tw,tx,kw.
20	enterovir$.tw,tx,kw.
21	rhinovir$.tw,tx,kw.
22	or/15-21
23	and/11,14
24	and/11,22
25	and/14,22
26	or/23-25
27	or/7,26
28	BLOOD GAS ANALYSIS.kw.
29	(BLOOD SPECIMEN COLLECTION or BLOOD SAMPLING).kw.
30	((capil??ar$ or arter$) adj3 blood adj3 (gas$ or oxygen or O2 or carbon dioxide or CO2)).tw,tx.
31	(ABG or SaO2 or SaCO2 or PO2 or PCO2 or PaO2 or PaCO2 or SpO2 or SpCO2).tw,tx.
32	or/28-31
33	and/4,27,32

Database(s): EBM Reviews - Health Technology Assessment

BRONC_capillary_blood_gas_RERUN1_hta_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40

#	Searches
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	BLOOD GAS ANALYSIS/
48	OXYGEN/bl [Blood]
49	CARBON DIOXIDE/ [Blood]
50	BLOOD SPECIMEN COLLECTION/
51	((capil??ar$ or arter$) adj3 blood adj3 (gas$ or oxygen or O2 or carbon dioxide or CO2)).tw.
52	(ABG or SaO2 or SaCO2 or PO2 or PCO2 or PaO2 or PaCO2 or SpO2 or SpCO2).tw.
53	or/47-52
54	and/7,46,53

Database(s): Embase

BRONC_capillary_blood_gas_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp NEWBORN/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
17	RESPIRATORY TRACT INFECTION/
18	exp LOWER RESPIRATORY TRACT INFECTION/
19	BRONCHUS DISEASE/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	or/16-22
24	exp ABNORMAL RESPIRATORY SOUND/
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/24-25

#	Searches
27	exp VIRUS INFECTION/
28	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
29	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
30	pneumovir$.ti,ab.
31	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
32	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
33	(paramyxovir$ or metapneumovir$).ti,ab.
34	ADENOVIRUS/ or ADENOVIRUS INFECTION/
35	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
36	(adenovir$ or mastadenovir$).ti,ab.
37	influenza$.ti,ab,hw.
38	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
39	enterovir$.ti,ab.
40	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
41	rhinovir$.ti,ab.
42	or/27-41
43	and/23,26
44	and/23,42
45	and/26,42
46	or/43-45
47	or/15,46
48	BLOOD GAS ANALYSIS/
49	BLOOD CARBON DIOXIDE TENSION/
50	BLOOD OXYGEN TENSTION/
51	ARTERIAL CARBON DIOXIDE TENSION/
52	ARTERIAL OXYGEN TENSION/
53	CARBON DIOXIDE/ec [Endogenous Compound]
54	OXYGEN/ec [Endogenous Compound]
55	*BLOOD SAMPLING/
56	((capil??ar$ or arter$) adj3 blood adj3 (gas$ or oxygen or O2 or carbon dioxide or CO2)).ti,ab.
57	(ABG or SaO2 or SaCO2 or PO2 or PCO2 or PaO2 or PaCO2 or SpO2 or SpCO2).ti,ab.
58	or/48-57
59	and/7,47,58
60	limit 59 to english language
61	conference abstract.pt.
62	letter.pt. or LETTER/
63	note.pt.
64	editorial.pt.
65	CASE REPORT/ or CASE STUDY/
66	(letter or comment* or abstracts).ti.
67	or/61-66
68	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
69	67 not 68
70	ANIMAL/ not HUMAN/
71	NONHUMAN/

#	Searches
72	exp ANIMAL EXPERIMENT/
73	exp EXPERIMENTAL ANIMAL/
74	ANIMAL MODEL/
75	exp RODENT/
76	(rat or rats or mouse or mice).ti.
77	or/69-76
78	60 not 77

F.5 What are the indications for fluids and nutritional support?

Database(s): Ovid MEDLINE(R)

BRONC_fluids_RERUN1_medline_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/

#	Searches
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp FEEDING METHODS/
48	exp FLUID THERAPY/
49	INFUSIONS, INTRAVENOUS/
50	INTUBATION, GASTROINTESTINAL/
51	((tube or tubal or intuba$ or enteral or parenteral or oral$ or nasogastric or gastrointestinal or intravenous$ or IV) adj3 (nutrition$ or fluid$ or feed$ or fed)).ti,ab.
52	(hydrat$ or rehydrat$ or fluid therap$ or hypodermoclysi$).ti,ab.
53	or/47-52
54	and/7,46,53
55	limit 54 to english language
56	LETTER/
57	EDITORIAL/
58	NEWS/
59	exp HISTORICAL ARTICLE/
60	ANECDOTES AS TOPIC/
61	COMMENT/
62	CASE REPORT/
63	(letter or comment* or abstracts).ti.
64	or/56-63
65	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
66	64 not 65
67	ANIMALS/ not HUMANS/
68	exp ANIMALS, LABORATORY/
69	exp ANIMAL EXPERIMENTATION/
70	exp MODELS, ANIMAL/
71	exp RODENTIA/
72	(rat or rats or mouse or mice).ti.
73	or/66-72
74	55 not 73

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_fluids_RERUN1_mip_240614 Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_fluids_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab,hw.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	((tube or tubal or intuba$ or enteral or parenteral or oral$ or nasogastric or gastrointestinal or intravenous$ or IV) adj3 (nutrition$ or fluid$ or feed$ or fed)).ti,ab.
27	(hydrat$ or rehydrat$ or fluid therap$ or hypodermoclysi$).ti,ab.
28	or/26-27
29	and/4,25,28

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_fluids_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/

#	Searches
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp FEEDING METHODS/
48	exp FLUID THERAPY/
49	INFUSIONS, INTRAVENOUS/
50	INTUBATION, GASTROINTESTINAL/
51	((tube or tubal or intuba$ or enteral or parenteral or oral$ or nasogastric or gastrointestinal or intravenous$ or IV) adj3 (nutrition$ or fluid$ or feed$ or fed)).ti,ab.
52	(hydrat$ or rehydrat$ or fluid therap$ or hypodermoclysi$).ti,ab.
53	or/47-52
54	and/7,46,53

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_fluids_RERUN1_cdsrdare_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,jw,rw.
3	p?ediatric$.tw,tx,jw,rw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx,kw.
6	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	or/8-10
12	(RESPIRAT$ adj2 SOUND?).kw.
13	(crepit$ or crackl$ or wheez$).tw,tx,kw.
14	or/12-13
15	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx,kw.
16	pneumovir$.tw,tx,kw.
17	(paramyxovir$ or metapneumovir$).tw,tx,kw.
18	(adenovir$ or mastadenovir$).tw,tx,kw.
19	influenza$.tw,tx,kw.
20	enterovir$.tw,tx,kw.
21	rhinovir$.tw,tx,kw.
22	or/15-21
23	and/11,14

#	Searches
24	and/11,22
25	and/14,22
26	or/23-25
27	or/7,26
28	FEEDING METHODS.kw.
29	FLUID THERAPY.kw.
30	INFUSIONS, INTRAVENOUS.kw.
31	INTUBATION, GASTROINTESTINAL.kw.
32	((tube or tubal or intuba$ or enteral or parenteral or oral$ or nasogastric or gastrointestinal or intravenous$ or IV) adj3 (nutrition$ or fluid$ or feed$ or fed)).tw,tx.
33	(hydrat$ or rehydrat$ or fluid therap$ or hypodermoclysi$).tw,tx.
34	or/28-33
35	and/4,27,34

Database(s): EBM Reviews - Health Technology Assessment

BRONC_fluids_RERUN1_hta_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.

#	Searches
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp FEEDING METHODS/
48	exp FLUID THERAPY/
49	INFUSIONS, INTRAVENOUS/
50	INTUBATION, GASTROINTESTINAL/
51	((tube or tubal or intuba$ or enteral or parenteral or oral$ or nasogastric or gastrointestinal or intravenous$ or IV) adj3 (nutrition$ or fluid$ or feed$ or fed)).tw.
52	(hydrat$ or rehydrat$ or fluid therap$ or hypodermoclysi$).tw.
53	or/47-52
54	and/7,46,53

Database(s): Embase

BRONC_fluids_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.

#	Searches
12	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
17	RESPIRATORY TRACT INFECTION/
18	exp LOWER RESPIRATORY TRACT INFECTION/
19	BRONCHUS DISEASE/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	or/16-22
24	exp ABNORMAL RESPIRATORY SOUND/
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/24-25
27	exp VIRUS INFECTION/
28	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
29	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
30	pneumovir$.ti,ab.
31	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
32	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
33	(paramyxovir$ or metapneumovir$).ti,ab.
34	ADENOVIRUS/ or ADENOVIRUS INFECTION/
35	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
36	(adenovir$ or mastadenovir$).ti,ab.
37	influenza$.ti,ab,hw.
38	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
39	enterovir$.ti,ab.
40	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
41	rhinovir$.ti,ab.
42	or/27-41
43	and/23,26
44	and/23,42
45	and/26,42
46	or/43-45
47	or/15,46
48	ENTERIC FEEDING/
49	exp FLUID THERAPY/
50	exp DIGESTIVE TRACT INTUBATION/
51	((tube or tubal or intuba$ or enteral or parenteral or oral$ or nasogastric or gastrointestinal or intravenous$ or IV) adj3 (nutrition$ or fluid$ or feed$ or fed)).ti,ab.
52	(hydrat$ or rehydrat$ or fluid therap$ or hypodermoclysi$).ti,ab.
53	or/48-52
54	and/7,47,53
55	limit 54 to english language
56	conference abstract.pt.

#	Searches
57	letter.pt. or LETTER/
58	note.pt.
59	editorial.pt.
60	CASE REPORT/ or CASE STUDY/
61	(letter or comment* or abstracts).ti.
62	or/56-61
63	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
64	62 not 63
65	ANIMAL/ not HUMAN/
66	NONHUMAN/
67	exp ANIMAL EXPERIMENT/
68	exp EXPERIMENTAL ANIMAL/
69	ANIMAL MODEL/
70	exp RODENT/
71	(rat or rats or mouse or mice).ti.
72	or/64-71
73	55 not 72

Database(s): CINAHL with Full Text

BRONC_fluids_RERUN1_cinahl_240614

#	Query
S35	S5 AND S25 AND S34
S34	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
S33	AB (hydrat* or rehydrat* or fluid therap* or hypodermoclysi*)
S32	TI (hydrat* or rehydrat* or fluid therap* or hypodermoclysi*)
S31	AB ((tube or tubal or intuba* or enteral or parenteral or oral* or nasogastric or gastrointestinal or intravenous* or IV) N3 (nutrition* or fluid* or feed* or fed))
S30	TI ((tube or tubal or intuba* or enteral or parenteral or oral* or nasogastric or gastrointestinal or intravenous* or IV) N3 (nutrition* or fluid* or feed* or fed))
S29	(MH "Intubation, Gastrointestinal")
S28	(MH "Infusions, Intravenous")
S27	(MH "Fluid Therapy+")
S26	(MH "Feeding Methods+")
S25	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
S24	TI (crepit* or crackl* or wheez*) or AB (crepit* or crackl* or wheez*)
S23	(MH "Respiratory Sounds")
S22	TI (LR#I* or ALR#I*) or AB (LR#I* or ALR#I*)
S21	AB (bronchi* N3 infect*) or AB (bronchi* N3 inflam*) or AB (bronchi* N3 disease*)
S20	TI (bronchi* N3 infect*) or TI (bronchi* N3 inflam*) or TI (bronchi* N3 disease*)
S19	AB (respiratory N3 infect*) or AB (respiratory N3 inflam*) or AB (respiratory N3 disease*)
S18	TI (respiratory N3 infect*) or TI (respiratory N3 inflam*) or TI (respiratory N3 disease*)
S17	(MH "Bronchial Diseases")
S16	(MH "Respiratory Tract Infections")
S15	(MH "Respiratory Tract Diseases")

#	Query
S14	TI (respiratory sync?tial vir* or RSV) or AB (respiratory sync?tial vir* or RSV)
S13	(MH "Respiratory Syncytial Virus Infections")
S12	(MH "Respiratory Syncytial Viruses")
S11	TI (bronchopneumon* or bronchit*) or AB (bronchopneumon* or bronchit*)
S10	(MH "Bronchopneumonia")
S9	(MH "Bronchitis+")
S8	TI (bronchiol*) or AB (bronchiol*)
S7	(MH "Bronchioles")
S6	(MH "Bronchiolitis")
S5	S1 OR S2 OR S3 OR S4
S4	TI (pediatric* or paediatric*) or AB (pediatric* or paediatric*) or SO (pediatric* or paediatric*)
S3	TI (infan* or neonat* or newborn* or baby or babies) OR AB (infan* or neonat* or newborn* or baby or babies) OR SO (infan* or neonat* or newborn* or baby or babies)
S2	TI (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR AB (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR SO (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#)
S1	(MH "Infant, Newborn+") OR (MH "Infant+") OR (MH "Child, Preschool") OR (MH "Child+") OR (MH "Pediatrics+")

F.6 What are the criteria for a) referral to secondary care, b) hospital admission for observation or treatment, c) discharge from hospital?

Database(s): Ovid MEDLINE(R)

BRONC_referral_RERUN2_medline_180814

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	bronchiol$.ti,ab.
12	or/8-11
13	"REFERRAL AND CONSULTATION"/
14	HEALTH KNOWLEDGE, ATTITUDES, PRACTICE/
15	DECISION MAKING/
16	(refer$ or consult$).ti,ab.

#	Searches
17	HOSPITALIZATION/ or PATIENT ADMISSION/ or PATIENT DISCHARGE/ or PATIENT READMISSION/ or PATIENT TRANSFER/
18	CHILD, HOSPITALIZED/
19	"EPISODE OF CARE"/
20	((hospital or secondary care) adj3 (admit$ or admission?)).ti,ab.
21	SECONDARY CARE/
22	(readmit$ or readmission?).ti,ab.
23	or/13-22
24	and/7,12,23
25	limit 24 to english language
26	LETTER/
27	EDITORIAL/
28	NEWS/
29	exp HISTORICAL ARTICLE/
30	ANECDOTES AS TOPIC/
31	COMMENT/
32	CASE REPORT/
33	(letter or comment* or abstracts).ti.
34	or/26-33
35	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
36	34 not 35
37	ANIMALS/ not HUMANS/
38	exp ANIMALS, LABORATORY/
39	exp ANIMAL EXPERIMENTATION/
40	exp MODELS, ANIMAL/
41	exp RODENTIA/
42	(rat or rats or mouse or mice).ti.
43	or/36-42
44	25 not 43

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_referral_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchitis or bronchopneumonia).ti,ab.
6	bronchiol$.ti,ab.
7	or/5-6
8	(decision or decide or deciding).ti,ab.
9	(refer$ or consult$).ti,ab.
10	(hospitaliz$ or hospitalis$).ti,ab.

#	Searches
11	((patient? or hospital) adj5 (admission or admited or readmission or readmit or discharge or transfer$)).ti,ab.
12	(secondary care adj3 (admit$ or admission?)).ti,ab.
13	(readmit$ or readmission?).ti,ab.
14	(episode? adj2 care).ti,ab.
15	or/8-14
16	and/4,7,15

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_referral_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	bronchiol$.ti,ab.
12	or/8-11
13	"REFERRAL AND CONSULTATION"/
14	HEALTH KNOWLEDGE, ATTITUDES, PRACTICE/
15	DECISION MAKING/
16	(refer$ or consult$).ti,ab.
17	HOSPITALIZATION/ or PATIENT ADMISSION/ or PATIENT DISCHARGE/ or PATIENT READMISSION/ or PATIENT TRANSFER/
18	CHILD, HOSPITALIZED/
19	"EPISODE OF CARE"/
20	((hospital or secondary care) adj3 (admit$ or admission?)).ti,ab.
21	SECONDARY CARE/
22	(readmit$ or readmission?).ti,ab.
23	or/13-22
24	and/7,12,23

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_referral_RERUN1_cdsrdare_240614

#	Searches
1	CHILD.tw.
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,jw,rw.
3	INFANT.kw.
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,jw,rw.
5	PEDIATRICS.kw.
6	p?ediatric$.tw,tx,jw,rw.
7	or/1-6
8	BRONCHIOLITIS.kw.
9	BRONCHIOLES.kw.
10	(BRONCHITIS or BRONCHOPNEUMONIA).kw.
11	bronchiol$.tw,tx.
12	or/8-11
13	"REFERRAL AND CONSULTATION".kw.
14	HEALTH KNOWLEDGE, ATTITUDES, PRACTICE.kw.
15	DECISION MAKING.kw.
16	(refer$ or consult$).tw,tx.
17	(HOSPITALIZATION or PATIENT ADMISSION or PATIENT DISCHARGE or PATIENT READMISSION or PATIENT TRANSFER).kw.
18	CHILD, HOSPITALIZED.kw.
19	"EPISODE OF CARE".kw.
20	((hospital or secondary care) adj3 (admit$ or admission?)).tw,tx.
21	SECONDARY CARE.kw.
22	(readmit$ or readmission?).tw,tx.
23	or/13-22
24	and/7,12,23

Database(s): EBM Reviews - Health Technology Assessment

BRONC_referral_RERUN1_hta_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/

#	Searches
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	bronchiol$.tw.
12	or/8-11
13	"REFERRAL AND CONSULTATION"/
14	HEALTH KNOWLEDGE, ATTITUDES, PRACTICE/
15	DECISION MAKING/
16	(refer$ or consult$).tw.
17	HOSPITALIZATION/ or PATIENT ADMISSION/ or PATIENT DISCHARGE/ or PATIENT READMISSION/ or PATIENT TRANSFER/
18	CHILD, HOSPITALIZED/
19	"EPISODE OF CARE"/
20	((hospital or secondary care) adj3 (admit$ or admission?)).tw.
21	SECONDARY CARE/
22	(readmit$ or readmission?).tw.
23	or/13-22
24	and/7,12,23

Database(s): Embase

BRONC_referral_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	bronchiol$.ti,ab.
11	or/8-10
12	PATIENT REFERRAL/
13	(refer$ or consult$).ti,ab.
14	MEDICAL DECISION MAKING/
15	HOSPITALIZATION/
16	HOSPITALIZED CHILD/ or HOSPITALIZED INFANT/
17	((hospital or secondary care) adj3 (admit$ or admission?)).ti,ab.
18	HOSPITAL ADMISSION/
19	HOSPITAL DISCHARGE/
20	SECONDARY HEALTH CARE/
21	HOSPITAL READMISSION/
22	(readmit$ or readmission?).ti,ab.
23	or/12-22

#	Searches
24	and/7,11,23
25	limit 24 to english language
26	conference abstract.pt.
27	letter.pt. or LETTER/
28	note.pt.
29	editorial.pt.
30	CASE REPORT/ or CASE STUDY/
31	(letter or comment* or abstracts).ti.
32	or/26-31
33	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
34	32 not 33
35	ANIMAL/ not HUMAN/
36	NONHUMAN/
37	exp ANIMAL EXPERIMENT/
38	exp EXPERIMENTAL ANIMAL/
39	ANIMAL MODEL/
40	exp RODENT/
41	(rat or rats or mouse or mice).ti.
42	or/34-41
43	25 not 42

F.7 When is pulse oximetry oxygen saturation monitoring (Sp_{O2}) indicated in bronchiolitis?

Database(s): Ovid MEDLINE(R)

BRONC_SpO2_monitoring_RERUN1_medline__240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/

#	Searches
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp OXIMETRY/
48	OXYGEN/an, bl [Analysis, Blood]
49	(oximet$ or S?O2 or O?SAT?).ti,ab.
50	((oxygen$ or O2) adj3 (saturat$ or monitor$)).ti,ab.
51	or/47-50
52	and/7,46,51
53	limit 52 to english language
54	LETTER/
55	EDITORIAL/
56	NEWS/
57	exp HISTORICAL ARTICLE/
58	ANECDOTES AS TOPIC/
59	COMMENT/
60	CASE REPORT/
61	(letter or comment* or abstracts).ti.
62	or/54-61

#	Searches
63	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
64	62 not 63
65	ANIMALS/ not HUMANS/
66	exp ANIMALS, LABORATORY/
67	exp ANIMAL EXPERIMENTATION/
68	exp MODELS, ANIMAL/
69	exp RODENTIA/
70	(rat or rats or mouse or mice).ti.
71	or/64-70
72	53 not 71

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_SpO2_monitoring_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab,hw.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	(oximet$ or S?O2 or O?SAT?).ti,ab.
27	((oxygen$ or O2) adj3 (saturat$ or monitor$)).ti,ab.
28	or/26-27
29	and/4,25,28
30	limit 29 to english language

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_SpO2_monitoring_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40

#	Searches
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp OXIMETRY/
48	OXYGEN/an, bl [Analysis, Blood]
49	(oximet$ or S?O2 or O?SAT?).ti,ab.
50	((oxygen$ or O2) adj3 (saturat$ or monitor$)).ti,ab.
51	or/47-50
52	and/7,46,51

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_SpO2_monitoring_RERUN1_cdsrdare_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,jw,rw.
3	p?ediatric$.tw,tx,jw,rw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx,kw.
6	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	or/8-10
12	(RESPIRAT$ adj2 SOUND?).kw.
13	(crepit$ or crackl$ or wheez$).tw,tx,kw.
14	or/12-13
15	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx,kw.
16	pneumovir$.tw,tx,kw.
17	(paramyxovir$ or metapneumovir$).tw,tx,kw.
18	(adenovir$ or mastadenovir$).tw,tx,kw.
19	influenza$.tw,tx,kw.
20	enterovir$.tw,tx,kw.
21	rhinovir$.tw,tx,kw.
22	or/15-21
23	and/11,14
24	and/11,22
25	and/14,22
26	or/23-25
27	or/7,26
28	(oximet$ or S?O2 or O?SAT?).tw,tx,kw.

#	Searches
29	((oxygen$ or O2) adj3 (saturat$ or monitor$)).tw,tx,kw.
30	or/28-29
31	and/4,27,30

Database(s): EBM Reviews - Health Technology Assessment

BRONC_SpO2_monitoring_RERUN1_hta_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw,hw.

#	Searches
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp OXIMETRY/
48	OXYGEN/an, bl [Analysis, Blood]
49	(oximet$ or S?O2 or O?SAT?).tw.
50	((oxygen$ or O2) adj3 (saturat$ or monitor$)).tw.
51	or/47-50
52	and/7,46,51

Database(s): Embase

BRONC_SpO2_monitoring_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
17	RESPIRATORY TRACT INFECTION/
18	exp LOWER RESPIRATORY TRACT INFECTION/
19	BRONCHUS DISEASE/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	or/16-22
24	exp ABNORMAL RESPIRATORY SOUND/

#	Searches
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/24-25
27	exp VIRUS INFECTION/
28	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
29	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
30	pneumovir$.ti,ab.
31	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
32	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
33	(paramyxovir$ or metapneumovir$).ti,ab.
34	ADENOVIRUS/ or ADENOVIRUS INFECTION/
35	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
36	(adenovir$ or mastadenovir$).ti,ab.
37	influenza$.ti,ab,hw.
38	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
39	enterovir$.ti,ab.
40	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
41	rhinovir$.ti,ab.
42	or/27-41
43	and/23,26
44	and/23,42
45	and/26,42
46	or/43-45
47	or/15,46
48	exp OXIMETRY/
49	OXYGEN SATURATION/
50	OXYGEN/an, ec [Drug Analysis, Endogenous Compound]
51	(oximet$ or S?O2 or O?SAT?).ti,ab.
52	((oxygen$ or O2) adj3 (saturat$ or monitor$)).ti,ab.
53	or/48-52
54	and/7,47,53
55	limit 54 to english language
56	conference abstract.pt.
57	letter.pt. or LETTER/
58	note.pt.
59	editorial.pt.
60	CASE REPORT/ or CASE STUDY/
61	(letter or comment* or abstracts).ti.
62	or/56-61
63	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
64	62 not 63
65	ANIMAL/ not HUMAN/
66	NONHUMAN/
67	exp ANIMAL EXPERIMENT/
68	exp EXPERIMENTAL ANIMAL/
69	ANIMAL MODEL/

#	Searches
70	exp RODENT/
71	(rat or rats or mouse or mice).ti.
72	or/64-71
73	55 not 72

F.8 What are the indications for chest radiography in bronchiolitis?

Database(s): Ovid MEDLINE(R)

BRONC_CXR_RERUN2_Medline_180814

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw,nw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw,nw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw,nw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/

#	Searches
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RADIOGRAPHY/
48	exp RADIOGRAPHY, THORACIC/
49	((chest or bronch$ or thora$) adj3 (radiogra$ or roentgenogram? or x ray? or xray?)).ti,ab.
50	CXR.ti,ab.
51	or/47-50
52	and/46,51
53	BRONCHIOLITIS/ra
54	or/52-53
55	and/7,54
56	limit 55 to english language
57	LETTER/
58	EDITORIAL/
59	NEWS/
60	exp HISTORICAL ARTICLE/
61	ANECDOTES AS TOPIC/
62	COMMENT/
63	CASE REPORT/
64	(letter or comment* or abstracts).ti.
65	or/57-64
66	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
67	65 not 66
68	ANIMALS/ not HUMANS/
69	exp ANIMALS, LABORATORY/
70	exp ANIMAL EXPERIMENTATION/
71	exp MODELS, ANIMAL/
72	exp RODENTIA/
73	(rat or rats or mouse or mice).ti.
74	or/67-73
75	56 not 74

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_CXR_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$ or respirat$ sound?).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab,hw.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	or/24-25
27	((chest or bronch$ or thora$) adj3 (radiogra$ or roentgenogram? or x ray? or xray?)).ti,ab.
28	CXR.ti,ab.
29	or/27-28
30	and/4,26,29

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_CXR_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.

#	Searches
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RADIOGRAPHY/
48	exp RADIOGRAPHY, THORACIC/
49	((chest or bronch$ or thora$) adj3 (radiogra$ or roentgenogram? or x ray? or xray?)).ti,ab.
50	CXR.ti,ab.
51	or/47-50

#	Searches
52	and/46,51
53	BRONCHIOLITIS/ra
54	or/52-53
55	and/7,54

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_CXR_RERUN1_cdsrdare_240614

#	Searches
1	CHILD.kw.
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,jw,rw.
3	INFANT.kw.
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,jw,rw.
5	PEDIATRICS.kw.
6	p?ediatric$.tw,tx,jw,rw.
7	or/1-6
8	BRONCHIOLITIS.kw.
9	BRONCHIOLES.kw.
10	(BRONCHITIS or BRONCHOPNEUMONIA).kw.
11	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx.
12	RESPIRATORY SYNCYTIAL VIRUSES.kw.
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS.kw.
14	(respiratory sync#tial vir$ or RSV).tw,tx.
15	or/8-14
16	RESPIRATORY TRACT DISEASES.kw.
17	RESPIRATORY TRACT INFECTIONS.kw.
18	BRONCHIAL DISEASES.kw.
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx.
20	low$ respiratory tract$.tw,tx.
21	(LR?I$ or ALR?I$).tw,tx.
22	or/16-21
23	RESPIRATORY SOUNDS.kw.
24	(crepit$ or crackl$ or wheez$).tw,tx.
25	or/23-24
26	VIRUS DISEASES.kw.
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx.
28	(PNEUMOVIRUS or PNEUMOVIRUS INFECTIONS).kw.
29	pneumovir$.tw,tx.
30	(PARAMYXOVIRIDAE or PARAMYXOVIRIDAE INFECTIONS).kw.
31	METAPNEUMOVIRUS.kw.
32	(paramyxovir$ or metapneumovir$).tw,tx.
33	(ADENOVIRIDAE or ADENOVIRIDAE INFECTIONS).kw.
34	(MASTADENOVIRUS or ADENOVIRUSES, HUMAN or ADENOVIRUS INFECTIONS, HUMAN).kw.

#	Searches
35	(adenovir$ or mastadenovir$).tw,tx.
36	influenza$.tw,tx.
37	(ENTEROVIRUS or ENTEROVIRUS INFECTIONS).kw.
38	enterovir$.tw,tx.
39	(RHINOVIRUS or PICORNAVIRIDAE INFECTIONS).kw.
40	rhinovir$.tw,tx.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RADIOGRAPHY.kw.
48	RADIOGRAPHY, THORACIC.kw.
49	((chest or bronch$ or thora$) adj3 (radiogra$ or roentgenogram? or x ray? or xray?)).tw,tx.
50	CXR.tw,tx.
51	or/47-50
52	and/46,51

Database(s): EBM Reviews - Health Technology Assessment

BRONC_CXR_RERUN1_hta_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.

#	Searches
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	RADIOGRAPHY/
48	exp RADIOGRAPHY, THORACIC/
49	((chest or bronch$ or thora$) adj3 (radiogra$ or roentgenogram? or x ray? or xray?)).tw.
50	CXR.tw.
51	or/47-50
52	and/46,51
53	BRONCHIOLITIS/ra
54	or/52-53
55	and/7,54

Database(s): Embase

BRONC_CXR_RERUN1_embase_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.

#	Searches
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
17	RESPIRATORY TRACT INFECTION/
18	exp LOWER RESPIRATORY TRACT INFECTION/
19	BRONCHUS DISEASE/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	or/16-22
24	exp ABNORMAL RESPIRATORY SOUND/
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/24-25
27	exp VIRUS INFECTION/
28	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
29	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
30	pneumovir$.ti,ab.
31	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
32	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
33	(paramyxovir$ or metapneumovir$).ti,ab.
34	ADENOVIRUS/ or ADENOVIRUS INFECTION/
35	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
36	(adenovir$ or mastadenovir$).ti,ab.
37	influenza$.ti,ab,hw.
38	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
39	enterovir$.ti,ab.
40	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
41	rhinovir$.ti,ab.
42	or/27-41
43	and/23,26
44	and/23,42
45	and/26,42
46	or/43-45
47	or/15,46
48	and/7,47
49	THORAX RADIOGRAPHY/

#	Searches
50	((chest or bronch$ or thora$) adj3 (radiogra$ or roentgenogram or x ray? or xray?)).ti,ab.
51	CXR.ti,ab.
52	or/49-51
53	and/48,52
54	limit 53 to english language
55	conference abstract.pt.
56	letter.pt. or LETTER/
57	note.pt.
58	editorial.pt.
59	CASE REPORT/ or CASE STUDY/
60	(letter or comment* or abstracts).ti.
61	or/55-60
62	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
63	61 not 62
64	ANIMAL/ not HUMAN/
65	NONHUMAN/
66	exp ANIMAL EXPERIMENT/
67	exp EXPERIMENTAL ANIMAL/
68	ANIMAL MODEL/
69	exp RODENT/
70	(rat or rats or mouse or mice).ti.
71	or/63-70
72	54 not 71

F.9 What is the efficacy of chest physiotherapy in the management of bronchiolitis?

Database(s): Ovid MEDLINE(R)

BRONC_physio_RERUN1_medline_240614

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.

#	Searches
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp CHILD/
22	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
23	exp INFANT/
24	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
25	exp PEDIATRICS/
26	p?ediatric$.ti,ab,jw.
27	or/21-26
28	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
29	BRONCHIOLES/
30	bronchiol$.ti,ab.
31	BRONCHITIS/
32	BRONCHOPNEUMONIA/
33	(bronchopneumon$ or bronchit$).ti,ab.
34	exp RESPIRATORY SYNCYTIAL VIRUSES/
35	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
36	(respiratory sync#tial vir$ or RSV).ti,ab.
37	RESPIRATORY TRACT DISEASES/
38	RESPIRATORY TRACT INFECTIONS/
39	BRONCHIAL DISEASES/
40	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
41	low$ respiratory tract$.ti,ab.
42	(LR?I$ or ALR?I$).ti,ab.
43	RESPIRATORY SOUNDS/
44	(crepit$ or crackl$ or wheez$).ti,ab.
45	or/28-44
46	RESPIRATORY THERAPY/
47	exp PHYSICAL THERAPY MODALITIES/
48	((chest or thora$) adj3 (physiotherap$ or physical therap$)).ti,ab.
49	DRAINAGE, POSTURAL/
50	(postur$ adj3 drain$).ti,ab.
51	PERCUSSION/
52	((chest or thora$) adj3 percuss$).ti,ab.
53	VIBRATION/
54	CHEST WALL OSCILLATION/
55	vibrat$.ti,ab.
56	((chest or thora$) adj3 (shak$ or oscillat$)).ti,ab.
57	BREATHING EXERCISES/

#	Searches
58	((direct$ or induc$ or provok$ or assist$) adj3 cough$).ti,ab.
59	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).ti,ab.
60	(breath$ adj3 exercis$).ti,ab.
61	or/46-60
62	and/27,45,61
63	limit 62 to english language
64	LETTER/
65	EDITORIAL/
66	NEWS/
67	exp HISTORICAL ARTICLE/
68	ANECDOTES AS TOPIC/
69	COMMENT/
70	CASE REPORT/
71	(letter or comment* or abstracts).ti.
72	or/64-71
73	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
74	72 not 73
75	ANIMALS/ not HUMANS/
76	exp ANIMALS, LABORATORY/
77	exp ANIMAL EXPERIMENTATION/
78	exp MODELS, ANIMAL/
79	exp RODENTIA/
80	(rat or rats or mouse or mice).ti.
81	or/74-80
82	63 not 81
83	and/20,82

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_physio_RERUN1_mip_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(bronchopneumon$ or bronchit$).ti,ab.
7	(respiratory sync#tial vir$ or RSV).ti,ab.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	(crepit$ or crackl$ or wheez$).ti,ab.
12	or/5-11
13	((chest or thora$) adj3 (physiotherap$ or physical therap$)).ti,ab.

#	Searches
14	(postur$ adj3 drain$).ti,ab.
15	((chest or thora$) adj3 percuss$).ti,ab.
16	vibrat$.ti,ab.
17	((chest or thora$) adj3 (shak$ or oscillat$)).ti,ab.
18	((direct$ or induc$ or provok$ or assist$) adj3 cough$).ti,ab.
19	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).ti,ab.
20	(breath$ adj3 exercis$).ti,ab.
21	or/13-20
22	and/4,12,21

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_physio_RERUN1_cctr_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	RESPIRATORY THERAPY/
27	exp PHYSICAL THERAPY MODALITIES/
28	((chest or thora$) adj3 (physiotherap$ or physical therap$)).ti,ab.
29	DRAINAGE, POSTURAL/
30	(postur$ adj3 drain$).ti,ab.

#	Searches
31	PERCUSSION/
32	((chest or thora$) adj3 percuss$).ti,ab.
33	VIBRATION/
34	CHEST WALL OSCILLATION/
35	vibrat$.ti,ab.
36	((chest or thora$) adj3 (shak$ or oscillat$)).ti,ab.
37	BREATHING EXERCISES/
38	((direct$ or induc$ or provok$ or assist$) adj3 cough$).ti,ab.
39	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).ti,ab.
40	(breath$ adj3 exercis$).ti,ab.
41	or/26-40
42	and/7,25,41

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_physio_RERUN1_cdsrdare_240614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	(bronchopneumon$ or bronchit$).tw,tx,kw.
7	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,kw.
9	low$ respiratory tract$.ti,kw.
10	(LR?I$ or ALR?I$).tw,tx.
11	(crepit$ or crackl$ or wheez$).ti,kw.
12	or/5-11
13	RESPIRATORY THERAPY.kw.
14	(PHYSICAL THERAPY MODALITIES or PHYSIOTHERAPY).kw.
15	((chest or thora$) adj3 (physiotherap$ or physical therap$)).tw,tx.
16	(postur$ adj3 drain$).tw,tx,kw.
17	PERCUSSION.kw.
18	((chest or thora$) adj3 percuss$).tw,tx.
19	vibrat$.tw,tx,kw.
20	((chest or thora$) adj3 (shak$ or oscillat$)).tw,tx,kw.
21	((direct$ or induc$ or provok$ or assist$) adj3 cough$).tw,tx,kw.
22	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).tw,tx,kw.
23	(breath$ adj3 exercis$).tw,tx,kw.
24	or/13-23

#	Searches
25	and/4,12,24

Database(s): EBM Reviews - Health Technology Assessment

BRONC_physio_RERUN1_hta_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).tw.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).tw.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
21	low$ respiratory tract$.tw.
22	(LR?I$ or ALR?I$).tw.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/8-24
26	RESPIRATORY THERAPY/
27	exp PHYSICAL THERAPY MODALITIES/
28	((chest or thora$) adj3 (physiotherap$ or physical therap$)).tw.
29	DRAINAGE, POSTURAL/
30	(postur$ adj3 drain$).tw.
31	PERCUSSION/
32	((chest or thora$) adj3 percuss$).tw.
33	VIBRATION/
34	CHEST WALL OSCILLATION/
35	vibrat$.tw.
36	((chest or thora$) adj3 (shak$ or oscillat$)).tw.
37	BREATHING EXERCISES/
38	((direct$ or induc$ or provok$ or assist$) adj3 cough$).tw.

#	Searches
39	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).tw.
40	(breath$ adj3 exercis$).tw.
41	or/26-40
42	and/7,25,41

Database(s): Embase

BRONC_physio_RERUN1_embase_240614

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	or/11,21
23	exp CHILD/
24	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
25	exp INFANT/
26	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
27	exp PEDIATRICS/
28	p?ediatric$.ti,ab,jx,ec.
29	or/23-28
30	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
31	BRONCHIOLE/
32	bronchiol$.ti,ab.
33	BRONCHITIS/
34	BRONCHOPNEUMONIA/

#	Searches
35	(bronchopneumon$ or bronchit$).ti,ab.
36	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
37	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
38	(respiratory sync#tial vir$ or RSV).ti,ab.
39	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
40	RESPIRATORY TRACT INFECTION/
41	exp LOWER RESPIRATORY TRACT INFECTION/
42	BRONCHUS DISEASE/
43	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
44	low$ respiratory tract$.ti,ab.
45	(LR?I$ or ALR?I$).ti,ab.
46	exp ABNORMAL RESPIRATORY SOUND/
47	(crepit$ or crackl$ or wheez$).ti,ab.
48	or/30-47
49	exp PHYSIOTHERAPY/
50	((chest or thora$) adj3 (physiotherap$ or physical therap$)).ti,ab.
51	POSTURAL DRAINAGE/
52	(postur$ adj3 drain$).ti,ab.
53	PERCUSSION/
54	((chest or thora$) adj3 percuss$).ti,ab.
55	exp VIBRATION/
56	THORACIC OSCILLATION/
57	vibrat$.ti,ab.
58	((chest or thora$) adj3 (shak$ or oscillat$)).ti,ab.
59	BREATHING EXERCISE/
60	ASSISTED COUGH/
61	INCREASED EXHALATION TECHNIQUE/
62	((direct$ or induc$ or provok$ or assist$) adj3 cough$).ti,ab.
63	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).ti,ab.
64	(breath$ adj3 exercis$).ti,ab.
65	or/49-64
66	and/29,48,65
67	limit 66 to english language
68	conference abstract.pt.
69	letter.pt. or LETTER/
70	note.pt.
71	editorial.pt.
72	CASE REPORT/ or CASE STUDY/
73	(letter or comment* or abstracts).ti.
74	or/68-73
75	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
76	74 not 75
77	ANIMAL/ not HUMAN/
78	NONHUMAN/
79	exp ANIMAL EXPERIMENT/

#	Searches
80	exp EXPERIMENTAL ANIMAL/
81	ANIMAL MODEL/
82	exp RODENT/
83	(rat or rats or mouse or mice).ti.
84	or/76-83
85	67 not 84
86	and/22,85

Database(s): AMED (Allied and Complementary Medicine)

BRONC_physio_RERUN1_amed_240614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	PEDIATRICS/
6	p?ediatric$.ti,ab,jx.
7	or/1-6
8	bronchiol$.ti,ab.
9	BRONCHITIS/
10	(bronchopneumon$ or bronchit$).ti,ab.
11	(respiratory sync#tial vir$ or RSV).ti,ab.
12	RESPIRATORY TRACT INFECTIONS/
13	BRONCHIAL DISEASE/
14	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
15	low$ respiratory tract$.ti,ab.
16	(LR?I$ or ALR?I$).ti,ab.
17	RESPIRATORY SOUNDS/
18	(crepit$ or crackl$ or wheez$).ti,ab.
19	or/8-18
20	RESPIRATORY THERAPY/
21	PHYSICAL THERAPY MODALITIES/
22	exp CHEST PHYSIOTHERAPY/
23	((chest or thora$) adj3 (physiotherap$ or physical therap$)).ti,ab.
24	DRAINAGE, POSTURAL/
25	(postur$ adj3 drain$).ti,ab.
26	((chest or thora$) adj3 percuss$).ti,ab.
27	VIBRATION/
28	vibrat$.ti,ab.
29	((chest or thora$) adj3 (shak$ or oscillat$)).ti,ab.
30	exp BREATHING EXERCISES/
31	((direct$ or induc$ or provok$ or assist$) adj3 cough$).ti,ab.
32	((forced or passive or compress$ or prolong$ or slow$ or accelerat$ or increas$) adj3 (exhal$ or expirat$)).ti,ab.

#	Searches
33	(breath$ adj3 exercis$).ti,ab.
34	or/20-33
35	and/7,19,34

Database(s): CINAHL with Full Text

BRONC_physio_RERUN1_cinahl_240614

#	Query	Limiters/Expanders
S80	S40 AND S60 AND S79	Limiters - English Language; Exclude MEDLINE records Search modes - Boolean/Phrase
S79	S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78	Search modes - Boolean/Phrase
S78	TI (breath* N3 exercis*) or AB (breath* N3 exercis*)	Search modes - Boolean/Phrase
S77	AB (forced or passive or compress* or prolong* or slow* or accelerat* or increas*) and AB (exhal* or expirat*)	Search modes - Boolean/Phrase
S76	TI (forced or passive or compress* or prolong* or slow* or accelerat* or increas*) and TI (exhal* or expirat*)	Search modes - Boolean/Phrase
S75	AB (direct* cough* or induc* cough* or provok* cough* or assist* cough*)	Search modes - Boolean/Phrase
S74	TI (direct* cough* or induc* cough* or provok* cough* or assist* cough*)	Search modes - Boolean/Phrase
S73	MH BREATHING EXERCISES+	Search modes - Boolean/Phrase
S72	TI (vibrat* or shak* or oscillat*) or AB (vibrat* or shak* or oscillat*)	Search modes - Boolean/Phrase
S71	MH VIBRATION	Search modes - Boolean/Phrase
S70	TI (thora* N3 percuss*) or AB (thora* N3 percuss*)	Search modes - Boolean/Phrase
S69	TI (chest N3 percuss*) or AB (chest N3 percuss*)	Search modes - Boolean/Phrase
S68	MH PERCUSSION	Search modes - Boolean/Phrase
S67	TI (postur* N3 drain*) or AB (postur* N3 drain*)	Search modes - Boolean/Phrase
S66	MH DRAINAGE, POSTURAL	Search modes - Boolean/Phrase
S65	TI (physical therap* or physiotherap*) or AB (physical therap* or physiotherap*)	Search modes - Boolean/Phrase
S64	MH PEDIATRIC PHYSICAL THERAPY	Search modes - Boolean/Phrase
S63	MH CHEST PHYSICAL THERAPY+	Search modes - Boolean/Phrase
S62	MH PHYSICAL THERAPY	Search modes - Boolean/Phrase
S61	MH RESPIRATORY THERAPY	Search modes - Boolean/Phrase
S60	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	Search modes - Boolean/Phrase
S59	TI (crepit* or crackl* or wheez*) or AB (crepit* or crackl* or wheez*)	Search modes - Boolean/Phrase
S58	(MH "Respiratory Sounds")	Search modes - Boolean/Phrase
S57	TI (LR#I* or ALR#I*) or AB (LR#I* or ALR#I*)	Search modes - Boolean/Phrase
S56	AB (bronchi* N3 infect*) or AB (bronchi* N3 inflam*) or AB (bronchi* N3 disease*)	Search modes - Boolean/Phrase
S55	TI (bronchi* N3 infect*) or TI (bronchi* N3 inflam*) or TI (bronchi* N3 disease*)	Search modes - Boolean/Phrase

#	Query	Limiters/Expanders
S54	AB (respiratory N3 infect*) or AB (respiratory N3 inflam*) or AB (respiratory N3 disease*)	Search modes - Boolean/Phrase
S53	TI (respiratory N3 infect*) or TI (respiratory N3 inflam*) or TI (respiratory N3 disease*)	Search modes - Boolean/Phrase
S52	(MH "Bronchial Diseases")	Search modes - Boolean/Phrase
S51	(MH "Respiratory Tract Infections")	Search modes - Boolean/Phrase
S50	(MH "Respiratory Tract Diseases")	Search modes - Boolean/Phrase
S49	TI (respiratory sync?tial vir* or RSV) or AB (respiratory sync?tial vir* or RSV)	Search modes - Boolean/Phrase
S48	(MH "Respiratory Syncytial Virus Infections")	Search modes - Boolean/Phrase
S47	(MH "Respiratory Syncytial Viruses")	Search modes - Boolean/Phrase
S46	TI (bronchopneumon* or bronchit*) or AB (bronchopneumon* or bronchit*)	Search modes - Boolean/Phrase
S45	(MH "Bronchopneumonia")	Search modes - Boolean/Phrase
S44	(MH "Bronchitis+")	Search modes - Boolean/Phrase
S43	TI (bronchiol*) or AB (bronchiol*)	Search modes - Boolean/Phrase
S42	(MH "Bronchioles")	Search modes - Boolean/Phrase
S41	(MH "Bronchiolitis")	Search modes - Boolean/Phrase
S40	S36 OR S37 OR S38 OR S39	Search modes - Boolean/Phrase
S39	TI (pediatric* or paediatric*) or AB (pediatric* or paediatric*) or SO (pediatric* or paediatric*)	Search modes - Boolean/Phrase
S38	TI (infan* or neonat* or newborn* or baby or babies) OR AB (infan* or neonat* or newborn* or baby or babies) OR SO (infan* or neonat* or newborn* or baby or babies)	Search modes - Boolean/Phrase
S37	TI (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR AB (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR SO (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#)	Search modes - Boolean/Phrase
S36	(MH "Infant, Newborn+") OR (MH "Infant+") OR (MH "Child, Preschool") OR (MH "Child+") OR (MH "Pediatrics+")	Search modes - Boolean/Phrase
S35	S5 AND S25 AND S34	Limiters - Published Date: 20140101-20141231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase
S34	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33	Search modes - Boolean/Phrase
S33	AB (hydrat* or rehydrat* or fluid therap* or hypodermoclysi*)	Search modes - Boolean/Phrase
S32	TI (hydrat* or rehydrat* or fluid therap* or hypodermoclysi*)	Search modes - Boolean/Phrase
S31	AB ((tube or tubal or intuba* or enteral or parenteral or oral* or nasogastric or gastrointestinal or intravenous* or IV) N3 (nutrition* or fluid* or feed* or fed))	Search modes - Boolean/Phrase
S30	TI ((tube or tubal or intuba* or enteral or parenteral or oral* or nasogastric or gastrointestinal or intravenous* or IV) N3 (nutrition* or fluid* or feed* or fed))	Search modes - Boolean/Phrase
S29	(MH "Intubation, Gastrointestinal")	Search modes - Boolean/Phrase
S28	(MH "Infusions, Intravenous")	Search modes - Boolean/Phrase

#	Query	Limiters/Expanders
S27	(MH "Fluid Therapy+")	Search modes - Boolean/Phrase
S26	(MH "Feeding Methods+")	Search modes - Boolean/Phrase
S25	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	Search modes - Boolean/Phrase
S24	TI (crepit* or crackl* or wheez*) or AB (crepit* or crackl* or wheez*)	Search modes - Boolean/Phrase
S23	(MH "Respiratory Sounds")	Search modes - Boolean/Phrase
S22	TI (LR#I* or ALR#I*) or AB (LR#I* or ALR#I*)	Search modes - Boolean/Phrase
S21	AB (bronchi* N3 infect*) or AB (bronchi* N3 inflam*) or AB (bronchi* N3 disease*)	Search modes - Boolean/Phrase
S20	TI (bronchi* N3 infect*) or TI (bronchi* N3 inflam*) or TI (bronchi* N3 disease*)	Search modes - Boolean/Phrase
S19	AB (respiratory N3 infect*) or AB (respiratory N3 inflam*) or AB (respiratory N3 disease*)	Search modes - Boolean/Phrase
S18	TI (respiratory N3 infect*) or TI (respiratory N3 inflam*) or TI (respiratory N3 disease*)	Search modes - Boolean/Phrase
S17	(MH "Bronchial Diseases")	Search modes - Boolean/Phrase
S16	(MH "Respiratory Tract Infections")	Search modes - Boolean/Phrase
S15	(MH "Respiratory Tract Diseases")	Search modes - Boolean/Phrase
S14	TI (respiratory sync?tial vir* or RSV) or AB (respiratory sync?tial vir* or RSV)	Search modes - Boolean/Phrase
S13	(MH "Respiratory Syncytial Virus Infections")	Search modes - Boolean/Phrase
S12	(MH "Respiratory Syncytial Viruses")	Search modes - Boolean/Phrase
S11	TI (bronchopneumon* or bronchit*) or AB (bronchopneumon* or bronchit*)	Search modes - Boolean/Phrase
S10	(MH "Bronchopneumonia")	Search modes - Boolean/Phrase
S9	(MH "Bronchitis+")	Search modes - Boolean/Phrase
S8	TI (bronchiol*) or AB (bronchiol*)	Search modes - Boolean/Phrase
S7	(MH "Bronchioles")	Search modes - Boolean/Phrase
S6	(MH "Bronchiolitis")	Search modes - Boolean/Phrase
S5	S1 OR S2 OR S3 OR S4	Search modes - Boolean/Phrase
S4	TI (pediatric* or paediatric*) or AB (pediatric* or paediatric*) or SO (pediatric* or paediatric*)	Search modes - Boolean/Phrase
S3	TI (infan* or neonat* or newborn* or baby or babies) OR AB (infan* or neonat* or newborn* or baby or babies) OR SO (infan* or neonat* or newborn* or baby or babies)	Search modes - Boolean/Phrase
S2	TI (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR AB (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR SO (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#)	Search modes - Boolean/Phrase
S1	(MH "Infant, Newborn+") OR (MH "Infant+") OR (MH "Child, Preschool") OR (MH "Child+") OR (MH "Pediatrics+")	Search modes - Boolean/Phrase

Database(s): PEDro

Field	Searches
Title and abstract	Bronchiol [automatic truncation applied]

F.10 What is the efficacy of antibiotic treatment?

Database(s): Ovid MEDLINE(R)

BRONC_antibiotics_RERUN1_medline_280514

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp CHILD/
22	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
23	exp INFANT/
24	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
25	exp PEDIATRICS/
26	p?ediatric$.ti,ab,jw.
27	or/21-26
28	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
29	BRONCHIOLES/
30	BRONCHITIS/ or BRONCHOPNEUMONIA/
31	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
32	exp RESPIRATORY SYNCYTIAL VIRUSES/
33	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/

#	Searches
34	(respiratory sync#tial vir$ or RSV).ti,ab.
35	or/28-34
36	RESPIRATORY TRACT DISEASES/
37	RESPIRATORY TRACT INFECTIONS/
38	BRONCHIAL DISEASES/
39	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
40	low$ respiratory tract$.ti,ab.
41	(LR?I$ or ALR?I$).ti,ab.
42	or/36-41
43	RESPIRATORY SOUNDS/
44	(crepit$ or crackl$ or wheez$).ti,ab.
45	or/43-44
46	exp VIRUS DISEASES/
47	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
48	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
49	pneumovir$.ti,ab.
50	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
51	METAPNEUMOVIRUS/
52	(paramyxovir$ or metapneumovir$).ti,ab.
53	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
54	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
55	(adenovir$ or mastadenovir$).ti,ab.
56	influenza$.ti,ab,hw.
57	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
58	enterovir$.ti,ab.
59	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
60	rhinovir$.ti,ab.
61	or/46-60
62	and/42,45
63	and/42,61
64	and/45,61
65	or/62-64
66	or/35,65
67	exp ANTI-BACTERIAL AGENTS/
68	(antibiotic$ or antibacteri$ or anti bacteri$ or antimycobacteri$ or anti mycobacteri$ or bacteriocid$).ti,ab.
69	exp MACROLIDES/
70	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).mp.
71	exp CEPHALOSPORINS/
72	(ce??alosporin$ or ce??alexin or ce??aclor or ce??epime or ce??otaxime or ce??am#cin$ or ce??otetan or ce??oxitin or ce??metazole or ce??pirome or ce??podoxime or ce??tazidime or ce??triaxone or ce??amandole or ce??azolin).mp.
73	exp PENICILLINS/

#	Searches
74	(penicil?in$ or amox#cil?in or co amox#clav or coamox#clav or ampicil?in or benzylpenicil?in or cloxacil?in or dicloxacil?in or flucloxacil?in or floxacil?in or piperacil?in or ticarcil?in or sulbactam).mp.
75	exp FLUOROQUINOLONES/
76	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).mp.
77	exp TETRACYCLINES/
78	(tetracycline$ or doxycycline or met?acycline or minocycline).mp.
79	(amikacin or gentam#cin$ or neom#cin or netilm#cin).mp.
80	(clindam#cin or lincom#cin).mp.
81	(chloram??enicol or amantadine).mp.
82	exp TRIMETHOPRIM/
83	(cotrimoxazole or co trimoxazole or trimethoprim).mp.
84	or/67-83
85	and/27,66,84
86	limit 85 to english language
87	LETTER/
88	EDITORIAL/
89	NEWS/
90	exp HISTORICAL ARTICLE/
91	ANECDOTES AS TOPIC/
92	COMMENT/
93	CASE REPORT/
94	(letter or comment* or abstracts).ti.
95	or/87-94
96	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
97	95 not 96
98	ANIMALS/ not HUMANS/
99	exp ANIMALS, LABORATORY/
100	exp ANIMAL EXPERIMENTATION/
101	exp MODELS, ANIMAL/
102	exp RODENTIA/
103	(rat or rats or mouse or mice).ti.
104	or/97-103
105	86 not 104
106	and/20,105

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_antibiotics_RERUN1_mip_280514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.

#	Searches
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	(antibiotic$ or antibacteri$ or anti bacteri$ or antimycobacteri$ or anti mycobacteri$ or bacteriocid$).ti,ab.
27	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).mp.
28	(ce??alosporin$ or ce??alexin or ce??aclor or ce??epime or ce??otaxime or ce??am#cin$ or ce??otetan or ce??oxitin or ce??metazole or ce??pirome or ce??podoxime or ce??tazidime or ce??triaxone or ce??amandole or ce??azolin).mp.
29	(penicil?in$ or amox#cil?in or co amox#clav or coamox#clav or ampicil?in or benzylpenicil?in or cloxacil?in or dicloxacil?in or flucloxacil?in or floxacil?in or piperacil?in or ticarcil?in or sulbactam).mp.
30	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).mp.
31	(tetracycline$ or doxycycline or met?acycline or minocycline).mp.
32	(amikacin or gentam#cin$ or neom#cin or netilm#cin).mp.
33	(clindam#cin or lincom#cin).mp.
34	(chloram??enicol or amantadine).mp.
35	(cotrimoxazole or co trimoxazole or trimethoprim).mp.
36	or/26-35
37	and/4,25,36

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_antibiotics_RERUN1_mip_280514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	(antibiotic$ or antibacteri$ or anti bacteri$ or antimycobacteri$ or anti mycobacteri$ or bacteriocid$).ti,ab.
27	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).mp.
28	(ce??alosporin$ or ce??alexin or ce??aclor or ce??epime or ce??otaxime or ce??am#cin$ or ce??otetan or ce??oxitin or ce??metazole or ce??pirome or ce??podoxime or ce??tazidime or ce??triaxone or ce??amandole or ce??azolin).mp.
29	(penicil?in$ or amox#cil?in or co amox#clav or coamox#clav or ampicil?in or benzylpenicil?in or cloxacil?in or dicloxacil?in or flucloxacil?in or floxacil?in or piperacil?in or ticarcil?in or sulbactam).mp.
30	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).mp.
31	(tetracycline$ or doxycycline or met?acycline or minocycline).mp.
32	(amikacin or gentam#cin$ or neom#cin or netilm#cin).mp.
33	(clindam#cin or lincom#cin).mp.
34	(chloram??enicol or amantadine).mp.
35	(cotrimoxazole or co trimoxazole or trimethoprim).mp.
36	or/26-35

#	Searches
37	and/4,25,36

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_antibiotics_RERUN1_cdsrdare_280514

#	Searches
1	CHILD.kw.
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
3	INFANT.kw.
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
5	PEDIATRICS.kw.
6	p?ediatric$.tw,tx,kw,jw,rw.
7	or/1-6
8	BRONCHIOLITIS.kw.
9	BRONCHIOLES.kw.
10	(BRONCHITIS or BRONCHOPNEUMONIA).kw.
11	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx,kw.
12	RESPIRATORY SYNCYTIAL VIRUSES.kw.
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS.kw.
14	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES.kw.
17	RESPIRATORY TRACT INFECTIONS.kw.
18	BRONCHIAL DISEASES.kw.
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
20	low$ respiratory tract$.tw,tx,kw.
21	(LR?I$ or ALR?I$).tw,tx,kw.
22	or/16-21
23	RESPIRATORY SOUNDS.kw.
24	(crepit$ or crackl$ or wheez$).tw,tx,kw.
25	or/23-24
26	VIRUS DISEASES.kw.
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx,kw.
28	(PNEUMOVIRUS or PNEUMOVIRUS INFECTIONS).kw.
29	pneumovir$.tw,tx,kw.
30	(PARAMYXOVIRIDAE or PARAMYXOVIRIDAE INFECTIONS).kw.
31	METAPNEUMOVIRUS.kw.
32	(paramyxovir$ or metapneumovir$).tw,tx,kw.
33	(ADENOVIRIDAE or ADENOVIRIDAE INFECTIONS).kw.
34	(MASTADENOVIRUS or ADENOVIRUSES, HUMAN or ADENOVIRUS INFECTIONS, HUMAN).kw.
35	(adenovir$ or mastadenovir$).tw,tx,kw.
36	influenza$.tw,tx,kw.
37	(ENTEROVIRUS or ENTEROVIRUS INFECTIONS).kw.

#	Searches
38	enterovir$.tw,tx,kw.
39	(RHINOVIRUS or PICORNAVIRIDAE INFECTIONS).kw.
40	rhinovir$.tw,tx,kw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	ANTI-BACTERIAL AGENTS.kw.
48	(antibiotic$ or antibacteri$ or anti bacteri$ or antimycobacteri$ or anti mycobacteri$ or bacteriocid$).tw,tx,kw.
49	MACROLIDES.kw.
50	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).mp.
51	CEPHALOSPORINS.kw.
52	(ce??alosporin$ or ce??alexin or ce??aclor or ce??epime or ce??otaxime or ce??am#cin$ or ce??otetan or ce??oxitin or ce??metazole or ce??pirome or ce??podoxime or ce??tazidime or ce??triaxone or ce??amandole or ce??azolin).mp.
53	PENICILLINS.kw.
54	(penicil?in$ or amox#cil?in or co amox#clav or coamox#clav or ampicil?in or benzylpenicil?in or cloxacil?in or dicloxacil?in or flucloxacil?in or floxacil?in or piperacil?in or ticarcil?in or sulbactam).mp.
55	FLUOROQUINOLONES.kw.
56	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).mp.
57	TETRACYCLINES.kw.
58	(tetracycline$ or doxycycline or met?acycline or minocycline).mp.
59	(amikacin or gentam#cin$ or neom#cin or netilm#cin).mp.
60	(clindam#cin or lincom#cin).mp.
61	(chloram??enicol or amantadine).mp.
62	TRIMETHOPRIM.kw.
63	(cotrimoxazole or co trimoxazole or trimethoprim).mp.
64	or/47-63
65	and/7,46,64

Database(s): EBM Reviews - Health Technology Assessment

BRONC_antibiotics_RERUN1_hta_280514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6

#	Searches
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp ANTI-BACTERIAL AGENTS/
48	(antibiotic$ or antibacteri$ or anti bacteri$ or antimycobacteri$ or anti mycobacteri$ or bacteriocid$).tw.
49	exp MACROLIDES/
50	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).tw,hw.

#	Searches
51	exp CEPHALOSPORINS/
52	(ce??alosporin$ or ce??alexin or ce??aclor or ce??epime or ce??otaxime or ce??am#cin$ or ce??otetan or ce??oxitin or ce??metazole or ce??pirome or ce??podoxime or ce??tazidime or ce??triaxone or ce??amandole or ce??azolin).tw,hw.
53	exp PENICILLINS/
54	(penicil?in$ or amox#cil?in or co amox#clav or coamox#clav or ampicil?in or benzylpenicil?in or cloxacil?in or dicloxacil?in or flucloxacil?in or floxacil?in or piperacil?in or ticarcil?in or sulbactam).tw,hw.
55	exp FLUOROQUINOLONES/
56	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).tw,hw.
57	exp TETRACYCLINES/
58	(tetracycline$ or doxycycline or met?acycline or minocycline).tw,hw.
59	(amikacin or gentam#cin$ or neom#cin or netilm#cin).tw,hw.
60	(clindam#cin or lincom#cin).tw,hw.
61	(chloram??enicol or amantadine).tw,hw.
62	exp TRIMETHOPRIM/
63	(cotrimoxazole or co trimoxazole or trimethoprim).tw,hw.
64	or/47-63
65	and/7,46,64

Database(s): Embase

BRONC_antibiotics_RERUN1_embase_280514

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/

#	Searches
21	or/12-20
22	or/11,21
23	exp CHILD/
24	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
25	exp INFANT/
26	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
27	exp PEDIATRICS/
28	p?ediatric$.ti,ab,jx,ec.
29	or/23-28
30	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
31	BRONCHIOLE/
32	BRONCHITIS/ or BRONCHOPNEUMONIA/
33	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
34	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
35	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
36	(respiratory sync#tial vir$ or RSV).ti,ab.
37	or/30-36
38	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
39	RESPIRATORY TRACT INFECTION/
40	exp LOWER RESPIRATORY TRACT INFECTION/
41	BRONCHUS DISEASE/
42	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
43	low$ respiratory tract$.ti,ab.
44	(LR?I$ or ALR?I$).ti,ab.
45	or/38-44
46	exp ABNORMAL RESPIRATORY SOUND/
47	(crepit$ or crackl$ or wheez$).ti,ab.
48	or/46-47
49	exp VIRUS INFECTION/
50	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
51	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
52	pneumovir$.ti,ab.
53	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
54	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
55	(paramyxovir$ or metapneumovir$).ti,ab.
56	ADENOVIRUS/ or ADENOVIRUS INFECTION/
57	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
58	(adenovir$ or mastadenovir$).ti,ab.
59	influenza$.ti,ab,hw.
60	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
61	enterovir$.ti,ab.
62	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
63	rhinovir$.ti,ab.
64	or/49-63
65	and/45,48

#	Searches
66	and/45,64
67	and/48,64
68	or/65-67
69	or/37,68
70	exp ANTIBIOTIC AGENT/
71	(antibiotic$ or antibacteri$ or anti bacteri$ or antimycobacteri$ or anti mycobacteri$ or bacteriocid$).ti,ab.
72	exp MACROLIDE/
73	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).mp.
74	exp CEPHALOSPORIN/
75	(ce??alosporin$ or ce??alexin or ce??aclor or ce??epime or ce??otaxime or ce??am#cin$ or ce??otetan or ce??oxitin or ce??metazole or ce??pirome or ce??podoxime or ce??tazidime or ce??triaxone or ce??amandole or ce??azolin).mp.
76	exp PENICILLIN DERIVATIVE/
77	SULBACTAM/
78	(penicil?in$ or amox#cil?in or co amox#clav or coamox#clav or ampicil?in or benzylpenicil?in or cloxacil?in or dicloxacil?in or flucloxacil?in or floxacil?in or piperacil?in or ticarcil?in or sulbactam).mp.
79	exp QUINOLONE DERIVATIVE/
80	exp QUINOLINE DERIVED ANTIINFECTIVE AGENT/
81	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).mp.
82	exp TETRACYCLINE DERIVATIVE/
83	(tetracycline$ or doxycycline or met?acycline or minocycline).mp.
84	(amikacin or gentam#cin$ or neom#cin or netilm#cin).mp.
85	(clindam#cin or lincom#cin).mp.
86	(chloram??enicol or amantadine).mp.
87	(cotrimoxazole or co trimoxazole or trimethoprim).mp.
88	or/70-87
89	and/29,69,88
90	limit 89 to english language
91	conference abstract.pt.
92	letter.pt. or LETTER/
93	note.pt.
94	editorial.pt.
95	CASE REPORT/ or CASE STUDY/
96	(letter or comment* or abstracts).ti.
97	or/91-96
98	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
99	97 not 98
100	ANIMAL/ not HUMAN/
101	NONHUMAN/
102	exp ANIMAL EXPERIMENT/
103	exp EXPERIMENTAL ANIMAL/
104	ANIMAL MODEL/
105	exp RODENT/

#	Searches
106	(rat or rats or mouse or mice).ti.
107	or/99-106
108	90 not 107
109	and/22,108

F.11 What is the efficacy of combined bronchodilator and corticosteroid therapy?

No separate search run (results of corticosteroids search and bronchodilators search combined)

F.12 What is the efficacy of inhaled/systemic corticosteroid therapy?

Database(s): Ovid MEDLINE(R)

BRONC_corticosteroids_RERUN1_medline_280514

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp CHILD/
22	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
23	exp INFANT/
24	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
25	exp PEDIATRICS/

#	Searches
26	p?ediatric$.ti,ab,jw.
27	or/21-26
28	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
29	BRONCHIOLES/
30	BRONCHITIS/ or BRONCHOPNEUMONIA/
31	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
32	exp RESPIRATORY SYNCYTIAL VIRUSES/
33	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
34	(respiratory sync#tial vir$ or RSV).ti,ab.
35	or/28-34
36	RESPIRATORY TRACT DISEASES/
37	RESPIRATORY TRACT INFECTIONS/
38	BRONCHIAL DISEASES/
39	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
40	low$ respiratory tract$.ti,ab.
41	(LR?I$ or ALR?I$).ti,ab.
42	or/36-41
43	RESPIRATORY SOUNDS/
44	(crepit$ or crackl$ or wheez$).ti,ab.
45	or/43-44
46	exp VIRUS DISEASES/
47	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
48	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
49	pneumovir$.ti,ab.
50	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
51	METAPNEUMOVIRUS/
52	(paramyxovir$ or metapneumovir$).ti,ab.
53	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
54	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
55	(adenovir$ or mastadenovir$).ti,ab.
56	influenza$.ti,ab,hw.
57	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
58	enterovir$.ti,ab.
59	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
60	rhinovir$.ti,ab.
61	or/46-60
62	and/42,45
63	and/42,61
64	and/45,61
65	or/62-64
66	or/35,65
67	exp ADRENAL CORTEX HORMONES/
68	(cortico$ or glucocortico$ or steroid$).ti,ab.
69	BUDESONIDE/
70	(budesonide or budelin or pulmicort).mp.

#	Searches
71	BECLOMETHASONE/
72	(beclomet?asone or asmabec or becodisk$ or clenil modulite or qvar).mp.
73	exp BETAMETHASONE/
74	(betamethasone or betnesol).mp.
75	exp DEXAMETHASONE/
76	(dexamethasone or dexsol or martapen).mp.
77	(flunisolide or syntaris).mp.
78	(fluticasone or flixotide).mp.
79	exp HYDROCORTISONE/
80	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).mp.
81	(mometasone or asmanex).mp.
82	exp PREDNISOLONE/
83	(prednisolone or deltacortril or methylprednisolone or medrone or solumedrone or depomedrone).mp.
84	PREDNISONE/
85	(prednisone or lodotra or methylprednisone or meprednisone).mp.
86	exp TRIAMCINOLONE/
87	(triamcinolone or kenalog or adcortyl or nasacort).mp.
88	or/67-87
89	and/27,66,88
90	limit 89 to english language
91	LETTER/
92	EDITORIAL/
93	NEWS/
94	exp HISTORICAL ARTICLE/
95	ANECDOTES AS TOPIC/
96	COMMENT/
97	CASE REPORT/
98	(letter or comment* or abstracts).ti.
99	or/91-98
100	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
101	99 not 100
102	ANIMALS/ not HUMANS/
103	exp ANIMALS, LABORATORY/
104	exp ANIMAL EXPERIMENTATION/
105	exp MODELS, ANIMAL/
106	exp RODENTIA/
107	(rat or rats or mouse or mice).ti.
108	or/101-107
109	90 not 108
110	and/20,109

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_corticosteroids_RERUN1_mip_290514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	or/5-6
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	or/8-10
12	(crepit$ or crackl$ or wheez$).ti,ab.
13	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
14	pneumovir$.ti,ab.
15	(paramyxovir$ or metapneumovir$).ti,ab.
16	(adenovir$ or mastadenovir$).ti,ab.
17	influenza$.ti,ab.
18	enterovir$.ti,ab.
19	rhinovir$.ti,ab.
20	or/13-19
21	and/11-12
22	and/11,20
23	and/12,20
24	or/21-23
25	or/7,24
26	(cortico$ or glucocortico$ or steroid$).ti,ab.
27	(budesonide or budelin or pulmicort).mp.
28	(beclomet?asone or asmabec or becodisk$ or clenil modulite or qvar).mp.
29	(betamethasone or betnesol).mp.
30	(dexamethasone or dexsol or martapen).mp.
31	(flunisolide or syntaris).mp.
32	(fluticasone or flixotide).mp.
33	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).mp.
34	(mometasone or asmanex).mp.
35	(prednisolone or deltacortril or methylprednisolone or medrone or solumedrone or depomedrone).mp.
36	(prednisone or lodotra or methylprednisone or meprednisone).mp.
37	(triamcinolone or kenalog or adcortyl or nasacort).mp.
38	or/26-37
39	and/4,25,38

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_corticosteroids_RERUN1_cctr_290514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).ti,ab.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
20	low$ respiratory tract$.ti,ab.
21	(LR?I$ or ALR?I$).ti,ab.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.ti,ab.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).ti,ab.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).ti,ab.
36	influenza$.ti,ab,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.ti,ab.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.ti,ab.
41	or/26-40

#	Searches
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp ADRENAL CORTEX HORMONES/
48	(cortico$ or glucocortico$ or steroid$).ti,ab.
49	BUDESONIDE/
50	(budesonide or budelin or pulmicort).mp.
51	BECLOMETHASONE/
52	(beclomet?asone or asmabec or becodisk$ or clenil modulite or qvar).mp.
53	exp BETAMETHASONE/
54	(betamethasone or betnesol).mp.
55	exp DEXAMETHASONE/
56	(dexamethasone or dexsol or martapen).mp.
57	(flunisolide or syntaris).mp.
58	(fluticasone or flixotide).mp.
59	exp HYDROCORTISONE/
60	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).mp.
61	(mometasone or asmanex).mp.
62	exp PREDNISOLONE/
63	(prednisolone or deltacortril or methylprednisolone or medrone or solumedrone or depomedrone).mp.
64	PREDNISONE/
65	(prednisone or lodotra or methylprednisone or meprednisone).mp.
66	exp TRIAMCINOLONE/
67	(triamcinolone or kenalog or adcortyl or nasacort).mp.
68	or/47-67
69	and/7,46,68

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_corticosteroids_RERUN1_cdsrdare_290514

#	Searches
1	CHILD.kw.
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,jw,rw.
3	INFANT.kw.
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,jw,rw.
5	PEDIATRICS.kw.
6	p?ediatric$.tw,tx,jw,rw.
7	or/1-6
8	BRONCHIOLITIS.kw.
9	BRONCHIOLES.kw.

#	Searches
10	(BRONCHITIS or BRONCHOPNEUMONIA).kw.
11	(bronchiol$ or bronchitis or bronchopneumonia).tw,tx.
12	RESPIRATORY SYNCYTIAL VIRUSES.kw.
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS.kw.
14	(respiratory sync#tial vir$ or RSV).tw,tx.
15	or/8-14
16	RESPIRATORY TRACT DISEASES.kw.
17	RESPIRATORY TRACT INFECTIONS.kw.
18	BRONCHIAL DISEASES.kw.
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx.
20	low$ respiratory tract$.tw,tx.
21	(LR?I$ or ALR?I$).tw,tx.
22	or/16-21
23	RESPIRATORY SOUNDS.kw.
24	(crepit$ or crackl$ or wheez$).tw,tx.
25	or/23-24
26	VIRUS DISEASES.kw.
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw,tx.
28	(PNEUMOVIRUS or PNEUMOVIRUS INFECTIONS).kw.
29	pneumovir$.tw,tx.
30	(PARAMYXOVIRIDAE or PARAMYXOVIRIDAE INFECTIONS).kw.
31	METAPNEUMOVIRUS.kw.
32	(paramyxovir$ or metapneumovir$).tw,tx.
33	(ADENOVIRIDAE or ADENOVIRIDAE INFECTIONS).kw.
34	(MASTADENOVIRUS or ADENOVIRUSES, HUMAN or ADENOVIRUS INFECTIONS, HUMAN).kw.
35	(adenovir$ or mastadenovir$).tw,tx.
36	influenza$.tw,tx,kw.
37	(ENTEROVIRUS or ENTEROVIRUS INFECTIONS).kw.
38	enterovir$.tw,tx.
39	(RHINOVIRUS or PICORNAVIRIDAE INFECTIONS).kw.
40	rhinovir$.tw,tx.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	ADRENAL CORTEX HORMONES.kw.
48	(cortico$ or glucocortico$ or steroid$).tw,tx.
49	BUDESONIDE.kw.
50	(budesonide or budelin or pulmicort).mp.
51	BECLOMETHASONE.kw.
52	(beclomet?asone or asmabec or becodisk$ or clenil modulite or qvar).mp.
53	BETAMETHASONE.kw.
54	(betamethasone or betnesol).mp.

#	Searches
55	DEXAMETHASONE.kw.
56	(dexamethasone or dexsol or martapen).mp.
57	(flunisolide or syntaris).mp.
58	(fluticasone or flixotide).mp.
59	HYDROCORTISONE.kw.
60	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).mp.
61	(mometasone or asmanex).mp.
62	PREDNISOLONE.kw.
63	(prednisolone or deltacortril or methylprednisolone or medrone or solumedrone or depomedrone).mp.
64	PREDNISONE.kw.
65	(prednisone or lodotra or methylprednisone or meprednisone).mp.
66	TRIAMCINOLONE.kw.
67	(triamcinolone or kenalog or adcortyl or nasacort).mp.
68	or/47-67
69	and/7,46,68

Database(s): EBM Reviews - Health Technology Assessment

BRONC_corticosteroids_RERUN1_hta_290514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.

#	Searches
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw,hw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	exp ADRENAL CORTEX HORMONES/
48	(cortico$ or glucocortico$ or steroid$).tw.
49	BUDESONIDE/
50	(budesonide or budelin or pulmicort).tw,hw.
51	BECLOMETHASONE/
52	(beclomet?asone or asmabec or becodisk$ or clenil modulite or qvar).tw,hw.
53	exp BETAMETHASONE/
54	(betamethasone or betnesol).tw,hw.
55	exp DEXAMETHASONE/
56	(dexamethasone or dexsol or martapen).tw,hw.
57	(flunisolide or syntaris).tw,hw.
58	(fluticasone or flixotide).tw,hw.
59	exp HYDROCORTISONE/
60	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).tw,hw.
61	(mometasone or asmanex).tw,hw.
62	exp PREDNISOLONE/
63	(prednisolone or deltacortril or methylprednisolone or medrone or solumedrone or depomedrone).tw,hw.
64	PREDNISONE/
65	(prednisone or lodotra or methylprednisone or meprednisone).tw,hw.
66	exp TRIAMCINOLONE/
67	(triamcinolone or kenalog or adcortyl or nasacort).tw,hw.
68	or/47-67

#	Searches
69	and/7,46,68

Database(s): Embase

BRONC_corticosteroids_RERUN1_embase_290514

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	or/11,21
23	exp CHILD/
24	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
25	exp INFANT/
26	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
27	exp PEDIATRICS/
28	p?ediatric$.ti,ab,jx.
29	or/23-28
30	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
31	BRONCHIOLE/
32	BRONCHITIS/ or BRONCHOPNEUMONIA/
33	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
34	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
35	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
36	(respiratory sync#tial vir$ or RSV).ti,ab.
37	or/30-36

#	Searches
38	RESPIRATORY TRACT DISEASE/
39	RESPIRATORY TRACT INFECTION/
40	exp LOWER RESPIRATORY TRACT INFECTION/
41	BRONCHUS DISEASE/
42	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,ab.
43	low$ respiratory tract$.ti,ab.
44	(LR?I$ or ALR?I$).ti,ab.
45	or/38-44
46	exp ABNORMAL RESPIRATORY SOUND/
47	(crepit$ or crackl$ or wheez$).ti,ab.
48	or/46-47
49	exp VIRUS INFECTION/
50	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
51	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
52	pneumovir$.ti,ab.
53	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
54	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
55	(paramyxovir$ or metapneumovir$).ti,ab.
56	ADENOVIRUS/ or ADENOVIRUS INFECTION/
57	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
58	(adenovir$ or mastadenovir$).ti,ab.
59	influenza$.ti,ab,hw.
60	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
61	enterovir$.ti,ab.
62	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
63	rhinovir$.ti,ab.
64	or/49-63
65	and/45,48
66	and/45,64
67	and/48,64
68	or/65-67
69	or/37,68
70	exp CORTICOSTEROID/
71	(cortico$ or glucocortico$ or steroid$).ti,ab.
72	BUDESONIDE/
73	(budesonide or budelin or pulmicort).mp.
74	BECLOMETASONE/
75	(beclomet?asone or asmabec or becodisk$ or clenil modulite or qvar).mp.
76	BETAMETHASONE/
77	(betamethasone or betnesol).mp.
78	DEXAMETHASONE/
79	(dexamethasone or dexsol or martapen).mp.
80	FLUNISOLIDE/
81	(flunisolide or syntaris).mp.
82	FLUTICASONE/ or FLUTICASONE PROPIONATE/

#	Searches
83	(fluticasone or flixotide).mp.
84	HYDROCORTISONE/
85	(hydrocortisone or efcortesol or solu cortef or solucortef or corlan).mp.
86	MOMETASONE FUROATE/
87	(mometasone or asmanex).mp.
88	PREDNISOLONE/ or METHYLPREDNISOLONE/
89	(prednisolone or deltacortril or methylprednisolone or medrone or solumedrone or depomedrone).mp.
90	PREDNISONE/ or METHYLPREDNISONE/
91	(prednisone or lodotra or methylprednisone or meprednisone).mp.
92	TRIAMCINOLONE/ or TRIAMCINOLONE ACETONIDE/
93	(triamcinolone or kenalog or adcortyl or nasacort).mp.
94	or/70-93
95	and/29,69,94
96	limit 95 to english language
97	conference abstract.pt.
98	letter.pt. or LETTER/
99	note.pt.
100	editorial.pt.
101	CASE REPORT/ or CASE STUDY/
102	(letter or comment* or abstracts).ti.
103	or/97-102
104	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
105	103 not 104
106	ANIMAL/ not HUMAN/
107	NONHUMAN/
108	exp ANIMAL EXPERIMENT/
109	exp EXPERIMENTAL ANIMAL/
110	ANIMAL MODEL/
111	exp RODENT/
112	(rat or rats or mouse or mice).ti.
113	or/105-112
114	96 not 113
115	and/22,114

F.13 What is the efficacy of inhaled bronchodilators (adrenaline, salbutamol, irpratropium bromide)?

Database(s): Ovid MEDLINE(R)

BRONC_bronchodilators_RERUN1_medline_290514

#	Searches
1	META-ANALYSIS/

#	Searches
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp CHILD/
22	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
23	exp INFANT/
24	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
25	exp PEDIATRICS/
26	p?ediatric$.ti,ab,jw.
27	or/21-26
28	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
29	BRONCHIOLES/
30	bronchiol$.ti,ab.
31	exp RESPIRATORY SYNCYTIAL VIRUSES/
32	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
33	(respiratory sync#tial vir$ or RSV).ti,ab.
34	RESPIRATORY SOUNDS/
35	(crepit$ or crackl$ or wheez$).ti,ab.
36	or/28-35
37	exp BRONCHODILATOR AGENTS/
38	(bronch$ adj3 dilat$).ti,ab.
39	(bronchodilat$ or broncholyt$).ti,ab.
40	exp ADRENERGIC AGENTS/
41	EPINEPHRINE/
42	(adrenalin$ or epinephrin$).mp.
43	adrenergic$.ti,ab.
44	ALBUTEROL/
45	(salbutamol or albuterol).mp.

#	Searches
46	IPRATROPIUM/
47	ipratropium.mp.
48	TERBUTALINE/
49	terbutalin$.mp.
50	or/37-49
51	and/27,36,50
52	limit 51 to english language
53	LETTER/
54	EDITORIAL/
55	NEWS/
56	exp HISTORICAL ARTICLE/
57	ANECDOTES AS TOPIC/
58	COMMENT/
59	CASE REPORT/
60	(letter or comment* or abstracts).ti.
61	or/53-60
62	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
63	61 not 62
64	ANIMALS/ not HUMANS/
65	exp ANIMALS, LABORATORY/
66	exp ANIMAL EXPERIMENTATION/
67	exp MODELS, ANIMAL/
68	exp RODENTIA/
69	(rat or rats or mouse or mice).ti.
70	or/63-69
71	52 not 70
72	and/20,71

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_bronchodilators_RERUN1_mip_290514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(respiratory sync#tial vir$ or RSV).ti,ab.
7	(crepit$ or crackl$ or wheez$).ti,ab.
8	or/5-7
9	(bronch$ adj3 dilat$).ti,ab.
10	(bronchodilat$ or broncholyt$).ti,ab.
11	(adrenalin$ or epinephrin$).mp.
12	adrenergic$.ti,ab.

#	Searches
13	(salbutamol or albuterol).mp.
14	ipratropium.mp.
15	terbutalin$.mp.
16	or/9-15
17	and/4,8,16

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_bronchodilators_RERUN1_cctr_290514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	exp RESPIRATORY SYNCYTIAL VIRUSES/
12	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
13	(respiratory sync#tial vir$ or RSV).ti,ab.
14	RESPIRATORY SOUNDS/
15	(crepit$ or crackl$ or wheez$).ti,ab.
16	or/8-15
17	exp BRONCHODILATOR AGENTS/
18	(bronch$ adj3 dilat$).ti,ab.
19	(bronchodilat$ or broncholyt$).ti,ab.
20	exp ADRENERGIC AGENTS/
21	EPINEPHRINE/
22	(adrenalin$ or epinephrin$).mp.
23	adrenergic$.ti,ab.
24	ALBUTEROL/
25	(salbutamol or albuterol).mp.
26	IPRATROPIUM/
27	ipratropium.mp.
28	TERBUTALINE/
29	terbutalin$.mp.
30	or/17-29
31	and/7,16,30

Database of Abstracts of Reviews of Effects

BRONC_bronchodilators_RERUN1_cdsrdare_290514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
7	RESPIRATORY SOUNDS.kw.
8	(crepit$ or crackl$ or wheez$).tw,tx,kw.
9	or/5-8
10	(bronch$ adj3 dilat$).tw,tx,kw.
11	(bronchodilat$ or broncholyt$).tw,tx.
12	(adrenalin$ or epinephrin$).tw,tx,kw.
13	adrenergic$.tw,tx,kw.
14	(salbutamol or albuterol).tw,tx,kw.
15	ipratropium.tw,tx,kw.
16	terbutalin$.tw,tx,kw.
17	or/10-16
18	and/4,9,17

Database(s): EBM Reviews - Health Technology Assessment

BRONC_bronchodilators_RERUN1_hta_290514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	exp RESPIRATORY SYNCYTIAL VIRUSES/
12	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
13	(respiratory sync#tial vir$ or RSV).tw.
14	RESPIRATORY SOUNDS/
15	(crepit$ or crackl$ or wheez$).tw.
16	or/8-15
17	exp BRONCHODILATOR AGENTS/
18	(bronch$ adj3 dilat$).tw.
19	(bronchodilat$ or broncholyt$).tw.
20	exp ADRENERGIC AGENTS/
21	EPINEPHRINE/
22	(adrenalin$ or epinephrin$).tw.
23	adrenergic$.tw.
24	ALBUTEROL/
25	(salbutamol or albuterol).tw.
26	IPRATROPIUM/
27	ipratropium.tw.
28	TERBUTALINE/
29	terbutalin$.tw.
30	or/17-29
31	and/7,16,30

Database(s): Embase

BRONC_bronchodilators_RERUN1_embase_290514

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	or/11,21
23	exp CHILD/
24	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
25	exp INFANT/
26	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
27	exp PEDIATRICS/
28	p?ediatric$.ti,ab,jx,ec.
29	or/23-28
30	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
31	BRONCHIOLE/
32	bronchiol$.ti,ab.
33	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
34	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
35	(respiratory sync#tial vir$ or RSV).ti,ab.
36	exp ABNORMAL RESPIRATORY SOUND/
37	(crepit$ or crackl$ or wheez$).ti,ab.
38	or/30-37
39	exp BRONCHODILATING AGENT/
40	(bronch$ adj3 dilat$).ti,ab.

#	Searches
41	(bronchodilat$ or broncholyt$).ti,ab.
42	exp ADRENERGIC RECEPTOR STIMULATING AGENT/
43	ADRENALIN/
44	(adrenalin$ or epinephrin$).mp.
45	adrenergic$.ti,ab.
46	SALBUTAMOL/
47	(salbutamol or albuterol).mp.
48	IPRATROPIUM/
49	ipratropium.mp.
50	TERBUTALINE/ or TERBUTALINE SULFATE/
51	terbutalin$.mp.
52	or/39-51
53	and/29,38,52
54	limit 53 to english language
55	conference abstract.pt.
56	letter.pt. or LETTER/
57	note.pt.
58	editorial.pt.
59	CASE REPORT/ or CASE STUDY/
60	(letter or comment* or abstracts).ti.
61	or/55-60
62	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
63	61 not 62
64	ANIMAL/ not HUMAN/
65	NONHUMAN/
66	exp ANIMAL EXPERIMENT/
67	exp EXPERIMENTAL ANIMAL/
68	ANIMAL MODEL/
69	exp RODENT/
70	(rat or rats or mouse or mice).ti.
71	or/63-70
72	54 not 71
73	and/22,72

F.14 What is the efficacy of nebulised hypertonic saline?

Database(s): Ovid MEDLINE(R)

BRONC_saline_RERUN1_medline_300514

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp CHILD/
22	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
23	exp INFANT/
24	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
25	exp PEDIATRICS/
26	p?ediatric$.ti,ab,jw.
27	or/21-26
28	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
29	BRONCHIOLES/
30	bronchiol$.ti,ab.
31	BRONCHITIS/
32	BRONCHOPNEUMONIA/
33	(bronchopneumon$ or bronchit$).ti,ab.
34	exp RESPIRATORY SYNCYTIAL VIRUSES/
35	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
36	(respiratory sync#tial vir$ or RSV).ti,ab.
37	RESPIRATORY TRACT DISEASES/
38	RESPIRATORY TRACT INFECTIONS/

#	Searches
39	BRONCHIAL DISEASES/
40	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,ab.
41	low$ respiratory tract$.ti,ab.
42	(LR?I$ or ALR?I$).ti,ab.
43	RESPIRATORY SOUNDS/
44	(crepit$ or crackl$ or wheez$).ti,ab.
45	or/28-44
46	SALINE SOLUTION, HYPERTONIC/
47	SODIUM CHLORIDE/
48	(hyperton$ adj3 (saline or solution?)).ti,ab.
49	(saline or sodium chloride or NaCl).ti,ab.
50	or/46-49
51	and/27,45,50
52	limit 51 to english language
53	LETTER/
54	EDITORIAL/
55	NEWS/
56	exp HISTORICAL ARTICLE/
57	ANECDOTES AS TOPIC/
58	COMMENT/
59	CASE REPORT/
60	(letter or comment* or abstracts).ti.
61	or/53-60
62	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
63	61 not 62
64	ANIMALS/ not HUMANS/
65	exp ANIMALS, LABORATORY/
66	exp ANIMAL EXPERIMENTATION/
67	exp MODELS, ANIMAL/
68	exp RODENTIA/
69	(rat or rats or mouse or mice).ti.
70	or/63-69
71	52 not 70
72	and/20,71

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_saline_RERUN1_mip_300514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(bronchopneumon$ or bronchit$).ti,ab.

#	Searches
7	(respiratory sync#tial vir$ or RSV).ti,ab.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	(crepit$ or crackl$ or wheez$).ti,ab.
12	or/5-11
13	(hyperton$ adj3 (saline or solution?)).ti,ab.
14	(saline or sodium chloride or NaCl).ti,ab.
15	or/13-14
16	and/4,12,15

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_saline_RERUN1_cctr_300514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	SALINE SOLUTION, HYPERTONIC/
27	SODIUM CHLORIDE/
28	(hyperton$ adj3 (saline or solution?)).ti,ab.
29	(saline or sodium chloride or NaCl).ti,ab.
30	or/26-29

#	Searches
31	and/7,25,30

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_saline_RERUN1_cdsrdare_300514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	(bronchopneumon$ or bronchit$).tw,tx,kw.
7	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	RESPIRATORY SOUND?.kw.
12	(crepit$ or crackl$ or wheez$).tw,tx.
13	or/5-12
14	(hyperton$ adj3 (saline or solution?)).tw,tx,kw.
15	(saline or sodium chloride or NaCl).tw,tx,kw.
16	or/14-15
17	and/4,13,16

Database(s): EBM Reviews - Health Technology Assessment

BRONC_saline_RERUN1_hta_300514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).tw.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/

#	Searches
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).tw.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).tw.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).tw.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/8-24
26	SALINE SOLUTION, HYPERTONIC/
27	SODIUM CHLORIDE/
28	(hyperton$ adj3 (saline or solution?)).tw.
29	(saline or sodium chloride or NaCl).tw.
30	or/26-29
31	and/7,25,30

Database(s): Embase

BRONC_saline_RERUN1_embase_300514

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/

#	Searches
21	or/12-20
22	or/11,21
23	exp CHILD/
24	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
25	exp INFANT/
26	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
27	exp PEDIATRICS/
28	p?ediatric$.ti,ab,jx,ec.
29	or/23-28
30	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
31	BRONCHIOLE/
32	bronchiol$.ti,ab.
33	BRONCHITIS/
34	BRONCHOPNEUMONIA/
35	(bronchopneumon$ or bronchit$).ti,ab.
36	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
37	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
38	(respiratory sync#tial vir$ or RSV).ti,ab.
39	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
40	RESPIRATORY TRACT INFECTION/
41	exp LOWER RESPIRATORY TRACT INFECTION/
42	BRONCHUS DISEASE/
43	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,ab.
44	low$ respiratory tract$.ti,ab.
45	(LR?I$ or ALR?I$).ti,ab.
46	exp ABNORMAL RESPIRATORY SOUND/
47	(crepit$ or crackl$ or wheez$).ti,ab.
48	or/30-47
49	HYPERTONIC SOLUTION/
50	SODIUM CHLORIDE/
51	(hyperton$ adj3 (saline or solution?)).ti,ab.
52	(saline or sodium chloride or NaCl).ti,ab.
53	or/49-52
54	and/29,48,53
55	limit 54 to english language
56	conference abstract.pt.
57	letter.pt. or LETTER/
58	note.pt.
59	editorial.pt.
60	CASE REPORT/ or CASE STUDY/
61	(letter or comment* or abstracts).ti.
62	or/56-61
63	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
64	62 not 63
65	ANIMAL/ not HUMAN/

#	Searches
66	NONHUMAN/
67	exp ANIMAL EXPERIMENT/
68	exp EXPERIMENTAL ANIMAL/
69	ANIMAL MODEL/
70	exp RODENT/
71	(rat or rats or mouse or mice).ti.
72	or/64-71
73	55 not 72
74	and/22,73

F.15 What is the efficacy of heliox?

Database(s): Ovid MEDLINE(R)

BRONC_heliox_RERUN1_medline_270514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	HELIUM/
27	(helium$ or heliox$).ti,ab,nm.
28	(He O2 or HeO2 or Hx).ti,ab.
29	or/26-28

#	Searches
30	and/7,25,29
31	limit 30 to english language
32	LETTER/
33	EDITORIAL/
34	NEWS/
35	exp HISTORICAL ARTICLE/
36	ANECDOTES AS TOPIC/
37	COMMENT/
38	CASE REPORT/
39	(letter or comment* or abstracts).ti.
40	or/32-39
41	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
42	40 not 41
43	ANIMALS/ not HUMANS/
44	exp ANIMALS, LABORATORY/
45	exp ANIMAL EXPERIMENTATION/
46	exp MODELS, ANIMAL/
47	exp RODENTIA/
48	(rat or rats or mouse or mice).ti.
49	or/42-48
50	31 not 49

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_heliox_RERUN1_mip_270514

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(bronchopneumon$ or bronchit$).ti,ab.
7	(respiratory sync#tial vir$ or RSV).ti,ab.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	(crepit$ or crackl$ or wheez$).ti,ab.
12	or/5-11
13	(helium$ or heliox$).ti,ab.
14	(He O2 or HeO2 or Hx).ti,ab.
15	or/13-14
16	and/4,12,15

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_heliox_RERUN1_cctr_270514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	exp BRONCHIOLITIS/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	HELIUM/
27	(helium$ or heliox$).ti,ab,nm.
28	(He O2 or HeO2 or Hx).ti,ab.
29	or/26-28
30	and/7,25,29

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_heliox_RERUN1_cdsrdare_270514

#	Searches
1	CHILD.kw.
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
3	INFANT.kw.
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.

#	Searches
5	PEDIATRICS.kw.
6	p?ediatric$.tw,tx,kw,jw,rw.
7	or/1-6
8	BRONCHIOLITIS.kw.
9	BRONCHIOLES.kw.
10	bronchiol$.tw,tx,kw.
11	BRONCHITIS.kw.
12	BRONCHOPNEUMONIA.kw.
13	(bronchopneumon$ or bronchit$).tw,tx,kw.
14	RESPIRATORY SYNCYTIAL VIRUSES.kw.
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS.kw.
16	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
17	RESPIRATORY TRACT DISEASES.kw.
18	RESPIRATORY TRACT INFECTIONS.kw.
19	BRONCHIAL DISEASES.kw.
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
21	low$ respiratory tract$.tw,tx,kw.
22	(LR?I$ or ALR?I$).tw,tx,kw.
23	RESPIRATORY SOUNDS.kw.
24	(crepit$ or crackl$ or wheez$).tw,tx,kw.
25	or/8-24
26	HELIUM.kw.
27	(helium$ or heliox$).tw,tx,kw.
28	(He O2 or HeO2 or Hx).tw,tx,kw.
29	or/26-28
30	and/7,25,29

Database(s): EBM Reviews - Health Technology Assessment

BRONC_heliox_RERUN1_hta_270514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	exp BRONCHIOLITIS/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).tw.

#	Searches
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).tw.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
21	low$ respiratory tract$.tw.
22	(LR?I$ or ALR?I$).tw.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/8-24
26	HELIUM/
27	(helium$ or heliox$).tw.
28	(He O2 or HeO2 or Hx).tw.
29	or/26-28
30	and/7,25,29

Database(s): Embase

BRONC_heliox_RERUN1_embase_270514

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	exp BRONCHIOLITIS/
9	BRONCHIOLE/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASE/
18	RESPIRATORY TRACT INFECTION/
19	exp LOWER RESPIRATORY TRACT INFECTION/
20	BRONCHUS DISEASE/
21	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
22	low$ respiratory tract$.ti,ab.
23	(LR?I$ or ALR?I$).ti,ab.

#	Searches
24	exp ABNORMAL RESPIRATORY SOUND/
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/8-25
27	HELIUM/
28	(helium$ or heliox$).ti,ab.
29	(He O2 or HeO2 or Hx).ti,ab.
30	or/27-29
31	and/7,26,30
32	limit 31 to english language
33	conference abstract.pt.
34	letter.pt. or LETTER/
35	note.pt.
36	editorial.pt.
37	CASE REPORT/ or CASE STUDY/
38	(letter or comment* or abstracts).ti.
39	or/33-38
40	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
41	39 not 40
42	ANIMAL/ not HUMAN/
43	NONHUMAN/
44	exp ANIMAL EXPERIMENT/
45	exp EXPERIMENTAL ANIMAL/
46	ANIMAL MODEL/
47	exp RODENT/
48	(rat or rats or mouse or mice).ti.
49	or/41-48
50	32 not 49

F.16 What is the efficacy of Montelukast?

Database(s): Ovid MEDLINE(R)

BRONC_montelukast_RERUN1_medline_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/

#	Searches
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	LEUKOTRIENE ANTAGONISTS/
27	(leu#otriene$ or antileu#otriene$ or LTRA).ti,ab.
28	(montelukast or singulair).ti,ab,rn.
29	or/26-28
30	and/7,25,29
31	limit 30 to english language
32	LETTER/
33	EDITORIAL/
34	NEWS/
35	exp HISTORICAL ARTICLE/
36	ANECDOTES AS TOPIC/
37	COMMENT/
38	CASE REPORT/
39	(letter or comment* or abstracts).ti.
40	or/32-39
41	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
42	40 not 41
43	ANIMALS/ not HUMANS/
44	exp ANIMALS, LABORATORY/
45	exp ANIMAL EXPERIMENTATION/
46	exp MODELS, ANIMAL/
47	exp RODENTIA/
48	(rat or rats or mouse or mice).ti.
49	or/42-48
50	31 not 49

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_montelukast_RERUN1_mip_170614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(bronchopneumon$ or bronchit$).ti,ab.
7	(respiratory sync#tial vir$ or RSV).ti,ab.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	(crepit$ or crackl$ or wheez$).ti,ab.
12	or/5-11
13	(leu#otriene$ or antileu#otriene$ or LTRA).ti,ab.
14	(montelukast or singulair).ti,ab,rn.
15	or/13-14
16	and/4,12,15
17	limit 16 to english language

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_montelukast_RERUN1_cctr_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/

#	Searches
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	LEUKOTRIENE ANTAGONISTS/
27	(leu#otriene$ or antileu#otriene$ or LTRA).ti,ab.
28	(montelukast or singulair).ti,ab,rn.
29	or/26-28
30	and/7,25,29

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_montelukast_RERUN1_cdsrdare_170614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	(bronchopneumon$ or bronchit$).tw,tx,kw.
7	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	RESPIRATORY SOUND$.kw.
12	(crepit$ or crackl$ or wheez$).tw,tx,kw.
13	or/5-12
14	(leu#otriene$ or antileu#otriene$ or LTRA).tw,tx,kw.
15	(montelukast or singulair).tw,tx,kw.
16	or/14-15
17	and/4,13,16

Database(s): EBM Reviews - Health Technology Assessment

BRONC_montelukast_RERUN1_hta_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).tw.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).tw.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
21	low$ respiratory tract$.tw.
22	(LR?I$ or ALR?I$).tw.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/8-24
26	LEUKOTRIENE ANTAGONISTS/
27	(leu#otriene$ or antileu#otriene$ or LTRA).tw.
28	(montelukast or singulair).tw.
29	or/26-28
30	and/7,25,29

Database(s): Embase

BRONC_montelukast_RERUN1_embase_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASE/
18	RESPIRATORY TRACT INFECTION/
19	exp LOWER RESPIRATORY TRACT INFECTION/
20	BRONCHUS DISEASE/
21	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
22	low$ respiratory tract$.ti,ab.
23	(LR?I$ or ALR?I$).ti,ab.
24	exp ABNORMAL RESPIRATORY SOUND/
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/8-25
27	MONTELUKAST/
28	(leu#otriene$ or antileu#otriene$ or LTRA).ti,ab.
29	(montelukast or singulair).ti,ab,rn.
30	or/27-29
31	and/7,26,30
32	limit 31 to english language
33	conference abstract.pt.
34	letter.pt. or LETTER/
35	note.pt.
36	editorial.pt.
37	CASE REPORT/ or CASE STUDY/
38	(letter or comment* or abstracts).ti.
39	or/33-38
40	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
41	39 not 40
42	ANIMAL/ not HUMAN/

#	Searches
43	NONHUMAN/
44	exp ANIMAL EXPERIMENT/
45	exp EXPERIMENTAL ANIMAL/
46	ANIMAL MODEL/
47	exp RODENT/
48	(rat or rats or mouse or mice).ti.
49	or/41-48
50	32 not 49

F.17 What is the efficacy of oxygen supplementation (non-humidified, humidified and high-flow) and of CPAP?

Database(s): Ovid MEDLINE(R)

BRONC_O2_supplementation_RERUN1_medline_130614

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp CHILD/
22	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
23	exp INFANT/
24	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
25	exp PEDIATRICS/
26	p?ediatric$.ti,ab,jw.

#	Searches
27	or/21-26
28	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
29	BRONCHIOLES/
30	bronchiol$.ti,ab.
31	BRONCHITIS/
32	BRONCHOPNEUMONIA/
33	(bronchopneumon$ or bronchit$).ti,ab.
34	exp RESPIRATORY SYNCYTIAL VIRUSES/
35	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
36	(respiratory sync#tial vir$ or RSV).ti,ab.
37	RESPIRATORY TRACT DISEASES/
38	RESPIRATORY TRACT INFECTIONS/
39	BRONCHIAL DISEASES/
40	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
41	low$ respiratory tract$.ti,ab.
42	(LR?I$ or ALR?I$).ti,ab.
43	RESPIRATORY SOUNDS/
44	(crepit$ or crackl$ or wheez$).ti,ab.
45	or/28-44
46	OXYGEN INHALATION THERAPY/
47	exp POSITIVE-PRESSURE RESPIRATION/
48	OXYGEN/
49	((oxygen$ or O2) adj3 (therap$ or supplement$ or humidif$ or unhumidif$ or high flow or insufflat$ or inhal$)).ti,ab.
50	high flow nasal cannul$.ti,ab.
51	(CPAP or nCPAP or nmCPAP or npCPAP or n-CPAP or nm-CPAP or np-CPAP or PEEP or IMV or PPV or HFNC).ti,ab.
52	(positive adj3 pressure adj3 (ventilat$ or respirat$ or breath$ or airway?)).ti,ab.
53	(airway pressure release adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
54	positive end expiratory pressur$.ti,ab.
55	continuous distend$ pressur$.ti,ab.
56	(intermittent adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
57	or/46-56
58	and/27,45,57
59	limit 58 to english language
60	LETTER/
61	EDITORIAL/
62	NEWS/
63	exp HISTORICAL ARTICLE/
64	ANECDOTES AS TOPIC/
65	COMMENT/
66	CASE REPORT/
67	(letter or comment* or abstracts).ti.
68	or/60-67
69	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
70	68 not 69

#	Searches
71	ANIMALS/ not HUMANS/
72	exp ANIMALS, LABORATORY/
73	exp ANIMAL EXPERIMENTATION/
74	exp MODELS, ANIMAL/
75	exp RODENTIA/
76	(rat or rats or mouse or mice).ti.
77	or/70-76
78	59 not 77
79	and/20,78

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_O2_supplementation_RERUN1_mip_130614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(bronchopneumon$ or bronchit$).ti,ab.
7	(respiratory sync#tial vir$ or RSV).ti,ab.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	(crepit$ or crackl$ or wheez$).ti,ab.
12	or/5-11
13	((oxygen$ or O2) adj3 (therap$ or supplement$ or humidif$ or unhumidif$ or high flow or insufflat$ or inhal$)).ti,ab.
14	high flow nasal cannul$.ti,ab.
15	(CPAP or nCPAP or nmCPAP or npCPAP or n-CPAP or nm-CPAP or np-CPAP or PEEP or IMV or PPV or HFNC).ti,ab.
16	(positive adj3 pressure adj3 (ventilat$ or respirat$ or breath$ or airway?)).ti,ab.
17	(airway pressure release adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
18	positive end expiratory pressur$.ti,ab.
19	continuous distend$ pressur$.ti,ab.
20	(intermittent adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
21	or/13-20
22	and/4,12,21

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_O2_supplementation_RERUN1_cctr_130614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	OXYGEN INHALATION THERAPY/
27	exp POSITIVE-PRESSURE RESPIRATION/
28	OXYGEN/
29	((oxygen$ or O2) adj3 (therap$ or supplement$ or humidif$ or unhumidif$ or high flow or insufflat$ or inhal$)).ti,ab.
30	high flow nasal cannul$.ti,ab.
31	(CPAP or nCPAP or nmCPAP or npCPAP or n-CPAP or nm-CPAP or np-CPAP or PEEP or IMV or PPV or HFNC).ti,ab.
32	(positive adj3 pressure adj3 (ventilat$ or respirat$ or breath$ or airway?)).ti,ab.
33	(airway pressure release adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
34	positive end expiratory pressur$.ti,ab.
35	continuous distend$ pressur$.ti,ab.
36	(intermittent adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
37	or/26-36
38	and/7,25,37

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_O2_supplementation_RERUN1_cdsrdare_130614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	(bronchopneumon$ or bronchit$).tw,tx,kw.
7	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	(crepit$ or crackl$ or wheez$).tw,tx,kw.
12	or/5-11
13	OXYGEN.kw.
14	PRESSURE SUPPORT VENTILATION.kw.
15	((oxygen$ or O2) adj3 (therap$ or supplement$ or humidif$ or unhumidif$ or high flow or insufflat$ or inhal$)).tw,tx,kw.
16	high flow nasal cannul$.tw,tx.
17	(CPAP or nCPAP or nmCPAP or npCPAP or n-CPAP or nm-CPAP or np-CPAP or PEEP or IMV or PPV or HFNC).tw,tx.
18	(positive adj3 pressure adj3 (ventilat$ or respirat$ or breath$ or airway?)).tw,tx,kw.
19	(airway pressure release adj3 (ventilat$ or respirat$ or breath$)).tw,tx.
20	positive end expiratory pressure.tw,tx,kw.
21	continuous distend$ pressur$.tw,tx.
22	(intermittent adj3 (ventilat$ or respirat$ or breath$)).tw,tx,kw.
23	or/13-22
24	and/4,12,23

Database(s): EBM Reviews - Health Technology Assessment

BRONC_O2_supplementation_RERUN1_hta_130614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/

#	Searches
10	bronchiol$.tw.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).tw.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).tw.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
21	low$ respiratory tract$.tw.
22	(LR?I$ or ALR?I$).tw.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/8-24
26	OXYGEN INHALATION THERAPY/
27	exp POSITIVE-PRESSURE RESPIRATION/
28	OXYGEN/
29	((oxygen$ or O2) adj3 (therap$ or supplement$ or humidif$ or unhumidif$ or high flow or insufflat$ or inhal$)).tw.
30	high flow nasal cannul$.tw.
31	(CPAP or nCPAP or nmCPAP or npCPAP or n-CPAP or nm-CPAP or np-CPAP or PEEP or IMV or PPV or HFNC).tw.
32	(positive adj3 pressure adj3 (ventilat$ or respirat$ or breath$ or airway?)).tw.
33	(airway pressure release adj3 (ventilat$ or respirat$ or breath$)).tw.
34	positive end expiratory pressur$.tw.
35	continuous distend$ pressur$.tw.
36	(intermittent adj3 (ventilat$ or respirat$ or breath$)).tw.
37	or/26-36
38	and/7,25,37

Database(s): Embase

BRONC_O2_supplementation_RERUN1_embase_130614

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.

#	Searches
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	or/11,21
23	exp CHILD/
24	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
25	exp INFANT/
26	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
27	exp PEDIATRICS/
28	p?ediatric$.ti,ab,jx,ec.
29	or/23-28
30	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
31	BRONCHIOLE/
32	bronchiol$.ti,ab.
33	BRONCHITIS/
34	BRONCHOPNEUMONIA/
35	(bronchopneumon$ or bronchit$).ti,ab.
36	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
37	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
38	(respiratory sync#tial vir$ or RSV).ti,ab.
39	RESPIRATORY TRACT DISEASE/
40	RESPIRATORY TRACT INFECTION/
41	exp LOWER RESPIRATORY TRACT INFECTION/
42	BRONCHUS DISEASE/
43	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
44	low$ respiratory tract$.ti,ab.
45	(LR?I$ or ALR?I$).ti,ab.
46	exp ABNORMAL RESPIRATORY SOUND/
47	(crepit$ or crackl$ or wheez$).ti,ab.
48	or/30-47
49	OXYGEN THERAPY/
50	OXYGEN BREATHING/
51	OXYGEN/
52	INTERMITTENT MANDATORY VENTILATION/
53	INTERMITTENT POSITIVE PRESSURE VENTILATION/

#	Searches
54	POSITIVE END EXPIRATORY PRESSURE/
55	PRESSURE SUPPORT VENTILATION/
56	((oxygen$ or O2) adj3 (therap$ or supplement$ or humidif$ or unhumidif$ or high flow or insufflat$ or inhal$)).ti,ab.
57	high flow nasal cannul$.ti,ab.
58	(CPAP or nCPAP or nmCPAP or npCPAP or n-CPAP or nm-CPAP or np-CPAP or PEEP or IMV or PPV or HFNC).ti,ab.
59	(positive adj3 pressure adj3 (ventilat$ or respirat$ or breath$ or airway?)).ti,ab.
60	(airway pressure release adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
61	positive end expiratory pressure.ti,ab.
62	continuous distend$ pressur$.ti,ab.
63	(intermittent adj3 (ventilat$ or respirat$ or breath$)).ti,ab.
64	or/49-63
65	and/29,48,64
66	limit 65 to english language
67	conference abstract.pt.
68	letter.pt. or LETTER/
69	note.pt.
70	editorial.pt.
71	CASE REPORT/ or CASE STUDY/
72	(letter or comment* or abstracts).ti.
73	or/67-72
74	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
75	73 not 74
76	ANIMAL/ not HUMAN/
77	NONHUMAN/
78	exp ANIMAL EXPERIMENT/
79	exp EXPERIMENTAL ANIMAL/
80	ANIMAL MODEL/
81	exp RODENT/
82	(rat or rats or mouse or mice).ti.
83	or/75-82
84	66 not 83
85	and/22,84

F.18 What is the efficacy of suction to remove secretions from the upper respiratory tract?

Database(s): Ovid MEDLINE(R)

BRONC_suction_RERUN1_medline_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	SUCTION/
27	DRAINAGE/
28	exp NOSE/
29	exp PHARYNX/
30	exp MOUTH/
31	NASAL OBSTRUCTION/
32	SPUTUM/
33	MUCUS/
34	or/28-33
35	and/27,34
36	((suction$ or aspiration or aspirator? or drain$) adj3 (nose? or nasal$ or nostril? or nare? or rhino$ or nasopharyn$ or epipharyn$ or oropharyn$ or hypopharyn$ or laryngopharyn$ or pharyn$ or laryn$ or trache$ or mouth? or oral$ or airway? or respiratory tract? or sputum or sputa or muc?us or secretion? or rhinorrh?ea)).ti,ab.
37	((suction$ or aspirat$ or drain$) adj3 (bulb? or device? or mechanical$ or manual$ or catheter$ or pump?)).ti,ab.

#	Searches
38	or/26,35-37
39	and/7,25,38
40	limit 39 to english language
41	LETTER/
42	EDITORIAL/
43	NEWS/
44	exp HISTORICAL ARTICLE/
45	ANECDOTES AS TOPIC/
46	COMMENT/
47	CASE REPORT/
48	(letter or comment* or abstracts).ti.
49	or/41-48
50	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
51	49 not 50
52	ANIMALS/ not HUMANS/
53	exp ANIMALS, LABORATORY/
54	exp ANIMAL EXPERIMENTATION/
55	exp MODELS, ANIMAL/
56	exp RODENTIA/
57	(rat or rats or mouse or mice).ti.
58	or/51-57
59	40 not 58

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations

BRONC_suction_RERUN1_mip_170614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
2	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
3	p?ediatric$.ti,ab,jw.
4	or/1-3
5	bronchiol$.ti,ab.
6	(bronchopneumon$ or bronchit$).ti,ab.
7	(respiratory sync#tial vir$ or RSV).ti,ab.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
9	low$ respiratory tract$.ti,ab.
10	(LR?I$ or ALR?I$).ti,ab.
11	(crepit$ or crackl$ or wheez$).ti,ab.
12	or/5-11
13	((suction$ or aspiration or aspirator? or drain$) adj3 (nose? or nasal$ or nostril? or nare? or rhino$ or nasopharyn$ or epipharyn$ or oropharyn$ or hypopharyn$ or laryngopharyn$ or pharyn$ or laryn$ or trache$ or mouth? or oral$ or airway? or respiratory tract? or sputum or sputa or muc?us or secretion? or rhinorrh?ea)).ti,ab.

#	Searches
14	((suction$ or aspirat$ or drain$) adj3 (bulb? or device? or mechanical$ or manual$ or catheter$ or pump?)).ti,ab.
15	or/13-14
16	and/4,12,15

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_suction_RERUN1_cctr_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
21	low$ respiratory tract$.ti,ab.
22	(LR?I$ or ALR?I$).ti,ab.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).ti,ab.
25	or/8-24
26	SUCTION/
27	DRAINAGE/
28	exp NOSE/
29	exp PHARYNX/
30	exp MOUTH/
31	NASAL OBSTRUCTION/
32	SPUTUM/
33	MUCUS/
34	or/28-33
35	and/27,34

#	Searches
36	((suction$ or aspiration or aspirator? or drain$) adj3 (nose? or nasal$ or nostril? or nare? or rhino$ or nasopharyn$ or epipharyn$ or oropharyn$ or hypopharyn$ or laryngopharyn$ or pharyn$ or laryn$ or trache$ or mouth? or oral$ or airway? or respiratory tract? or sputum or sputa or muc?us or secretion? or rhinorrh?ea)).ti,ab.
37	((suction$ or aspirat$ or drain$) adj3 (bulb? or device? or mechanical$ or manual$ or catheter$ or pump?)).ti,ab.
38	or/26,35-37
39	and/7,25,38

Database(s): EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Database of Abstracts of Reviews of Effects

BRONC_suction_RERUN1_cdsrdare_170614

#	Searches
1	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,tx,kw,jw,rw.
2	(infan$ or neonat$ or newborn$ or baby or babies).tw,tx,kw,jw,rw.
3	p?ediatric$.tw,tx,kw,jw,rw.
4	or/1-3
5	bronchiol$.tw,tx,kw.
6	(bronchopneumon$ or bronchit$).tw,tx,kw.
7	(respiratory sync#tial vir$ or RSV).tw,tx,kw.
8	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw,tx,kw.
9	low$ respiratory tract$.tw,tx.
10	(LR?I$ or ALR?I$).tw,tx.
11	RESPIRATORY SOUND$.kw.
12	(crepit$ or crackl$ or wheez$).tw,tx,kw.
13	or/5-12
14	SUCTION.kw.
15	((suction$ or aspiration or aspirator? or drain$) adj3 (nose? or nasal$ or nostril? or nare? or rhino$ or nasopharyn$ or epipharyn$ or oropharyn$ or hypopharyn$ or laryngopharyn$ or pharyn$ or laryn$ or trache$ or mouth? or oral$ or airway? or respiratory tract? or sputum or sputa or muc?us or secretion? or rhinorrh?ea)).tw,tx,kw.
16	((suction$ or aspirat$ or drain$) adj3 (bulb? or device? or mechanical$ or manual$ or catheter$ or pump?)).tw,tx,kw.
17	or/14-16
18	and/4,13,17

Database(s): EBM Reviews - Health Technology Assessment

BRONC_suction_RERUN1_hta_170614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,jx,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,jx,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,jx,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	bronchiol$.tw.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).tw.
14	exp RESPIRATORY SYNCYTIAL VIRUSES/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
16	(respiratory sync#tial vir$ or RSV).tw.
17	RESPIRATORY TRACT DISEASES/
18	RESPIRATORY TRACT INFECTIONS/
19	BRONCHIAL DISEASES/
20	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
21	low$ respiratory tract$.tw.
22	(LR?I$ or ALR?I$).tw.
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/8-24
26	SUCTION/
27	DRAINAGE/
28	(suction$ or aspiration or aspirator? or drain$).tw.
29	or/26-28
30	and/7,25,29

Database(s): Embase

BRONC_suction_RERUN2_embase_130814

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
5	exp PEDIATRICS/
6	p?ediatric$.ti,ab,jx,ec.

#	Searches
7	or/1-6
8	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
9	BRONCHIOLE/
10	bronchiol$.ti,ab.
11	BRONCHITIS/
12	BRONCHOPNEUMONIA/
13	(bronchopneumon$ or bronchit$).ti,ab.
14	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
15	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
16	(respiratory sync#tial vir$ or RSV).ti,ab.
17	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
18	RESPIRATORY TRACT INFECTION/
19	exp LOWER RESPIRATORY TRACT INFECTION/
20	BRONCHUS DISEASE/
21	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
22	low$ respiratory tract$.ti,ab.
23	(LR?I$ or ALR?I$).ti,ab.
24	exp ABNORMAL RESPIRATORY SOUND/
25	(crepit$ or crackl$ or wheez$).ti,ab.
26	or/8-25
27	SUCTION/
28	SUCTION DRAINAGE/
29	exp AIRWAY SUCTION DEVICE/
30	ASPIRATION/
31	exp NOSE/
32	exp PHARYNX/
33	exp MOUTH/
34	NOSE OBSTRUCTION/
35	SPUTUM/
36	MUCUS/ or BRONCHUS MUCUS/ or NOSE MUCUS/ or TRACHEA MUCUS/
37	NOSE SECRETION/
38	RHINORRHEA/
39	or/31-38
40	and/30,39
41	((suction$ or aspiration or aspirator? or drain$) adj3 (nose? or nasal$ or nostril? or nare? or rhino$ or nasopharyn$ or epipharyn$ or oropharyn$ or hypopharyn$ or laryngopharyn$ or pharyn$ or laryn$ or trache$ or mouth? or oral$ or airway? or respiratory tract? or sputum or sputa or muc?us or secretion? or rhinorrh?ea)).ti,ab.
42	((suction$ or aspirat$ or drain$) adj3 (bulb? or device? or mechanical$ or manual$ or catheter$ or pump?)).ti,ab.
43	or/27-29,40-42
44	and/7,26,43
45	limit 44 to english language
46	conference abstract.pt.
47	letter.pt. or LETTER/
48	note.pt.

#	Searches
49	editorial.pt.
50	CASE REPORT/ or CASE STUDY/
51	(letter or comment* or abstracts).ti.
52	or/46-51
53	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
54	52 not 53
55	ANIMAL/ not HUMAN/
56	NONHUMAN/
57	exp ANIMAL EXPERIMENT/
58	exp EXPERIMENTAL ANIMAL/
59	ANIMAL MODEL/
60	exp RODENT/
61	(rat or rats or mouse or mice).ti.
62	or/54-61
63	45 not 62

Database(s): CINAHL with Full Text

BRONC_suction_RERUN1_cinahl_170614

#	Query
S29	S5 AND S25 AND S28
S28	S26 OR S27
S27	TI (suction* or aspiration or aspirator? or drain*) or AB (suction* or aspiration or aspirator? or drain*)
S26	(MH "Suction+") OR (MH "Drainage+")
S25	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
S24	TI (crepit* or crackl* or wheez*) or AB (crepit* or crackl* or wheez*)
S23	(MH "Respiratory Sounds")
S22	TI (LR#I* or ALR#I*) or AB (LR#I* or ALR#I*)
S21	AB (bronchi* N3 infect*) or AB (bronchi* N3 inflam*) or AB (bronchi* N3 disease*)
S20	TI (bronchi* N3 infect*) or TI (bronchi* N3 inflam*) or TI (bronchi* N3 disease*)
S19	AB (respiratory N3 infect*) or AB (respiratory N3 inflam*) or AB (respiratory N3 disease*)
S18	TI (respiratory N3 infect*) or TI (respiratory N3 inflam*) or TI (respiratory N3 disease*)
S17	(MH "Bronchial Diseases")
S16	(MH "Respiratory Tract Infections")
S15	(MH "Respiratory Tract Diseases")
S14	TI (respiratory sync?tial vir* or RSV) or AB (respiratory sync?tial vir* or RSV)
S13	(MH "Respiratory Syncytial Virus Infections")
S12	(MH "Respiratory Syncytial Viruses")
S11	TI (bronchopneumon* or bronchit*) or AB (bronchopneumon* or bronchit*)
S10	(MH "Bronchopneumonia")
S9	(MH "Bronchitis+")
S8	TI (bronchiol*) or AB (bronchiol*)
S7	(MH "Bronchioles")
S6	(MH "Bronchiolitis")

#	Query
S5	S1 OR S2 OR S3 OR S4
S4	TI (p#ediatric*) or AB (p#ediatric*)
S3	TI (infan* or neonat* or newborn* or baby or babies) OR AB (infan* or neonat* or newborn* or baby or babies)
S2	TI (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#) OR AB (child* or preschool* or toddler* or kid# or kindergar* or boy# or girl#)
S1	(MH "Infant, Newborn+") OR (MH "Infant+") OR (MH "Child, Preschool") OR (MH "Child+") OR (MH "Pediatrics+")

F.19 Health economics

Database(s): Ovid MEDLINE(R)

BRONC_HE_global_RERUN1_medline_060614

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	exp CHILD/
23	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
24	exp INFANT/
25	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
26	exp PEDIATRICS/
27	p?ediatric$.ti,ab,jw.
28	or/22-27
29	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
30	BRONCHIOLES/
31	BRONCHITIS/ or BRONCHOPNEUMONIA/

#	Searches
32	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
33	exp RESPIRATORY SYNCYTIAL VIRUSES/
34	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
35	(respiratory sync#tial vir$ or RSV).ti,ab.
36	or/29-35
37	RESPIRATORY TRACT DISEASES/
38	RESPIRATORY TRACT INFECTIONS/
39	BRONCHIAL DISEASES/
40	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
41	low$ respiratory tract$.ti,ab.
42	(LR?I$ or ALR?I$).ti,ab.
43	or/37-42
44	RESPIRATORY SOUNDS/
45	(crepit$ or crackl$ or wheez$).ti,ab.
46	or/44-45
47	exp VIRUS DISEASES/
48	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
49	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
50	pneumovir$.ti,ab.
51	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
52	METAPNEUMOVIRUS/
53	(paramyxovir$ or metapneumovir$).ti,ab.
54	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
55	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
56	(adenovir$ or mastadenovir$).ti,ab.
57	influenza$.ti,ab,hw.
58	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
59	enterovir$.ti,ab.
60	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
61	rhinovir$.ti,ab.
62	or/47-61
63	and/43,46
64	and/43,62
65	and/46,62
66	or/63-65
67	or/36,66
68	and/28,67
69	limit 68 to english language
70	and/21,69
71	LETTER/
72	EDITORIAL/
73	NEWS/
74	exp HISTORICAL ARTICLE/
75	ANECDOTES AS TOPIC/
76	COMMENT/

#	Searches
77	CASE REPORT/
78	(letter or comment* or abstracts).ti.
79	or/71-78
80	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
81	79 not 80
82	ANIMALS/ not HUMANS/
83	exp ANIMALS, LABORATORY/
84	exp ANIMAL EXPERIMENTATION/
85	exp MODELS, ANIMAL/
86	exp RODENTIA/
87	(rat or rats or mouse or mice).ti.
88	or/81-87
89	70 not 88

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials

BRONC_HE_global_RERUN1_cctr_130614

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	exp CHILD/
23	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
24	exp INFANT/
25	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
26	exp PEDIATRICS/
27	p?ediatric$.ti,ab,jw.

#	Searches
28	or/22-27
29	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
30	BRONCHIOLES/
31	BRONCHITIS/ or BRONCHOPNEUMONIA/
32	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
33	exp RESPIRATORY SYNCYTIAL VIRUSES/
34	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
35	(respiratory sync#tial vir$ or RSV).ti,ab.
36	or/29-35
37	RESPIRATORY TRACT DISEASES/
38	RESPIRATORY TRACT INFECTIONS/
39	BRONCHIAL DISEASES/
40	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).ti,ab.
41	low$ respiratory tract$.ti,ab.
42	(LR?I$ or ALR?I$).ti,ab.
43	or/37-42
44	RESPIRATORY SOUNDS/
45	(crepit$ or crackl$ or wheez$).ti,ab.
46	or/44-45
47	exp VIRUS DISEASES/
48	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
49	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
50	pneumovir$.ti,ab.
51	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
52	METAPNEUMOVIRUS/
53	(paramyxovir$ or metapneumovir$).ti,ab.
54	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
55	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
56	(adenovir$ or mastadenovir$).ti,ab.
57	influenza$.ti,ab,hw.
58	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
59	enterovir$.ti,ab.
60	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
61	rhinovir$.ti,ab.
62	or/47-61
63	and/43,46
64	and/43,62
65	and/46,62
66	or/63-65
67	or/36,66
68	and/28,67
69	limit 68 to english language
70	and/21,69
71	LETTER/
72	EDITORIAL/

#	Searches
73	NEWS/
74	exp HISTORICAL ARTICLE/
75	ANECDOTES AS TOPIC/
76	COMMENT/
77	CASE REPORT/
78	(letter or comment* or abstracts).ti.
79	or/71-78
80	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
81	79 not 80
82	ANIMALS/ not HUMANS/
83	exp ANIMALS, LABORATORY/
84	exp ANIMAL EXPERIMENTATION/
85	exp MODELS, ANIMAL/
86	exp RODENTIA/
87	(rat or rats or mouse or mice).ti.
88	or/81-87
89	70 not 88

Database(s): EBM Reviews - NHS Economic Evaluation Database, EBM Reviews - Health Technology Assessment

BRONC_HE_global_RERUN1_nhseed_130614

#	Searches
1	exp CHILD/
2	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).tw,rw.
3	exp INFANT/
4	(infan$ or neonat$ or newborn$ or baby or babies).tw,rw.
5	exp PEDIATRICS/
6	p?ediatric$.tw,rw.
7	or/1-6
8	BRONCHIOLITIS/ or BRONCHIOLITIS, VIRAL/
9	BRONCHIOLES/
10	BRONCHITIS/ or BRONCHOPNEUMONIA/
11	(bronchiol$ or bronchitis or bronchopneumonia).tw.
12	exp RESPIRATORY SYNCYTIAL VIRUSES/
13	RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/
14	(respiratory sync#tial vir$ or RSV).tw.
15	or/8-14
16	RESPIRATORY TRACT DISEASES/
17	RESPIRATORY TRACT INFECTIONS/
18	BRONCHIAL DISEASES/
19	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$ or illness$)).tw.
20	low$ respiratory tract$.tw.
21	(LR?I$ or ALR?I$).tw.
22	or/16-21

#	Searches
23	RESPIRATORY SOUNDS/
24	(crepit$ or crackl$ or wheez$).tw.
25	or/23-24
26	exp VIRUS DISEASES/
27	((virus or viral) adj3 (infect$ or diseas$ or illness$)).tw.
28	PNEUMOVIRUS/ or PNEUMOVIRUS INFECTIONS/
29	pneumovir$.tw.
30	PARAMYXOVIRIDAE/ or PARAMYXOVIRIDAE INFECTIONS/
31	METAPNEUMOVIRUS/
32	(paramyxovir$ or metapneumovir$).tw.
33	ADENOVIRIDAE/ or ADENOVIRIDAE INFECTIONS/
34	MASTADENOVIRUS/ or ADENOVIRUSES, HUMAN/ or ADENOVIRUS INFECTIONS, HUMAN/
35	(adenovir$ or mastadenovir$).tw.
36	influenza$.tw.
37	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTIONS/
38	enterovir$.tw.
39	RHINOVIRUS/ or PICORNAVIRIDAE INFECTIONS/
40	rhinovir$.tw.
41	or/26-40
42	and/22,25
43	and/22,41
44	and/25,41
45	or/42-44
46	or/15,45
47	and/7,46
48	limit 47 to english language

Database(s): Embase

BRONC_HE_global_RERUN2_embase_120814

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.

#	Searches
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	exp CHILD/
19	(child$ or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jx.
20	exp INFANT/
21	(infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jx.
22	exp PEDIATRICS/
23	p?ediatric$.ti,ab,jx,ec.
24	or/18-23
25	BRONCHIOLITIS/ or VIRAL BRONCHIOLITIS/
26	BRONCHIOLE/
27	BRONCHITIS/ or BRONCHOPNEUMONIA/
28	(bronchiol$ or bronchitis or bronchopneumonia).ti,ab.
29	RESPIRATORY SYNCYTIAL PNEUMOVIRUS/
30	RESPIRATORY SYNCYTIAL VIRUS INFECTION/
31	(respiratory sync#tial vir$ or RSV).ti,ab.
32	or/25-31
33	RESPIRATORY TRACT DISEASE/ or ACUTE RESPIRATORY TRACT DISEASE/
34	RESPIRATORY TRACT INFECTION/
35	exp LOWER RESPIRATORY TRACT INFECTION/
36	BRONCHUS DISEASE/
37	((respiratory or bronchi$) adj3 (infect$ or inflam$ or diseas$)).ti,ab.
38	low$ respiratory tract$.ti,ab.
39	(LR?I$ or ALR?I$).ti,ab.
40	or/33-39
41	exp ABNORMAL RESPIRATORY SOUND/
42	(crepit$ or crackl$ or wheez$).ti,ab.
43	or/41-42
44	exp VIRUS INFECTION/
45	((virus or viral) adj3 (infect$ or diseas$ or illness$)).ti,ab.
46	PNEUMOVIRINAE/ or PNEUMOVIRUS INFECTION/
47	pneumovir$.ti,ab.
48	PARAMYXOVIRUS/ or PARAMYXOVIRUS INFECTION/
49	exp METAPNEUMOVIRUS/ or exp METAPNEUMOVIRUS INFECTION/
50	(paramyxovir$ or metapneumovir$).ti,ab.
51	ADENOVIRUS/ or ADENOVIRUS INFECTION/
52	exp MASTADENOVIRUS/ or HUMAN ADENOVIRUS INFECTION/
53	(adenovir$ or mastadenovir$).ti,ab.
54	influenza$.ti,ab,hw.
55	exp ENTEROVIRUS/ or ENTEROVIRUS INFECTION/
56	enterovir$.ti,ab.
57	exp RHINOVIRUS/ or RHINOVIRUS INFECTION/
58	rhinovir$.ti,ab.

#	Searches
59	or/44-58
60	and/40,43
61	and/40,59
62	and/43,59
63	or/60-62
64	or/32,63
65	and/24,64
66	limit 65 to english language
67	and/17,66
68	conference abstract.pt.
69	letter.pt. or LETTER/
70	note.pt.
71	editorial.pt.
72	CASE REPORT/ or CASE STUDY/
73	(letter or comment* or abstracts).ti.
74	or/68-73
75	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
76	74 not 75
77	ANIMAL/ not HUMAN/
78	NONHUMAN/
79	exp ANIMAL EXPERIMENT/
80	exp EXPERIMENTAL ANIMAL/
81	ANIMAL MODEL/
82	exp RODENT/
83	(rat or rats or mouse or mice).ti.
84	or/76-83
85	67 not 84

Appendix G: Summary of identified studies

Protocol question	total papers identified	duplicates	weeded out	abandoned	excluded	included
1. What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions?	2235	1	2185	0	31	7

Protocol question	total papers identified	duplicates	weeded out	abandoned	excluded	included
2. What are the risk factors for severe bronchiolitis?	3554	3	3430	1	66	43
3. At the time of assessment, what clinical features predict deterioration?	1347	0	1318	0	20	8
4. What are the indications for capillary blood gas testing?	349	0	346	0	3	0
5. What are the indications for fluids and nutritional support?	443	0	435	2	3	2
6. What are the criteria for a) referral to secondary care, b) hospital admission for observation or treatment, c) discharge from hospital?	1646	0	1632	0	9	5
7. What are the indications for SpO2 monitoring?	754	0	744	0	9	1
8. What are the indications for chest radiography?	1384	0	1360	0	16	4
9. What is the efficacy of chest physiotherapy in the management of bronchiolitis?	605	1	582	4	8	7
10. What is the efficacy of antibiotic treatment?	1121	0	1105	0	1	8
11. What is the efficacy of inhaled bronchodilator therapy?	1540	0	1494	0	19	24
12. What is the efficacy of inhaled corticosteroid therapy?	1551	0	1542	0	4	4

Protocol question	total papers identified	duplicates	weeded out	abandoned	excluded	included
13. What is the efficacy of systemic corticosteroid therapy?	1527	1	1504	0	8	13
14. What is the efficacy of nebulised hypertonic saline?	431	0	397	1	9	18
15. What is the efficacy of heliox?	139	0	125	1	4	7
16. What is the efficacy of combined bronchodilator and corticosteroid therapy?	1647	1	1617	2	15	11
17. What is the efficacy of Montelukast?	603	0	587	0	4	2
18. What is the efficacy of oxygen supplementation, including humidified oxygen, CPAP or humidified high-flow oxygen?	721	0	681	1	13	3
19. What is the efficacy of suction to remove secretions from the upper respiratory tract?	462	0	455	1	6	0

Appendix H: Summary of excluded studies

H.1 What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions?

Study	Reason for Exclusion
Ahmad,S.A., Mujawar,Q., Al,OthmanM, Salleh,H.B., Alsarfandi,M.A., Clinical profile of bronchiolitis in infants younger than 90 days in Saudi Arabia, Journal of Emergencies, Trauma and Shock, 7, 49-52, 2014	Non-comparative study
Bamberger,E., Srugo,I., Abu,Raya B., Segal,E., Chaim,B., Kassis,I., Kugelman,A., Miron,D., What is the clinical relevance of respiratory syncytial virus bronchiolitis?: findings from a multi-center, prospective study, European Journal of Clinical Microbiology and Infectious Diseases, 31, 3323-3330, 2012	Examines difference between RSV bronchiolitis and other forms.
Bordley,W.C., Viswanathan,M., King,V.J., Sutton,S.F., Jackman,A.M., Sterling,L., Lohr,K.N., Diagnosis and Testing in Bronchiolitis: A Systematic Review, Archives of Pediatrics and Adolescent Medicine, 158, 119-126, 2004	General descriptive review of the literature.
Brooke,A.M., Lambert,P.C., Burton,P.R., Clarke,C., Luyt,D.K., Simpson,H., The natural history of respiratory symptoms in preschool children, American Journal of Respiratory and Critical Care Medicine, 152, 1872-1878, 1995	Mixed patient group, including non-bronchiolitis.
Che,D., Caillere,N., Brosset,P., Vallejo,C., Josseran,L., Burden of infant bronchiolitis: data from a hospital network, Epidemiology and Infection, 138, 573-575, 2010	Description of treatment patterns for Bronchiolitis.
Checchia,P., Identification and management of severe respiratory syncytial virus. [37 refs], American Journal of Health-System Pharmacy, 65, S7-12, 2008	General review of Bronchiolitis identification and treatment.
Constantopoulos,A.G., Kafetzis,D.A., Syrogiannopoulos,G.A., Roilides,E.J., Malaka-Zafiriu,E.E., Sbyrakis,S.S., Marcopoulos,M.L., Burden of respiratory syncytial viral infections on paediatric hospitals: a two-year prospective epidemiological study, European Journal of Clinical Microbiology and Infectious Diseases, 21, 102-107, 2002	RSV including non-bronchiolitis.
Deshpande,S.A., Northern,V., The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area, Archives of Disease in Childhood, 88, 1065-1069, 2003	Description of hospitalised infants; does not examine symptoms.
Duarte-Dorado,D.M., Madero-Orostegui,D.S., Rodriguez-Martinez,C.E., Nino,G., Validation of	Study does not examine individual symptoms of bronchiolitis.

Study	Reason for Exclusion
a scale to assess the severity of bronchiolitis in a population of hospitalized infants, Journal of Asthma, 50, 1056-1061, 2013	
Flaherman,V.J., Ragins,A.I., Li,S.X., Kipnis,P., Masaquel,A., Escobar,G.J., Frequency, duration and predictors of bronchiolitis episodes of care among infants >=32weeks gestation in a large integrated healthcare system: a retrospective cohort study, BMC Health Services Research, 12, 144-, 2012	Describes duration of interaction with health service rather than of symptoms.
Flaherman,V.J., Ragins,A.I., Li,S.X., Kipnis,P., Masaquel,A., Escobar,G.J., Frequency, duration and predictors of bronchiolitis episodes of care among infants >32weeks gestation in a large integrated healthcare system: a retrospective cohort study, BMC Health Services Research, 12, 144-, 2012	examines the duration of hospital stay based on risk factors.
Hall,C.B., Simoes,E.A.F., Anderson,L.J., Clinical and epidemiologic features of respiratory syncytial virus, Challenges and Opportunities for Respiratory Syncytial Virus Vaccines, 372, 39-57, 2013	Descriptive review. No analysis of symptoms.
Hervas,D., Reina,J., Yanez,A., del Valle,J.M., Figuerola,J., Hervas,J.A., Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis, European Journal of Clinical Microbiology and Infectious Diseases, 31, 1975-1981, 2012	Description of hospiyalisation patterns
Houben,M.L., Bont,L., Wilbrink,B., Belderbos,M.E., Kimpen,J.L., Visser,G.H., Rovers,M.M., Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study, Pediatrics, 127, 35-41, 2011	Examines risk-factors for bronchiolitis
Koehoorn,M., Karr,C.J., Demers,P.A., Lencar,C., Tamburic,L., Brauer,M., Descriptive epidemiological features of bronchiolitis in a population-based cohort, Pediatrics, 122, 1196-1203, 2008	Does not describe the clinical course of Bronchiolitis, but examines the risk-factors.
Leung,A.K., Kellner,J.D., Davies,H.D., Respiratory syncytial virus bronchiolitis. [67 refs], Journal of the National Medical Association, 97, 1708-1713, 2005	General descriptive review of Bronchiolitis.
Mai,T.V., Selby,A.M., Simpson,J.M., Isaacs,D., Use of simple clinical parameters to assess severity of bronchiolitis, Journal of Paediatrics and Child Health, 31, 465-468, 1995	Examines association between symptoms and severity of bronchiolitis
Mansbach,J.M., Clark,S., Christopher,N.C., LoVecchio,F., Kunz,S., Acholonu,U., Camargo,C.A.,Jr., Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department, Pediatrics, 121, 680-688, 2008	Examines criteria for discharge
Marlais,M., Evans,J., Abrahamson,E., Clinical predictors of admission in infants with acute bronchiolitis, Archives of Disease in Childhood, 96, 648-652, 2011	Examines predictors for admission to hospital; not symptoms of bronchiolitis.

Study	Reason for Exclusion
McCallum,G.B., Morris,P.S., Wilson,C.C., Versteegh,L.A., Ward,L.M., Chatfield,M.D., Chang,A.B., Severity scoring systems: are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis?, Pediatric Pulmonology, 48, 797-803, 2013	Examines reliability of a single score. This score is included in review by Gajdos, 2009.
Mellis,C., Respiratory noises: how useful are they clinically?. [42 refs], Pediatric Clinics of North America, 56, 1-17, 2009	Does not examine Bronchiolitis.
Mulholland,E.K., Olinsky,A., Shann,F.A., Clinical findings and severity of acute bronchiolitis, Lancet, 335, 1259-1261, 1990	Examines severity of bronchiolitis
Plint,A.C., Johnson,D.W., Wiebe,N., Bulloch,B., Pusic,M., Joubert,G., Pianosi,P., Turner,T., Thompson,G., Klassen,T.P., Practice variation among pediatric emergency departments in the treatment of bronchiolitis, Academic Emergency Medicine, 11, 353-360, 2004	Description of patient management but not outcomes of interest
Schroeder,A.R., Mansbach,J.M., Stevenson,M., Macias,C.G., Fisher,E.S., Barcega,B., Sullivan,A.F., Espinola,J.A., Piedra,P.A., Camargo,C.A.,Jr., Apnea in children hospitalized with bronchiolitis, Pediatrics, 132, e1194-e1201, 2013	Study focuses on factors causing apnea, rather than apnea as a symptom.
Shaw,K.N., Bell,L.M., Sherman,N.H., Outpatient assessment of infants with bronchiolitis, American Journal of Diseases of Children, 145, 151-155, 1991	Examines risk factors for severity of disease but not symptoms.
Sritippayawan,S., Deerojanawong,J., Prapphal,N., Clinical score and arterial oxygen saturation in children with wheezing associated respiratory illness (WARI), Journal of the Medical Association of Thailand, 83, 1215-1222, 2000	Mixed clinical group; not just Bronchiolitis.
Walsh,P., Gonzales,A., Satar,A., Rothenberg,S.J., The interrater reliability of a validated bronchiolitis severity assessment tool, Pediatric Emergency Care, 22, 316-320, 2006	Examines interrater reliability of a score and symptoms and signs.
Walsh-Kelly,C.M., Hennes,H.M., Do clinical variables predict pathologic radiographs in the first episode of wheezing?, Pediatric Emergency Care, 18, 8-11, 2002	Does not describe symptoms of bronchiolitis.
Wang,E.E., Milner,R.A., Navas,L., Maj,H., Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections, American Review of Respiratory Disease, 145, 106-109, 1992	Examines inter-observer agreement in respiratory symptomss for Bronchiolitis.
Weigl,J.A., Puppe,W., Schmitt,H.J., Can respiratory syncytial virus etiology be diagnosed clinically? A hospital-based case-control study in children under two years of age, European Journal of Epidemiology, 18, 431-439, 2003	Mixed patient group, including non-bronchiolitis

H.2 What are the risk factors for severe bronchiolitis?

Study	Reason for Exclusion
Allen,U., Asner,S., Stephens,D., Pedulla,P., Richardson,S.E., Robinson,J., Risk factors and outcomes for respiratory syncytial virus-related infections in immunocompromised children, Pediatric Infectious Disease Journal, 32, 1073-1076, 2013	No relevant data, study focuses on comparison of community acquired versus nosocomial RSV infection
Al-Muhsen,S.Z., Clinical profile of Respiratory Syncytial Virus (RSV) bronchiolitis in the intensive care unit at a tertiary care hospital, Current Pediatric Research, 14, 75-80, 2010	Non-comparative study
Al-Shawwa,B., Al-Huniti,N., Weinberger,M., bu-Hasan,M., Clinical and therapeutic variables influencing hospitalisation for bronchiolitis in a community-based paediatric group practice, Primary Care Respiratory Journal, 16, 93-97, 2007	Study does not reported adjusted odds ratios
Andres,S., Bauer,G., Rodriguez,S., Novali,L., Micheli,D., Farina,D., Hospitalization due to respiratory syncytial virus infection in patients under 2 years of age with hemodynamically significant congenital heart disease, Jornal de Pediatria, 88, 246-252, 2012	Study does not report adjusted odds ratios
Aujard,Y., Fauroux,B., Risk factors for severe respiratory syncytial virus infection in infants, Respiratory Medicine, 96 Suppl B, S9-14, 2002	Review article: individual studies checked for inclusion
Berger,T.M., Aebi,C., Duppenthaler,A., Stocker,M., Swiss Pediatric,Surveillance Unit, Prospective population-based study of RSV-related intermediate care and intensive care unit admissions in Switzerland over a 4-year period (2001-2005), Infection, 37, 109-116, 2009	Nothing to suggest the relative risks reported in the study are adjusted
Bloemers,B.L., van Furth,A.M., Weijerman,M.E., Gemke,R.J., Broers,C.J., van den,Ende K., Kimpen,J.L., Strengers,J.L., Bont,L.J., Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study, Pediatrics, 120, e1076-e1081, 2007	Nothing to suggest the odds ratios reported in the study are adjusted.
Bradley,J.P., Bacharier,L.B., Bonfiglio,J., Schechtman,K.B., Strunk,R., Storch,G., Castro,M., Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy, Pediatrics, 115, e7-14, 2005	Results are not in the form of relative risks/odds ratios but a predicted decrease in oxygen saturation
Broughton,S., Roberts,A., Fox,G., Pollina,E., Zuckerman,M., Chaudhry,S., Greenough,A., Prospective study of healthcare utilisation and respiratory morbidity due to RSV infection in prematurely born infants, Thorax, 60, 1039-1044, 2005	Though this study splits the subjects into 3 groups (no LRTI, RSV positive LRTI and RSV negative LRTI), it is seems as though all subjects (including those with no LRTI) were included in the risk factor analysis: therefore, population not as specified in protocol
Carbonell-Estrany,X., Figueras-Aloy,J., Law,B.J., Infeccion Respiratoria Infantil por Virus Respiratorio Sincitial Study Group, Pediatric Investigators Collaborative Network on Infections in Canada Study Group., Identifying	Commentary comparing the PICNIC and FLIP studies

Study	Reason for Exclusion
risk factors for severe respiratory syncytial virus among infants born after 33 through 35 completed weeks of gestation: different methodologies yield consistent findings, Pediatric Infectious Disease Journal, 23, S193-S201, 2004	
Corsello,G., Di Carlo,P., Salsa,L., Gabriele,B., Meli,L., Bruno,S., Titone,L., Respiratory syncytial virus infection in a Sicilian pediatric population: risk factors, epidemiology, and severity, Allergy and Asthma Proceedings, 29, 205-210, 2008	All subjects hospitalised
Das,P.K., Saha,J.B., Basu,K., Lahiri,S., Sarkar,G.N., Some clinico-epidemiological aspect of bronchiolitis among infants and young children--a hospital based study, Indian Journal of Public Health, 47, 66-71, 2003	Study does not report adjusted odds ratios
Dharmage,S.C., Rajapaksa,L.C., Fernando,D.N., Risk factors of acute lower respiratory tract infections in children under five years of age, Southeast Asian Journal of Tropical Medicine and Public Health, 27, 107-110, 1996	This study examines risk factors for acute lower respiratory tract infections in general - there is no subgroup analysis for bronchiolitis
Duppenthaler,A., Ammann,R.A., Gorgievski-Hrisoho,M., Pfammatter,J.P., Aebi,C., Low incidence of respiratory syncytial virus hospitalisations in haemodynamically significant congenital heart disease, Archives of Disease in Childhood, 89, 961-965, 2004	Study does not report adjusted relative risks
Eriksson,M., Bennet,R., Rotzen-Ostlund,M., von,Sydow M., Wirgart,B.Z., Population-based rates of severe respiratory syncytial virus infection in children with and without risk factors, and outcome in a tertiary care setting, Acta Paediatrica, 91, 593-598, 2002	Nothing to suggest the odds ratios reported are adjusted.
Fjaerli,H.O., Farstad,T., Bratlid,D., Hospitalisations for respiratory syncytial virus bronchiolitis in Akershus, Norway, 1993-2000: a population-based retrospective study, BMC Pediatrics, 4, 25-, 2004	All hospitalised
Flaherman,V.J., Ragins,A.I., Li,S.X., Kipnis,P., Masaquel,A., Escobar,G.J., Frequency, duration and predictors of bronchiolitis episodes of care among infants >=32weeks gestation in a large integrated healthcare system: a retrospective cohort study, BMC Health Services Research, 12, 144-, 2012	Not specifically looking at severe bronchiolitis, also includes infants with a range of conditions (bronchiolitis, pneumonia, parainfluenza)
Fleming,P.F., Richards,S., Waterman,K., Davis,P.G., Kamlin,C.O., Stewart,M., Sokol,J., Medical retrieval and needs of infants with bronchiolitis: an analysis by gestational age, Journal of Paediatrics and Child Health, 49, E227-E231, 2013	No relevant data
Flores,P., Rebelo-de-Andrade,H., Goncalves,P., Guiomar,R., Carvalho,C., Sousa,E.N., Noronha,F.T., Palminha,J.M., Bronchiolitis caused by respiratory syncytial virus in an area	Nothing to suggest the odds ratios reported in the study are adjusted odds ratios. Also includes subjects with previous history of wheeze.

Study	Reason for Exclusion
of portugal: epidemiology, clinical features, and risk factors, European Journal of Clinical Microbiology and Infectious Diseases, 23, 39-45, 2004	
Fryzek,J.P., Martone,W.J., Groothuis,J.R., Trends in chronologic age and infant respiratory syncytial virus hospitalization: an 8-year cohort study, Advances in Therapy, 28, 195-201, 2011	Study reports crude relative risks (not adjusted)
Gooch,K.L., Notario,G.F., Schulz,G., Gudkov,K.M., Buesch,K., Khong,H., Campbell,A., Comparison of risk factors between preterm and term infants hospitalized for severe respiratory syncytial virus in the Russian Federation, International Journal of Women's Health, 3, 133-138, 2011	All hospitalised subjects
Gouyon,J.B., Roze,J.C., Guillermet-Fromentin,C., Glorieux,I., Adamon,L., DI Maio,M., Miloradovich,T., Anghelescu,D., Pinquier,D., Escande,B., Elleau,C., Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study, Epidemiology and Infection, 141, 816-826, 2013	Results of multivariate analysis is presented in the form of beta coefficients not odds ratios
Hacimustafaoglu,M., Celebi,S., Bozdemir,S.E., Ozgur,T., Ozcan,I., Guray,A., Cakir,D., RSV frequency in children below 2 years hospitalized for lower respiratory tract infections, Turkish Journal of Pediatrics, 55, 130-139, 2013	No relevant data
Hall,C.B., Weinberg,G.A., Blumkin,A.K., Edwards,K.M., Staat,M.A., Schultz,A.F., Poehling,K.A., Szilagyi,P.G., Griffin,M.R., Williams,J.V., Zhu,Y., Grijalva,C.G., Prill,M.M., Iwane,M.K., Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age, Pediatrics, 132, e341-e348, 2013	Study does not report adjusted incidence rate ratios but unadjusted ones
Hall,C.B., Weinberg,G.A., Iwane,M.K., Blumkin,A.K., Edwards,K.M., Staat,M.A., Auinger,P., Griffin,M.R., Poehling,K.A., Erdman,D., Grijalva,C.G., Zhu,Y., Szilagyi,P., The burden of respiratory syncytial virus infection in young children, New England Journal of Medicine, 360, 588-598, 2009	Odds ratios in the form of forest plots (numbers not reported)
Hayes,E.B., Hurwitz,E.S., Schonberger,L.B., Anderson,L.J., Respiratory syncytial virus outbreak on American Samoa. Evaluation of risk factors, American Journal of Diseases of Children, 143, 316-321, 1989	Study does not report adjusted odds ratios
Heikkinen,T., Valkonen,H., Lehtonen,L., Vainionpaa,R., Ruuskanen,O., Hospital admission of high risk infants for respiratory syncytial virus infection: implications for palivizumab prophylaxis, Archives of Disease in Childhood: Fetal and Neonatal Edition, 90, F64-F68, 2005	Study does not report adjusted odds ratios

Study	Reason for Exclusion
Holberg,C.J., Wright,A.L., Martinez,F.D., Ray,C.G., Taussig,L.M., Lebowitz,M.D., Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life, American Journal of Epidemiology, 133, 1135-1151, 1991	This study looks at risk factors for RSV-LRI and not specifically severe infection
Holman,R.C., Curns,A.T., Cheek,J.E., Bresee,J.S., Singleton,R.J., Carver,K., Anderson,L.J., Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population, Pediatrics, 114, e437-e444, 2004	Study does not report adjusted odds ratios
Holman,R.C., Shay,D.K., Curns,A.T., Lingappa,J.R., Anderson,L.J., Risk factors for bronchiolitis-associated deaths among infants in the United States, Pediatric Infectious Disease Journal, 22, 483-490, 2003	Though results of multivariate analysis are reported, data for risk factors of interest are not examined
Horn,S.D., Smout,R.J., King,J., Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes, Journal of Pediatrics, 143, S133-S141, 2003	Study analysed records of all children with bronchiolitis/RSV pneumonia/viral pneumonia, unspecified. The study also includes subjects with a history of wheezing and history of hospitalisation for RSV/bronchiolitis.
Howidi,M., Rajah,J., Abushrar,Z., Parsons,H., The severity of respiratory syncytial virus bronchiolitis in young infants in the United Arab Emirates, Journal of Tropical Pediatrics, 53, 22-26, 2007	This study reports multiple regression analysis for predictors of duration of oxygen therapy but in the form of beta coefficients not odds ratios
Jeena,P.M., Ayannusi,O.E., Annamalai,K., Naidoo,P., Coovadia,H.M., Guldner,P., Risk factors for admission and the role of respiratory syncytial virus-specific cytotoxic T-lymphocyte responses in children with acute bronchiolitis, South African Medical Journal, Suid-Afrikaanse Tydskrif Vir Geneeskunde. 93, 291-294, 2003	Only p values of multivariate analysis are reported. Also, includes previous wheezers.
Jones,L.L., Hashim,A., McKeever,T., Cook,D.G., Britton,J., Leonardi-Bee,J., Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis, Respiratory Research, 12, 5-, 2011	Systematic review and meta-analyses which combines both adjusted and unadjusted odds ratios. Individual studies have been checked for inclusion.
Kristensen,K., Dahm,T., Frederiksen,P.S., Ibsen,J., Iyore,E., Jensen,A.M., Kjaer,B.B., Olofsson,K., Pedersen,P., Poulsen,S., Epidemiology of respiratory syncytial virus infection requiring hospitalization in East Denmark, Pediatric Infectious Disease Journal, 17, 996-1000, 1998	Study does not report adjusted odds ratios.
Lacaze-Masmonteil,T., Truffert,P., Pinquier,D., Daoud,P., Goldfarb,G., Vicaut,E., Fauroux,B., Lower respiratory tract illness and RSV prophylaxis in very premature infants, Archives of Disease in Childhood, 89, 562-567, 2004	Study does not report adjusted odds ratios
Lanari,M., Giovannini,M., Giuffre,L., Marini,A., Rondini,G., Rossi,G.A., Merolla,R., Zuccotti,G.V., Salvioli,G.P.,	All hospitalised

Study	Reason for Exclusion
Investigators,R.A.D.A., Study Group., Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity, Pediatric Pulmonology, 33, 458-465, 2002	
Lanari,M., Silvestri,M., Rossi,G.A., Respiratory syncytial virus risk factors in late preterm infants, Journal of Maternal-Fetal and Neonatal Medicine, 22, 102-107, 2009	Review article comparing the PICNIC, FLIP and Osservatorio VRS studies
Leung,T.F., Lam,D.S., Miu,T.Y., Hon,K.L., Chau,C.S., Ku,S.W., Lee,R.S., Chow,P.Y., Chiu,W.K., Ng,D.K., Hong Kong Society of Paediatric Respirology (HKSPR) RSV Concern Group., Epidemiology and risk factors for severe respiratory syncytial virus infections requiring pediatric intensive care admission in Hong Kong children, Infection, 42, 343-350, 2014	No data for risk factors of interest
Lloyd,P.C., May,L., Hoffman,D., Riegelman,R., Simonsen,L., The effect of birth month on the risk of respiratory syncytial virus hospitalization in the first year of life in the United States, Pediatric Infectious Disease Journal, 33, e135-e140, 2014	No risk factors of interest
Lowther,S.A., Shay,D.K., Holman,R.C., Clarke,M.J., Kaufman,S.F., Anderson,L.J., Bronchiolitis-associated hospitalizations among American Indian and Alaska Native children, Pediatric Infectious Disease Journal, 19, 11-17, 2000	Study does not report adjusted rate ratios
McConnochie,K.M., Roghmann,K.J., Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis, American Journal of Diseases of Children, 140, 806-812, 1986	This study is not looking at risk factors for 'severe' bronchiolitis
Meert,K., Heidemann,S., Abella,B., Sarnaik,A., Does prematurity alter the course of respiratory syncytial virus infection?, Critical Care Medicine, 18, 1357-1359, 1990	Study does not report adjusted odds ratios
Paes,B., Mitchell,I., Yi,H., Li,A., Lanctot,K.L., CARESS,Investigators, Hospitalization for respiratory syncytial virus illness in Down syndrome following prophylaxis with palivizumab, Pediatric Infectious Disease Journal, 33, e29-e33, 2014	No relevant data
Park,H.W., Lee,B.S., Kim,A.R., Yoon,H.S., Kim,B.I., Song,E.S., Kim,W.T., Lim,J., Kim,S., Jin,H.S., Byun,S., Chee,D.H., Kim,K.S., Epidemiology of respiratory syncytial virus infection in infants born at less than thirty-five weeks of gestational age, Pediatric Infectious Disease Journal, 31, e99-104, 2012	Only p values of multivariate analysis are reported.
Pineros,J.G., Baquero,H., Bastidas,J., Garcia,J., Ovalle,O., Patino,C.M., Restrepo,J.C., Respiratory syncytial virus infection as a cause of hospitalization in population under 1 year in	No relevant data in the form of adjusted odds ratios/relative risks

Study	Reason for Exclusion
Colombia, Jornal de Pediatria, 89, 544-548, 2013	
Reeve,C.A., Whitehall,J.S., Buettner,P.G., Norton,R., Reeve,D.M., Francis,F., Predicting respiratory syncytial virus hospitalisation in Australian children, Journal of Paediatrics and Child Health, 42, 248-252, 2006	No risk factors of interest
Resch,B., Manzoni,P., Lanari,M., Severe respiratory syncytial virus (RSV) infection in infants with neuromuscular diseases and immune deficiency syndromes. [53 refs], Paediatric Respiratory Reviews, 10, 148-153, 2009	Review article: individual studies checked for inclusion
Resch,B., Pasnocht,A., Gusenleitner,W., Muller,W., Rehospitalisations for respiratory disease and respiratory syncytial virus infection in preterm infants of 29-36 weeks gestational age, Journal of Infection, 50, 397-403, 2005	This study looks at rehospitalisations for respiratory illness -this includes a wide range of conditions such as upper RTIs, acute bronchitis, bronchiolitis, pneumonia and pertussis. Although the study does have a section on RSV related hospitalisation, it is unclear whether these are adjusted odds ratios.
Riccetto,A.G., Ribeiro,J.D., Silva,M.T., Almeida,R.S., Arns,C.W., Baracat,E.C., Respiratory syncytial virus (RSV) in infants hospitalized for acute lower respiratory tract disease: incidence and associated risks, Brazilian Journal of Infectious Diseases, 10, 357-361, 2006	Nothing to suggest the relative risks reported are adjusted. Also, includes previous wheezers.
Sankaran,K., Tan,B., Respiratory syncytial viral infections in infants of 33 to 35 completed weeks of gestation, Perinatology, 12, 112-116, 2011	Review article: individual studies checked for inclusion
Simoes,E.A., King,S.J., Lehr,M.V., Groothuis,J.R., Preterm twins and triplets. A high-risk group for severe respiratory syncytial virus infection, American Journal of Diseases of Children, 147, 303-306, 1993	This study looks at risk factors for bronchiolitis not severe bronchiolitis
Singleton,R., Karron,R.A., Kruse,D.G., Harrison,L.H., DeSmet,I.J., Davidson,N.M., Petersen,K.M., RSV-associated hospitalizations in Alaska Native infants, International Journal of Circumpolar Health, 57 Suppl 1, 255-259, 1998	No relevant data
Sommer,C., Resch,B., Simoes,E.A., Risk factors for severe respiratory syncytial virus lower respiratory tract infection, Open Microbiology Journal, 5, 144-154, 2011	Review article: individual studies checked for inclusion
Spencer,N., Logan,S., Scholey,S., Gentle,S., Deprivation and bronchiolitis, Archives of Disease in Childhood, 74, 50-52, 1996	Nothing to suggest odds ratio reported is an adjusted one.
Stensballe,L.G., An epidemiological study of respiratory syncytial virus associated hospitalizations in Denmark, Respiratory Research, 3 Suppl 1, S34-S39, 2002	Protocol for a study initiated in 2001
Szabo,S.M., Gooch,K.L., Bibby,M.M., Vo,P.G., Mitchell,I., Bradt,P., Levy,A.R., The risk of mortality among young children hospitalized for severe respiratory syncytial virus infection,	British Library unable to supply

Study	Reason for Exclusion
Paediatric Respiratory Reviews, 13 Suppl 2, S1-S8, 2013	
Tabarani,C.M., Bonville,C.A., Suryadevara,M., Branigan,P., Wang,D., Huang,D., Rosenberg,H.F., Domachowske,J.B., Novel inflammatory markers, clinical risk factors and virus type associated with severe respiratory syncytial virus infection, Pediatric Infectious Disease Journal, 32, e437-e442, 2013	Results are not presented in the form of adjusted odds ratios but p values
Tissing,W.J., van Steensel-Moll,H.A., Offringa,M., Risk factors for mechanical ventilation in respiratory syncytial virus infection, European Journal of Pediatrics, 152, 125-127, 1993	Multivariate analysis is not reported in the form of odds ratios but beta coefficients
Voets,S., van Berlaer,G., Hachimi-Idrissi,S., Clinical predictors of the severity of bronchiolitis, European Journal of Emergency Medicine, 13, 134-138, 2006	Nothing to suggest relative risks reported are adjusted ones - also no confidence intervals presented.
von Linstow,M.L., Hogh,M., Nordbo,S.A., Eugen-Olsen,J., Koch,A., Hogh,B., A community study of clinical traits and risk factors for human metapneumovirus and respiratory syncytial virus infection during the first year of life, European Journal of Pediatrics, 167, 1125-1133, 2008	Sample size of 11 subjects for risk factor analysis
Wang,E.E., Law,B.J., Stephens,D., Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection, Journal of Pediatrics, 126, 212-219, 1995	Age range of enrolled subjects was 6 days to 18.4 years therefore unlikely to be bronchiolitis. Also, subjects older than 2 years who had asthma only were excluded - unclear whether subjects with asthma plus other underlying conditions were hence included.
Weigl,J.A., Puppe,W., Schmitt,H.J., Incidence of respiratory syncytial virus-positive hospitalizations in Germany, European Journal of Clinical Microbiology and Infectious Diseases, 20, 452-459, 2001	No confidence intervals
Yorita,K.L., Holman,R.C., Steiner,C.A., Effler,P.V., Miyamura,J., Forbes,S., Anderson,L.J., Balaraman,V., Severe bronchiolitis and respiratory syncytial virus among young children in Hawaii, Pediatric Infectious Disease Journal, 26, 1081-1088, 2007	Descriptive and also includes children up to 4 years
Yusuf,S., Caviness,A.C., kunle-Ojo,A.O., Risk factors for admission in children with bronchiolitis from pediatric emergency department observation unit, Pediatric Emergency Care, 28, 1132-1135, 2012	Risk factors specified by GDG were not examined in the multivariate analysis
Zachariah,P., Ruttenber,M., Simoes,E.A., Down syndrome and hospitalizations due to respiratory syncytial virus: a population-based study, Journal of Pediatrics, 160, 827-831, 2012	Nothing to suggest odds ratios reported are adjusted

H.3 At the time of assessment, what clinical features predict deterioration?

Study	Reason for Exclusion
Blanken,M.O., Koffijberg,H., Nibbelke,E.E., Rovers,M.M., Bont,L., Dutch RSV,Neonatal Network, Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study, PLoS ONE, 8, e59161-, 2013	The study uses a prediction rule for hospitalization based on presence of risk factors (family atopy, birth period, breastfeeding, and siblings).
Bordley,W.C., Viswanathan,M., King,V.J., Sutton,S.F., Jackman,A.M., Sterling,L., Lohr,K.N., Diagnosis and Testing in Bronchiolitis: A Systematic Review, Archives of Pediatrics and Adolescent Medicine, 158, 119-126, 2004	Used for references
Brand,H.K., Ferwerda,G., Preijers,F., de,Groot R., Neeleman,C., Staal,F.J., Warris,A., Hermans,P.W., CD4+ T-cell counts and interleukin-8 and CCL-5 plasma concentrations discriminate disease severity in children with RSV infection, Pediatric Research, 73, 187-193, 2013	The study doesn't present adjusted ORs.
Brown,L., Reiley,D.G., Jeng,A., Green,S.M., Bronchiolitis: Can objective criteria predict eligibility for brief hospitalization?, CJEM Canadian Journal of Emergency Medical Care, 5, 239-244, 2003	Wrong comparison (no admission/severity, but LOS)
El-Radhi,A.S., Barry,W., Patel,S., Association of fever and severe clinical course in bronchiolitis, Archives of Disease in Childhood, 81, 231-234, 1999	Nothing to suggest the odds ratios reported in the study are adjusted odds ratios.
Evans,J., Marlais,M., Abrahamson,E., Clinical predictors of nasal continuous positive airway pressure requirement in acute bronchiolitis, Pediatric Pulmonology, 47, 381-385, 2012	The study doesn't present adjusted ORs.
Flores,P., Rebelo-de-Andrade,H., Goncalves,P., Guiomar,R., Carvalho,C., Sousa,E.N., Noronha,F.T., Palminha,J.M., Bronchiolitis caused by respiratory syncytial virus in an area of portugal: epidemiology, clinical features, and risk factors, European Journal of Clinical Microbiology and Infectious Diseases, 23, 39-45, 2004	Nothing to suggest the odds ratios reported in the study are adjusted odds ratios. Also includes subjects with previous history of wheeze.
Hall,C.B., Hall,W.J., Speers,D.M., Clinical and physiological manifestations of bronchiolitis and pneumonia. Outcome of respiratory syncytial virus, American Journal of Diseases of Children, 133, 798-802, 1979	Results not shown separately for children with bronchiolitis and pneumonia
Kneyber,M.C.J., Brandenburg,A.H., De,GrootR, Joosten,K.F.M., Rothbarth,P.H., Ott,A., Moll,H.A., Risk factors for respiratory syncytial virus associated apnoea, European Journal of Pediatrics, 157, 331-335, 1998	Results not reported separately for children with bronchiolitis
Laham,F.R., Trott,A.A., Bennett,B.L., Kozinetz,C.A., Jewell,A.M., Garofalo,R.P., Piedra,P.A., LDH concentration in nasal-wash	The study doen't report a clear definition of hypoxia and therefore results cannot be interpreted correctly.

Study	Reason for Exclusion
fluid as a biochemical predictor of bronchiolitis severity, Pediatrics, 125, e225-e233, 2010	
Lind,I., Gill,J.H., Calabretta,N., What are hospital admission criteria for infants with bronchiolitis?, Journal of Family Practice, 55, 67-69, 2006	Evidence summary (useful references)
Mai,T.V., Selby,A.M., Simpson,J.M., Isaacs,D., Use of simple clinical parameters to assess severity of bronchiolitis, Journal of Paediatrics and Child Health, 31, 465-468, 1995	Nothing to suggest the estimates reported in the study are adjusted.
Mansbach,J.M., Clinical features can help predict which infants with bronchiolitis will need hospital admission, Journal of Pediatrics, 160, 174-175, 2012	Commentary
Mansbach,J.M., Clark,S., Christopher,N.C., LoVecchio,F., Kunz,S., Acholonu,U., Camargo,C.A.,Jr., Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department, Pediatrics, 121, 680-688, 2008	The study reports clinical characteristics and presentation at ED according to disposition (admitted/discharged). However, they then say that among those who were sent home, 49% had worsening that led to hospital admission. Therefore, we cannot rely on initial assessment to identify predictors of admission. The authors also present analysis for criteria of discharge.
Marlais,M., Evans,J., Abrahamson,E., Clinical predictors of admission in infants with acute bronchiolitis, Archives of Disease in Childhood, 96, 648-652, 2011	The study reports unadjusted ORs only
Mella,C., Suarez-Arrabal,M.C., Lopez,S., Stephens,J., Fernandez,S., Hall,M.W., Ramilo,O., Mejias,A., Innate immune dysfunction is associated with enhanced disease severity in infants with severe respiratory syncytial virus bronchiolitis, Journal of Infectious Diseases, 207, 564-573, 2013	No definition provided for severity score
Mulholland,E.K., Olinsky,A., Shann,F.A., Clinical findings and severity of acute bronchiolitis, Lancet, 335, 1259-1261, 1990	Severity defined based on oxygen saturation (not right comparison)
Semple,M.G., Taylor-Robinson,D.C., Lane,S., Smyth,R.L., Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study, PLoS ONE [Electronic Resource], 6, e22425-, 2011	Nothing to suggest the odds ratios reported in the study are adjusted odds ratios.
Shaw,K.N., Bell,L.M., Sherman,N.H., Outpatient assessment of infants with bronchiolitis, American Journal of Diseases of Children, 145, 151-155, 1991	Vague definition of disease severity.
Voets,S., van,Berlaer G., Hachimi-Idrissi,S., Clinical predictors of the severity of bronchiolitis, European Journal of Emergency Medicine, 13, 134-138, 2006	The study presents unadjusted estimates only.

H.4 What are the indications for capillary blood gas testing?

Study	Reason for Exclusion
Mulholland,E.K., Olinsky,A., Shann,F.A., Clinical findings and severity of acute bronchiolitis, Lancet, 335, 1259-1261, 1990	Non-comparative study

Study	Reason for Exclusion
REYNOLDS,E.O., RECOVERY FROM BRONCHIOLITIS AS JUDGED BY ARTERIAL BLOOD GAS TENSION MEASUREMENTS, Journal of Pediatrics, 63, 1182-1184, 1963	No relevant data, study compares the arterial oxygen and carbon dioxide tensions of a group of 25 babies with bronchiolitis at the height of their illnesses with the levels found 14 days later.
Wohl,M.E., Present capacity to evaluate pulmonary function relevent to bronchiolitis. [15 refs], Pediatric Research, 11, 252-253, 1977	Review article - no relevant data

H.5 What are the indications for fluids and nutritional support?

Study	Reason for Exclusion
Kennedy,N., Flanagan,N., Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis?. [7 refs], Archives of Disease in Childhood, 90, 320-321, 2005	Review article: no relevant studies
Oakley,E., Babl,F., Borland,M., Acworth,J., Neutze,J., Prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis, Academic Emergency Medicine, 19, 710-711, 2012	Conference abstract
Paediatric Research in Emergency Department, Oakley,E., Babl,F.E., Acworth,J., Borland,M., Kreiser,D., Neutze,J., Theophilos,T., Donath,S., South,M., Davidson,A., A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol): the comparative rehydration in bronchiolitis study (CRIB), BMC Pediatrics, 10, 37-, 2010	Protocol of a study later published (Oakley 2013)

H.6 What are the criteria for a) referral to secondary care, b) hospital admission for observation or treatment, c) discharge from hospital?

Study	Reason for Exclusion
Brown,L., Reiley,D.G., Jeng,A., Green,S.M., Bronchiolitis: Can objective criteria predict eligibility for brief hospitalization?, CJEM Canadian Journal of Emergency Medical Care, 5, 239-244, 2003	Intervention and comparator based on length of hospital stay
Damore,D., Mansbach,J.M., Clark,S., Ramundo,M., Camargo,C.A.,Jr., Prospective multicenter bronchiolitis study: predicting intensive care unit admissions, Academic Emergency Medicine, 15, 887-894, 2008	Compare ICU admission to regular floor admission which is not specified in the protocol
Kemper,A.R., Kennedy,E.J., Dechert,R.E., Saint,S., Hospital readmission for bronchiolitis, Clinical Pediatrics, 44, 509-513, 2005	Only report the incidence rate for readmission, no outcomes can be extracted

Study	Reason for Exclusion
Lind,I., Gill,J.H., Calabretta,N., What are hospital admission criteria for infants with bronchiolitis?, Journal of Family Practice, 55, 67-69, 2006	Review risk factors for deterioration
Marlais,M., Evans,J., Abrahamson,E., Clinical predictors of admission in infants with acute bronchiolitis, Archives of Disease in Childhood, 96, 648-652, 2011	Unadjusted odds ratios
Norwood,A., Mansbach,J.M., Clark,S., Waseem,M., Camargo,C.A.,Jr., Prospective multicenter study of bronchiolitis: predictors of an unscheduled visit after discharge from the emergency department, Academic Emergency Medicine, 17, 376-382, 2010	Unadjusted odds ratios
Roback,M.G., Baskin,M.N., Failure of oxygen saturation and clinical assessment to predict which patients with bronchiolitis discharged from the emergency department will return requiring admission, Pediatric Emergency Care, 13, 9-11, 1997	Unable to calculate odds ratios from the data provided
Sandweiss,D.R., Corneli,H.M., Kadish,H.A., Barriers to discharge from a 24-hour observation unit for children with bronchiolitis, Pediatric Emergency Care, 26, 892-896, 2010	Outcomes reported cannot be used to calculate odds ratios
Voets,S., van,Berlaer G., Hachimi-Idrissi,S., Clinical predictors of the severity of bronchiolitis, European Journal of Emergency Medicine, 13, 134-138, 2006	Unadjusted odds ratios

H.7 When is pulse oximetry oxygen saturation (Sp_{O2}) monitoring indicated in bronchiolitis?

Study	Reason for Exclusion
Flett,K.B., Breslin,K., Braun,P.A., Hambidge,S.J., Outpatient course and complications associated with home oxygen therapy for mild bronchiolitis, Pediatrics, 133, 769-775, 2014	Pulse oximetry monitoring is not reported as a management preference and is not discussed in relation to the sub questions listed in the protocol.
Mallory,M.D., Shay,D.K., Garrett,J., Bordley,W.C., Bronchiolitis management preferences and the influence of pulse oximetry and respiratory rate on the decision to admit, Pediatrics, 111, e45-e51, 2003	Pulse oximetry monitoring is not reported as a management preference and is not discussed in relation to the sub questions listed in the protocol.
Maneker,A.J., Petrack,E.M., Krug,S.E., Contribution of routine pulse oximetry to evaluation and management of patients with respiratory illness in a pediatric emergency department, Annals of Emergency Medicine, 25, 36-40, 1995	All patients received pulse oximetry monitoring population considered included infants with asthma and pneumonia
Mulholland,E.K., Olinsky,A., Shann,F.A., Clinical findings and severity of acute bronchiolitis, Lancet, 335, 1259-1261, 1990	All patients received pulse oximetry on admission.
Pavon,D., Castro-Rodriguez,J.A., Rubilar,L., Girardi,G., Relation between pulse oximetry and clinical score in children with acute wheezing	All infants received pulse oximetry monitoring and authors studied both children with asthma and bronchiolitis.

Study	Reason for Exclusion
less than 24 months of age, Pediatric Pulmonology, 27, 423-427, 1999	
Rosen,L.M., Yamamoto,L.G., Wiebe,R.A., Pulse oximetry to identify a high-risk group of children with wheezing, American Journal of Emergency Medicine, 7, 567-570, 1989	Mixed patient population (asthma, pneumonia, bronchopulmonary dysplasia) and all infants received pulse oximetry monitoring.
Schroeder,A.R., Marmor,A.K., Pantell,R.H., Newman,T.B., Impact of pulse oximetry and oxygen therapy on length of stay in bronchiolitis hospitalizations, Archives of Pediatrics and Adolescent Medicine, 158, 527-530, 2004	All patients received continuous pulse oximetry.
Sritippayawan,S., Deerojanawong,J., Prapphal,N., Clinical score and arterial oxygen saturation in children with wheezing associated respiratory illness (WARI), Journal of the Medical Association of Thailand, 83, 1215-1222, 2000	Includes infants with LRTI and reactive airway disease all infants received pulse oximetry monitoring.
Yamamoto,L.G., Wiebe,R.A., Rosen,L.M., Ringwood,J.W., Uechi,C.M., Miller,N.C., Beardsly,E.S., Toshi,A.S., Sugimoto,S.P., MacPherson,K.A., Oxygen saturation changes during the pediatric emergency department treatment of wheezing, American Journal of Emergency Medicine, 10, 274-284, 1992	Mixed patient population (asthma, pneumonia, BPD).

H.8 What are the indications for chest radiography in bronchiolitis?

Study	Reason for Exclusion
Alford,B.A., Armstrong,P., Radiographic evaluation of the child who wheezes. [59 refs], Current Problems in Diagnostic Radiology, 12, 1-38, 1983	Experts opinion without critical appraisal of the literature.
Cao,Millicent Amy, Choy,Joleen P., Mohanakrishnan,Narayana Lakshmi, Bain,Roger F., van Driel,Mieke L., Chest radiographs for acute lower respiratory tract infections, Cochrane Database of Systematic Reviews, -, 2013	Population considered: adults and children who met the WHO case definition for Pneumonia.
Catalano,D., Sperandeo,M., Trovato,G., Re: Caiulo VA, Gargani L, Caiulo S, Fisicaro A, Moramarco F, Latini G, Picano E. Lung ultrasound in bronchiolitis: comparison with chest X-ray. Eur J Pediatr. 2011;170: 1427-33, European Journal of Pediatrics, 173, 405-, 2014	Commentary.
Coblentz,C.L., Babcook,C.J., Alton,D., Riley,B.J., Norman,G., Observer variation in detecting the radiologic features associated with bronchiolitis, Investigative Radiology, 26, 115-118, 1991	This study takes into account the inter and intra observer agreement in reading CXR.
Dawson,K.P., Mogridge,N., Acute bronchiolitis: a three year study, New Zealand Medical Journal, 102, 528-529, 1989	This study was requested and used to get more baseline information about patients included by Dawson et al.
Ecochard-Dugelay,E., Beliah,M., Perreaux,F., de,Laveaucoupet J., Bouyer,J., Epaud,R., Labrune,P., Ducou-Lepointe,H., Gajdos,V.,	All children received CXR and the study doesn't report data for outcomes highlighted in the review protocol.

Study	Reason for Exclusion
Clinical predictors of radiographic abnormalities among infants with bronchiolitis in a paediatric emergency department, BMC Pediatrics, 14, 143-, 2014	
Farah,M.M., Padgett,L.B., McLario,D.J., Sullivan,K.M., Simon,H.K., First-time wheezing in infants during respiratory syncytial virus season: chest radiograph findings, Pediatric Emergency Care, 18, 333-336, 2002	Descriptive study, no comparison made.
Friis,B., Eiken,M., Hornsleth,A., Jensen,A., Chest X-ray appearances in pneumonia and bronchiolitis. Correlation to virological diagnosis and secretory bacterial findings, Acta Paediatrica Scandinavica, 79, 219-225, 1990	Some of the children participating to the study conformed to the diagnosis of acute bronchiolitis; however the paper does not report results separately for children with bronchiolitis so conclusions cannot be drawn.
Kneyber,M.C., Moons,K.G., de,Groot R., Moll,H.A., Predictors of a normal chest x-ray in respiratory syncytial virus infection, Pediatric Pulmonology, 31, 277-283, 2001	This study considers infants with RSV infection, but it doesn't mention bronchiolitis nor it reports results for children with bronchiolitis.
McMillan,J.A., Tristram,D.A., Weiner,L.B., Higgins,A.P., Sandstrom,C., Brandon,R., Prediction of the duration of hospitalization in patients with respiratory syncytial virus infection: use of clinical parameters, Pediatrics, 81, 22-26, 1988	Population includes children with laboratory documented RSV infection. There is no mention of bronchiolitis in this study.
Nasr,S.Z., Strouse,P.J., Soskolne,E., Maxvold,N.J., Garver,K.A., Rubin,B.K., Moler,F.W., Efficacy of recombinant human deoxyribonuclease I in the hospital management of respiratory syncytial virus bronchiolitis, Chest, 120, 203-208, 2001	CXR findings were not used to assess disease severity or to determine management of the illness.
Roback,M.G., Dreitlein,D.A., Chest radiograph in the evaluation of first time wheezing episodes: review of current clinical practice and efficacy, Pediatric Emergency Care, 14, 181-184, 1998	Population included children with asthma and children with pneumonia.
Schuh,S., Lalani,A., Allen,U., Manson,D., Babyn,P., Stephens,D., MacPhee,S., Mokanski,M., Khaikin,S., Dick,P., Evaluation of the utility of radiography in acute bronchiolitis, Journal of Pediatrics, 150, 429-433, 2007	This study uses the same study participants as Yong et al. without adding useful results. In data extraction, information from this study have been linked to the paper by Yong.
Swingler,GH, Radiologic differentiation between bacterial and viral lower respiratory infection in children: a systematic literature review, Clinical Pediatrics, 39, 627-33, 2000	The study considers children with LRTI and data are not reported separately for children with bronchiolitis.
Williams,C., Bartram,T., Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 4: Chest x-rays in bronchiolitis, Emergency Medicine Journal, 29, 514-515, 2012	Report; used for references.
Wilmott,R.W., Do we need chest radiographs in infants with uncomplicated bronchiolitis?, Journal of Pediatrics, 150, A2-, 2007	Commentary

H.9 What is the efficacy of chest physiotherapy in the management of bronchiolitis?

Study	Reason for Exclusion
Belcastro,M.R., Backes,C.R., Chila,A.G., Bronchiolitis: A pilot study of osteopathic manipulative treatment, bronchodilators, and other therapy, Journal of the American Osteopathic Association, 83, 672-676, 1984	Study design does not meet the protocol (non randomised).
Figuls,Marta, GineGarriga,Maria, Granados Rugeles,Claudia, Perrotta,Carla, Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old, Cochrane Database of Systematic Reviews, -, 2012	Update, only used to check references.
Frasson,T., Nascimento,G., Frasson,F., Rossi,M., Rodrigues,A., Goncalves,W., Abreu,G., Increase in induced expiratory flow reduces peripheral hypoxemia in children with acute bronchiolitis, Pediatric Critical Care Medicine, 13, 618-, 2012	We haven't been able to find any full text articles with similar titles and the same author (probably the full text hasn't been published yet).
Postiaux,G., Hankard,R., Saulnier,J.P., Karolewicz,S., Benielli,J., Le,Dinahet T., Louis,J., Chest physical therapy in infant acute viral bronchiolitis: should we really surrender?, Archives de Pediatrie, 21, 452-453, 2014	Commentary.
Postiaux,G., Louis,J., Gerroldt,J., Kotik,A.-C., Lemuhot,A., Patte,C., Effects of a new chest physiotherapy protocol in infant RSV bronchiolitis, a RCT [Abstract], European Respiratory Society Annual Congress, Berlin, Germany, October 4-8, [E1772]p. 2008., -	No full text available was found for this abstract.
Postiaux,G., Zwaenepoel,B., Louis,J., Chest physical therapy in acute viral bronchiolitis: an updated review, Respiratory Care, 58, 1541-1545, 2013	Summary.
Pupin,M.K., Riccetto,A.G., Ribeiro,J.D., Baracat,E.C., Comparison of the effects that two different respiratory physical therapy techniques have on cardiorespiratory parameters in infants with acute viral bronchiolitis, Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia, 35, 860-867, 2009	Study design does not meet the protocol (non randomised).
Rochat,I., Leis,P., Bouchardy,M., Oberli,C., Sourial,H., Friedli-Burri,M., Perneger,T., Argiroffo,C.B., Erratum: Chest physiotherapy using passive expiratory techniques does not reduce bronchiolitis severity: A randomised controlled trial (European Journal of Pediatrics DOI: 10.1007/s00431-011-1562-y), European Journal of Pediatrics, 171, 603-, 2012	Letter (erratum).
Rochat,I., Leis,P., Bouchardy,M., Oberli,C., Sourial,H., Friedli-Burri,M., Pernegger,T., Argiroffo,C.B., Chest physiotherapy in bronchiolitis: A randomised trial assessing passive expiratory manoeuvres, Paediatric Respiratory Reviews, 11, S85-S86, 2010	Abstract only.

Study	Reason for Exclusion
Salyer,John, Bronchiolitis and the Respiratory Therapist: Some Convenient Truths, AARC Times, 35, 30-32, 2011	Expert's opinion.

H.10 What is the efficacy of antibiotic treatment?

Study	Reason for Exclusion
McCallum,G.B., Morris,P.S., Chang,A.B., Antibiotics for persistent cough or wheeze following acute bronchiolitis in children, Cochrane Database of Systematic Reviews, 12, CD009834-, 2012	Not antibiotics for treatment of acute bronchiolitis but chronic cough following bronchiolitis

H.11 What is the efficacy of inhaled bronchodilator therapy?

Study	Reason for Exclusion
Alario,A.J., Lewander,W.J., Dennehy,P., Seifer,R., Mansell,A.L., The efficacy of nebulized metaproterenol in wheezing infants and young children, American Journal of Diseases of Children, 146, 412-418, 1992	Included patients with asthma, wheezing or bronchiolitis (no distinction made)
Barlas,C., Kiper,N., Gocmen,A., Ozcelik,U., Dilber,E., Anadol,D., Ustacelebi,S., Haliloglu,M., Racemic adrenaline and other treatment regimens in mild and moderate bronchiolitis: <ORIGINAL> HAFIF VE ORTA SIDDETTEKI BRONSIOLIT VAKALARINDA RASEMIK ADRENALIN VE DIGER TEDAVI YONTEMLERININ KARSILASTIRILMASI, Cocuk Sagligi Ve Hastaliklari Dergisi, 41, 155-165, 1998	Mist tent used as placebo
bul-Ainine,A., Luyt,D., Short term effects of adrenaline in bronchiolitis: a randomised controlled trial, Archives of Disease in Childhood, 86, 276-279, 2002	Data in article has been presented in graphs (numbers not reported).
Emmett,G.A., Bronchodilators for bronchiolitis-should they be used routinely?: ..reducing waste in child health one intervention at a time Eco-Paediatrics, Evidence-Based Child Health, 9, 301-302, 2014	Commentary
Everard,Mark, Bara,Anna, Kurian,Matthew, N'Diaye,Tracy, Ducharme,Francine, Mayowe,Varaidzo, Anticholinergic drugs for wheeze in children under the age of two years, Cochrane Database of Systematic Reviews, -, 2009	This study looks at wheezy infants, not bronchiolitis specifically
Fernandes,R.M., On-demand, not scheduled, nebulization (epinephrine or saline) improves important clinical outcomes in hospitalized infants with bronchiolitis, Journal of Pediatrics, 163, 1529-1530, 2013	Commentary

Study	Reason for Exclusion
Gadomski,Anne M., Brower,Melissa, Bronchodilators for bronchiolitis, Cochrane Database of Systematic Reviews, -, 2010	This cochrane review has grouped together all bronchodilators (other than epinephrine) and does not assess all outcomes specified by the GDG. However, data such as missing standard deviations and data for certain outcomes not available in individual studies has been extracted from here.
Gupta,N., Puliyel,A., Manchanda,A., Puliyel,J., Nebulized hypertonic-saline vs epinephrine for bronchiolitis; proof of concept study of cumulative sum (CUSUM) analysis, Indian Pediatrics, 49, 543-547, 2012	Comparator is hypertonic saline not placebo
Hartling,L., Fernandes,R.M., Bialy,L., Milne,A., Johnson,D., Plint,A., Klassen,T.P., Vandermeer,B., Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis, BMJ, 342, d1714-, 2011	Network meta-analysis
Hartling,Lisa, Bialy,Liza M., Vandermeer,Ben, Tjosvold,Lisa, Johnson,David W., Plint,Amy C., Klassen,Terry P., Patel,Hema, Fernandes,Ricardo M., Epinephrine for bronchiolitis, Cochrane Database of Systematic Reviews, -, 2011	This cochrane review does not assess all outcomes specifed by the GDG
Kadir,M.A., Mollah,A.H., Basak,R., Choudhury,A.M., Ahmed,S., Comparative efficacy of combined nebulized salbutamol with ipratropium bromide and nebulized adrenaline to treat children with acute bronchiolitis, Mymensingh Medical Journal: MMJ, 18, 208-214, 2009	No placebo group (group A combined nebulised salbutamol and ipratropium bromide, group B nebbulised L-adrenaline)
Kuyucu,S., Unal,S., Kuyucu,N., Yilgor,E., Additive effects of dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis, Pediatrics International, 46, 539-544, 2004	This study did not include a bronchodilator vs placebo comparison but a comparison relevant to the combined corticosteroids bronchodilator review
Levin,D.L., Garg,A., Hall,L.J., Slogic,S., Jarvis,J.D., Leiter,J.C., A prospective randomized controlled blinded study of three bronchodilators in infants with respiratory syncytial virus bronchiolitis on mechanical ventilation, Pediatric Critical Care Medicine, 9, 598-604, 2008	Population includes children with bronchiolitis requiring mechanical ventilation and admitted in ICU.
Mallol,J., Barrueto,L., Girardi,G., Munoz,R., Puppo,H., Ulloa,V., Toro,O., Quevedo,F., Use of nebulized bronchodilators in infants under 1 year of age: analysis of four forms of therapy, Pediatric Pulmonology, 3, 298-303, 1987	Patients admitted with acute wheezing. Made no distinction between bronchiolitis or asthma.
Okutan,V., Akin,R., Yanik,A., Ozcan,O., Gokcay,E., Effectiveness of nebulised adrenaline and salbutamol in the treatment of infants with bronchiolitis, Bulletin of Gulhane Military Medical Academy, 40, 199-204, 1998	British Library unable to supply
Sanchez,I., De,Koster J., Powell,R.E., Wolstein,R., Chernick,V., Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with	No placebo group, compared a crossover of inhaled racemic epinephrine with salbutamol

Study	Reason for Exclusion
bronchiolitis, Journal of Pediatrics, 122, 145-151, 1993	
Schweich,P.J., Hurt,T.L., Walkley,E.I., Mullen,N., Archibald,L.F., The use of nebulized albuterol in wheezing infants, Pediatric Emergency Care, 8, 184-188, 1992	Population is wheezing infants including recurrent wheezers. There is no mention of bronchiolitis in this study.
Tal,A., Bavilski,C., Yohai,D., Bearman,J.E., Gorodischer,R., Moses,S.W., Dexamethasone and salbutamol in the treatment of acute wheezing in infants, Pediatrics, 71, 13-18, 1983	Included bronchiolitis or asthma or WARI (no distinction made)
Wang,E.E., Milner,R., Allen,U., Maj,H., Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial, Archives of Disease in Childhood, 67, 289-293, 1992	Data is presented in graph format without accompanying numbers. Although data for certain outcomes is available in the cochrane review, this has been presented for all bronchodilators together rather than for each bronchodilator group
Study	Reason for Exclusion
McCallum,G.B., Morris,P.S., Chang,A.B., Antibiotics for persistent cough or wheeze following acute bronchiolitis in children, Cochrane Database of Systematic Reviews, 12, CD009834-, 2012	Not antibiotics for treatment of acute bronchiolitis but chronic cough following bronchiolitis

H.12 What is the efficacy of inhaled corticosteroid therapy?

Study	Reason for Exclusion
Alansari,K., Sakran,M., Davidson,B.L., Ibrahim,K., Alrefai,M., Zakaria,I., Oral dexamethasone for bronchiolitis: a randomized trial, Pediatrics, 132, e810-e816, 2013	Examines a combined therapy
AndersonJames,Sophie, Marchant,Julie M., Acworth,Jason P., Turner,Cathy, Chang,Anne B., Inhaled corticosteroids for subacute cough in children, Cochrane Database of Systematic Reviews, -, 2013	Not children with bronchiolitis
Barlas,C., Kiper,N., Gocmen,A., Ozcelik,U., Dilber,E., Anadol,D., Ustacelebi,S., Haliloglu,M., Racemic adrenaline and other treatment regimens in mild and moderate bronchiolitis: <ORIGINAL> HAFIF VE ORTA SIDDETTEKI BRONSIOLIT VAKALARINDA RASEMIK ADRENALIN VE DIGER TEDAVI YONTEMLERININ KARSILASTIRILMASI, Cocuk Sagligi Ve Hastaliklari Dergisi, 41, 155-165, 1998	Mist tent used as placebo
Hartling,L., Fernandes,R.M., Bialy,L., Milne,A., Johnson,D., Plint,A., Klassen,T.P., Vandermeer,B., Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis, BMJ, 342, d1714-, 2011	Network meta-analysis

H.13 What is the efficacy of systemic corticosteroid therapy?

Study	Reason for Exclusion
Alansari,K., Sakran,M., Davidson,B.L., Ibrahim,K., Alrefai,M., Zakaria,I., Oral dexamethasone for bronchiolitis: a randomized trial, Pediatrics, 132, e810-e816, 2013	Examines a combined therapy

Study	Reason for Exclusion
Barlas,C., Kiper,N., Gocmen,A., Ozcelik,U., Dilber,E., Anadol,D., Ustacelebi,S., Haliloglu,M., Racemic adrenaline and other treatment regimens in mild and moderate bronchiolitis: <ORIGINAL> HAFIF VE ORTA SIDDETTEKI BRONSIOLIT VAKALARINDA RASEMIK ADRENALIN VE DIGER TEDAVI YONTEMLERININ KARSILASTIRILMASI, Cocuk Sagligi Ve Hastaliklari Dergisi, 41, 155-165, 1998	Mist tent used as placeb
Bentur,L., Shoseyov,D., Feigenbaum,D., Gorichovsky,Y., Bibi,H., Dexamethasone inhalations in RSV bronchiolitis: a double-blind, placebo-controlled study, Acta Paediatrica, 94, 866-871, 2005	Inhaled therapy, not systemic
Ermers,M.J., Rovers,M.M., van Woensel,J.B., Kimpen,J.L., Bont,L.J., RSV Corticosteroid Study Group., The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial, BMJ, 338, b897-, 2009	Examines post-bronchiolitis wheeze
Garrison,M.M., Christakis,D.A., Harvey,E., Cummings,P., Davis,R.L., Systemic corticosteroids in infant bronchiolitis: A meta-analysis, Pediatrics, 105, E44-, 2000	Superseded by Cochrane review with search date of Jan 2013
Hartling,L., Fernandes,R.M., Bialy,L., Milne,A., Johnson,D., Plint,A., Klassen,T.P., Vandermeer,B., Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis, BMJ, 342, d1714-, 2011	Network meta-analysis
Mallol,J., Barrueto,L., Girardi,G., Toro,O., Bronchodilator effect of fenoterol and ipratropium bromide in infants with acute wheezing: use of MDI with a spacer device, Pediatric Pulmonology, 3, 352-356, 1987	Not specific to bronchiolitis.
Tal,A., Bavilski,C., Yohai,D., Bearman,J.E., Gorodischer,R., Moses,S.W., Dexamethasone and salbutamol in the treatment of acute wheezing in infants, Pediatrics, 71, 13-18, 1983	Include infants with recurrent wheeze and asthma

H.14 What is the efficacy of nebulised hypertonic saline?

Study	Reason for Exclusion
Ater,D., Shai,H., Bar,B.E., Fireman,N., Tasher,D., Dalal,I., Ballin,A., Mandelberg,A., Hypertonic saline and acute wheezing in preschool children, Pediatrics, 129, e1397-e1403, 2012	"Recruited 2 to 6 year old children to better exclude infants with RSV bronchiolitis"
Bueno,Campana M., Olivares,Ortiz J., Notario,Munoz C., Ruperez,Lucas M., Fernandez,Rincon A., Patino,Hernandez O., Calvo,Rey C., High flow therapy versus hypertonic saline in bronchiolitis: randomised controlled trial, Archives of Disease in Childhood, 99, 511-515, 2014	Wrong comparator.

Study	Reason for Exclusion
Canty,W.B., Colomb-Lippa,D., Using hypertonic saline to manage bronchiolitis in infants, Journal of the American Academy of Physician Assistants, 27, 45-49, 2014	Descriptive review.
Chen,Y-J., Lee,W-L., Wang,C-M., Chou,H-H., Nebulized hypertonic saline treatment reduces both rate and duration of hospitalization for acute bronchiolitis in infants: an updated meta-analysis (Provisional abstract), Pediatrics and Neonatology, Article in Press, 1-8, 2014	The Meta-analysis includes 11 RCTs and all of them have already been considered in our review.
Grewal,S., Klassen,T.P., The tale of 2 trials: disentangling contradictory evidence on hypertonic saline for acute bronchiolitis, JAMA Pediatrics, 168, 607-609, 2014	Commentary.
Kim,H., Ater,D., Shai,H., Bar,B.E., Hypertonic saline and wheezing in preschool children, Journal of emergency medicine, 43, e379, 2012-, 2012	Abstract and comment on Ater et al., 2012 study
Mathew,J.L., Shivbalan,S., Sehgal,V., 7% Hypertonic saline in acute bronchiolitis: A Randomized Controlled Trial: Source citation: Jacobs JD, Foster M, Wan J, Pershad J. Pediatrics 2014;133:E8, Indian Pediatrics, 51, 221-222, 2014	Commentary.
Mitchell,M.D., Schast,A.P., Umscheid,C.A., Nebulized hypertonic saline treatment for infants with bronchiolitis, Penn Medicine's Center for Evidence-based Practice, 2013	Review of existing guidelines.
Oymar,K., Skjerven,H.O., Mikalsen,I.B., Acute bronchiolitis in infants, a review, Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 22, 23-, 2014	Wrong comparator.
Ralston,S., Repeated dosing of nebulised 5% saline improves respiratory scores in inpatients with mild to moderate bronchiolitis at 48 h, Evidence-Based Medicine, 16, 82-83, 2011	Comment on Al-Ansari et al., 2010 study

H.15 What is the efficacy of heliox?

Study	Reason for Exclusion
Braun Filho,L.R., Amantea,S.L., Becker,A., Vitola,L., Marta,V.F., Krumenauer,R., Use of helium-oxygen mixture (Heliox) in the treatment of obstructive lower airway disease in a pediatric emergency department, Jornal de Pediatria, 86, 424-428, 2010	Included 2 months to 12 years with diagnoses of asthmatic crisis or viral bronchiolitis
Kneyber,M.C., van,Heerde M., Twisk,J.W., Plotz,F.B., Markhors,D.G., Heliox reduces respiratory system resistance in respiratory syncytial virus induced respiratory failure, Critical Care (London, England), 13, R71-, 2009	Mechanically ventilated
Martinon-Torres,F., Rodriguez-Nunez,A., Martinon-Sanchez,J.M., Heliox therapy in infants with acute bronchiolitis, Pediatrics, 109, 68-73, 2002	Not blinded or randomised

Study	Reason for Exclusion
Moraa,Irene, Sturman,Nancy, McGuire,Treasure, van Driel,Mieke L., Heliox for croup in children, Cochrane Database of Systematic Reviews, -, 2013	Children with croup (no mention to bronchiolitis).
Petrocheilou,A., Tanou,K., Kalampouka,E., Malakasioti,G., Giannios,C., Kaditis,A.G., Viral croup: Diagnosis and a treatment algorithm, Pediatric Pulmonology, 49, 421-429, 2014	Not relevant to population indicated by the protocol.
Verma,N., Lodha,R., Kabra,S.K., Recent advances in management of bronchiolitis, Indian Pediatrics, 50, 939-949, 2013	Descriptive review.

H.16 What is the efficacy of combined bronchodilator and corticosteroid therapy?

Study	Reason for Exclusion
Ahronheim,S., Combination therapy with epinephrine and dexamethasone for bronchiolitis, Canadian Journal of Emergency Medicine, 12, 443-445, 2010	Commentary of Plint et al, 2009
Chao,L.C., Lin,Y.Z., Wu,W.F., Huang,F.Y., Efficacy of nebulized budesonide in hospitalized infants and children younger than 24 months with bronchiolitis, Acta Paediatrica Taiwanica, 44, 332-335, 2003	This study included children with acute wheezing, bronchiolitis or asthma. Bronchiolitis was not defined and no attempt was made to distinguish between bronchiolitis and infantile asthma.
Corneli,H.M., Zorc,J.J., Mahajan,P., Shaw,K.N., Holubkov,R., Reeves,S.D., Ruddy,R.M., Malik,B., Nelson,K.A., Bregstein,J.S., Brown,K.M., Denenberg,M.N., Lillis,K.A., Cimpello,L.B., Tsung,J.W., Borgialli,D.A., Baskin,M.N., Teshome,G., Goldstein,M.A., Monroe,D., Dean,J.M., Kuppermann,N., Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network (PECARN), A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis.[Erratum appears in N Engl J Med. 2008 Oct 30;359(18):1972. Note: Majahan, Prashant [corrected to Mahajan, Prashant]], New England Journal of Medicine, 357, 331-339, 2007	This was not a combined therapy review - bronchildilator given at discretion of physician.
de,Boeck K., Van der,Aa N., Van,Lierde S., Corbeel,L., Eeckels,R., Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study, Journal of Pediatrics, 131, 919-921, 1997	Unclear whether outcomes of interest were measured before or after bronchodilator administration
Fernandes,R.M., Bialy,L.M., Vandermeer,B., Tjosvold,L., Plint,A.C., Patel,H., Johnson,D.W., Klassen,T.P., Hartling,L., Glucocorticoids for acute viral bronchiolitis in infants and young children.[Update of Cochrane Database Syst Rev. 2010;(10):CD004878; PMID: 20927740], Cochrane Database of Systematic Reviews, 6, CD004878-, 2013	Not all comparisons/outcomes of interest have been examined in this Cochrane review: the individual studies within this Cochrane review have been checked for inclusion and analysed as necessary

Study	Reason for Exclusion
Fiandeiro,P.T., Epinephrine and dexamethasone reduce hospital admission in children with bronchiolitis, Thorax, 64, 975-, 2009	Summary of the study by Plint et al, 2009
Frohna,J.G., Frey,U., Combination of epinephrine and dexamethasone may reduce hospitalization in children with bronchiolitis, Journal of Pediatrics, 155, 761-762, 2009	Commentary of Plint et al, 2009
Hartling,L., Fernandes,R.M., Bialy,L., Milne,A., Johnson,D., Plint,A., Klassen,T.P., Vandermeer,B., Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis, BMJ, 342, d1714-, 2011	Network meta-analysis
Hartling,Lisa, Bialy,Liza M., Vandermeer,Ben, Tjosvold,Lisa, Johnson,David W., Plint,Amy C., Klassen,Terry P., Patel,Hema, Fernandes,Ricardo M., Epinephrine for bronchiolitis, Cochrane Database of Systematic Reviews, -, 2011	Not all comparisons/outcomes of interest have been examined in this Cochrane review: the individual studies within this Cochrane review have been checked for inclusion and analysed as necessary
Mallol,J., Barrueto,L., Girardi,G., Munoz,R., Puppo,H., Ulloa,V., Toro,O., Quevedo,F., Use of nebulized bronchodilators in infants under 1 year of age: analysis of four forms of therapy, Pediatric Pulmonology, 3, 298-303, 1987	The population includes children with acute wheezing, bronchiolitis or asthma. No distinction between bronchiolitis and asthma was made.
Springer,C., Bar-Yishay,E., Uwayyed,K., Avital,A., Vilozni,D., Godfrey,S., Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis, Pediatric Pulmonology, 9, 181-185, 1990	Study design - not randomised
Tal,A., Bavilski,C., Yohai,D., Bearman,J.E., Gorodischer,R., Moses,S.W., Dexamethasone and salbutamol in the treatment of acute wheezing in infants, Pediatrics, 71, 13-18, 1983	The study population includes subjects with bronchiolitis, asthma and recurrent wheezers
Teeratakulpisarn,J., Limwattananon,C., Tanupattarachai,S., Limwattananon,S., Teeratakulpisarn,S., Kosalaraksa,P., Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: a randomized, double-blind, placebo-controlled trial, Pediatric Pulmonology, 42, 433-439, 2007	Not a combined therapy review
Zhang,L., Ferruzzi,E., Bonfanti,T., Auler,M.I., D'avila,N.E., Faria,C.S., Costa,M.M., Long and short-term effect of prednisolone in hospitalized infants with acute bronchiolitis, Journal of Paediatrics and Child Health, 39, 548-551, 2003	Subjects were assigned to steroid plus standard care. Standard care was defined as oxygen therapy, fluid replacement and nebulised fenoterol as judged by the paediatrician. Therefore unclear whether all subjects received fenoterol and whether this can be considered as combination therapy.
Zuerlein,N., Portnoy,J., Efficacy of combined corticosteroid (CS) and beta-agonist (BA) therapy for treatment of bronchiolitis in infants, Annals of Allergy, Vol.64, pp.85, 1990., -, -32676	Abstract only

H.17 What is the efficacy of montelukast?

Study	Reason for Exclusion
Bisgaard,H., Flores-Nunez,A., Goh,A., Azimi,P., Halkas,A., Malice,M.P., Marchal,J.L., Dass,S.B., Reiss,T.F., Knorr,B.A., Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children, American Journal of Respiratory and Critical Care Medicine, 178, 854-860, 2008	Long-term post-viral symptoms
Bisgaard,H., Skoner,D., Boza,M.L., Tozzi,C.A., Newcomb,K., Reiss,T.F., Knorr,B., Noonan,G., Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. [18 refs], Pediatric Pulmonology, 44, 568-579, 2009	Safety in paediatric asthma patients.
Khoshoo,V., Ross,G., Edell,D., Effect of interventions during acute respiratory syncytial virus bronchiolitis on subsequent long term respiratory morbidity. [34 refs], Pediatric Infectious Disease Journal, 21, 468-472, 2002	Literature review across all treatments. Two studies on Montelukast - a case study and laboratory study.
Zou,Y., Zhang,J., Ma,C., Li,J., Zai,J., Guo,Y.S., Clinical efficacy of montelukast sodium in treating infantile wheezing, European Review for Medical and Pharmacological Sciences, 18, 775-780, 2014	Includes children without bronchiolitis.

H.18 What is the efficacy of oxygen supplementation (non-humidified, humidified and high-flow) and of CPAP?

Study	Reason for Exclusion
Beggs,Sean, Wong,Hame Zee, Kaul,Sheena, Ogden,Kathryn J., Walters,AE Julia, High-flow nasal cannula therapy for infants with bronchiolitis, Cochrane Database of Systematic Reviews, -, 2014	Review includes individual studies assessed for this review.
Bressan,S., Balzani,M., Krauss,B., Pettenazzo,A., Zanconato,S., Baraldi,E., High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: a pilot study, European Journal of Pediatrics, 172, 1649-1656, 2013	Non-comparative study.
Bueno,Campana M., Olivares,Ortiz J., Notario,Munoz C., Ruperez,Lucas M., Fernandez,Rincon A., Patino,Hernandez O., Calvo,Rey C., High flow therapy versus hypertonic saline in bronchiolitis: randomised controlled trial, Archives of Disease in Childhood, 99, 511-515, 2014	Comparison between HHHFNC and HS not relevant to the review protocol.
Donlan,M., Fontela,P.S., Puligandla,P.S., Use of continuous positive airway pressure (CPAP) in acute viral bronchiolitis: a systematic review, Pediatric Pulmonology, 46, 736-746, 2011	Descriptive review
Essouri,S., Laurent,M., Chevret,L., Durand,P., Ecochard,E., Gajdos,V., Devictor,D., Tissieres,P., Improved clinical and economic outcomes in severe bronchiolitis with pre-	Retrospective economic analysis.

Study	Reason for Exclusion
emptive nCPAP ventilatory strategy, Intensive Care Medicine, 40, 84-91, 2014	
Kallappa,C., Hufton,M., Millen,G., Ninan,T.K., Use of high flow nasal cannula oxygen (HFNCO) in infants with bronchiolitis on a paediatric ward: a 3-year experience, Archives of Disease in Childhood, 99, 790-791, 2014	No comparison specified. Children received HFNCO and clinical features were reported.
Martinon-Torres,F., Rodriguez-Nunez,A., Martinon-Sanchez,J.M., Nasal continuous positive airway pressure with heliox versus air oxygen in infants with acute bronchiolitis: a crossover study, Pediatrics, 121, e1190-e1195, 2008	Used a combined therapy so not able to identify effect of CPAP. Non-randomised study.
Metge,P., Grimaldi,C., Hassid,S., Thomachot,L., Loundou,A., Martin,C., Michel,F., Comparison of a high-flow humidified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: experience in a pediatric intensive care unit, European Journal of Pediatrics, 173, 953-958, 2014	Retrospective review of medical charts. Study found no difference in length of stay, RR, PCO2, FiO2, and duration of oxygen support.
Milesi,C., Baleine,J., Matecki,S., Durand,S., Combes,C., Novais,A.R., Cambonie,G., Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study.[Erratum appears in Intensive Care Med. 2013 Jun;39(6):1170 Note: Combonie, Gilles [corrected to Cambonie, Gilles]], Intensive Care Medicine, 39, 1088-1094, 2013	Non-comparative case-series
Oymar,K., Bardsen,K., Continuous positive airway pressure for bronchiolitis in a general paediatric ward; a feasibility study, BMC Pediatrics, 14, 122-, 2014	All children received CPAP.
Sood,R., Stolfi,A., Rowin,M., Use of high flow high humidity nasal cannula therapy for infants with bronchiolitis, Journal of Investigative Medicine, 60, 453-, 2012	Abstract based on interim analysis. Full trial will not be published until 2015.
Umoren,Rachel, Odey,Friday, Meremikwu,Martin M., Steam inhalation or humidified oxygen for acute bronchiolitis in children up to three years of age, Cochrane Database of Systematic Reviews, -, 2011	No studies identified on o2 supplementation.
Unger,S., Cunningham,S., Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis, Pediatrics, 121, 470-475, 2008	Non-comparative retrospective analysis. Suggests O2 supplementation increases length of stay

H.19 What is the efficacy of suction to remove secretions from the upper respiratory tract?

Study	Reason for Exclusion
de,CastroG, Remondini,R., dos,SantosA, do,PradoC, Analysis of symptoms, clinical signs and oxygen support in patients with bronchiolitis before and after chest physiotherapy during hospitalizationAnalise dos sintomas, sinais	Many airway clearance techniques applied, no relevant outcomes can be extracted

Study	Reason for Exclusion
clinicos e suporte de oxigenio em pacientes com bronquiolite antes e apos fisioterapia respiratoria durante a internacao hospitalar, Revista Paulista de Pediatria, 29, 599-605, 2011	
Gajdos,V., Katsahian,S., Beydon,N., Abadie,V., de,Pontual L., Larrar,S., Epaud,R., Chevallier,B., Bailleux,S., Mollet-Boudjemline,A., Bouyer,J., Chevret,S., Labrune,P., Effectiveness of chest physiotherapy in infants hospitalized with acute bronchiolitis: a multicenter, randomized, controlled trial, PLoS Medicine / Public Library of Science, 7, e1000345-, 2010	Both groups could receive nasal suction
Gomes,E.L.F.D., Postiaux,G., Medeiros,D.R.L., Monteiro,K.K.D.S., Sampaio,L.M.M., Costa,D., Chest physical therapy is effective in reducing the clinical score in bronchiolitis: Randomized controlled trialA fisioterapia respiratoria e eficaz na reducao de escore clinico na bronquiolite: Ensaio controlado randomizado, Revista Brasileira de Fisioterapia, 16, 241-247, 2012	All groups could receive upper airway suctioning during hospitalisation
Jarvis,K., Pirvu,D., Barbee,K., Berg,N., Meyer,M., Gaulke,L., Pate,B.M., Roberts,C., Change to a standardized airway clearance protocol for children with bronchiolitis leads to improved care, Journal of Pediatric Nursing, 29, 252-257, 2014	Examines protocol for suction rather than specific intervention.
Mussman,G.M., Parker,M.W., Statile,A., Sucharew,H., Brady,P.W., Suctioning and length of stay in infants hospitalized with bronchiolitis, JAMA Pediatrics, 167, 414-421, 2013	Retrospective study examining different levels of nasal suction. - Study does not examine children who received no nasal suction. - Study is unable to demonstrate nature of relationship between nasal suction and length of stay. - Study unavble to allow for clinical severity of children.
Unger,S., Cunningham,S., Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis, Pediatrics, 121, 470-475, 2008	Retrospective cohort observational study, no comparative data presented

Appendix I: Evidence tables

I.1 What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions?

Study details	Demographics & setting	Methods	Results	Limitations & comments
Full citation El-Radhi,A.S., Barry,W., Patel,S., Association of fever and severe clinical course in bronchiolitis, Archives of Disease in Childhood, 81, 231-234, 1999 Ref Id 206773 Country/ies where the study was carried out UK Source of funding Not stated Aim of the study Assess the extent of fever in bronchiolitis, whether the clinical course varies between febrile and afebrile infants with bronchiolitis, and whether fever in brochiolitis is beneficial or harmful. Study type Prospective cohort study	Characteristics 90 infants recruited 59 boys, 31 girls Mean age 4.4 months (SD 2.7, range 1 to 11.75 months) RSV present in 55 infants Inclusion criteria Infants aged over 1 month Diagnosis of bronchiolitis based on: presence of acute upper respiratory infection followed by acute onset of respiratory distress with cough, breathlessness, and wheeze, and clinical signs of chest overinflation, tachypnoea, rhonchi or crepitations occuring during winter epidemic of brochiolitis Only infants with their first episode of bronchiolitis. Exclusion criteria None stated	Methods Setting Single hospital Duration November 1997 to February 1998 Management All infants managed according to local hospital protocol Outcomes: Axillary temperature measured at admission and discharge. Fever defined as >38C Severity measured on McItiosh scale (infants who requird mechanical ventilation were classified as very severe, those who require oxygen supplementation as severe, and those who required admission for observation without oxygen requirement as mild) RSV measured based on nasopharyngel aspirates	Results Comparison of febrile and afrebile infants N = 28, 62 Age (months) 5.3 (1 - 10.25), 4.0 (1 - 11.75), p = 0.033 Clinical severity severe: 20, 18, p < 0.005 Radiograph abormal (segmental/lobar collapse/consolidation): 17, 9, p< 0.005 No deaths reported Body temperature in febrile infants: < 38C = 1 < 39C = 16 < 40C = 9 => 40 = 2	Limitations Bias assessed using NICE checklist for prognostic study - Analysis does not account for confounders Other information

Study details	Demographics & setting	Methods	Results	Limitations & comments
		Chest radiograph within 24 hours of admission Statistics: T-test or X2		
Full citation Swingler,G.H., Hussey,G.D., Zwarenstein,M., Duration of illness in ambulatory children diagnosed with bronchiolitis, Archives of Pediatrics and Adolescent Medicine, 154, 997-1000, 2000 Ref Id 208276 Country/ies where the study was carried out South Africa Source of funding Not stated Aim of the study To measure the duration of illness in ambulatory children diagnosed with bronchiolitis and to examine clinical predicators of duration of illness. Study type Prospective cohort based on a RCT population examinig chest radiography.	Characteristics Median (IQR) age, months = 6.0 (3.8 to 9.9) Gender male, % = 51.4% Median duration of symptoms before enrollment, days = 4 (2 to 6) Median (IQR) respiratory rate = 60 (54 to 63) Inclusion criteria Aged 2 to 23 months Clinical diagnosis of Bronchiolitis by a physician based on definition of: first contact with illness with cough plus tachypnea (based on WHO criteria) Exclusion criteria Poor drinking, chest indrawing, cyanosis, abnormal level of consciousness or stridor	Methods Baseline data collection Age, sex, respiratory rate. Setting Outpatients clinic at a children's hospital Follow-up Follow-up by twice weekly structured interviews via telephone or at clinic Follow-up for 28 days Lost to follow-up if no responses after 3 attempts Resolution based on parent assessment Statistical analysis X2 or Cox proportional hazards regression model	Results Enrollment 512 assessed 258 with Bronchiolitis 181 Follow-ups attempted 133 Follow-ups achieved Management Standard physician directed management for children with Bronchiolitis Results Outcomes defined by GDG: At what ages does bronchiolitis typical occur? What are the typical symptoms of bronchiolitis? What is the typical duration of symptoms? How due symptoms change during the course of a bronchiolitis episode? When do symptoms peak?	Limitations Based on NICE prognostic study quality checklist 1.1 Limited to mild Bronchiolitis. Study designed as an RCT 1.2 High loss to follow-up not explained (26.5%) or analysed Other information

Study details	Demographics & setting	Methods	Results	Limitations & comments
			Median duration of illness = 12 days (95% CI 11 to 14 days). 39% of children were still symptomatic after 14 days, 18% after 21 days and 9% after 28 days. (Graph showing duration of symptoms available)	
Full citation Petruzella,F.D., Gorelick,M.H., Duration of illness in infants with bronchiolitis evaluated in the emergency department, Pediatrics, 126, 285-290, 2010 Ref Id 207879 Country/ies where the study was carried out USA Source of funding Not stated Aim of the study To describe the duration of illness in infants with first-time Bronchiolitis who present to an emergency department and assess the burden of the illness on caregivers and families. Study type Prospective Cohort study	Characteristics Infants enrolled from November 2007 to March 2008. Age, median (IQR), months = 4 (3 to 7) Gender, % male = 59 Smoker living at home, % = 37 History of eczema = 13% Family history of atopy = 72% History of prematurity = 21% RSV+ = 74% RDAI score, median (IQR) = 5 (3 to 9) Discharged from ED, % = 67% Inclusion criteria 12 months or younger Clinical diagnosis of Bronchiolitis - tachypnea, crackles, wheezing and/or retractions and a history of previous upper airway infection (nasal congestion or rhinorrhea)	Methods Setting Emergency Dpeartment of Children's Hospital Sampling Convenience sample Baseline data collection Demographics - Age, gender, race and ethnicity Risk factors - prematurity, cardiac disease and pulmonary disease, atopy or family hisotry of asthma Duration based on asking "How many days ago did this illness start? Severity measured using RADI score Follow-up Weekly telephone interview on Days lost at work Symptom diary	Results Enrollment 112 enrolled. 9 excluded with pneumonia and 8 lost to follow-up. 95 available for analysis Results Outcomes defined by GDG: At what ages does bronchiolitis typical occur? What are the typical symptoms of bronchiolitis? What is the typical duration of symptoms? How due symptoms change during the course of a bronchiolitis episode? When do symptoms peak? Median time to resolution of symptoms 15 days	Limitations No limitations based on NICE prognostic study checklist Other information

Study details	Demographics & setting	Methods	Results	Limitations & comments
	Exclusion criteria Previous episode of wheezing or asthma Previous bronchodilator use Treatment with corticosteriods within 14 days of current illness Immunosuppression Imunodeficiency Diagnosis of croup or pneumonia by physician Caregiver about to understand and speak English	Outcomes Primary - time from onset to resolution of symptoms (free from cough for a 24-hour period) RSV status tested based on nasal swab Statistical analysis Descriptive statistics X2 used to compare characeteristics Sample size calculation Sample size calculation based on detecting illness duration with 95% CI < 1 day. Based on Swingler study this would be 50 infants.	25% of infants continued to be symptomatic at day 20 At end of follow-up period 11% of infants continued to be symptomatic (Graph showing duration of symptoms) (Further analysis based on risk-factors for length of stay, not reported as not specified for this question.)	
Full citation Thompson,M., Vodicka,T.A., Blair,P.S., Buckley,D.I., Heneghan,C., Hay,A.D., TARGET Programme Team., Duration of symptoms of respiratory tract infections in children: systematic review, BMJ, 347, f7027-, 2013 Ref Id 297669 Country/ies where the study was carried out	Characteristics Study examine a range of respiratory infections Inclusion criteria Various specific respiratory conditions and symptoms, including bronchiolitis. Definition not described. Exclusion criteria Chronic, recurrent or complicated infections, induced infections or	Methods Review methods Search on PubMed, DARE and CINAHL until July 2012 English lanaguage only Double data extraction Quality assessment based on Cochrane frameworks for RCTs and observational studies Pooled means and 95% confidence intervals	Results Included studies 4 bronchiolitis studies identified Patel, 2003 - RCT of 61 infants followed up until symptoms resolution. Median duration 8.4 days Plint, 2009 - RCT of 201 infants followed-up for 22 days. Median duration 13.3 days (IQR 8.2 to 19.5) Petruzella, 2010 - observational study of 95 infants followed-up unitl	Limitations Quality assessment using NICE checklist for systematic reviews None bias to report. Other information

Study details	Demographics & setting	Methods	Results	Limitations & comments
Review; analysis undertaken in USA and UK Source of funding NIRH grant Aim of the study To determine the expected duration of common respiratory tract infections in children in primary and emergency care. Study type Systematic review	conditions associated with a high risk of infection. Compared two active treatments or prophylatci or adjuvant treatment Retrospective study design		symptoms resolution. Median duration 15 days (IQR 11-20) Plint, 2004 - oberservational study of 163 infants followed-up for 3 weeks. Median duration 12 days (IQR 8 to 20) Pooled results Time for symptoms to resolve in 50% of infants was 13 days Time for symptoms to resolve in 90% of infants was 21 days (estimate)	
Full citation Tsolia,M.N., Kafetzis,D., Danelatou,K., Astral,H., Kallergi,K., Spyridis,P., Karpathios,T.E., Epidemiology of respiratory syncytial virus bronchiolitis in hospitalized infants in Greece, European Journal of Epidemiology, 18, 55-61, 2003 Ref Id 210627 Country/ies where the study was carried out Greece Source of funding Not stated Aim of the study	Characteristics 636 infants enrolled 473 tested for RSV 291 RSV+ and 182 RSV- Inclusion criteria Admitted to hospital Age 1 year ir less Diagnosis of bronchiolitis - three of the following: tachypnea (>50 resp/min), use of accessory respiratory muscles, prolonged expiration or wheezing, diffuse crackling rales and hyperinflation with ot without peribronchial thickening, atelectasis or infiltrates on X-ray. First epiosde of bronchiolitis Exclusion criteria	Methods Setting Two children's departments Ethical approval Informed consent and local ethics approval obtained Study dates February 1997 to June 2000 Data collection Chart review RSV diagnosed nasopharyngeal wash Statistical analysis Mann-Whitney test	Results Outcomes - What are the typical symptoms of bronchiolitis Symptom: RSC+ (n = 291), RSV- (n = 182) Tachypnea (=> 50 per min): 75.5%, 69.5% Retractions: 71%, 65% Crackles: 75%, 63% Fever: 30%, 25.5% Age (months) median: 2.8, 4.5 No data on the following outcomes - At what ages does bronchiolitis typical occur?	Limitations Quality assessment based on NICE checklist - Admission based on symptoms of Bronchiolitis - High proportion of eligible infants did not have RSV test - Reliability assessing outcomes not reported Other information

Study details	Demographics & setting	Methods	Results	Limitations & comments
The aim of this study was to examine the frequency, clinical characteristics, severity and impact of RSV infection on infants under 1 hospitalised with bronchiolitis. Study type Cohort study	Not stated	X2 or Fisher's exact test	- What is the typical duration of symptoms - How due symptoms change during the course of a bronchiolitis episodes - When do symptoms peak?	
Full citation Gajdos,V., Beydon,N., Bommenel,L., Pellegrino,B., de,Pontual L., Bailleux,S., Labrune,P., Bouyer,J., Inter-observer agreement between physicians, nurses, and respiratory therapists for respiratory clinical evaluation in bronchiolitis, Pediatric Pulmonology, 44, 754-762, 2009 Ref Id 206897 Country/ies where the study was carried out France Source of funding Not stated Aim of the study To assess the inter-observer agreement for evaluations to determine if clinical evaluation	Characteristics Age range 12 days to 15.5 months, median 2.1 months Inclusion criteria Children aged under 18 months admitted for bronchiolitis - defined as constellation of clinical symptoms and signs includng viral upper respiratory prodrome followed by respiratory effort and wheezing. Exclusion criteria None stated	Methods Setting Four children's hospitals Study dates September 2003 to January 2005 Assessment Assessment by medical doctors, nurses and respiratory therapists Using 4 point scale for respiratory rate, retraction signs and wheezing (maximum 12 points) Statistical analysis Weight kappa to measure concordance beyond chance.	Results What are the typical symptoms of bronchiolitis? Review of litearture Review of clinical scores for bronchiolitis identified 13 scores (including one developed by authors. Alll scores included measures of: 13 of 13 used respiratory rate 13 fo 13 used retraction signs 13 of 13 Wheezing 4 of 13 used general appearance 3 of 13 used cyanosis 7 of 13 used other measures, usually oxygen saturation 7 of 13 studies undertook validity testing on scores. Evaluation Authors score	Limitations Evaluation of bias based on NICE checklists - Diagnosis of bronchiolitis based on clinical signs - No gold standard test of bronchiolitis - Review of existing scores did not appear to be systematic Other information Information from review used to identify commonly used symptoms.

Study details	Demographics & setting	Methods	Results	Limitations & comments
was reliable for use in real life and trial settings Study type Diagnostic validation study of a clinical score			Based on 180 (360 pairs)evaluations had 93.1 agreement, weighted kappa 0.72 (0.66 to 0.78 - Respiatory rate 94.9 0.81 (0.72 to 0.91) - Retraction signs 93.1 0.77 (0.68 to 0.84) - Wheezing 91.3 0.73 (0.63 to 0.80) Data no presented on - At what ages does bronchiolitis typical occur? - What are the typical symptoms of bronchiolitis? - What is the typical duration of symptoms? - How due symptoms change during the course of a bronchiolitis episode? - When do symptoms peak?	
Full citation Mansbach,J.M., McAdam,A.J., Clark,S., Hain,P.D., Flood,R.G., Acholonu,U., Camargo,C.A.,Jr., Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department, Academic Emergency Medicine, 15, 111-118, 2008 Ref Id 210386	Characteristics Study conducted between December 2005 and March 2006 Demographics divided by virus causing bronchiolitis Characteristic: RSV only, RV only, RSV and RV, Other Age (months), median (IQR): 4.9 (2.4 to 9.4), 7.5 (3.4 to 10.8), 7.3 (5.1 to 11.7), 7.3 (4.2 to 10.5) Male (%): 59, 78, 64, 58	Methods Ethics approval Informed consent and local ethics approval Setting 14 emergency departments recruited over 2 to 3 weeks Patient management	Results Outcomes defined by GDG: At what ages does bronchiolitis typical occur? What are the typical symptoms of bronchiolitis? What is the typical duration of symptoms? How due symptoms change during the course of a bronchiolitis episode?	Limitations Quality assessment based on NICE prognostic study checklist Study population includes infants with previous wheeze

Study details	Demographics & setting	Methods	Results	Limitations & comments
Country/ies where the study was carried out USA Source of funding Thrasher Research Fund and MedImmune Grant Aim of the study Describe the epidemiology of the viruses causing bronchiolitis in the emergency department and whether there are distinguishing clinical characteristcis. Study type Prospective cohort	History of wheezing (%): 23, 52, 21, 33 Inclusion criteria Physician diagnosed bronchiolitis - defined based on AAP position papaer as "children with bronchiolitis typically have rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring" Children aged less than 2 years Acute tachypnea, retractions and abnormal breath sounds Exclusion criteria Pneuonia Previous enrollment	As prescribed by physician Virology testing nasopharyngeal samples sent for testing to identify virus Data collection Baseline and 2-week telephone follow-up Demographics, medical history, and treatment Statistical analysis Chi2, t-test and Kruskal-Wallis Rank Test Two tail p-value at 0.05 Cohort had 83% power to detect a 30% difference in history of wheeze between RSV and RV groups.	When do symptoms peak? Outcome: RSV only, RV only, RSV and RV, Other Relapse within 2-weeks (%):12, 8, 15, 13 Duration of symptoms (days)(from onset to 2 week follow-up): 8 (4 to 10), 3 (2 to 8), 6 (2 to 9), 8 (2 to 9) Presence of cough (%): 90, 92, 93, 91 Presence of wheeze (%): 73, 73, 79, 63	Duration of symptoms censored at 2 weeks Other information

I.2 What are the risk factors for severe bronchiolitis? (Adjusted OR studies only)

Study details	Participants	Factors	Results	Comments
Full citation Al-Shehri,M.A., Sadeq,A., Quli,K., Bronchiolitis in Abha, Southwest Saudi Arabia: viral etiology and predictors for hospital admission, West African Journal of Medicine, 24, 299-304, 2005	Cases A random sample of children aged ≤5 years old, suffering from bronchiolitis who were admitted to the pediatric ward at Assir Central Hospital from September 1997 to October 2001	Factors 1) Prematurity (not defined) 2) Congenital heart defects (not defined) 3) CLD (not defined) 4) History of exposure to smoking 5) Aged ≤1 year	Odds ratios Predictors of hospitalisation for infants with bronchiolitis from September 1997 to October 2001 Controls, n(%); cases, n(%); p value; Crude odds ratio (95% CI); adjusted* odds ratio (95% CI)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Exclusion criteria not reported

Study details	Participants	Factors	Results	Comments
Ref Id 206250 Country/ies where the study was carried out South west Saudi Arabia Study type Prospective, matched case-control Study dates Sample admitted to the pediatric ward from September 1997 to October 2001 Aim of the study To determine the viral etiology and predictors for hospital admission of children with bronchiolitis in Abba city Source of funding Not reported	n=51 Diagnostic criteria - Clinical features including bronchiolitis clinical score (based on accessory muscle and wheeze findings) were recorded at the time of presentation - Oxygen saturation was measured by pulse oximetry - Nasopharyngeal aspirate was obtained from each hospitalised child at the time of hospital admission for respiratory virus diagnosis - For virology study, all clinical specimens were analysed for verification of the presence of respiratory viruses Controls - Children aged ≤5 years, diagnosed clinically as having bronchiolitis in the emergency room but did not need admission at the time of diagnosis - Control subjects age and sex matched to case-patients n=115 Inclusion criteria	6) Breast feeding: exclusive breast milk, mixed breast and formula milk, never breast milk	1) Prematurity NR; NR; 4.97 (3.81 to 5.16); 3.44 (2.27 to 4.33) 2) Congenital heart defects NR; NR; 1.21 (1.10 to 2.32); 1.11 (0.85 to 1.95) 3) CLD NR; NR; 4.53 (2.42 to 5.46); 3.12 (2.19 to 3.78) 4) History of exposure to smoking 15(13); 19(37); p=0.01 4.18 (3.47 to 5.14); 2.51 (2.11 to 3.73) 5) Aged ≤1 year 57(49.5); 33(65); p=0.01 9.52 (7.86 to 10.74); 3.44 (2.27 to 4.33) 6) Breast feeding - Exclusive breast milk: 43(37); 4(7); p=0.01; 0.75 (0.46 to 1.24); 0.43 (0.22 to 1.13) - Mixed breast and formula milk: 6.45 (4.31 to 8.33); 4.15 (3.68 to 5.24) - Never breast milk: 8.05 (6.37 to 5.14); 2.51 (2.11 to 3.73) * Adjusted for prematurity, congenital heart defects, chronic lung diseases, atopic child, father, mother, parents, breastfeeding, history of exposure to smoking, age (one year or less)	- Unclear how the bronchiolitis clinical score was used to determine need for hospitalisation - Prematurity not defined Indirectness Does the study match the review protocol in terms of: Population: Yes, but included children ≤5 years of age Outcome: Yes Indirectness: Some Other information Setting Assir Central Hospital pediatric emergency room and pediatric ward Sample size calculation Not reported Outcome Bronchiolitis hospitalisation Data sources Not reported

Study details	Participants	Factors	Results	Comments
	See above (cases and controls section) Exclusion criteria Not reported Statistical method - Comparison of proportions was performed with the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables - Mann-Whitney test used to compare averages - To estimate which risk factors were independently related to hospital admission, the risk factors were included in multivariate forward stepwise logistic regression analysis Demographics Controls; cases; p value Male/female 65/50; 27/24; p=0.09 Age, months, mean±SD 8.8±3.9; 7.6±3.5; p=0.12 >1 sibling, n(%) 79(69); 38(74); p=0.68			

Study details	Participants	Factors	Results	Comments
	Low monthly income, n(%) 30(26); 13(25); p=0.57 Weight, kg, mean±SD 11.9±6.8; 12.6±5.5; p=0.34 Oxygen saturation, mean±SD 90.0±1.24; 86.4±4.7; p=0.001 Bronchiolitis clinical score, mean±SD 2.2±0.80; 4.5±1.5; p=0.01 Types of viruses, age and sex distribution of infants admitted with bronchiolitis, n(%) <6 months; 6-12 months; 12-24 months; total number - RSV: 15(75); 2(25); 1(6); 18(40) - Influenza virus A: 0; 1(13); 4(23); 5(11) - Influenza virus B: 1(5); 0; 2(12); 3(7) - Adenovirus: 4(20); 2(25); 4(24); 10(22) - Parainfluenza virus 1: 0; 0; 2(12); 2(4) - Parainfluenza virus 2: 0; 0; 1(6); 1(2) - Parainfluenza virus 3: 0; 3(37); 3(50); 6(14)			

Study details	Participants	Factors	Results	Comments
	- Total: 20(100); 8(100); 17(100); 45(100) Clinical course and hospital stay - 8 infants admitted to PICU, 7 of those were <6 months old - Of those admitted to PICU, RSV was isolated in 50% of these infants and 62% of these infants were exclusively on aritfical milk - 4 infants admitted to PICU needed mechanical ventilation and 3 of those were <3 months old - 82% of infants were discharged within 5 days of admission (95% CI: 80.92 to 83.47) - 9 infants stayed >7 days, 5 of those infants were infected with RSV and the remaining were infected with adenovirus, none of them was exclusively on breast milk Complications - 14 (27%) infants who were admitted developed complications: gastroenteritis (6), aspiration pneumonitis (5), sepsis (3)			

Study details	Participants	Factors	Results	Comments
	- One infant with aspiration pneumonitis, sepsis and pneumorthorax died			
Full citation Bockova,J., O'Brien,K.L., Oski,J., Croll,J., Reid,R., Weatherholtz,R.C., Santosham,M., Karron,R.A., Respiratory syncytial virus infection in Navajo and White Mountain Apache children, Pediatrics, 110, e20-, 2002 Ref Id 206403 Country/ies where the study was carried out Southwestern US Study type Prospective cohort Study dates Three RSV seasons (October 1 to March 31) from 1997 to 2000 Aim of the study To estimate RSV hospitalisation rates among Navajo and White Mountain Apache children younger than 2 years Source of funding	Cases - Children <2 years of age admitted with severe respiratory symptoms or apnea between October 1 and March 31 of 1997 through 2000 - Severity score ≥3 n=45 Diagnostic criteria - Nasopharyngeal aspirates were collected from all children who were hospitalised with an ALRI or apnea at the 4 participating hospitals to indicate RSV status - Nasopharyngeal aspirates were tested within 2 hours of collection using commercial RSV-specific enzyme immunoassay kits (Abbot test pack used from 1997 to 1999, Directigen test pack used from 1999 to 2000) Severity score - Published by McConnochie et al., 1990	Factors 1) Age <6 months 2) Prematurity (gestational age <36 weeks) 3) Gender (male)	Odds ratios Cases, n; controls, n 1) Age <6 months: 37; 337 2) Gestational age <36 weeks: 5; 58 3) Gender (male): 25; 418 Risk factors for severe RSV among Navajo and Apache children <2 years old hospitalised for RSV infection from 1997 to 2000 Crude odds ratio (95% CI); adjusted* odds ratio (95% CI) 1) Age <6 months 6.8 (3.1 to 17.0); 6.6 (3.0 to 14.4) 2) Prematurity 1.7 (0.5 to 4.5); 1.8 (0.7 to 5.1) 3) Gender (male) 1.2 (0.6 to 2.3); 1.2 (0.6 to 2.2) *Adjusted for age, prematurity, gender, underlying conditions (CHD, CLD of prematurity, reactive airway disease, 2 or more previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: - Included infants with apnea - Underlying conditions not reported separately for cases and controls - Study personnel were only avaliable to collect aspirates from 9 to 5 Monday to Friday, but infants presenting outside of this time had a test on the next business day Loss to follow-up: 876 of 913 eligible infants had chart reviews completed for assessment Indirectness Does the study match the review protocol in terms of: Population: Include Navajo and Apache children, children with mild respiratory symptoms or apnea Outcome: Yes Indirectness: Some

Study details	Participants	Factors	Results	Comments
Supported by Wyeth Lederle Vaccines	- 1 point each was assigned for apnea, pH <7.35, PC02 >45, oxygen saturation <87% and length of stay >5 days - 2 points were assigned for mechanical ventilation - Severity index for each subject was the sum of the points, the maximum score is 7 Controls - Children <2 years of age admitted with mild respiratory symptoms or apnea between October 1 and March 31 of 1997 through 2000 - Severity score <3 n=831 Inclusion criteria See above (cases and controls section) Exclusion criteria - 37 infants with RSV associated hospitalisation were excluded because they had incompete chart reviews to determine disease severity			Other information Setting 3 of the 5 Navajo hospitals and at the White Mountain Apache hospital Sample size calculation Not reported Outcome Severe RSV disease Data source Hospital-based surveillance Other Underlying conditions defined as having ≥1 of the following: CHD, CLD of prematurity, reactive airway disease, ≥2 previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency, this data has not been extracted because these conditions have been grouped together

Study details	Participants	Factors	Results	Comments
	Statistical method - Simple and multivariate logistic regression analyses were used to examine the risk factors for disease severity while controlling for other potential confounders - Calculate crude and adjusted odds ratios - Colinearity of the covariates assessed by using variance inflation factors fitting the child's medical record number as the response variable - Pearson's goodness-of-fit test was used to check the fit of the logistic model Demographics ALRI hospitalisations attributable to RSV infection: <2 years of age: 913(49.7%) <1 year of age: 642(48.6%) Infants who had been previously admitted for RSV associated ALRI: <2 years of age: 44(4.8%) <1 year of age: 18(2.8%) (Severity of disease and inclusion in analysis not described for these infants)			

Study details	Participants	Factors	Results	Comments
	Duration of hospital stay, days Ranged: 0 to 31 Mean (95% CI): 4.1 (3.8 to 4.3) Median: 3 % of cases with severe disease according to age, months <1: 16.3 1 to 2: 10.1 3 to 4: 7.9 5 to 6: 2.9 7 to 8: 1.3 9 to 10: 0 11 to 12: 3.8 13 to 23: 1.4 Underlying conditions - 23 required ventilatory support - 1 died - 63 were born <36 weeks gestation - 3 had CLD - 11 had CHD - 49 had reactive airway disease or ≥2 previous hospitalisations for respiratory infection - Cases: 1 - Controls: 62			

Study details	Participants	Factors	Results	Comments
Full citation Boyce,T.G., Mellen,B.G., Mitchel,E.F.,Jr., Wright,P.F., Griffin,M.R., Rates of hospitalization for respiratory syncytial virus infection among children in medicaid, Journal of Pediatrics, 137, 865-870, 2000 Ref Id 262376 Country/ies where the study was carried out USA Study type Retrospective cohort study Study dates July 1 1989 to June 30 1993 Aim of the study To determine rates of hospitalisation associated with RSV infection among children with and without specific medical conditions Source of funding Supported by a grant from the National Institute of	Cases Children were put into 4 mutually exclusive high-risk groups with the following priority: BPD, CHD, prematurity and all other conditions combined*. All other children were considered as low risk and served as the reference group. *Data for all other conditions combined has not been extracted as this was not of interest in the protocol of this review question Diagnostic criteria - Tennessee Medicaid data files from 1989 to 1993 include enrollment dates, demographic characteristics and medical services and are linked to birth certificates - All children were classifed into mutually exclusive groups with the use of birth certificate data and International classification of Diseases, 9th revision Controls	Factors 1) Bronchopulmonary dysplasia (BPD)* 2) Congenital heart disease (CHD)* 3) Prematurity: ≤28 weeks gestational age, 29 to <33 weeks gestational age, 33 to <36 weeks gestational age** 4) Male sex 5) White race *Not defined but identification based on the presence of specific ICD-9 codes found in Medicaid data files **If gestational age was missing from the birth certificate, (~15% of children), this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population	Odds ratios Adjusted incidence rate ratios of risk for RSV hospitalisation in the first year of life (95%CI) 1) BPD: 10.7 (8.4 to 13.6)* 2) CHD: 2.8 (2.3 to 3.3)* 3) Prematurity: ≤28 weeks gestational age: 2.4 (1.8 to 3.3), 29 to <33 weeks gestational age: 2.2 (1.8 to 2.7), 33 to <36 weeks gestational age: 1.8 (1.6 to 2.1)* 4) Male sex: 1.3 (1.2 to 1.4)* 5) White race: 1.3 (1.2 to 1.4)* *Raw data not reported, odds ratio adjusted for BPD, CHD, gestational age, number of siblings, presence of other conditions, male sex, white race, rural residence, maternal smoking and maternal education <12 years (other conditions identified included asthma, previous respiratory hospitalisation, cystic fibrosis, cancer, human immunodeficiency virus infection, immunodeficiency, use of chronic oral steroids, chronic renal disease, diabetes, congenital anomalies of the respiratory system, tracheoesophageal fistula, esophageal atresia and stenosis, neonatal respiratory	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Some risk factors (BPD, CHD) and outcome (RSV hospitalisation) based on reliability of coding systems - Gestational age missing for ~15% of children - if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population - Database contains information only on children enrolled in Medicaid therefore may not be generalisable - Exclusion criteria not reported Indirectness Does the study match the review protocol in terms of: Population: No, only children enrolled in Medicaid included Outcome: Yes Indirectness: Some Other information

Study details	Participants	Factors	Results	Comments
Allergy and Infectious Diseases	Children born at term with no underlying medical condition - the 'low risk' group Inclusion criteria - Children <3 years enrolled at birth in Tennessee Medicaid from July 1 1989 to June 30 1993 - Children hospitalised for an RSV infection remained in the study, allowing >1 hospitalisation per child - RSV season defined as occurring from November 1 through April 30 Exclusion criteria Not reported Statistical method - Incidence rates were calculated by dividing the number of RSV-associated hospitalisations per selected time period by the child-years during that period - Rates were then annualized to provide the estimated number of RSV associated hospitalisations per 1000 children - For each high risk group, incidence rate ratios were calculated by dividing the rate of RSV associated		distress syndrome and other respiratory conditions of the fetus and newborn).	Setting Hospitals Sample size calculation Not reported Outcome RSV hospitalisation* *Based on presence of ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis. Data sources Tennessee Medicaid data files (see diagnostic criteria section) Other information - Maternal smoking was also presented as a risk factor in this study - however this data has not been extracted as it unclear whether this is smoking during or after pregnancy (this review question was interested in family smoking which has been interpreted as household smoking not smoking during pregnancy) - There were 3553 RSV associated hospitalisations in the 80,037 child years during noninfluenza RSV season for an overall rate of 44.4

Study details	Participants	Factors	Results	Comments
	hospitalisation among children in that risk group by the corresponding rate among children at low risk - Adjusted incidence rate ratios were calculated with Stata version 5 with Poisson regression models Demographics Gender, % male 51 Ethnicity, % Black: 44 White: 56 Age <3 years			hospitalisations per 1000 child years during the first 3 years of life
Full citation Bulkow,L.R., Singleton,R.J., Karron,R.A., Harrison,L.H., Alaska RSV Study Group., Risk factors for severe respiratory syncytial virus infection among Alaska native children, Pediatrics, 109, 210-216, 2002 Ref Id 262400 Country/ies where the study was carried out Southwest Alaska Study type	Cases Acute respiratory infection in a child <3 years of age from the YK Delta and requiring admission to the YKDRH or an Anchorage hospital between October 1, 1993 and September 30, 1996, with a positive RSV nasopharyngeal culture or antigen test during hospitalisation n=204 Diagnostic criteria	Factors 1) Breast feeding (ever breastfed, ever breastfed more than half of feedings, breastfed within 2 week of age of admission, breastfed within 8 week of age of admission)	Odds ratios Cases, n(%); controls, n(%) 1) Breast feeding - Ever breastfed: 128(63); 272/337 (81) - Ever breastfed more than half of feedings: 103/195 (53); 245/327 (75) - Breastfed within 8 week of age of admission: 65(32); 171(51) Results of conditional multiple logisitic regression: risk factors for RSV hospitalisation among Alaska Native children <3 years of age from October 1, 1993 to September 30, 1996	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: 166 eligible case patients were not recruited (reasons given in cases section) Prognostic factor: Diagnose RSV, do not define bronchiolitis Statistical analysis: - 95% CIs not reported

Study details	Participants	Factors	Results	Comments
Retrospective, matched case-control Study dates 1st October 1993 to 30th September 1996 Aim of the study The incidence of hospitalisation for RSV infection among Alaska Native children is much higher than among non-Native populations in the US, this study was conducted to better understand factors associated with hospitalisation attributable to RSV infection in this high-risk population Source of funding Funded by grants from the Indian Health Serivce and Wyeth-Lederle Vaccines and Pediatrics and in-kind donation of RSV test pack kits from Abbott Laboratories	- Each nasopharyngeal aspirate was tested for RSV by rapid antigen enzyme immunoassay test pack or by direct flurescent antibody - The rest of each sample was snap frozen and transported to a virology laboratory where it was cultured for RSV - Virus isolates were identified by an indirect immunofluoresence assay - RSV culture-negative specimens were retested by rapid enzyme immunoassay test - Cord serum specimens were tested for RSV-neutralising antibody by complement-enchanced plaque-reduction neutralisation assay The severity of the case-patient's illness was classified by using a published severity index (McConnochie et al., 1990), this score ranges from 0 to 7 with a point each for oxygen saturation <87%, pH <7.35, Pc02 >45mmHg, apnea during hospital stay, and hospital stay >5 days, and 2 points for mechanical ventilation		Odds ratio* (p value) Complete data set n=542; age <6 months n=279; age ≥6 months n=263 1) Breastfeeding - Ever breastfed: -; - ; 0.25 (p=0.001) - Ever breastfed more than half of feedings: 0.38 (p=0.001); 0.33 (p=0.001); - - Breastfed within 8 week of admission age: 0.44 (p=0.004); - ; 0.27 (p=0.004) *Adjusted for high risk infants, ≥4 others aged <12 years in household, ≥2 persons/room in household	Outcome of interest: Report the odds ratio for a high risk infant (gestational age ≤36 weeks, chronic lung disease, heart disease, or other systemic medical condition that impaires respiratory function) but do not report these factors separately Indirectness Does the study match the review protocol in terms of: Population: No, study includes Alaska Native Children, the lifestyle of households in the study is primarily subsistence with a heavy reliance on local fishing and hunting Outcome: Yes Indirectness: None Other information Setting YK Delta regional Hospital (YKDRK) and 2 referral hospitals Sample size calculation Not reported Outcome RSV hospitalisation Data sources

Study details	Participants	Factors	Results	Comments
	Controls - Selected from a master list of YK Delta children, constructed from births at YKDRH or Anchorage hospitals and updated with children born in the villages - Could not have had an acute respiratory infection hospitalisation during the year of the case-patient's hospitalisation n=338 Matching - Attempted to match 2 control subjects to each case-patient using a caliper method, based on the case-patient's date of birth and village/region of residence - A list of possible control subjects was generated for each case-patient, moving outward in time in both directions from the case-patient's date of birth, but within the case-patient's village, for up to 30 days difference in birth date - If ≥2 eligible control subjects could not be identified within the village, infants from the same			YK Delta registry for high-risk infants with chronic medical conditions Other This study examines prematurity, CLD and heart disease, these have been grouped together as "high risk" infants and therefore not extracted

Study details	Participants	Factors	Results	Comments
	subregion were added beginning again at the case-patient's birth date and moving outward in both directions - Infants who were hospitalised for a respiratory infection during the study year before the case-patient's date of illness were deleted from the list and were not eligible to be control subjects - 74 (36.3%) case-patients were matched to 1 control subject, 126 (61.8%) to 2 control subjects and 4(2.0%) to 3 control subjects Inclusion criteria - Considered eligible for the study based only on their first RSV hospitalisation during that year - See above (cases and controls section) Exclusion criteria 61 of 431 hospitalisations were readmissions during the same RSV study year and were excluded 166 eligible case-patients were not recurited:			

Study details	Participants	Factors	Results	Comments
	- 13 had parents who were not approached or refused to participate - 4 moved from the study area - The remaining were not contacted because adequately matched control subjects could not be identified or because travel logisistics resulted in a long delay before recruitment could begin Statistical method - Cases and controls were compared by using conditional logistic regression - Matched bivariate analysis was done with a single predictor variable and multivariate analysis with multiple predictor variables - Conditional multivariate regression models were developed by using a forward stepwise approach - Any risk factor that was statsistically significant ($p<0.05$) in any of the bivariate subgroup analyses was considered for entry into the multivariate model - All p value reported are two-sided			

Study details	Participants	Factors	Results	Comments
	- No adjustments were made for multiple comparisons Demographics Case-patients included, n(%) - 6(2.9) who were mechanically ventilated - 9(4.4) who had apnea during their hospital stay - 28(13.7) with Pc02 >45mmHg - 31(15.2) with oxygen saturation <87% - 23(11.3) with pH <7.35 - 104(51.0) who were hospitalised for >5 days Male 108(53) Definite case 166(81) Severity* 0: 88(43) 1-2: 95(47) ≥3: 21(10) Age, months <2: 43(21) <6: 108(53) <12: 161(79) Pre-existing high risk conditions			

Study details	Participants	Factors	Results	Comments
	(% of case-patients or control subjects with specific condition of all case-patients or control subjects with any high-risk condition) Cases, n(%); controls, n(%) Prematurity (≤36 weeks' gestational age) - Required mechanical ventilation: 2(6); 0 - Required oxygen but not mechanical ventilation: 5(15); 3(38) - No oxygen or mechanical ventilation: 14(44); 4(50) - Total: 21(66); 7(88) Lung disease - Congenital lung disease requiring surgery or treatment: 3(9); 0 - Previous mechanical ventilation (other than for prematurity): 1(3); 0 - Total: 4(12); 0 Significant congenital or heart condition 6(19); 1(12) Other systematic condition (including Down syndrome, traumatic encephalopathy, congenital hypothyroidism			

Study details	Participants	Factors	Results	Comments
	and low birth weight at full-term) 4(12); 0 Overall total of pre-exisiting high risk conditions Cases 38 Controls 8 *Published by McConnochie et al., 1990, the score ranges from 0 to 7, with a point each for oxygen saturation <87%, pH <7.35, Pc02 >45mmHg, apnea during hospital stay, and hospital stay >5 days, and 2 points for mechanical ventilation			
Full citation Carbonell-Estrany,X., Quero,J., Bustos,G., Cotero,A., Domenech,E., Figueras-Aloy,J., Fraga,J.M., Garcia,L.G., Garcia-Alix,A., Del Rio,M.G., Krauel,X., Sastre,J.B., Narbona,E., Roques,V., Hernandez,S.S., Zapatero,M., Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a	Cases Children who were rehospitalised for RSV infection n=53 (118 rehospitalisations) Diagnostic criteria - Rapid antigen testing, by either enzyme-linked immunosorbent assay or immunofluorescence techniques, was used in 97% of cases in which investigation for RSV	Factors 1) Increasing gestational age 2) Chronic lung disease (infants who still required oxygen therapy at 36 weeks postconceptional age - premature infants)	Odds ratios Adjusted* odds ratios (95%CI) for RSV hospitalisation 1) Increasing gestational age: 0.85 (0.72 to 0.99), p<0.047 2) Chronic lung disease: 3.1 (1.22 to 7.91), p<0.016 Rehospitalisation RSV infection - 8/53 (15%), No rehospitalisation RSV infection - 27/509 (5.3%) *Adjusted for gestational age, birth weight, family history of asthma, clinical risk index for	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Identification of a causative pathogen was attempted in 89 (75.4%) of all hospital admissions; therefore not all subjects tested Indirectness Does the study match the review protocol in terms of:

Study details	Participants	Factors	Results	Comments
prospective study. IRIS Study Group, Pediatric Infectious Disease Journal, 19, 592-597, 2000 Ref Id 262435 Country/ies where the study was carried out Spain Study type Multicenter, prospective cohort study Study dates Children born between April 1 1998 to March 31 1999 Aim of the study To collect data on hospitalisation for RSV infections and presumptive risk factors for rehospitalisation among premature infants in Spain Source of funding Supported by an unrestricted grant of Abbott Laboratories	infection was performed - Viral cultures were performed as the only test in 3% of cases with positive RSV results Controls Children who were not rehospitalised for RSV infection* n= 584-53 = 541** *21 patients who had one admission without RSV identification have been excluded **Calculated by NCC-WCH technical team based on data reported in the article Inclusion criteria - Date of birth between April 1 1998 and March 31 1999 - ≤32 weeks of gestational age - Date of hospital discharge before April 1 1999 Exclusion criteria - Administration of prophylactic treatment: n=55 - Lost to follow-up: n=41 Statistical method - Incidence of RSV readmission was the result		babies, month of discharge, chronic lung disease and siblings at school age	Population: no, all premature infants <33 weeks Outcome: yes Indirectness: some Other information Setting Fourteen Spanish neonatal units Sample size calculation Not reported, however of 680 children enrolled, 96 excluded, 5 additional children died during the study (but only 1 related to RSV infection), leaving 584 evaluable patients Outcome RSV rehospitalisation Data sources The study included an initial visit in which demographic data, gestational age, birth weight, sex, race, family history of allergy, neonatal pathology, procedures and score of the clinical risk index for babies at 12 hours after birth were recorded. Infants were followed at monthly intervals throughout the respiratory season through either outpatient visits (40% of cases) or telephone calls (60% cases). In patients hospitalised

Study details	Participants	Factors	Results	Comments
	of applying the same percent of positive RSV test found in hospitalised patients in which RSV test was performed, to the whole hospitalised population - All variables in the univariate analysis that were significant at p<0.10 were included in a multivariate analysis with a logistic regression procedure and forward stepwise selection - Odds ratios and 95%CIs were calculated from beta coefficients and standard errors of the regression model Demographics Age at entry RSV season in days, median (IQR) 76 (37 to 137) Sex, number of cases (%) Boys: 301 (51.5) Girls: 283 (48.5) Birthweight in grams, mean (SD) 1408 (357) Gestational age, median (IQR) 30 (29 to 32) Ethnicity, n (%) Caucasian: 537 (91.9)			for acute respiratory illness, RSV testing, length of stay in hospital, admission to ICU, ICU length of stay, days on assisted ventilation and treatment modalities were either recorded prospectively (if admitted in the same study hospital) or collected retrospectively from the discharge summary if hospitalised elsewhere. Any omissions or questions arising from questionnaire information were discussed and verified with the treating physician. At the final follow up visit, potential risk factors for RSV infection were recorded.

Study details	Participants	Factors	Results	Comments
	Others: 47 (8.1) Multiple delivery, n (%) Yes: 180 (30.8) No: 404 (69.2) Chronic lung disease, n (%) 38 (6.5) Neonatal comorbidity, n (%) Respiratory: 326 (55.8) Cardiac (including PDA): 50 (8.5) Neurologic: 68 (11.6) Leukomalacia: Periventricular noncystic - 10 (1.7), Periventricular cystic - 14 (2.4) Haemorrhage Peri- and intraventricular - 29 (4.9) Cogenital malformations - 19 (3.2) Immunodeficiency - 6 (1) Others - 167 (28.6)			
Full citation Carbonell-Estrany,X., Quero,J., Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons, Pediatric Infectious Disease Journal, 20, 874-879, 2001 Ref Id 262436	Cases Subjects with rehospitalisation for RSV infection n= 207 Diagnostic criteria RSV testing was performed in 187 infants (90%), 118 of	Factors 1) Increasing gestational age 2) Age at entry RSV season 3) Tobacco smoke exposure	Odds ratios Adjusted odds ratio* (95%CI) for risk of rehospitalisation for RSV illness 1) Increasing gestational age: 0.87 (0.77 to 0.97); p=0.019 2) Age > 3 months at the start of the RSV season (versus age <3 months): 0.44 (0.25 to 0.77); p=0.004, Rehospitalisation: 24/309**, No rehospitalisation: 285/309**	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV

Study details	Participants	Factors	Results	Comments
Country/ies where the study was carried out Spain Study type Prospective cohort study Study dates April 1 1999 to April 31 2000 Aim of the study To collect data on hospitalisation rates for RSV illness during the season of 1999 to 2000 in nonprophylaxed premature infants ≤32 weeks gestational age in Spain and compare this with previously published data collected in the season of 1998 to 1999 Source of funding Supported by an unrestricted grant of Abbott Laboratories, Spain	whom were RSV positive (63%) Controls Subjects without rehospitalisation for RSV infection (no other details reported) n=999-207=792* *Calculated by NCC-WCH technical team Inclusion criteria - All premature infants born at ≤32 weeks gestational age, discharged from the neonatal intensive care unit - ≤6 months of age at the onset of the respiratory season in Spain (October) Exclusion criteria - Receiving one or more doses of palivizumab Statistical method - All variables in the univariate that were significant at P<0.10 were included in a multivariate analysis with a logistic regression procedure and forward stepwise selection - Odds ratios (95%CIs) were calculated from the beta		3) Tobacco smoke exposure (yes versus no): 1.63 (1.05 to 2.56); p= 0.031, Rehospitalisation: 45/87**, No rehospitalisation: 269/812** *Adjusted for gestational age, weight at birth, CRIB index, age at entry RSV season, month of discharge, smoke exposure, and siblings at school age **Numbers for multivariate analysis not reported so the raw numbers have been extracted from the univariate analysis	illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999) - 54/207 lost to follow up (26%) Indirectness Does the study match the review protocol in terms of: Population: no all premature infants Outcome: yes Indirectness: some Other information Setting 26 Spanish neonatal units Sample size calculation Not reported, 1206 infants were followed, 207 of these were excluded (54 lost to follow up, 153 received one or more doses of palivizumab), therefore a total of 999 subjects Outcome Unclear if RSV hospitalisation or rehospitalisation Data sources Parents of study subjects were contacted on a monthly basis to collect data on the incidence

Study details	Participants	Factors	Results	Comments
	coefficients and standard errors of the regression model Demographics 1999 season (n=584), 2000 season (n=999) Age at start of RSV season in days, median (interquartile range) 1999 season - 76 (37 to 137) 2000 season - 66 (41 to 115) p: NS Sex* 1999 season - Boys: 301 (51.5), Girls: 283 (48.5), p: NS 2000 season - Boys: 521 (52.1), Girls: 478 (47.8), p: NS *Values are number of cases (percent) unless otherwise stated Birthweight in grams, mean (SD) 1999 season - 1408 (357) 2000 season - 1440 (365) p: NS Gestational age, median (interquartile range) 1999 season: 30 (29 to 32)			of RSV infection throughout the respiratory season. 19% of these follow-up contacts were by clinic visits, 81% by telephone.

Study details	Participants	Factors	Results	Comments
	2000 season: 30 (29 to 32) p: NS Ethnic group, Caucasian 1999 season: 537 (91.9) 2000 season: 910 (92.9) p: NS Multiple delivery, n (%) yes 1999 season: 180 (30.8) 2000 season: 365 (37.4) p: 0.022 Chronic lung disease 1999 season: 38 (6.5) 2000 season: 38 (3.8) p: 0.03 Oxygen therapy in days, median (interquartile range) 1999 season: 5 (2 to 17) 2000 season: 5 (2 to 12) p: NS Mechanical ventilation in days, median (interquartile range) 1999 season: 3 (1 to 7) 2000 season: 3 (2 to 6) p: NS			
Full citation Chan,P., Goh,A., Respiratory syncytial virus infection in young Malaysian children, Singapore Medical Journal, 40, 336-340, 1999	Cases Moderate (5-8) or severe (9-12) RDAI score n=68	Factors 1) <3 months of age 2) Premature (<36 weeks gestation)	Odds ratios Multiple logistic regression analysis of independent risk factors associated with respiratory distress in 185 patients	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample:

Study details	Participants	Factors	Results	Comments
Ref Id 262478 Country/ies where the study was carried out Malasyia Study type Retrospective cohort Study dates Three year period between 1 January 1993 and 31 December 1995 Aim of the study To determine the clinical profile and risk factors for respiratory distress in young Malaysian children with RSV infection Source of funding Not reported	Diagnostic criteria - Nasopharyngeal secretion was collected from patients - RSV was identified by immunofluoresence, and/or viral culture - RDAI score based on: respiratory rate, use of accessory muscle, cyanosis and auscultation findings. Each patient's parameter was given a score based on the clinical status on admission and then added up, giving a RDAI score. Controls Mild RDAI score (0-4) n=117 Inclusion criteria - <24 months of age - RSV infection - Clinical features of LRTI: cough, tachypnoa, breathlessness, crepitations and rhonchi on auscultation Exclusion criteria Not reported Statistical method		Cases, n/N (%); Controls, n/N (%); odds ratio* (95% CI) 1) <3 months of age 21/68** (31%); 12/117** (10%); 4.5 (1.2 to 17.6) P value: 0.001 2) Premature (<36 weeks) NR; NR; 5.1 (1.0 to 25.0) P value: 0.02 *Adjusted for age <3 months, family history of asthma, underlying illness, prematurity **Calculated by NCC-WCH based on data reported in the article	- Unclear if cases include moderate and severe RDAI scores - Outcome of interest: The risk factors were not reported separately for underlying illnesses Indirectness Does the study match the review protocol in terms of: Population: Race/ethnicity include Malay, Chinese and Indian Outcome: Yes Indirectness: None Other information Setting University Hospital Kuala Lumpur Sample size calculation Not reported but 185 enrolled Outcome Respiratory distress due to RSV infection Data source Medical hospital records

Study details	Participants	Factors	Results	Comments
	- Significance tested with Student t-test or chi-squared test - Multiple logistic regression analysis with the elimination of confounding factors was used to study the various risk factors independently for association with moderate and severe respiratory distress as defined by RDAI score - Relative risk estimate described as an odds ratio Demographics - Malays made up 56% of the patients followed by Chinese (19%) and Indians (21%) - Using RDAI score, 117(63%) had mild distress and 53(29%) had moderate distress - All 15(8%) patients who had severe distress were admitted to PICU, of whom 12(80%) required assisted ventilation for respiratory failure - One 5-month old Indian child developed acute respiratory distress syndrome and had an underlying primary immunodeficiency died			

Study details	Participants	Factors	Results	Comments
	Duration of hospital stay, days Mean±SD: 7.0±5.0 Range: 2 to 30 Median: 5 n(%) of underlying illnesses in children with RSV infection (n=47) Prematurity (<36 weeks gestation): 19(40) CHD: 10(21) CLD: 3(6) Immunodeficiency: 2(4) Others including cerebal palsy, infantile spasm, spinal muscular atrophy, aplastic anaemia and Russel silver syndrom: 13(29)			
Full citation Chan,P.W., Lok,F.Y., Khatijah,S.B., Risk factors for hypoxemia and respiratory failure in respiratory syncytial virus bronchiolitis, Southeast Asian Journal of Tropical Medicine and Public Health, 33, 806-810, 2002 Ref Id 206532 Country/ies where the study was carried out Malaysia	Cases Aged <24 months with a clincal diagnosis of viral bronchiolitis with respiratory failure n=7 Diagnostic criteria - RSV isolated in the naso-pharyngeal secretion by immunofluorescence and/or viral culture - Severe RSV bronchiolitis requiring intubation and	Factors 1) Prematurity (<37 weeks gestation)	Odds ratios Multivariate logistic regression analysis of prematurity as a risk factor for the development of hypoxemia in RSV bronchiolitis No hypoxemia, n(%); hypoxemia, n(%); odds ratio* (95%CI); p value 1) Prematurity 14(7.6); 11(35.5); 1.17 (1.06 to 1.55); <0.01 Multivariate logistic regression analysis of prematurity as a risk factor for the development of respiratory failure in RSV	Limitations Based on NICE guidelines manual 2012 checklist: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: - Small sample size for cases, likely to be underpowered - Study dates and exclusion criteria not reported - Unclear what confounders were adjusted for in multivariate analysis

Study details	Participants	Factors	Results	Comments
Study type Retrospective cohort Study dates Not reported, reviewed the medical records of 216 children admitted consecutively who fulfilled the criteria Aim of the study To examine the incidence of, and identity the risk factors associated with, the development of hypoxemia and respiratory failure in RSV bronchiolitis Source of funding Not reported	positive pressure ventilation was considered as repiratory failure - Children admitted with bronchiolitis would have a routine oxygen saturation measurement, a measurement <90% in room air was used as the definition of hypoxemia Controls Aged <24 months with a clincal diagnosis of viral bronchiolitis without respiratory failure n=209 Inclusion criteria See above (cases and controls section) Exclusion criteria Not reported Statistical method - Children who were delivered at gestational age <37 weeks were considered as premature, in this category, the corrected age at admission was used for analysis - Univariate analysis was initally performed to examine		bronchiolitis No respiratory failure, n(%); respiratory failure, n(%); odds ratio* (95%CI); p value 1) Prematurity 21(10.0); 4(57.1); 1.14 (1.02 to 2.07); 0.02 *Unclear what factors were adjusted for	Indirectness Does the study match the review protocol in terms of: Population: Yes, but conducted in Malaysia where the ethnicity was Malay, Chinese or Indian Outcome: Yes, but hypoxemia is not specified in the protocol Indirectness: None Other information Setting University of Malaya Medical Centre - a university-affiliated hospital in Kuala Lumpur Sample size calculation Not reported Outcome - Respiratory failure from RSV bronchiolitis - Hypoxemia from RSV bronchiolitis Data source Medical records, no further details reported

Study details	Participants	Factors	Results	Comments
	risk factors associated with hypoxemia and respiratory failure in the study population using chi-squared or Fisher's Exact test - Multivariate logisitc regression analysis with backward stepwise process was done with variables identified by univariate analysis Demographics - Children whos weight was <3rd centile for age were considered as failing to thrive - Socioeconomic status was determined according to the UK Registrar's Classification of Occupational class ranks based on fathers' occupation and was divided into 5 categories (1= leading professional and business, 5= non-skilled) - 16 children had congenital heart disease of which none was an anatomically cyanotic cardiac lesion - None of the children were known to have an underlying chronic haemotological disorder - Hypoxemia was suffered by 31 (14.3%) children			

Study details	Participants	Factors	Results	Comments
	admitted with RSV bronchiolitis - 7 (3.2%) children developed repiratory failure due to RSV bronchiolitis			
Full citation Cilla,G., Sarasua,A., Montes,M., Arostegui,N., Vicente,D., Perez-Yarza,E., Perez-Trallero,E., Risk factors for hospitalization due to respiratory syncytial virus infection among infants in the Basque Country, Spain, Epidemiology and Infection, 134, 506-513, 2006 Ref Id 262533 Country/ies where the study was carried out Spain Study type Retrospective cohort Study dates Records of infants born between July 1996 and June 2000 Aim of the study To identify the % of infants with risk factors, the importance of these factors	Cases Infants <2 years of age hospitalised in the Hospital Donostia (Gipuzkoa, Basque Country) for virologically confirmed RSV infection N=357 infants representing 361 episodes of hospitalisation (4 infants hospitalised twice) Diagnostic criteria The presence of RSV in nasopharyngeal aspirate was investigated through a commercial enzyme immunoassay Controls General infant population composed of infants living >24 hours after delivery in the same period and geographical area N=13986 Inclusion criteria - Aged <2 years	Factors 1) Gestational age, weeks (<33, 33 to 35, 36 to 37, ≥38) 2) Haemodynamically unstable heart disease	Odds ratios Logistic regression (multivariate analysis) of risk factors for RSV hospitalisation among infants born in Gipuzkoa between July 1996 and June 2000 hospitalised for RSV infection in the first 2 years of life Cases, n(%); Controls, n(%); Odds ratio* (95% CI); p value 1) Gestational age <37 weeks (reference ≥37 weeks) NR; NR; 1.61 (1.07 to 2.42); p=0.022 2) Haemodynamically unstable heart disease 4 (1.1); 22 (0.2); 12.77 (3.89 to 41.89); p<0.001 *Adjusted for haemodynamically unstable heart disease, maternal age, period of birth, birth weight, gestational age and rural/urban residence	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Loss to follow-up: 2, 1, 10 and 10 observations lost in the series of hospitalisated infants in the variables: gestational age, birthweight, maternal age and residence respectively. 271 (75.9%) responded to the postal survey Study sample: - Number of controls not explained, assume to include all those that fit the criteria - No indication that controls have been tested for RSV Indirectness Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information

Study details	Participants	Factors	Results	Comments
in hospitalisation, and the foreseeable impact of current indications for palivizumab prophylaxis Source of funding No declarations of interest	- Born between July 1996 and June 2000 - Hospitalised in the Hospital Donostia for virologically confirmed, community-acquired RSV infection for >24 hours - Discharge diagnosis of acute respiratory infection Exclusion criteria - Nosocomial RSV infection - Those whose demographic data or data on the cause of hospitalisation were lacking (n=11) - Born or resident outside the catchment area Statistical method - Risk factors compared using chi-squared test or Fisher's exact test - Variables with a value of p<0.25 were included in the logistic regression model - Backward stepwise selection to determine independent associations between hospitalisation for RSV infection and the variables analysed Demographics Race			Setting Hospital Donostia (Gizpuzkoa) Sample size calculation Not reported Outcome RSV hospitalisation Data sources - General infant population obtained from the Basque Institute of Statistics - Records of infants with congenital heart disease and/or bronchopulmonary dysplasia were obtained from the registries of the Department of Pediatrics of the Hospital Donostia - Exposure to tabacco smoke and nursery school attendence was studied through a questionnaire sent by post in 2003

Study details	Participants	Factors	Results	Comments
	16 (4.5%) cases were from gypsy families, one was from Maghreb and the remaining were Caucasian Cardiac malformations - 8 (2.2%) cases had congenital cardiac malformations, three of these had required surgical treatment (one with atrioventricular septal defect in the context of Down syndrome, another with Di George syndrome and complex congenital heart disease and another with tetralogy of Fallot), a fourth was under medical treatment for atrioventricular septal defect pending clinical course and possible surgical correction, the four remaining infants had no haemogynamic compromise (artrial septal defect or patent ductus arteriosus) - 108 (0.8%) controls had congenital heart defects, of which 22 (0.2%) had haemodynamic compromise Underlying diseases - 8 controls were diagnosed with bronchopulmonary dysplasia			

Study details	Participants	Factors	Results	Comments
	- Cases: one had a congenital bronchial cyst requiring lobectomy, a second had laryngotracheomalacia, a third had severe neuromuscular disease due to mitochondrial myopathy and another had a thoracic neuroblastoma - None had diabetes mellitus or chronic renal disease Tabacco smoke - 30.3% of mothers regulary smoked during pregnancy, n: 82 cases and 271 controls - 26.8% of infants were exposed to smoke after birth because ≥1 parents smoked regulary at home, n: 154 cases and 271 controls Nursey school attendance 49 (18%) infants were attending nursery school when the first episode of hospitalisation for RSV infection occured Admitted to PICU - 23 (6.4%) infants were admitted to PICU - Of these, 19 were aged <3 months, 6 weighed <2500g at birth (two born <37 weeks gestation and one with			

Study details	Participants	Factors	Results	Comments
	bronchial cyst), one had a congenital heart disease with haemodynamic compromise, and the remaining 12 had no known risk factors Palivizumab 10(2.8%) infants had risk factors that made them suitable candidates for palivizumab prophylaxis according to the indications of the American Academy of Pediatrics (AAP)			
Full citation Damore,D., Mansbach,J.M., Clark,S., Ramundo,M., Camargo,C.A.,Jr., Prospective multicenter bronchiolitis study: predicting intensive care unit admissions, Academic Emergency Medicine, 15, 887-894, 2008 Ref Id 206669 Country/ies where the study was carried out USA Study type Prospective cohort Study dates	Cases Infants admitted to the ICU from the emergency department with a diagnosis of bronchiolitis n=50 Diagnostic criteria - AAP 2006 position statement says children with bronchiolitis typically have "rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring" - 98% of the children in this study (1423 of 1456) met the AAP definition of bronchiolitis and had a	Factors 1) Age <2 months	Odds ratios Odds ratio* (95% CI) for multivariate predictors of ICU admission compared to regular floor admission in infants <2 years of age with a clinical diagnosis of bronchiolitis during the study period 1) Age <2 months (vs ≥12 months) 4.14 (2.05 to 8.34) Cases: 27/50 (53%); Controls: 138/533 (26%); p<0.001 *Adjusted for ED visit during past week, moderate/severe retractins, oral intake (adequate, inadequate, unknown)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Outcome of interest: Concomitant medical disorders grouped together Indirectness Does the study match the review protocol in terms of: Population: Yes, but over half received Medicaid insurance and some infants have a history of wheezing (26% of cases and 27% of controls) - unclear whether this might be family history of wheezing

Study details	Participants	Factors	Results	Comments
Two consecutive bronchiolitis seasons (December to March), from 2004 to 2006 Aim of the study To identify predictors of ICU admission among children hospitalised with bronchiolitis for ≥24 hours Source of funding Funded by Thrasher Research Fund and unrestricted data analysis grant from Merck	respiratory rate greater than normal, current wheezing, current cough, or mild/moderate/severe retractions - Among the 2% (33) without any of these factors, 15% had an oxygen saturation <96%, or their air entry was not normal Controls Infants admitted to the regular floor for >24 hours with a diagnosis of bronchiolitis n=533 Inclusion criteria - Infants <2 years old - Attending physician diagnosis of bronchiolitis - Ability of the parent or guardian to give informed consent Exclusion criteria Previous enrollment Statistical method - The association of factors with ICU admission was examined using chi-squared tests, Student t test and Kruskal-Wallis rank tests			Outcome: Yes Indirectness: Some Other information Setting - 30 emergency departments - The number of children enrolled at each site ranged from 11 to 158, median 37, IQR 29 to 50 Sample size calculation Not reported Outcome Bronchiolitis ICU admission Data source - Standardised questionnaire consisted of an ED interview, ED chart review and 2-week follow-up telephone interview - All forms were reviewed by site principal investigators, who are physicians, before submission to the coordinating centre in Boston Other Concomitant medical disorder (introduction refers to chronic lung disease, congenital heart disease and immunocompromised conditions) also reported as a

Study details	Participants	Factors	Results	Comments
	- All p values are two tailed - Multivariate logistic regression was used to identify independent predictors of ICU admission - Factors associated with ICU admission at p<0.20 were evaluated for inclusion in the multivariate analysis - When the final model was identified factors that had not yet been retained in the model were reevaluated for inclusion - The final model was adjusted for clustering by site, but did not differ from the unadjusted model which is presented Demographics Controls, n(%); cases, n(%) n calculated by NCC-WCH Age, months 0-1.9: 138(26); 26.5(53) 2-3.9: 112(21); 6(12) 4-5.9: (14); (2) 6-7.9: (11); (7) 8-9.9: (7); (5) 10-11.9: (6); (2) ≥12 (reference): (15); (19) p=0.006 Male			risk factor, but the disorders are not reported separately

Study details	Participants	Factors	Results	Comments
	304(57); 29(58) p=0.98 Race/ethnicity White (reference): 218(41); 27(54) African American: 139(26); 9(18) Hispanic: 176(33); 14(28) p=0.28 Medicaid insurance 304(57); 30(59) Concomitant medical disorder 101(19); 13(26) p=0.35 Birth weight, pounds <3 (reference): (4); (2) 3-5: (7); (7) >5: (89); (90) p=0.87 Premature 69(13); 5(10) p=0.57 Breast-fed 288(54); 31.5(63) p=0.25			

Study details	Participants	Factors	Results	Comments
	Ever hospitalised 123(23); 8.5(17) p=0.38 Ever intubated 53(10); 2.5(5) p=0.24 Abnormal x-ray findings 362(68); 38(76) p=0.37 Viral test results RSV-positive: (41); (53) p=0.11 Influenza A positive: (2); (5) p=0.13 Influenza B positive: (0.2); (2) p=0.02 Adenovirus positive: (0.4); (0) p=0.69 Duration of symptoms ≥4 days 293(55); 20(40) p=0.048 History of wheezing 27(144); 26(13)			
Full citation	Cases	Factors	Odds ratios	Limitations

Study details	Participants	Factors	Results	Comments
Doering,G., Gusenleitner,W., Belohradsky,B.H., Burdach,S., Resch,B., Liese,J.G., The risk of respiratory syncytial virus-related hospitalizations in preterm infants of 29 to 35 weeks' gestational age, Pediatric Infectious Disease Journal, 25, 1188-1190, 2006 Ref Id 262649 Country/ies where the study was carried out Austria and Germany Study type Retrospective cohort Study dates The Munich RSV study cohort: November 1, 1998 to October 31, 1999. The Austrian RSV study cohort: June 1, 2001 to December 31, 2002. Aim of the study To evaluate risk factors for RSV hospitalisation in a large German-Austrian cohort of preterm children with a gestational age of 29 to 35 weeks	A cohort of 1236 preterm children with a gestational age of 29 to 35 weeks was formed by pooling the Munich RSV study cohort and the Austrian RSV study cohort n=1158 children remained in the pooled cohort as 78 were excluded because they received palivizumab. Diagnostic criteria - Definite RSV hospitalisation was assumed for all patients with an acute respiratory infection hospitalisation who had a positive RSV antigen test - Because RSV tests were not reguarly performed in all hospitals, an additional clinical case definition for RSV hospitalisation was used: children hospitalised between October and May with a clinical diagnosis of obstructive bronchitis, bronchiolitis, apnea or a diagnosis of pneumonia in the presence of wheezing were classifed as suffering from a probable RSV infection. Controls	1) Male gender 2) Neurologic disorder - the presence of 1 or more of the following diagnoses: intracranial hemorrhage (ICH), grade III or IV (periventricular hemorrhage), cystic periventricular leukomalacia (cPVL), cerebral infarction, hydrocephalus or other symptomatic neurologic conditions.	Adjusted* odds ratio (95% confidence interval) for the risk of RSV hospitalisation 1) Male gender: 2.8 (1.6 to 5.5), p<0.01 2) Neurologic problems: 3.6 (1.3 to 9.9), p=0.01 *Adjusted for male gender, neurologic problems, older sibling, discharge between october and december	Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Only 31 of 57 children had laboratory proven RSV hospitalisation. Among 26 of 57 children classified as probable RSV-H, 21 were not tested for RSV infection Indirectness Does the study match the review protocol in terms of: Population: No, all infants were preterm (29 to 35 weeks gestational age) and also an additional clinical case definition for RSV hospitalisation was used: children hospitalised between October and May with a clinical diagnosis of obstructive bronchitis, bronchiolitis, apnea or a diagnosis of pneumonia in the presence of wheezing were classifed as suffering from a probable RSV infection. Outcome: Yes Indirectness: Some Other information Setting Neonatal units

Study details	Participants	Factors	Results	Comments
Source of funding Study was supported by an unrestricted grant from Abbott Laboratories, Germany (3 of the authors participate in advisory board meetings concering the 'RSV Risk Assessment' sponsored by Abbott Int).	Though the comparison group is not explicitly stated, it seems as though those subjects hopsitalised for RSV infection were compared to those not hospitalised Inclusion criteria - The Munich RSV study cohort included 620 preterm children with a gestational age of 29 (29 + 0) to 35 (35 + 6) weeks who had been admitted to 9 neonatal intensive care units in Bavaria between November 1, 1998 and October 31, 1999 - The Austrian 29-32 RSV study cohort included 616 preterm children with a gestational age of 29 (29 + 0) to 32 (32 + 6) weeks, born between June 1, 2001 and December 31, 2002, who had been admitted to 20 neonatal units in Austria Exclusion criteria - Children who received palivizumab during the surveillance period - Children with suspected nosocomial RSV infection, who developed clinical respiratory symptoms or a			Sample size calculation Not reported Outcome RSV hospitalisation (definition used in study is stated in the diagnostic criteria section of this evidence table) Data sources Medical discharge letters of all acute respiratory infection hospitalisations during follow-up were analysed for RSV hospitalisations Additional information 57/1158 (4.9%) had a RSV hospitalisation during the follow up period

Study details	Participants	Factors	Results	Comments
	positive RSV test after day 3 of hospitalization Statistical method - Univariate and multivariate logistic regression analyses were used to assess independent risk factors for RSV hospitalisation - Variables with a level of statistical significance below 0.15 were included in the multivariate logistic regression model using the backward selection procedure Demographics Gestational age in weeks, range Munich cohort: 29 to 35 Austrian cohort: 29 to 32 Multiple births Children from the Munich RSV study were signficantly more likely to be twins or triplets (p=0.02) than children from the Austrian study Other No significant differences between the 2 populations were found for birthweight, gender, visit to child care, presence of older siblings, neurologic disorders, cardiac			

Study details	Participants	Factors	Results	Comments
	abnormalities or chronic lung disease (p values not reported)			
Full citation Figueras-Aloy,J., Carbonell-Estrany,X., Quero,J., IRIS Study Group., Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33-35 weeks in Spain, Pediatric Infectious Disease Journal, 23, 815-820, 2004 Ref Id 216321 Country/ies where the study was carried out Spain Study type Prospective case-control study Study dates Cases recruited during the RSV season October 2002 to April 2003. Controls selected and included in May to June 2003. Aim of the study	Cases - Preterm infants born between 33 and 35 weeks gestational age of either sex discharged during the infectious RSV season or age 6 months or younger at the start of the season (October 1 in Spain) - The patients were to have been born at or transferred immediately after birth to a participating hospital and were admitted to a hospital with a proven RSV lower respiratory tract infection n=189 cases included, 3 subsequently excluded because of refusal to participate (1 case) or loss to follow-up (2 cases), therefore 186 cases included in the analysis Diagnostic criteria RSV proven lower respiratory tract infection - immunofluorescence assay, enzyme-linked immunosorbent assay, virus culture	Factors 1) Breast feeding ≤2 months 2) Absolute chronologic age at start of RSV season: ≤10 weeks	Odds ratios Adjusted* odds ratio (95% confidence interval) for the risk of RSV hospitalisation - conditional* logistic regression 1) Absolute chronologic age at start of RSV season: ≤10 weeks Cases: 125/186 (67.2%), Controls: 131/371 (35.3%)** OR(95%CI): 3.95 (2.65 to 5.90) 2) Breast-feeding ≤2 months (vs ≥2 months) Cases: 159/186 (85.5%), Controls: 251/371 (67.6%)** OR (95%CI): 3.26 (1.96 to 5.42) *Adjusted for medical centre, breastfeeding, chronologic age at start of RSV season, school age siblings, residents and/or visitors at home ≥4 (without school age siblings and the subject him/herself), history of wheezing in the family **Data from univariate analysis	Limitations Based on NICE guidelines 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Current age of subjects not reported - Subjects previously hospitalised for prematurity - Data sources not reported Indirectness Does the study match the review protocol in terms of: Population: No, all infants were premature Outcome: Yes Indirectness: Some Other information Setting 50 participating Spanish hospitals Sample size calculation Based on data obtained in the IRIS Group study 1999-2000 and on the type of design considered (1 case/2 controls), the desirable number was determined to be at least 200 cases and 400 controls to

Study details	Participants	Factors	Results	Comments
To identify those risk factors most likely to lead to the development of RSV related respiratory infection and subsequent hospital admission among premature infants born at 33-35 weeks gestational age Source of funding Supported by an unrestricted grant from Abbott Laboratories	Controls - 33 to 35 weeks gestational age also of either sex identified at the end of the inclusion period for cases and randomly selected from among all premature children born at or transferred immediately after birth to a given participating hospital within the same time period and within the same gestational age limits as cases - Controls could not have been previously hospitalised for any acute respiratory illness during the RSV season - 2 controls for each cases and some additional ones if needed - Except for medical center, controls were not matched to cases n= 378 controls included, 6 subsquently excluded because they had been treated with palivizumab and 1 child excluded because s/he had been previously admitted as a case for RSV infection, therefore 371 controls included in the analysis Inclusion criteria			achieve α=0.05 and 1-ß=0.8 Outcome RSV hospitalisation Data sources This was not a retrospective review of records but a prospective case control study. Details of how the data was obtained is not reported.

Study details	Participants	Factors	Results	Comments
	See above (cases and controls section) Exclusion criteria - Previous inclusion in the study - Nosocomial RSV infection (appearing >5 days after admission) - Known renal impairment - Hepatic dysfunction or immunodeficiency - Chronic seizure disorder - Congenital heart disease with cyanosis or heart failure - Chromosomal anomalies - Congenital metabolic diseases - Major congenital anomalies - Subjects who had received palivizumab, investigational RSV vaccines or other investigational agents - Those previously hospitalised for acute respiratory illness - Patients with other chronic lung diseases except for bronchopulmonary dysplasia Statistical method - Bivariate calculation of ORs was used to determine the rates of each risk factor for cases and controls - Any variable for which p≤0.10 in any of the			

Study details	Participants	Factors	Results	Comments
	bivariate analyses was considered for entry into the multivariate model (conditional logistic regression analysis). Adjusted ORs were determined within the multivariate model to estimate the contribution of each factor after controlling for other factors in the model. Demographics Birthweight in grams, mean (SD) Cases: 2205 (379) Controls: 2128 (423) p=0.0297 Gestational age in weeks, n (%) 33 weeks - Cases: 50 (26.9), Controls: 77 (20.8), p=NS (0.204) 34 weeks - Cases: 60 (32.3), Controls: 141 (38) 35 weeks - Cases: 76 (40.9), Controls: 153 (41.1) Gender, n (%) male Cases: 117 (62.9) Controls: 202 (54.4) p=NS (0.057) Ethnic group, n (%) Caucasian - Cases: 158 (85.9), Controls: 348 (93.8)			

Study details	Participants	Factors	Results	Comments
	Non-Caucasian - Cases: 26 (14.2), Controls: 23 (6.2) p=not reported Multiple pregnancy, n (%) Cases: 64 (34.4) Controls: 134 (36.1) p=NS (0.761) Ventilation required, n (%) Cases: 25 (13.4) Controls: 33 (8.9) p=NS (0.131) NICU admittance, n (%) Cases: 51 (27.4) Controls: 79 (21.3) p=NS (0.132) Family history of allergy, n (%) Asthma Cases: 42 (22.6) Controls: 73 (19.7) Wheezing Cases: 66 (35.5) Controls: 89 (24) Allergic rhinitis Cases: 52 (28) Controls: 102 (27.5) Eczema Cases: 42 (22.6) Controls: 58 (15.6)			

Study details	Participants	Factors	Results	Comments
Full citation Figueras-Aloy,J., Carbonell-Estrany,X., Quero-Jimenez,J., Fernandez-Colomer,B., Guzman-Cabanas,J., Echaniz-Urcelay,I., Domenech-Martinez,E., IRIS Study Group., FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks, Pediatric Infectious Disease Journal, 27, 788-793, 2008 Ref Id 262746 Country/ies where the study was carried out Spain Study type Prospective cohort study (with 2 cohorts) Study dates 2 consecutive RSV seasons - October 2005 to April 2006 and October 2006 to April 2007 Aim of the study To validate the risk factors found in a previous	Cases - Male or female preterm infants born between 32 weeks (and 1 day) and 35 weeks (and 0 days) of gestational age, as determined at each participating site, discharged during the infectious RSV season or aged 6 months or less at the start of the season (October 1 in Spain) - The patients were to have been born at or transferred immediately after birth to a participating hospital and were admitted to a hospital with a proven RSV lower respiratory tract infection n=202 Diagnostic criteria RSV proven lower respiratory tract infection - immunofluorescence assay, enzyme-linked immunosorbent assay, virus culture Controls - The remaining premature infants seen, born at or transferred immediately after birth to one of the participating hospitals within the same period and within	Factors 1) Absolute chronologic age at start of RSV season: ≤10 weeks	Odds ratios Adjusted** odds ratios (95%CI) for risk of RSV hospitalisation, n/N (%) - logistic regression analysis 1) Absolute chronologic age at start of RSV season: ≤10 weeks Cases: 126/202 (62.4%), controls: 1944/5239 (37.1%) OR (95%CI): 2.99 (2.23 to 4.01) **Adjusted for school age siblings or day care attendance and tobacco smoking during pregnancy	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Unclear why ≤2 tobacco smokers at home was not examined in the logistic regression analysis although this variable had a p value ≤0.10 in the bivariate analysis - Refusal to participate or loss to follow-up in 777 subjects - Current age of subjects not reported - Subjects previously hospitalised for prematurity Indirectness Does the study match the review protocol in terms of: Population: No, all infants were premature Outcome: Yes Indirectness: Some Other information Setting 37 Spanish hospitals Sample size calculation Not reported howeve, a total of 6473 children fulfilled inclusion criteria, 1030 were excluded (refusal to participate or loss to

Study details	Participants	Factors	Results	Comments
epidemiologic case-control study (FLIP study) regarding hospitalisation as a result of RSV infection in premature infants born at 32 to 35 weeks of gestational age in Spain (This study was called the FLIP-2 study) Source of funding Supported by an unrestricted grant from Abbott Laboratories	the same gestational age limit as cases - Controls could not have been children hospitalised for any acute respiratory illness during the RSV season n=5239 Inclusion criteria See above (cases and controls section) Exclusion criteria - Previous inclusion in the study - Nosocomial RSV infection (infection appearing ≥5 days after admission) - Known renal impairment - Hepatic dysfunction or immunodeficiency - Chronic seizure disorder - Congenital heart disease with cyanosis or heart failure - Chromosomal anomalies - Congenital metabolic diseases - Major congenital anomalies - Subjects who participated in clinical trals that included blind treatments - Those previously hospitalised for acute respiratory illness - Patients with other chronic lung diseases except for			follow-up in 777 subjects, respiratory admissions that were not RSV positive in 235 subjects, death not related to respiratory processes in 3 subjects and incomplete data in 15 subjects) Outcome RSV hospitalisation (of the cases, 17.8% required ICU admission and 7.4% mechanical ventilation) Data sources At the time of hospital admission of premature infants born after April 1st, parents were informed about the study. Informed consent was subsequently obtained and data regarding kinship and risk factors were collected. After RSV season was over (month of May), all participant families were contacted (personal interview or phone call) to complete the risk factor report and also to collect data regarding possible hospital admissions for respiratory diseases in general.

Study details	Participants	Factors	Results	Comments
	bronchopulmonary dysplasia Statistical method - Bivariate calculation of ORs was used to determine the rates of each risk factor for cases and controls - Any variable for which p≤0.10 in any of the bivariate analyses was considered for entry into the multivariate model (logistic regression analysis). Adjusted odds ratios were determined within the multivariate model after controlling for other factors in the model. Demographics Birthweight in grams, mean (SD) Cases: 2047 (360) Controls: 2020 (400) p=0.304 Gestational age in weeks, mean (SD) Cases: 33.8 (0.8) Controls: 33.9 (0.9) p=not reported Gender - male, n (%) Cases: 121 (59.9) Controls: 2800 (53.4) p=0.083			

Study details	Participants	Factors	Results	Comments
	Multiple pregnanicies, n (%) Cases: 76 (37.6) Controls: 2052 (39.2) p=0.711 Bronchopulmonary dysplasia, n (%) Cases: 0 Controls: 4 (0.07) p=0.352 Family history of wheezing, n (%) Cases: 60 (29.7) Controls: 1346 (25.7)			
Full citation Garcia,C.G., Bhore,R., Soriano-Fallas,A., Trost,M., Chason,R., Ramilo,O., Mejias,A., Risk factors in children hospitalized with RSV bronchiolitis versus non-RSV bronchiolitis, Pediatrics, 126, e1453-e1460, 2010 Ref Id 206908 Country/ies where the study was carried out Texas Study type Retrospective cohort Study dates	Cases Based on disease severtiy (outcomes of care) of patients hospitalised with RSV and non-RSV bronchiolitis: Oxygen requirement RSV bronchiolitis n=1600 (56.3%) Non-RSV bronchiolitis n=675 (46.7%) Total cases n=2275 PICU requirement RSV bronchiolitis n=329 (11.6%) Non-RSV bronchiolitis n=119 (8.2%) Total cases n=448 Intubation requirement (Ventilatory support)	Factors 1) Gender (male) 2) Prematurity - <37 weeks 3) CHD - not defined 4) CLD - not defined 5) Race (Black, Hispanic, Other) Reference: White 6) Neuromuscular disorders - not defined	Odds ratios Odds ratio* (95% CI) for oxygen requirement (n=4285) in infants <2 years of age hospitalised with RSV or non-RSV bronchiolitis during the study period 1) Gender (male) 0.80 (0.71 to 0.91) p=0.0005 2) Prematurity 1.36 (1.17 to 1.59) p<0.0001 3) CHD 1.88 (1.32 to 2.67) p=0.0005 4) CLD 3.27 (2.14 to 5.00) p<0.0001 5) Race	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: Inclusion based on ICD-9 codes Statistical analysis: - Number of infants unclear in analysis of severity - Only odds ratios for significant results reported Indirectness Does the study match the review protocol in terms of: Population: Yes

Study details	Participants	Factors	Results	Comments
January 1, 2002 to December 31, 2007 Aim of the study To define the burden of hospitalisations related to RSV and non-RSV bronchiolitis in a tertiary-care children's hospital from 2002 to 2007 and to identify the risk factors associated with severe disease Source of funding Funded by the National Institutes of Health	RSV bronchiolitis n=171 (6%) Non-RSV bronchiolitis n=46 (3.2%) Total cases n=217 Diagnostic criteria - Inclusion identified via International Classification of Diseases, Ninth Revision codes with a primary diagnosis of RSV bronchiolitis (466.11) amd bronchiolitis attributable to other infectious organisms (466.19) - 4589 infants had a viral diagnostic test performed which included rapid antigen tests (enzyme immunoassay) for 1650, direct fluorescent antibody (DFA) test for 3559 and viral culture for 1766 - The hospitals policy states samples with negative rapid-test results were automatically tested by using a DFA assay, and samples that tested negative by rapid test and/or DFA test underwent viral culture, this policy was applied to 97% of included infants Controls		- Black: 0.49 (0.41 to 0.60), p<0.001 - Hispanic: 1.12 (0.96 to 1.31), p=0.149 - Other: 1.02 (0.76 to 1.39), p=0.879 6) Neuromuscular disorders 1.52 (0.87 to 2.64) p=0.139 Odds ratio* (95% CI) for PICU requirement (n=4285) in infants <2 years of age hospitalised with RSV or non-RSV bronchiolitis during the study period 1) Gender (male) NS 2) Prematurity 1.63 (1.29 to 2.05) p<0.0001 3) CHD 2.77 (1.89 to 4.05) p<0.0001 4) CLD 1.80 (1.12 to 2.89) p=0.01 5) Race - Black: 0.89 (0.65 to 1.23), p=0.486 - Hispanic: 1.01 (0.79 to 1.31), p=0.917 - Other: 1.59 (1.03 to 2.44), p=0.034 6) Neuromuscular disorders	Outcome: Disease severity based on care requirement Indirectness: None Other information Setting Children's Medical Center in Dallas Sample size calculation Not reported Outcome Disease severity: oxygen requirement, PICU, intubation and length of stay Data source Medical records Other - Referred to the group of patients with bronchiolitis caused by viruses other than RSV and those with negative viral testing results as the non-RSV bronchiolitis group (n=1445) - Sample size: non-RSV bronchiolitis group n=1445, RSV bronchiolitis group n=2840

Study details	Participants	Factors	Results	Comments
	Based on disease severity (outcomes of care) of patients hospitalised with RSV and non-RSV bronchiolitis: Number calculated by NCC-WCH assuming the total number included in analysis (oxygen and PICU n=4285 and intubation n=448) minus number of cases with care requirement equals the number of controls - No oxygen requirement n=2010 - No PICU requirement n=3837 - No intubation requirement n=231 Inclusion criteria - Infants <2 years of age - Hospitalised with RSV and non-RSV bronchiolitis at Children's Medical Center in Dallas from January 1, 2002 to December 31, 2007 - Viral test performed - Only the first hospitalisation was considered for analysis (255 infants had >1 hospitalisation accounting for 304 hospitalisations)		2.79 (1.43 to 5.46) p=0.003 Odds ratio* (95% CI) for intubation requirement (n=448) in infants <2 years of age hospitalised with RSV or non-RSV bronchiolitis during the study period 1) Gender (male) NS 2) Prematurity 1.54 (1.02 to 2.33) p=0.04 3) CHD NS 4) CLD NS 5) Race - Black: 1.73 (0.93 to 3.19), p=0.999 - Hispanic: 2.17 (1.32 to 3.58), p=0.136 - Other: 2.37 (1.06 to 5.29), p=0.252 6) Neuromuscular disorders NS NS: values not significant and not reported in the study * Adjusted for RSV, weight, age at hospitalisation, gender, race, prematurity, congenital heart defects, chronic lung disease,	

Study details	Participants	Factors	Results	Comments
	Exclusion criteria Multivariable linear regression was performed after log transformation and restricted to cases with values within 3SDs of the mean of log-transformed length of stay (25 cases of 4285 were excluded) Statistical method - Chi-squared test for trends was used to determine significant changes in hospitalisation rates over time - Associations between categorical and continuous variables were analysed by using the chi-squared tests with Yates correction for continuity or Fisher's exact tests and the 2-tailed Student t or Wilcoxon rank-sum tests - Statistical models were built by using multivariate logistic regression for binary outcome variables (supplemental oxygen, PICU and intubation) and linear regression models for the continuous outcome length of hospital stay - Multivariable logistic regression analysis was performed by constructing a		trisomy 21, congenital syndromes	

Study details	Participants	Factors	Results	Comments
	full stepwise sequence, and the final model was selected on the basis of the Akaike criteria - The final regression model was selected by using the backward elimination method Demographics - The virus most commonly identified was RSV in 2840 (66%) infants, followed by parainfluenza virus (3%), rhinovirus (3%), adenovirus (1%) and influenza virus A and B in <1% - >1 virus was identified in 24 (0.5%) infants, the most frequent association was RSV and rhinovirus - 5 deaths: 3 attributable to RSV (3-month old with CHD, 17-month old with Moebius syndrome, previously healthy 5-month old) and 2 to non-RSV (17-month old with CHD and 3-month old born at 33 weeks gestation who developed methicillin resistant Staphylococcus aureus pneumonia) RSV bronchiolitis (n=2840); non-RSV bronchiolitis (n=1445)			

Study details	Participants	Factors	Results	Comments
	Mean±SD or n(%) Gestational age 38.3±3.4; 37.4±4.3 p<0.001 Weight, kg 7.0±2.6; 7.6±2.8 p<0.001 Age, months 6.3±5.6; 8.0±6.0 p<0.001 Gender Male: 1619(57.01); 847(58.62) Female: 1221(42.99); 598(41.38) Race White: 643(22.64); 278(19.24) Black: 540(19.01); 319(22.08) Hispanic: 1504(52.96); 784(54.26) Other: 153(5.39); 64(4.43) CHD 91(3.20); 78(5.40) p<0.001 CLD			

Study details	Participants	Factors	Results	Comments
	58(2.04); 77(5.33) p<0.001 Immunodeficiencies 7(0.25); 5(0.35) p=0.761 Cystic fibrosis 2(0.007); 1(0.07) p=0.000 Prematurity, gestational age at birth, weeks Premature: 580(20.42); 418(28.93) p<0.001 ≤28: 71(2.50); 81(5.61) 29 to 32: 81(2.85); 85(5.88) 32 to 35: 194(6.83); 112(7.75) 35 to 37: 234(8.24); 140(9.69) Trisomy 21 34(1.20); 34(2.21) p=0.004 Neuromuscular disorders 34(1.20); 23(1.59) p=0.287 Congenital syndromes (Prader-Willi, trisomy 18, VACTERL association, Shwachman-Diamond,			

Study details	Participants	Factors	Results	Comments
	Noonan and Goldenhar, hemoglobinopathies, congenital lymphedema, congenital hypothyroidism and Kasabach Merritt) 46(1.62); 32(2.21) p=0.280 Respiratory tract morbidity (intubation ≥10 days for meconium aspiration syndrome, gastroschsis, congenital diaphragmatic hernia, tracheoesophageal fistula, pulmonary hypertension and spontaneous pneumothorax and upper airway normalities) 53(1.87); 34(2.35) p=0.286 Length of stay, median (IQR) 3(2 to 5); 2(2 to 4) p<0.001			
Full citation Gavin,N.I., Leader,S., Predictive accuracy of risk factors for RSV-related hospitalizations among infants in low-income families born at 32 to 35 weeks of gestation, Journal of Clinical Outcomes	Cases Infants born in 1997 at 32 to 35 weeks gestation who have had an RSV-related hospital stay: - Treatment with a date of service between their date of birth and first birthday	Factors 1) Gender (male)	Odds ratios Risk of RSV-related hospitalisation in infants born 32 to 35 weeks of gestation in 1997 who had continous Medicaid coverage in the first 12 months of life 1) Gender, male	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: - Few demographics reported

Study details	Participants	Factors	Results	Comments
Management, 14, 323-331, 2007 Ref Id 262805 Country/ies where the study was carried out USA (Texas) Study type Retrospective cohort Study dates 1997 Aim of the study To examine the accuracy of risk factors avaliable from administrative data to predict hospitalisation due to severe RSV infection among moderately premature infants in low-income families Source of funding Supported by MedImmune, Inc	- One of the following ICD-9-CM codes: 466.11 (acute bronchiolitis due to RSV), 079.6 (RSV infection), or 480.1 (pneumonia due to RSV) n=109 Diagnostic criteria Based on ICD-9-CM codes Controls Infants born in 1997 at 32 to 35 weeks gestation who have not had an RSV-related hospital stay n=1989 Inclusion criteria - See above (cases and controls section) - Living in Texas - Received continuous Medicaid coverage in the first 12 months of life Exclusion criteria - Infants with congenital anomalies reported on their birth certificates (n=834)		Unadjusted odds ratio (95% CI): 1.27 (0.86 to 1.88) Adjusted* odds ratio (95% CI): 1.07 (0.70 to 1.64) *Adjusted for race/ethnicity (non-Hispanic whie, non-Hispanic black, mixed race, and other/unknown), twin or multiple birth, Medicaid eligibility category, urban/rural residence, whether mother had adequate prenatal care, number of hospital beds per square mile in county, presence of NICU beds in county, % of foreign-born medical graduates in county, presence of a teaching hospital in the county, month of birth, birth weight, presence of siblings, unmarried mother, gender, birth stay ≥7 days, teenaged mother, NICU stay, maternal smoking during pregnancy, ventilator assistance at birth.	- Included infants with pneumonia due to RSV Prognostic factor: - Diagnosis based on ICD-9-CM codes Statistical analysis: Results and significance not reported for variables included in preliminary regressions Indirectness Does the study match the review protocol in terms of: Population: Include infants in low-income families who had continuous Medicaid coverage and moderately premature infants (32 to 35 weeks gestation), also included subjects with one of the following ICD-9-CM codes: 466.11 (acute bronchiolitis due to RSV), 079.6 (RSV infection), or 480.1 (pneumonia due to RSV) Outcome: Yes Indirectness: Some Other information Setting Inpatient and outpatient Sample size calculation Not reported

Study details	Participants	Factors	Results	Comments
	- On ≥2 Medicaid claims (n=5177) - Received RSV prophylaxis (n=46) Statistical method - Priminary multivariate logistic regressions investigated 27 risk factors for of the probability of an RSV-related hospital stay - Investigated 11 dichotomous variables as predictors of RSV hospitalisations, these were either listed in the AAP guidelines for RSV prophylaxis or proxies for those factors, factors that were consistently significant in preliminary regression or factors found to be significant in other studies Demographics % of infants with risk factor - Low birth weight: 61.7 - Presence of siblings: 60.0 - Male: 52.1 - Birth stay of ≥7 days: 20.8 - NICU stay: 15.5 - Ventilator assisted birth: 7.7 Gestational age			Outcome RSV-related hospitalisation Data source - Birth certificates - Medicaid enrollment and claims data - Linked data from the Area Resource File on the supply of medical care in the infant's county Other Also report the odds ratio for maternal smoking during pregnancy, this does not include the presence of environmental tobacco smoke in the household following the infant's birth

Study details	Participants	Factors	Results	Comments
	- Defined gestational age based on the clinical estimate unless this variable was missing from the infant's birth certificate, in which case it was based on the date of the mother's last menstrual cycle as reported on the birth certificate (n=535) - 2098 infants included in the study born at 32 to 35 weeks gestation			
Full citation Grimwood,K., Cohet,C., Rich,F.J., Cheng,S., Wood,C., Redshaw,N., Cunningham,C.W., Pearce,N., Kirman,J.R., Risk factors for respiratory syncytial virus bronchiolitis hospital admission in New Zealand, Epidemiology and Infection, 136, 1333-1341, 2008 Ref Id 206989 Country/ies where the study was carried out New Zealand Study type Retrospective cohort Study dates	Cases Hospitalised for bronchiolitis: - Aged <24 months in hospital Monday-Friday with community-acquired bronchiolitis during three consecutive RSV epidemic seasons (June/July to October 2003-2005) - RSV was confirmed in 141 (61.3%) of 230 infants hospitalised with bronchiolitits - Of the 141 positive samples, 135 (95.7%) were typed as RSV subgroup A or B - One infant had RSV subgroup B detected during his first admission and subgroup A was indentified 3 weeks later when he was	Factors 1) Gender (male) 2) Ethnicity (Maori, Pacific, Other, European) 3) Gestational age (<37 weeks) 4) Age at admission (<2 months) 5) Multiple birth	Odds ratios Odds ratios for RSV positive bronchiolitis hospitalisation compared with all live hospital births during the same period Cases, n(%); controls, n(%); crude rate ratios (95% CI); adjusted* rate ratio (95% CI) 1) Gender - Male: 82(58.2); 5816(51.6); 1.30 (0.93 to 1.82); 1.25 (0.89 to 1.75) - Female (reference): 59(41.8); 5454 (48.4) 2) Ethnicity - Māori: 49(34.8); 1533(13.6); 5.00 (3.35 to 7.44); 3.64 (2.27 to 5.85), p≤0.0001	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: - 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers - No indication that controls have been tested for RSV - Dates unclear, the controls include all live births in the region for 2003-2005, but control subjects were compared to patients hospitalised for bronchiolitis

Study details	Participants	Factors	Results	Comments
Three consecutive RSV epidemic seasons (June/July to October 2003-2005) Aim of the study To assess risk factors for RSV hospitalisation and disease severity in Wellington Source of funding No decalarations of interest	readmitted with a new episode of bronchiolitis Severity: Severe = assisted ventilation or continuous positive arirway pressure n=34 Diagnostic criteria - Bronchiolitis diagnosed based upon coryzal symptoms followed by signs of respiratory distress and fine, inspiratory crackles on auscultation - Hospital admission guidelines included ≥1 of the following: respiratory distress, apnoea, inability to feed, pulse oximetry <92% in air, underlying chronic medical conditions and adverse social circumstances from a lack of transport or telephone - The severity index score took oxygen requirement as the best single measure of illness severity in hospitalised infants with bronchiolitis - Nasopharyngeal aspirates were performed routinely on infants admitted with bronchiolitis. RSV antigen testing was conducted by		- Pacific: 37(26.2); 1207(10.7); 4.79 (3.12 to 7.35); 3.60 (2.14 to 6.06), p≤0.0001 - Other: 9(6.4); 1321(11.7); 1.06 (0.52 to 2.17); 1.09 (0.52 to 2.25) - European (Pakeha) (reference): 46(32.6); 7189(63.8) - No data: 0; 20(0.2) 3) Gestational age - <37 weeks: 32(22.7); 1178(10.5); 2.52 (1.70 to 3.71); 2.29 (1.48 to 3.56) - ≥37 weeks (reference): 109(77.3); 10092(89.5) 5) Multiple birth - Yes: 10(7.1); 524(4.6); 1.57 (0.83 to 2.96); 1.25 (0.62 to 2.54) - No (reference): 131(92.9); 10746(95.4) * Multivariate rate ratio adjusted for all variables listed here including mother smoking during pregnancy, month of birth and NZDepartment2001 score Risk factors for severe (assisted ventilation or continuous positive arirway pressure) compared with moderate/mild RSV bronchiolitis in hospitalised children	during 2003 and 2004 using the departmental database, the database for 2005 was incompete at the time of writing Indirectness Does the study match the review in terms of: Population: Yes Outcome: Yes Indirectness: None Other information Setting Wellington Hospital Sample size calculation Not reported Outcome - RSV hospitalisation - Severe compared with moderate/mild RSV bronchiolitits - Length of hospital stay Data sources - New Zealand Depravation Index used pooled 2001 census data for 9 dimensions of material and social status and was used as a proxy

Study details	Participants	Factors	Results	Comments
	direct immunofluorescence assay. Controls General infant population All live hospital births during 2003-2005 in the Wellington region n=11270 Severity Moderate = received supplemental oxygen Mild = no additional oxygen needed n=107 Inclusion criteria See above (cases and controls section) Exclusion criteria Not reported Statistical method - Analysis of RSV incidence were conducted using Poisson regression to estimate incidence rate ratios initally with univariate analysis, then with multiple regression analyses - Analyses of factors that affected severity in RSV-positive children were		Severe, n(%); moderate/mild, n(%); univariate* odds ratio (95% CI); adjusted** odds ratio (95% CI) 1) Gender - Male: 18(52.9); 64(59.8); 0.74 (0.34 to 1.63); 0.79 (0.34 to 1.85) - Female (reference): 16(47.1); 43(40.2) 2) Ethnicity - Māori: 12(35.3); 37(34.6); 1.21 (0.46 to 3.20); 1.34 (0.42 to 4.28) - Pacific: 9(26.5); 28(26.2); 1.28 (0.45 to 3.63); 1.42 (0.36 to 5.52) - Other: 3(8.8); 6(5.6); 1.68 (0.35 to 8.06); 1.95 (0.37 to 10.29) - European (Pakeha) (reference): 10(29.4); 36(33.6) 3) Gestational age - <37 weeks: 5(14.7); 27(25.2); 0.58 (0.20 to 1.67); 0.58 (0.19 to 1.78) - ≥37 weeks (reference): 29(85.3); 80(74.8) 4) Age at admission - <2 months: 13(38.2); 22(20.6); 2.36 (1.01 to 5.50); 2.50 (0.98 to 6.39)	measure for socioeconomic status and was determined from the infant's address - Wellington Women's Hospital Perinatal Information Management System database allowed comparisons to be made between subject and infant birth populations from the same region

Study details	Participants	Factors	Results	Comments
	conducted using logisitic regression to estimate prevalence odds ratios, initally only adjusted for year (termed univariate), then with multiple regression analyses including the factors of interest and factors that showed elevated risks in univariate analyses Demographics - Median age of infants hospitalised with RSV was 5.1 months (IQR 2.0 to 9.0) - Mean length of hospitalisation was 5.1 days (95% CI 4.5 to 5.7) - Median length of hospitalisation was 4.0 days (IQR 2.0 to 7.0) - 15 (10.6%) RSV-positive infants had a major underlying illness (cardiac, respiratory, Down's syndrome or achondroplasia) Cases, n(%); controls, n(%) Mother smoking during pregnancy Yes: 13(38.2); 35(33.0) No: 21(61.8); 71(67.0) Birth weight Low birth weight (≤10th centile): 7(10.9); 6(7.9)		- ≥2 months (reference): 21(61.8); 85(79.4) **Adjusted for year, gender, month of birth, age at admission, mother smoking during pregnancy, ethnicity, number of other children living in the house and gestational age Risk factors for length of stay (≥5 days vs. <5 days) in RSV-positive children hospitalised with bronchiolitits ≥5 days, n(%); <5 days, n(%); univariate* odds ratio (95% CI); adjusted*** odds ratio (95% CI) 1) Gender - Male: 40(62.5); 42(54.5); 1.39 (0.70 to 2.76); 2.25 (0.85 to 6.00) - Female (reference): 24(37.5); 35(45.5) 2) Ethnicity - Mãori: 22(34.4); 27(35.1); 1.34 (0.58 to 3.09); 1.44 (0.38 to 5.51) - Pacific: 19(29.7); 18(23.4); 1.86 (0.76 to 4.58); 2.21 (0.49 to 10.02) - Other: 5(7.8); 4(5.2); 1.79 (0.41 to 7.77); 2.43 (0.32 to 18.62) - European (Pakeha) (reference): 18(28.1); 28(36.4)	

Study details	Participants	Factors	Results	Comments
	Normal to high (>10th centile): 57(89.1); 70(92.1)		4) Age at admission - <2 months: 22(34.4); 38(49.4); 2.56 (1.15 to 5.71); 1.92 (0.63 to 5.83) - ≥2 months (reference): 42(65.6); 39(50.6) 5) Multiple birth - Yes: 8(12.5); 2(2.6); 5.35 (1.08 to 26.51); 6.52 (0.89 to 47.96) - No (reference): 56(87.5); 75(97.4) * Univariate adjusted for year *** Adjusted for year, gender, multiple birth, age at admission, ethnicity, number of other children living in the house, birth weight	
Full citation Hervas,D., Reina,J., Yanez,A., del Valle,J.M., Figuerola,J., Hervas,J.A., Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis, European Journal of Clinical Microbiology and Infectious Diseases, 31, 1975-1981, 2012 Ref Id 262969	Cases Subjects with acute bronchiolitis with the need for oxygen or ICU admission n=1428* for oxygen, 198* for ICU admission *Calculated by NCC-WCH technical team Diagnostic criteria - All children admitted for acute bronchiolitis are tested for RSV - RSV detection was done on nasopharyngeal aspirate	Factors 1) Congenital heart disease 2) Male sex 3) Gestational age <32 weeks, gestational age 32 to 36 weeks	Odds ratios Adjusted* odds ratios (95%CI) for oxygen need in children with non-RSV bronchiolitis Congenital heart disease: n.s** Male sex: 0.68 (0.51 to 0.91), p<0.001 Gestational age <32 weeks: n.s** Gestational age 32 to 36 weeks: n.s** Adjusted* odds ratios (95%CI) for oxygen need in children with RSV bronchiolitis Congenital heart disease: n.s** Male sex: n.s**	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist - Though risk factors for both oxygen need and ICU admission were examined separately, the study only presents odds ratios for signficant results - Based on reliability of coding systems Indirectness

Study details	Participants	Factors	Results	Comments
Country/ies where the study was carried out Spain Study type Retrospective review Study dates January 1 1995 to December 31 2006 Aim of the study To determine the epidemiology and outcomes of the infants hospitalised for bronchiolitis in an insular area of Spain Source of funding Not reported	or wash specimen by an enzyme-linked immunoassay and/or virus culture using HEp-2 cell lines - All bronchiolitis in which RSV was not detected were classified as non-RSV bronchiolitis Controls Subjects with acute bronchiolitis without the need for oxygen or ICU admission n=956* for no oxygen, 2186* for no ICU admission *Calculated by NCC-WCH technical team Inclusion criteria - Infants and young children admitted to the Department of Pediatrics with a diagnosis of acute bronchiolitis (acute bronchiolitis were identified via the ICD, 9th revision with the following discharge codes: acute bronchiolitis, RSV bronchiolitis, RSV pneumonia and RSV not otherwise specified) - Only those with a first episode of obstructive lower respiratory tract infection		Gestational age <32 weeks: n.s** Gestational age 32 to 36 weeks: n.s** Adjusted* odds ratios (95%CI) for ICU admission in children with non-RSV bronchiolitis Congenital heart disease: n.s** Male sex: n.s** Gestational age <32 weeks: 5.6 (1.89 to 16.59), p<0.01 Gestational age 32 to 36 weeks: n.s** Adjusted* odds ratios (95%CI) for ICU admission in children with RSV bronchiolitis Congenital heart disease: 3.08 (1.14 to 8.3), p<0.0001 Male sex: n.s** Gestational age <32 weeks: 4.92 (1.95 to 12.40), p<0.001 Gestational age 32 to 36 weeks: n.s** *Adjusted for nebulized epinephrine, nebulized salbutamol, year, congenital heart disease, atelectasis/condensation, age, male sex, gestational age **n.s= non-significant, study does not report odds ratios for nonsignificant results	Does study match review protocol in terms of: Population: no, includes children with ICD codes of acute bronchiolitis, RSV bronchiolitis, RSV pneumonia and RSV not otherwise specified Outcome: yes Indirectness: some Other information Setting Department of pediatrics of a university hospital Sample size calculation Not reported, however 2889 admitted with bronchiolitis, after exclusions, 2384 selected for study Outcome Oxygen need/ICU admission Data sources Data on premature infants was obtained from the neonatal unit registry, all other data from retrospective review of medical records

Study details	Participants	Factors	Results	Comments
	during the first 2 years of life were selected Exclusion criteria - All children with a previous episode of lower respiratory tract infection, n=401 - No information about RSV microbiology, n=19 - Erroneously codified, n=8 - >2 years of age, n=77 Statistical method - The independent association between risk factors for severe disease and outcome were analysed using a backward multivariate linear and logistic regression - A p value of <0.05 was considered statistically significant Demographics Male, n/N (%) 1391/2384 (58) Age in months, mean (range) 3.9 (0 to 23) <6 months, n/N (%) 1836/2384 (77) Hospital stay in days, median (range)			

Study details	Participants	Factors	Results	Comments
	5 (1 to 55) Previous history of prematurity, n (%) 246 (10.3) Comorbidities diagnosed during hospital stay, n (%) Acute otitis media: 351 (14.7) Urinary tract infection: 14 (0.6) Atelectases and/or condensations: 353 (16.8) During hospitalisation, other non-related morbidities included 1 cystic fibrosis, 2 congenital diaphragmatic hernia, 1 leukemia 1 aortic coarctation, 1 hypogammaglobulinemia and 1 ventricular septal defect			
Full citation Joffe,S., Escobar,G.J., Black,S.B., Armstrong,M.A., Lieu,T.A., Rehospitalization for respiratory syncytial virus among premature infants, Pediatrics, 104, 894-899, 1999 Ref Id 212485	Cases Infants rehospitalised for RSV between 1992 and 1996 n=55 Infants discharged before the beginning of the RSV season - 55 infants were hospitalised for laboratory proven RSV disease	Factors 1) Gestational age	Odds ratios Cases n=55 Controls n=1622 1) Gestational age Infants with gestational age 23 to 32 weeks were at greater risk of hospitalisation for RSV than those of 33 to 36 weeks Number hospitalised for RSV/Total number 23 to 32 weeks gestation - 32/438	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Prognostic factor: Diagnosis based on 12 ICD9-CM codes Indirectness Does the study match the review protocol in terms of:

Study details	Participants	Factors	Results	Comments
Country/ies where the study was carried out USA Study type Retrospective cohort Study dates 1992 to 1996 Aim of the study To characterise the epidemiology of severe RSV disease among premature infants and to identify high-risk subgroups Source of funding Funding for the Neonatal Minimum Data Set database was provided by the Kaiser Foundation Health Plan	between December 1 and March 31 - 3 infants were hospitalised twice for RSV, and 1 infant was hospitalised 3 times, for a total of 60 RSV-related hospitalisations - 30 admissions for a respiratory illness were associated with a negative RSV test, and no RSV test was performed during an additional 9 respiratory admissions - 99 total hospitalisations for respiratory illness Infants discharged during the RSV season - 27 were admitted before March 31 for laboratory proven RSV disease - No infant had more than one hospitalisation for RSV - 25 additional infants admitted for respiratory illness had a negative RSV test - 4 infants hospitalised for respiratory disease were not tested for RSV - 56 total hospitalisations for respiratory illness Diagnostic criteria		(7.3%), number hospitalised for RSV/Total 33 to 36 weeks gestation - 23/1283 (1.8%); Odds ratio* (95% CI): 2.6 (1.4 to 5.1) P value: 0.003 *Unclear what confounders were adjusted for	Population: No, all premature infants and also inclusion was based on the presence of ICD codes which included a broad range of conditions such as acute bronchitis and bronchiolitis, pneumonia, other diseases of lung Outcome: Yes Indirectness: Some Other information Setting 6 NICUs in Northern California Sample size calculation Not reported Outcome RSV hospitalisation and rehospitalisation Data source - Kaiser Permanente Neonatal Minimum Data Set (KPNMDS) - Kaiser Permanente Medical Care Plan database (KPMCP) Other - No infant in the cohort received RSV prophylaxis - Primary analysis (full-season cohort) assigned infants discharged from the nursery

Study details	Participants	Factors	Results	Comments
	- Linked the cohort of eligible infants to the KPMCP hospitalisation database to identify admissions potentially related to RSV - Admissions for which an acute respiratory or nonspecific viral diagnosis was listed were selected for chart review, these were based on 12 International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) codes and included a broad range of conditions such as acute bronchitis and bronchiolitis, pneumonia, other diseases of lung - We defined an illness as attributable to RSV if the infant was hospitalised for a respiratory indication and an RSV direct fluorescent antibody test performed between 7 days before and 3 days after admission was positive - RSV testing was performed at the discretion of the treating physician ; no institutional policy was in place - Viral cultures were rarely performed - All RSV tests were performed at the KPMCP regional virology laboratory			between December 1 of a given year and November 30 of the subsequent year to the following RSV season - Secondary analysis (partial-season cohort) was restricted to the subset of infants discharged from the NICU during an RSv season (December 31 to March 31), and included hospitalisations from the date of NICU discharge to the end of the concurrent RSV season

Study details	Participants	Factors	Results	Comments
	Controls Infants discharged from the NICU before the beginning of the RSV season n=1666 Inclusion criteria - Gestational age ≤36 weeks - Discharge alive from the NICU between July 1, 1992 and March 31, 1996 - No diagnosis of congenital heart disease other than patent ductus arteriosus - No diagnosis of cystic fibrosis - No diagnosis of congenital or acquired immunodeficiency - Considered to have complete follow-up (continuosly enrolled during the RSV season of interest) Exclusion criteria - See inclusion criteria - If RSV infection was incidental to rather than the cause of admission, the hospitalisation was not considered as a case Statistical method			

Study details	Participants	Factors	Results	Comments
	- The full and partial season cohorts were analysed separately - Bivariate analyses were performed using Pearson chi-squared or Student's t test - Bivaraite comparisons were two-tailed - Backwards stepwise multiple logistic regression was used to evaluate the simultaneous role of multiple risk factors and to assess interactions - Predictor variables that were statistically significant at p<0.10 in the bivariate analyses were included in the initial regression model; variables that were not significant at p<0.05 were seqentially dropped Demographics No episodes of nosocomial RSV Infants rehospitalised for RSV - Hospital days, median (mean): 4 (5.7) - Supplemental oxygen days, median (mean): 3 (4.8) - ICU admission: 18.4%			

Study details	Participants	Factors	Results	Comments
	- Received mechanical ventilation: 9.2% Infants discharged before the beginning of the RSV season (cases n=99, controls n=1622) Total n; % hospitalised for RSV Gestation, weeks 23 to 32: 438; 7.3 23 to 28: 99; 11.1 29 to 32: 339; 6.2 Birth weight, g <1500: 264; 8.7 ≥1500: 1457; 2.2 Oxygen therapy, days <28: 1597; 2.3 ≥28: 124; 14.5 Assisted ventilation, days <14: 1608; 2.4 ≥14: 113; 14.2 Maternal race White: 1065; 3.2 Asian: 220; 2.3 Black: 142; 2.1 Latino: 231; 4.3 Gender			

Study details	Participants	Factors	Results	Comments
	Female: 762; 3.3 Male: 959; 3.1 Multiple gestation No: 1334; 2.9 Yes: 387; 4.1 Date of NICU discharge December to August: 1238; 2.2 September to November: 483; 5.8			
Full citation Kaneko,M., Watanabe,J., Ueno,E., Hida,M., Sone,T., Risk factors for severe respiratory syncytial virus-associated lower respiratory tract infection in children, Pediatrics International, 43, 489-492, 2001 Ref Id 212487 Country/ies where the study was carried out Japan Study type Retrospective chart review Study dates All subjects hospitalised from July 1, 1995 to June 30, 1999	Cases Patients with severe RSV-LRI and required oxygen supplementation or mechanical ventilation n=20 Diagnostic criteria - RSV infection was diagnosed by enzyme-linked fluorescent immunoassay (ELFA) or enzyme immunoassay (EIA) via a nasopharyngeal secretion. Another method of detection of the virus included a fourfold or greater rise in complement fixation antibody titer to RSV between paired sera. - Indications for oxygen supplementation are the	Factors 1) Age <3 months 2) CHD - not defined, identified from patient records	Odds ratios Adjusted* odds ratio (95%CI) for severe RSV-LRI (i.e. requiring oxygen supplementation or mechanical ventilation) 1) Age <3 months: 59.9 (14.7 to 244.0), p<0.0001; severe group: 13/20 (65%), non-severe group: 6/137 (4.4%) 2) CHD: 99.2 (8.5 to 1160.1), p<0.0005; severe group: 6/20, non-severe group: 1/137** *Adjusted for age <3 months, CHD **Numbers from univariate analysis	Limitations - Small sample size may not have provided adequate power Indirectness Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information Setting Hospital Outcome Severe RSV-LRI: requiring oxygen supplementation or mechanical ventilation

Study details	Participants	Factors	Results	Comments
Aim of the study To look for independent risk factors for severe RSV-LRI that required oxygen supplementation or mechanical ventilation Source of funding Not reported	episodes of hypoxaemia (O2 saturation <90%) or signs of exhaustion such as an increasing respiratory rate and chest retraction. The CO2 retention, hypoxaemia or exacerbation of severe respiratory distress as indicated by chest retractions and respiratory rate >60 to 80/min, despite oxygen supplementation were considered indications for mechanical ventilation. Controls Patients who needed neither the treatment of oxygen supplementation nor mechanical ventilation during the disease course n=137 Inclusion criteria - All pediatric patients who were younger than 4 years and hospitalised with RSV-LRI from July 1, 1995 to June 30, 1999 Exclusion criteria - Patients with nosocomial infections Statistical method			Sample size calculation Not reported, 157 hospitalised during the study period were included Data sources Medical records of patients hospitalised with RSV-LRI were reviewed Other Of the 157 hospitalised patients, 20 (12.7%) were diagnosed with severe RSV-LRI

Study details	Participants	Factors	Results	Comments
	- Proportions for patients were compared with the Chi-square test or Fisher's exact test - A multivariate analysis was performed by logistic regression - Additionally, for the model of logistic regression, a Hosmer-Lemeshow goodness of fit was conducted and a perfect fit was obtained (p>0.05) - Multivariate logistic regression was used to examine the independent contribution of the variables to the probability of severe RSV-LRI that needed mechanical ventilation or oxygen supplementation - In a stepwise process, variables were eliminated from the multivariate model until no remaining candidate variable met a significance level of 0.10 Demographics Age in months, mean (standard error) Group 1 (non-severe RSV-LRI, n=137): 21.3 (1.1) Group 2 (oxygen supplementation, n=17): 11.3 (3.5) Group 3 (mechanical			

Study details	Participants	Factors	Results	Comments
	ventilation, n=3): 1.3 (0.3) Gender, n Group 1 (non-severe RSV-LRI, n=137): Male -78, Female-59 Group 2 (oxygen supplementation, n=17): Male -13, Female -4 Group 3 (mechanical ventilation, n=3): Male - 1, Female - 2			
Full citation Koehoorn,M., Karr,C.J., Demers,P.A., Lencar,C., Tamburic,L., Brauer,M., Descriptive epidemiological features of bronchiolitis in a population-based cohort, Pediatrics, 122, 1196-1203, 2008 Ref Id 207318 Country/ies where the study was carried out Canada Study type Retrospective cohort Study dates 1992 to 2002 Aim of the study To conduct a large, population-based,	Cases - Identified from the first health care encounter with a ICD-9CM code 466.1 (acute bronchiolitis) in the hospital discharge records - Only hospitalisations included, this data does not include emergency room visits unless they resulted in a hospital admission - Only the first hospitalisation for each infant was counted as the case n=1588 Diagnostic criteria Based on International Classification of Diseases, Ninth Revision, Clinical	Factors 1) Gender (male) 2) No breastfeeding initiation at hospital	Odds ratios Cases, n(%); controls, n(%); Adjusted* hazard rate ratios (95% CI) for bronchiolitis hospitalisation among infants in the Georgia Air Basin during the study period (1999 to 2002) 1) Male (reference: female): 960 (60.5); 46888 (51.3); 1.49 (1.34 to 1.64) 2) No breastfeeding initiation at hospital (reference: yes): 205 (12.9); 6766 (7.4); 1.33 (1.14 to 1.54) *Adjusted for all covariates in the model: gender, maternal age, maternal education, maternal smoking during pregnancy, breastfeeding initiation at hospital, First Nations status, older siblings, birth weight, congenital anomalies	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: Inclusion based on ICD-9-CM codes Indirectness Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information Setting Outpatient and inpatient records used to identify infants born in the Georgia Air Basin Sample size calculation

Study details	Participants	Factors	Results	Comments
epidemiological study of a comprehensive set of concurrent risk factors for bronchiolitis, including both hospitalisations and outpatient visits to physicians Source of funding Supported in part by Health Canada via an agreement with the British Columbia Centre for Disease Control to the Border Air Quality Study, and by the Centre for Health and Environmental Research at the University of British Columbia	Modification diagnosis (ICD-9-CM) code 466.1 Controls General population without a bronchiolitis encounter n=91438 Inclusion criteria - Born in the geographic area defined as the Georgia Air Basin, British Columbia between 1999 and 2002 - Follow-up monitoring was from the second to 12th month of life, the first month of life was exclude because bronchiolitis is uncommon in the first month Exclusion criteria - Muliple births and births of <25 weeks gestation (n=2606) - Missing data on maternal age or First Nations status (n=14488) - Incomplete residential history (n=9193) Statistical method - Cox-proportional hazards model used to investigate the association between risk factors and an infant's first			Not reported Outcome Bronchiolitis hospitalisation Data source - Medical services and hospitalisations data were provided and governed by the Mnistry of Health, Government of British Columbia, and vital statistics data by the British Columbia Vital Statistics Agency - Provinical perinatal database, goverened by the British Columbia Reproductive Care Program - The research database was constructed by merging vital statistics birth records (for cohort enumeration according to residential postal codes) with outpatient medical services billing records and inpatient hospital discharge records, for identification of cases for the period of 1999-2003 (allowing a minimum of a 1 year follow-up) - First nations status was avaliable from hospital discharge records for all births, with socioeconomic indicators for education and household income from Statistics Canada census data

Study details	Participants	Factors	Results	Comments
	clinical encounter related to bronchiolitis - Factors associated with bronchiolitis at the bivariate level were entered into the final multivariate model Demographics Cases, n(%); controls, n(%) Maternal smoking during pregnancy No: 1351(85.1); 83298(91.1) Yes: 237(14.9); 8140(8.9) First Nations status No: 1516(95.5); 90432(98.9) Yes: 72(4.5); 1006(1.1) Siblings No: 474(29.9); 42248(46.2) Yes: 1114(70.1); 49190(53.8) Birth weight <1500g: 42(2.6); 364(0.4) 1500 to 2500g: 122(7.7); 2859(3.1) 2500 to 4000g: 1239(78.0); 75363(82.4) ≥4000g: 185(11.7); 12852(14.1)			Other The study reported 2 case definitions: 1) Included all those with ICD of 466 (acute bronchitis and bronchiolitis) in the outpatient medical charts (general practitioner or specialist visit) or a principal diagnosis code of 466.1 (acute bronchiolitis) in the hospital discharge records 2) Limited to hospitalisations only with the more specific diagnosis code of 466.1 Only data relating to the second case definition has been extracted as this is more relevant to this review question of interest

Study details	Participants	Factors	Results	Comments
	Low birth weight complications No: 1386(87.3); 85391(93.4) Yes: 202(12.7); 6047(6.6) Congenital anomalies No: 1560(98.2); 90727(99.2) Yes: 28(1.8); 711(0.8) Preterm complications No: 1378(86.8); 85074(93.0) Yes: 210(13.2); 6364(7.0)			
Full citation Kristensen,K., Stensballe,L.G., Bjerre,J., Roth,D., Fisker,N., Kongstad,T., Svendsen,A.L., Nielsen,B.W., Risk factors for respiratory syncytial virus hospitalisation in children with heart disease, Archives of Disease in Childhood, 94, 785-789, 2009 Ref Id 212490 Country/ies where the study was carried out Denmark Study type Retrospective, matched case-control	Cases Those patients with heart disease diagnosed with RSV by using the RSV database (if found to have >1 positive RSV test, only the first hospitalisation was included in the study) Study population n=331 had a positive RSV test n=313 analysed Diagnostic criteria Based on International Classification of Diseases, version 10 diagnosis codes (ICD-10) Controls	Factors 1) Gender 2) Underlying condition - Down's syndrome 3) Preterm (gestational age <37 weeks)	Odds ratios Risk factors for RSV hospitalisation in children with heart disease during the period from January 1996 to April 2003 Cases, n; controls, n; odds ratio (95% CI); adjusted* odds ratio (95% CI) 1) Gender - Female: reference - Male: 165; 158; 1.10 (0.80 to 1.50); 1.14 (0.81 to 1.59) 2) Underlying condition - None (reference): 223; 263 - Down: 50; 18; 3.23 (1.82 to 5.74); 3.24 (1.80 to 5.80) - Other (including 4 cases and 3 controls of DiGeorge syndrome): 40; 32; 1.54 (0.93 to 2.57); 1.49 (0.88 to 2.52)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: Inclusion based on coding Prognostic factor: RSV diagnosis not described Indirectness Does the study match the review protocol in terms of: Population: Children with heart disease Outcome: Yes Indirectness: Children with heart disease. Children 0-14 years were enrolled, mean age at RSV diagnosis was 362 days (range: 15 to 2379 days)

Study details	Participants	Factors	Results	Comments
Study dates January 1996 to April 2003 Aim of the study To assess the risk and risk factors for RSV hospitalisation and determinants of the severity of RSV disease in children with heart disease Source of funding Supported by an unrestricted grant from Abbott Laboratories	- For each case child, one control child was drawn from the population of children registered with heart disease - Matched on centre and age - If >1 patient was avaliable the one with the lowest serial number in the Central Person Regiter was chosen, if a control child had died before RSV diagnosis in the case child another control was drawn - 22 controlled children were replaced by other control children because they had died before RSV hospitalisation in the case child n=313 Inclusion criteria Aged 0-14 years with ICD-10 codes DQ 20-38 (congenital malformations in the cardiovascular system) and DI 30-52 (other heart disease) seen as inpatients or outpatients during the period from January 1996 to April 2003 n=3239 children registered as having heart disease		3) Preterm - Term: reference - Gestational age <37 weeks: 49; 49; 1.00 (0.65 to 1.54); 1.03 (0.65 to 1.64) *Adjusted for underlying condition, type of heart disease and haemodynamic significance Determinants of severity of RSV infection in 283 children (nosocomially infected excluded) with heart disease: results of multivariate models Risk of needing supplemental oxygen (71 events), RR* (95% CI) - Preterm (reference: term): 1.88 (1.16 to 3.04) *Adjusted for age, cardiac decompensation	Other information Setting Hospitals - 3 centres for paediatric cardiology Sample size calculation Not reported Outcome RSV hospitalisation Data sources - Database as described in Stensballe et al., 2005 which covers 96% of all patients discharged with an RSV-specific diagnosis compared with the National Patient Registry - Information on death or emigration in the population of children with heart disease was drawn from the Central Person Register Other Though the paper reports on heart disease of various types, it is not specified that these are congenital heart diseases and therefore has not been extracted

Study details	Participants	Factors	Results	Comments
	Exclusion criteria - Contained insufficient information or could not be found (n=7) - Absence of heart disease (n=11) Statistical method - Matched case-control study analysed using conditional logistic regressions - First performed univariate analysis, then a multivariate model was built by backward elimination (significance level of 5%) taking hierarchy between the parameters into account - Computed the incidence of RSV hospitalisation in the age groups 0-5 months, 6-11 months, 12-17 months and 18-23 months (for a given group this was done by dividing the number of RSV hospitalisations in the group by the number of person-years experienced in the group by the population of children with heart disease) - Considered predictors of severity of infection using multivariate log-binomial regression, to estimate the relative risks for the cohort			

Study details	Participants	Factors	Results	Comments
	of hospitalised children, the exained predictors were age at infection along with the same variables as the case-control study - The time to discharge from hospital was modelled as a function of the same parameters using the Cox proportional hazards model with time to hospital as the underlying time scale Demographics - Median age at RSV diagnosis was 280 days, mean 362, range 15 to 2379 - 84 (27.5%) patients required supplemental oxygen, 79 (25.8%) were treated with CPAP and 12 (3.9%) were mechanically ventilated, none died - 23 (7.5%) patients were nosocomially infected - Median length of hospitalisation among children who were not nosocomially infected was 4 days, mean 6, range 0 to 74 Gestational age, median (range) Cases: 31 (24 to 36) Controls: 32 (24 to 36)			

Study details	Participants	Factors	Results	Comments
	Gender, males/females Cases: 165/148 Controls: 158/155 Heart disease: Cardiomyopathy, n Cases: hypertonic cardiomyopathy 3, dilated cardiomyopathy 10 Controls: dilated cardiomyopathy 3 Heart disease: Arrhythmia alone, n Cases: superventricular tachycardia 7, ventricular tachycardia 1, nodal tachycardia 1, focal arterial tachycardia 1 Controls: superventricular tachycardia 19			
Full citation Kristensen,K., Hjuler,T., Ravn,H., Simoes,E.A., Stensballe,L.G., Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study, Clinical Infectious Diseases, 54, 810-817, 2012	Cases Infants <24 months of age first hospitalised with RSV from January 1997 through June 2003 n=12,498 Diagnostic criteria Diagnosis coding based on the International Classification of Diseases, Tenth Revision (ICD-10).	Factors 1) BPD (ICD-10 code P27.0-P27.9) 2) Cystic fibrosis (ICD-10 code E84.0- E84.9) 3) CHD (ICD-10 code Q20.0-Q26.9) 4) Down syndrome (ICD-10 code Q90.0-Q90.9) 5) Neuromuscular disease: - encephalocele (ICD code Q01.0-Q01.9) - spina bifida and	Odds ratios Number with RSV hospitalisation/total number with risk factor (%) 1) BPD 89/504 (17.7) 2) Cystic fibrosis 13/72 (18.1) 3) CHD 292/2720 (10.7) 4) Down syndrome 78/399 (19.5)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - All variables were entered into 1 final multivariable model with no variable selection procedures - Study sample: Size cases and controls unclear

Study details	Participants	Factors	Results	Comments
Ref Id 204551 Country/ies where the study was carried out Denmark Study type Retrospective cohort Study dates January 1997 to June 2003 Aim of the study To assess the risk and severity of RSV hospitalisation in children with chronic conditions in this register-based, population-based cohort study Source of funding Supported by an unrestricted grant from Abbott Laboratories	RSV hospitalisation was defined by the first positive RSV test in the RSV database during the first 2 years of life. Controls Population of infants <24 months of age from January 1997 through June 2003 not hospitalised for RSV n=379,485 (calculated by NCC-WCH assuming the total population of 391, 983 included in analysis and subtracting those 12,498 hospitalised with RSV) Inclusion criteria See above (cases and controls section) Exclusion criteria - 472 children who were nosocomially infected i.e. had a positive RSV test ≥3 days after hospitalisation due to other cause - 262 children with insufficient data on duration on hospitalisation were excluded from this part of the analysis Statistical method	malformations of the spinal cord (ICD code Q05.0-Q05.9) - spinal muscular atrophy (ICD code G12.0-G12.9) - muscular dystrophy (ICD code G71.0-G71.3) - congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia (ICD code P94.1-P94.9) - cerebral palsy (ICD code G80.0-G80.9) 6) Congenital immunodeficiencies (ICD code D80.0-D82.9) *All of the above risk factors were based on ICD codes (definitions not reported)	5) Neuromuscular disease - encephalocele: 58/542 (10.7) - spina bifida and malformations of the spinal cord: 17/172 (9.9) - spinal muscular atrophy: 2/39 (5.1) - muscular dystrophy: 13/82 (15.9) - congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia: 23/344 (6.7) - cerebral palsy: 93/905 (10.3) 6) Congenital immunodeficiencies 26/122 (21.3) Adjusted* incidence rate ratios (95% CI) for risk of RSV hospitalisation in infants <24 months of age during the study period from January 1997 to June 2003 1) BPD 2.58 (2.06 to 3.24) P value: <0.001 2) Cystic fibrosis 4.32 (2.42 to 7.71) P value: <0.001 3) CHD 1.70 (1.45 to 1.99) P value: <0.001 4) Down syndrome 3.43 (2.66 to 4.42) P value: <0.001	- RSV diagnosis based on reliability of ICD coding systems Indirectness Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information Setting National population based study Sample size calculation Not reported Outcome RSV hospitalisation Data source Data obtained from the Danish RSV database, the National Patient and Birth Registries (ICD-10 codes), and the Civil Registration System

Study details	Participants	Factors	Results	Comments
	- The associations between chronic conditions and first RSV hospitalisation were analysed using a Cox regression model stratified for sex and exact date of birth using age as the underlying time variable - The associations are reported as incidence rate ratios with Wald type 95% CIs - All variables were entered in one final multivariate model with no variable selection procedures - Chronic conditions were adjusted for each other and for all potential confounders in one single model - Proportionality assumptions in the Cox model were tested using Schoenfeld residuals Demographics - Total of 10616(2.7%) had ≥1 diagnosis for chronic disease - Of the hospitalised RSV children 930 (8.8%) had a diagnosis for chronic disease - 7 of 11764 nonsocomially RSV infected children died during their course of RSV		5) Neuromuscular disease - encephalocele: 1.54 (1.14 to 2.08); p=0.005 - spina bifida and malformations of the spinal cord: 2.16 (1.31 to 3.55); p=0.002 - spinal muscular atrophy: 1.02 (0.24 to 4.27); p=0.983 - muscular dystrophy: 2.49 (1.36 to 4.56); p=0.003 - congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia: 1.21 (0.78 to 1.88); p=0.4 - cerebral palsy: 1.59 (1.27 to 1.99); p<0.001 6) Congenital immunodeficiencies 3.80 (2.49 to 5.80) P value<0.001 *Unclear what factors were adjusted for, all variables were entered into 1 final multivariable model with no variable selection procedures	

Study details	Participants	Factors	Results	Comments
	hospitalisation: neurological disease (1), Edwards syndrome (2), multiple malformations (1), malformations without specification (1) - During the study period 118 received ≥1 dose of palivizumab			
Full citation Law,B.J., Langley,J.M., Allen,U., Paes,B., Lee,D.S., Mitchell,I., Sampalis,J., Walti,H., Robinson,J., O'Brien,K., Majaesic,C., Caouette,G., Frenette,L., Le,Saux N., Simmons,B., Moisiuk,S., Sankaran,K., Ojah,C., Singh,A.J., Lebel,M.H., Bacheyie,G.S., Onyett,H., Michaliszyn,A., Manzi,P., Parison,D., The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation, Pediatric Infectious Disease Journal, 23, 806-814, 2004 Ref Id 236040	Cases Infants admitted to hospital for RSV-RTI n=140 infants hospitalised for respiratory tract illness n=66 "cases" had proven RSV infection Diagnostic criteria - RSV proven by viral culture and/or rapid test - The decision to admit a child to hospital for a respiratory illness was made by local nonstudy physicians responsible for each child's care and was not influenced by the child's participation in the study Controls Infants with no RTI hospital admissions during the study follow-up period	Factors 1) Gender (male) 2) ≥2 smokers in household	Odds ratios Incidence of hospitalisation for RSV infection 1) Gender (male) % hospitalised for RSV-RTI who have the risk factor: 4.8% (46 of 961 infants) % hospitalised for RSV-RTI who do not have the risk factor: 2.5% (20 of 796 infants) 2) ≥2 smokers in household % hospitalised for RSV-RTI who have the risk factor: 6.2% (20 of 321 infants) % hospitalised for RSV-RTI who do not have the risk factor: 3.2% (46 of 1437 infants) Final model of predictors of RSV hospitalisation based on factors present in baseline interview Adjusted* odds ratios (95% CI) 1) Gender (male) 1.91 (1.10 to 3.31) P value: 0.02 2) ≥2 smokers in household 1.71 (0.97 to 3.00)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Study sample: Not all infants tested for RSV, however risk factor analysis was restricted to the 66 infants hospitalised with proven RSV RTI - Controls not tested for RSV Indirectness Does the study match the review protocol in terms of: Population: Yes, but included infants at 33 to 35 weeks gestation Outcome: Yes Indirectness: Some Other information Setting

Study details	Participants	Factors	Results	Comments
Country/ies where the study was carried out Canada Study type Prospective cohort Study dates 2000 to 2002 Aim of the study To identify risk factors associated with hospitalisation for RSV infection in infants ≤35 weeks gestation, which could be used to preselect those children most likely to benefit from passive immunisation Source of funding Research grant provided by Abbott Laboratories	n=1692 Inclusion criteria - Infants born from Novmber 1 through to April 30 of the ensuring year (or to the end of the local RSV season if lasting longer than April 30) - Completed from 33 weeks and 0 days through 35 weeks and 6 days of gestation - Home residence lay within a geographical region defined by postal code for each study site Exclusion criteria - Infants given RSV immunoprophylaxis - If parents/guardians did not speak English (or French for participants from Quebec) or did not have a household telephone during the first study year Statistical method - Statistical significance for categoric risk factors was assessed with the chi-squared statistic - Simple logistic regression was used to assess the		P value: 0.064 *Adjusted for month of birth, gender, small for gestational age, subject attending day care, any preschool age siblings, ≥2 smokers in the household, >5 individuals in the home, eczema in the first degree relative	Hospitals: 657 infants were from 11 centres across 7 provinces in study year 1 and 1175 infants from 16 centres across 9 provinces in study year 2 Sample size calculation Sample size of 2000 to provide 880% power to detect a relative risk of ≥1.25 for individual risk factors at a 5% significance level Outcome RSV hospitalisation Data source - Parent/caregiver interviews were repeated monthly, by telephone or in person, after discharge home until the following May 31 or 1 month after the end of the local RSV season - Participating centre medical records were reviewed to abstract data on the nursery course and medical status at discharge and on any emergency room visits and/or hospitalisations for RTI episodes during the course of the study Follow-up

Study details	Participants	Factors	Results	Comments
	statistical significance of continuous risk factors - Within each of the 5 categories of risk factors, those that were significantly associated with hospitalisation for RSV infection in the univariate analysis (p<0.15) were included in multiple logistic regression models - Stepwise selection was used to determine the final logistic regression model Demographics Study population characteristics (n=1832), % - Caucasian: 85 - Male: 54.7 - 33 weeks gestation: 22.7 - 34 weeks gestation: 34.6 - 35 weeks gestation: 42.7 - >5 people living in household: 14 - No smokers: 60.3 - ≥2 smokers: 18.2 - No older siblings: 41 - Twin: 25.8 - Triplet: 2.5 - Received supplemental oxygen: 34 - Received assisted ventilation: 20			- 1860 enrolled, 4 not evaluable: no baseline interview (2), remained in hospital (2) - 1856 followed after discharge home, 24 excluded: lost to follow-up (13), withdrew consent (4), given palivizumab (1), deaths (5), apprehended (1) - 1832 were followed up for at least one month post-discharge and included in analysis - 72 had < complete follow-up: lost to follow-up (32), withdrew consent (14), given palivizumab (12), deaths (3), unknown/other (11) - 1760 (96.1%) completed all follow-up interviews

Study details	Participants	Factors	Results	Comments
	%; n/total with RSV test done - Emergency room visit: 37; 98/265 - Hospitalisation: 69; 96/140 %; n/total positive for RSV - Emergency room visit: 57.1; 56/98 - Hospitalisation: 69; 66/96 Length of hospital stay, days - Mean±SD: 14.0±10.2 - Range: 1 to 86 - Median: 12.0 Medical problems - At discharge 13.9% infants had ≥1 ongoing medical problems: - Apnea of prematurity (1.5%) - Feeding problems (1.6%) - Acyaotic heart disease (2.9%) - Anemia (0.8%)			
Full citation Liese,J.G., Grill,E., Fischer,B., Roeckl-Wiedmann,I., Carr,D., Belohradsky,B.H., Munich RSV Study Group., Incidence and risk factors of respiratory syncytial	Cases Those with RSV-RH n=37 Diagnostic criteria	Factors 1) Male gender 2) Chronic lung disease (defined as oxygen requirements beyond 36 weeks post-conceptual age)	Odds ratios Odds ratio (95%CI) for the risk of RSV-RH 1) Male gender, n/N (%) RSV-RH: 33/37 (89.2)* No RSV-RH: 342/680 (50.3)* Adjusted OR (95%CI): 8.7 (2.6	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported

Study details	Participants	Factors	Results	Comments
virus-related hospitalizations in premature infants in Germany, European Journal of Pediatrics, 162, 230-236, 2003 Ref Id 263303 Country/ies where the study was carried out Germany Study type Retrospective cohort study Study dates November 1 1998 to October 31 1999 Aim of the study To determine incidence and risk factors of RSV-related rehospitalisations (RSV-RH) of premature infants Source of funding Supported by an unrestricted grant from Abbott Laboratories	- Questionnaires sent to all parents, asking whether their child had been hospitalised between the date of discharge from primary neonatal care and May 30 2000 - Questionnaire contained questions regarding the presence of respiratory symptoms at the time of secondary hospitalisation, breastfeeding of the child, prophylactic treatment with monoclonal antibodies against RSV, number of siblings, day care attendance of the child and its siblings, family size, presence of allergic diseases in the family and presence of smokers. - For all children for whom rehospitalisation had been reported by the parents, detailed medical documentation and discharge letters were obtained from the hospitals - Definite RSV-RH was assumed for all patients with ARI-RH*, who had been hospitalised between October and May and had laboratory confirmation via a positive direct RSV antigen test using either an enzyme-linked immunnosorbent assay or an		to 29.1)** p<0.001 2) Chronic lung disease, n/N (%) RSV-RH: 8/37 (21.6)* No RSV-RH: 45/680 (6.6)* Adjusted OR (95%CI): 3.99 (1.4 to 11.2)** p=0.009 *Numbers reported for the univariate analysis **Adjusted for gender, birth weight, gestational age, mechanical ventilation, chronic lung disease, cardiac abnormalities, neurological abnormalities, multiple birth, month of discharge, breast feeding, number of siblings, siblings in day care group, family history of allergies	- Questionnaires - recall bias - Controls are infants who were not hospitalised - unclear if these controls were tested for RSV - Among the 24 infants with probable RSV-RH, 15 were not tested for RSV infection - Only significant results from multivariate analysis reported Indirectness Does the study match the review protocol in terms of: Population: No, all preterm infants. As RSV tests were not regularly performed in all hospitals where infants had been readmitted for ARI-RH, children were classified as having a probable rehospitalisation due to RSV infection, if they had been hospitalised between October and May with such clinical diagnoses typical for RSV infection as acute bronchitis, bronchiolitis, obstructive bronchitis, pneumonia or apnea. Outcome: Yes Indirectness: Some Other information Setting Nine neonatal units in

Study details	Participants	Factors	Results	Comments
	immunofluorescence technique - As RSV tests were not regularly performed in all hospitals where infants had been readmitted for ARI-RH, children were classified as having a probable rehospitalisation due to RSV infection, if they had been hospitalised between October and May with such clinical diagnoses typical for RSV infection as acute bronchitis, bronchiolitis, obstructive bronchitis, pneumonia or apnea *ARI-RH: when at least one of the following symptoms or diagnoses was documented at the time of hospital admission: cough, rhinitis, dyspnea, tachypnea, conjunctivitis, otitis, bronchitis, obstructive bronchitis, bronchiolitis, pneumonia, upper or lower respiratory tract infection Controls Those without RSV-RH n=680 Inclusion criteria - All neonates born at ≤35 weeks of gestation			Southern Germany Sample size calculation Not reported - 1103 infants were enrolled, 754 infants (68.4%) with completed questionnaires, 37 excluded because of prophylactic treatment with palivizumab or because they had been discharged from the NICU after May 30 2000 Outcome RSV-RH: among the 717 included, 37 (5.2%) were rehospitalised either for definite, laboratory-proven (n=13, 1.8%) or probable (n=24, 3.4%) RSV-RH Data sources Questionnaires, medical documentation and discharge letters Other 9 infants were tested negative but had a definite, documented clinical diagnosis of RSV infection

Study details	Participants	Factors	Results	Comments
	- Admitted to one of the nine participating neonatal intensive case units (NICU) between November 1 1998 and October 31 1999 - Discharge alive from NICU before May 30 2000 - Completed medical documentation of primary hospitalisation in NICU from computerized databases or medical discharge letters Exclusion criteria - Infants with suspected nosocomial RSV infection who developed clinical respiratory symptoms or a positive RSV antigen test after day 3 of hospitalisation - Prophylactic treatment with palivizumab or because they had been discharged from the NICU after May 30 2000 Statistical method - The probability of RSV-RH was calculated as the percentage of infants of the cohort who were admitted for RSV-RH - Univariate analyses were conducted to assess whether probable or definite RSV-RH were associated with any of the measured demographic variables and medical risk factors			

Study details	Participants	Factors	Results	Comments
	- Those variables with a p-value <0.2 were included as possible predictors in the modelling procedure - Multivariate analyses using logistic regression with backward selection were carried out to assess the independent influence of the different risk factors - For all statistical tests, a level of significance of 0.05 was used Demographics Gestational age in grams, mean (SD) 32 (3) Birthweight in grams, mean (SD) 1747 (570) Gender, n (%) Male: 375 (52.3) Female: 342 (47.7) Multiple births, n (%) Single births: 484 (67.5) Twin births: 189 (26.4) Triplet births: 44 (6.1) Mechanical ventilation, n (%) Chronic lung disease: 53 (7.4) Breastfeeding, n (%) 569 (79.5)			

Study details	Participants	Factors	Results	Comments
	*The above characteristics are for all 717 preterm infants			
Full citation Mansbach,J.M., Emond,J.A., Camargo,C.A.,Jr., Bronchiolitis in US emergency departments 1992 to 2000: epidemiology and practice variation, Pediatric Emergency Care, 21, 242-247, 2005 Ref Id 207526 Country/ies where the study was carried out USA Study type Retrospective cohort Study dates 1992 to 2000 Aim of the study To describe the epidemiology of US emergency department visits for bronchiolitis, including the characteristics of children presenting to the emergency department and	Cases - Children <2 years old from 1992 to 2000 presenting to the emergency department with bronchiolitits ICD-9-CM code 466 - From 1992 to 2000, bronchiolitis accounted for approximately 1,868,000 emergency department visits for children <2 years old Diagnostic criteria - Based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes - Code 466 captures both bronchiolitis and bronchitis, code 466.1 is for acute bronchiolitis (70% of the final sample had code 466.1) Controls - Patients <2 years old from 1992 to 2000 presenting to the emergency department without a bronchiolitis ICD-9-CM code	Factors 1) Gender 2) Race (White, Black, other) 3) Ethnicity (Non-hispanic, Hispanic)	Odds ratios Multivariate predictors of patients younger than 2 years with bronchiolitis being admitted to the hospital from the emergency department from 1992 to 2000 Odds ratio* (95% CI) 1) Gender - Female (reference) - Male: 1.2 (0.7 to 2.3); p=0.511 2) Race - White (reference) - Black: 1.6 (0.9 to 3.2); p=0.132 - Other: 0.3 (0.03 to 3.4); p=0.365 3) Ethnicity - Non-hispanic (reference) - Hispanic: 2.3 (1.1 to 5.0); p=0.029 - Missing/unknown: 2.1 (0.9 to 4.7); p=0.088 *Odds ratios adjusted for sex, race, ethnicity, insurance status, metropolitan statistical areas,	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: - Using code 466 includes patients with bronchitis and bronchiolitis - 70% of the final sample had the code 466.1 for acute bronchiolitis - Sample size not reported - Relies on coding system to diagnose - Exclusion criteria and diagnostic criteria not described Indirectness Does the study match the review protocol in terms of: Population: No, bronchiolitis cases were identified using an ICD code which captures both bronchiolitis and bronchitis, 70% of final sample had code for acute bronchioltis. Also, study is emergency

Study details	Participants	Factors	Results	Comments
the variability in bronchiolitis care in the emergency department Source of funding Educational grant from Merck	- Rates per 1000 US population were calculated using data from the US Census Bureau, and rates per 1000 emergency department visits were calculated using projected NHAMCS estimated Inclusion criteria - Beginning in 1995, NHAMCS included the age in days for patients who were younger than 1 year. Thus, analyses including patients younger than 6 months were restricted to 1995 to 2000. - See above (cases and controls section) Exclusion criteria Not reported Statistical method - Analysed using chi squared and logistic regression - Linear trends over time were tested with least-squares regression - Compared primary analysis for those children coded as 466 to those coded as 466.1, there were no		region, season and urgent/emergent visit	department based so generasability questionnable. Outcome: Yes Indirectness: Some Other information Setting Emergency departments Sample size calculation Not reported Outcome Admitted to hospital with bronchiolitis (determind by clinical code 466) from the emergency department Data sources - US Census Bureau and National Hospital Ambulatory Medical Care Survey (NHAMCS) - NHAMCS is a 4-stage probability sample of visits to randomly selected noninstitutional general and short-stay hospitals, excluding federal, military and Veteran Affairs hospitals in the USA - NHAMC is conducted anually and covers geographic primary sampling units, hospitals within primary sampling units, emergency departments within

Study details	Participants	Factors	Results	Comments
	differences in the multivariate analysis - 7 (1.5%) children had a primary diagnosis of asthma (code 493) and 16 (3.4%) had a diagnosis of asthma in any of the 3 diagnosis fields, there was no difference in the results when these children were removed from the analyses Demographics % cases (95% CI); % controls (95% CI) Sex - Female: 39 (31 to 48); 47 (45 to 48); p=0.01 - Male: 61 (53 to 69); 53 (52 to 55) Race - White: 71 (66 to 75); 71 (69 to 72); p=0.96 - Black: 26 (14 to 39); 26 (25 to 28) - Other: 3 (0 to 7); 3 (2 to 3) Ethnicity - Hispanic: 27 (21 to 33); 20 (19 to 21); p=0.008 - Non-hispanic: 67 (57 to 77); 72 (71 to 74)			hospitals, and patients within emergency departments - Hospital staff collected data during a randomly selected assigned 4-week data period for each of the sampled hospitals, for each year of the study period, when the data forms were completed they were sent to the National Centre for Health Statistics where they were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification

Study details	Participants	Factors	Results	Comments
	Insurance status - Private: 29 (22 to 37); 33 (32 to 35); p=0.03 - Medicare/Medicaid: 54 (46 to 63); 46 (44 to 47) - Other/unspecified: 6 (1 to 11); 7 (6 to 8) - Self-pay: 8 (4 to 12); 11 (10 to 12) - Unknown: 2 (0 to 5); 3 (2 to 3) Season - January to March: 49 (37 to 60); 28 (26 to 30); p<0.001 - April to June: 15 (10 to 20); 24 (22 to 25) - July to September: 10 (1 to 18); 23 (22 to 24) - October to December: 27 (21 to 32); 26 (24 to 27) Urgency - Urgent/emergent (waiting time < 15 minutes/<60 minutes): 50 (40 to 61); 40 (38 to 42); p<0.001 - Nonurgent/nonemergent (waiting time >60 minutes/>120 minutes): 50 (43 to 56); 60 (58 to 61) Time of presentation (for 1995 to 2000)			

Study details	Participants	Factors	Results	Comments
	0:00 to 7:59am: 19 (14 to 24); 15 (14 to 15); p=0.018 8:00am to 3:59pm: 37 (29 to 45); 34 (33 to 36) 4:00pm to 12:59pm: 43 (34 to 53); 50 (49 to 52) 19% (95% CI: 12 to 26) of the cohort were admitted to hospital			
Full citation Nielsen,H.E., Siersma,V., Andersen,S., Gahrn-Hansen,B., Mordhorst,C.H., Norgaard-Pedersen,B., Roder,B., Sorensen,T.L., Temme,R., Vestergaard,B.F., Respiratory syncytial virus infection--risk factors for hospital admission: a case-control study, Acta Paediatrica, 92, 1314-1321, 2003 Ref Id 263566 Country/ies where the study was carried out Denmark Study type Retrospective, matched case-control study Study dates 5 year period 1990 - 1994	Cases Children under 2 years of age admitted with verified RSV infection during the 5 year period from 1990 to 1994 from 2 Danish counties n=1252 individuals representing 1272 cases (20 children admitted twice) Diagnostic criteria - All children with symptoms of respiratory tract infection during the winter season were routinely tested for RSV - The RSV-positive patients were identified from the registers of the microbiological departments - The clinical charts were not reviewed - Detection of RSV antigen was performed by means of commercially available direct	Factors 1) Gestational age (prematurity: ≤32 weeks, 33-35 weeks, 35-37 weeks, 37-39 weeks)	Odds ratios Adjusted* odds ratio (95% confidence interval) for the risk of RSV disease hospitalisation, cases/controls in each category 1) Gestational age (prematurity) ≤32 weeks: 3.88 (2.74 to 7.75), 49/54 33-35 weeks: 1.73 (1.20 to 2.82), 61/139 35-37 weeks: 1.43 (1.10 to 1.97), 119/393 37-39 weeks: 1.18 (1.00 to 1.40), 419/1890 ≥40 weeks: Baseline, 602/3483 *Adjusted for the effects of the other risk factors (birthweight, number of older siblings, smoking in pregnancy, anti RSV titre)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Overlapping group intervals (eg: 33-35 weeks, 35-37 weeks) - No indication that controls have been tested for RSV Indirectness Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information Setting Hospitals Sample size calculation

Study details	Participants	Factors	Results	Comments
Aim of the study To carry out a study of risk factors for hospital admission because of RSV infection in Denmark in children aged less than 2 years of age Source of funding Supported by the Danish Lung Association, the Health Insurance Fund, the Dagmar Marshall Foundation and the Ronald McDonald Children's Charities.	immunofluorescence tests using monoclonal antibodies Controls 5 controls for each case drawn from the Central Office of Civil Registration, matched for sex, month and year of birth and municipality of residence at the time of the patient's admission to hospital n= not reported Inclusion criteria - See above (cases and controls section) Exclusion criteria - Patients in whom the positive sample was obtained more than two days after admission (nosocomial infection) - Infants living outside the 2 counties - Infants living in 2 municipalities within one of the counties but geographically isolated from the remainder of the country Statistical method - Analysis of risk factors was carried out by multivariate conditional logistic			Not reported Outcome RSV hospitalisation Data sources - The Central Office of Civil Registration supplied data on the controls - The Medical Birth Register supplied data on gestational age, birthweight and maternal smoking during pregnancy - Information on duration of hospital admission was obtained from hospital files - Statistics Denmark provided information on the population in the 2 counties Other Although this study also examines young age and gender as risk factors, the confidence intervals of relative risks/odds ratio have not been provided and the data to calculate confidence intervals is not presented - this data has therefore not been extracted

Study details	Participants	Factors	Results	Comments
	regression (using the SAS PHREG procedure) - The levels of the risk factors were divided into 4 equally sized classes in order to assess the effect of the level without assuming linearity. The division of gestational age, however was in unequally sized classes in accordance with the division used in other RSV studies. Demographics Gestational age in weeks, median (interquartile range) Cases: 39 (38 to 40) Controls: 40 (39 to 40) Birthweight in kg, median (interquartile range) Cases: 3.3 (2.9 to 3.7) Controls: 3.5 (3.1 to 3.8) Mothers smoking during pregnancy, % Cases: 44.7 Controls: 32.8			
Full citation Papenburg,J., Hamelin,M.E., Ouhoummane,N., Carbonneau,J., Ouakki,M., Raymond,F., Robitaille,L., Corbeil,J., Caouette,G., Frenette,L., De Serres,G.,	Cases Infants hospitalised for RSV n=460 Infants hospitalised for RSV with a disease severity score ≥2	Factors 1) Age <6 months 2) Prematurity (<37 weeks) 3) History of breast-feeding	Odds ratios Adjusted* odds ratio (95% CI) from multivariate logistic regression model for risk factors comparing setting (hospital vs. clinic) in infants <3 years of age	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample:

Study details	Participants	Factors	Results	Comments
Boivin,G., Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children, Journal of Infectious Diseases, 206, 178-189, 2012 Ref Id 263647 Country/ies where the study was carried out Canada Study type Prospective cohort study Study dates Four consecutive winter seasons (November to April) from 2006-2007 through 2009-2010 Aim of the study To prospectively evaluate human metapnemovirus (hMPV) disease severity determinants among hospitalised and community cases aged <3 years and to compare them to those for RSV Source of funding Supported by the Canadian Institutes of Health Research grant and a	Patients given 1 point for each of the following: admission to PICU, hospitalised for >5 days, require supplemental oxygen therapy (fraction of inhaled oxygen ≥0.3) n=83 Diagnostic criteria - Potential clinic subjects were identified by treating physicians trained regarding selection criteria and had a nasopharyngeal aspirate collected - Hospitalisation was defined as admission for >24 hours to a short-stay unit, pediatric ward, or PICU - Hospitalised subjects were identified by daily review of a registry of all nasopharyngeal apirates, which are collected rountinely in children hospitalised with RTI at this hospital - Mutiplex polymerase chain reaction microarray hybridization assay was used to detect hMPV and respiratory viruses Controls Infants with RSV not admitted to hospital (clinic)		presenting with an acute respiratory infection 1) Age <6 months (vs 18 to 36 months): 4.63 (2.94 to 7.28); cases: 270/460 (58.6%); controls: 30/141 (21.3%) 2) Prematurity (<37 weeks): 1.29 (0.68 to 2.43); cases: 57/460 (12.4%), controls: 16/141 (11.4%) 3) History of breast-feeding: 0.55(0.33 to 0.92); cases: 341/460 (74%); controls: 25/141 (17.7%) *Adjusted for each of the above as well ≥3 children in the household, presence of comorbidity and viral coinfection in the model Adjusted odds ratio (95% CI) from multivariate logistic regression model for risk factors comparing severity score* (≥2 vs. <2) in infants <3 years of age hospitalised with an acute respiratory infection 1) Age <6 months (vs 18 to 36 months): 2.26 (1.31 to 3.89) 2) Prematurity (<37 weeks): 3.08 (1.63 to 5.83) **Adjusted for each of the above as well as viral coinfection	- Enrollment restricted from to weekdays - Unclear if other underlying comorbidities unclude low birth weight and prematurity Indirectness Does the study match the review protocol in terms of: Population: Yes, but 34.5% of infants hospitalised for RSV were diagnosed with pneumonia Outcome: Yes Indirectness: Some Other information Setting Outpatients at the Sainte-Foy pediatric clinic and inpatients at the CHUQ Sample size calculation Not reported Outcome - Severity of RSV - RSV hospitalisation Data source - In both settings, standardised questionnaires were administered to the patient's parents/guardians at

Study details	Participants	Factors	Results	Comments
research grant from MedImmune	n=141 Infants hospitalised for RSV with a disease severity score <2 Patients given 1 point for each of the following: admission to PICU, hospitalised for >5 days, require supplemental oxygen therapy (fraction of inhaled oxygen ≥0.3) n=377 Inclusion criteria - Outpatients to the Sainte-Foy pediatric clinic or hospitalised at the Centre hospitalier universitaire de Quebec (CHUQ) for symptomatic acute RTI - Outpatients were required to manifest signs/symptoms of lower RTI, defined as the presence of cough and either fever (≥38 degrees) or suggestive findings on auscultation (rales/wheezing) - Study nurses enrolled patients from Monday to Friday Exclusion criteria Ineligible hospitalised patients who had a			enrollment and at 1-month follow-up telephone interview - Medical records of hospitalised subjects were reviewed after discharge Other - Recruitment was delayed until December in 2009-2010 because of resource reallocation associated with pandemic 2009 A/H1h1 influenza - Also report risk factors of severe hMPV

Study details	Participants	Factors	Results	Comments
	nasophayngeal aspirate collected: - RTI symptoms >7 days duration at recruitment (n=468) - Hospitalised in the preceding 14 days (n=107) - >3 years of age (n=418) - Not in hospital during recruitment times (n=209) - Already recruited for episode of RTI (n=18) - Refused to pariticipate (n=25) - Parents/guardians not avaliable (n=35) - Spoke neither French or English (n=5) - Unavailable for 1-month follow-up interview (n=12) - Insufficient specimen or specimen lost (n=10) Did not have a nasopharyngeal aspirate collected within 24 hours of presentation Statistical method - Proportions and distributions compared using chi-squared or Fisher exact test			

Study details	Participants	Factors	Results	Comments
	- Continuous compared using student or Wilcoxon rank-sum test - Univariate and multivariate logistic or log-binomial regression analyses were performed to examine the association between risk factors and disease severity - Variables with a univariate P value of ≤0.2 and potential confounding factors were considered for inclusion in multivariate logistic regression models Demographics Daignosis (>1 discharge diagnosis allowed), n(%) - Bronchiolitis RSV hospital: 389(84.6) RSV clinic: 78(55.3) - Pneumonia RSV hospital: 159(34.5) RSV clinic: 2(1.4) - Apnea RSV hospital: 6(1.3) RSV clinic: 0 - Others include: reactive aiway disease exacerbation, otitis media, URTI, croup, pharyngitis, sinusitis and cystic fibrosis exacerbation hMPV			

Study details	Participants	Factors	Results	Comments
	Clinic: 58 of 305 infants identified (19%) Hospitalised: 69 of 734 infants identified (9.4%) Hospital (n=734); clinic (n=305); RSV hospital (n=460); RSV clinic (n=141) Age, months - <6, n(%): 378(51.5); 62(20.3); 270(58.6); 30(21.3) - 6 to 11, n(%): 150 (20.4); 98 (32.1); 77 (16.7); 45 (31.9) - 12 to 17, n(%): 94 (13); 68 (22.3); 48 (10.4); 31 (22) 18 to 23, n(%): 57 (8); 50 (16.4); 32 (6.9); 23 (16.3) 24 to 29, n(%): 32 (4.3); 18 (6); 21 (4.6); 11 (7.8) 30 to 35, n(%): 23 (3.1); 9(3); 13 (2.8); 1 (0.7) - Mean±SD: 8.7±8.5; 12.8±7.4; 8.0±8.4; 12.5±7.2 - Median (IQR): 5.7 (1.8 to 13.3); 11.7 (6.9 to 18.0); 4.1 (1.7 to 11.9); 10.7(6.9 to 18.0) Female, n(%) 309(42.0); 119(39.0); 196(45.5); 56(39.7) Day care attendance, n(%)			

Study details	Participants	Factors	Results	Comments
	252(34.3); 182(60.0); 311(67.4); 81(57.5) Gestational age, weeks - Premature (<37), n(%): 107(14.6); 31(10.1); 57(12.4); 16(11.4) - Term (≥37), n(%): 627(85.4); 274(89.8); 401(87.0); 121(85.8) - 33 to 36, n(%): 77(10.5); 23(7.5); 46(10); 11(7.8) - 29 to 32, n(%): 23(3.1); 8(2.6); 7(1.5); 5(3.6) - <29, n(%): 7(0.9); 0; 4(0.9); 0 - Mean±SD: 38.3±2.5; 38.7±2.2; 38.5±2.2; 38.6±2.4 - Median (IQR): 39 (38 to 40); 39 (38 to 40); 39 (38 to 40); 39 (38 to 40) Birth weight, g - Low (<2500), n(%): 98(13.3); 25(8.2); 52(11.3); 15(10.6) - Mean±SD: 3173±697; 3324±657; 3226±656; 3318±735 - Median (IQR): 3214 (2772 to 3642); 3325 (3027 to 3677); 3221 (2786 to 3642); 3381(2972 to 3720) ≥1 smoker in the household, n(%)			

Study details	Participants	Factors	Results	Comments
	78(10.6); 8(2.6); 45(9.8); 2(1.4) History of breast-feeding, n(%) 537(73.1); 247(81.0); 13(25.0); 25(17.7) Underlying comorbidity, n(%) - Pulmonary disease: 38(5.2); 4(1.3); 17(3.7); 2(1.4) - Heart disease: 29(3.9); 4(1.3); 12(2.6); 1(0.7) - Renal disease: 11(1.5); 3(1.0); 6(1.3); 1(0.7) - Anemia: 4(0.5); 2(0.6); 2(0.4); 0 - Seizure disorder: 22(3.0); 4(1.3); 11(2.4); 0 - Trouble swallowing: 6(0.8); 0; 2(0.4); 0 - Diabetes: 7(0.9); 1(0.3); 3(0.65); 1(0.7) - Other: 42(5.7); 9(2.9); 23(5.0); 6(4.2) Palivizumab RSV immunoprophylaxis during that winter season, n(%) 30(4.1); 7(2.3); 9(2.0); 3(2.1)			
Full citation	Cases	Factors 1) Postnatal age<30 days	Odds ratios	Limitations

Study details	Participants	Factors	Results	Comments
Papoff,P., Moretti,C., Cangiano,G., Bonci,E., Roggini,M., Pierangeli,A., Scagnolari,C., Antonelli,G., Midulla,F., Incidence and predisposing factors for severe disease in previously healthy term infants experiencing their first episode of bronchiolitis, Acta Paediatrica, 100, e17-e23, 2011 Ref Id 207818 Country/ies where the study was carried out Italy Study type Prospective cohort Study dates Five epidemic seasons: October to May of 2004/2005, 2005/2006, 2006/2007, 2007/2008 and 2008/2009 Aim of the study To determine the incidence of severe bronchiolitis and factors predicting disease severity in previously healthy term infants <12 months of age hospitalised	Subjects with severe bronchiolitis n=16 Diagnostic criteria - Severe bronchiolitis was defined as need for ventilatory support in a PICU. - Infants were retrospectively grouped according to the worst severity of bronchiolitis experienced during their admission: 1) Group 0: conservative treatment, no need for supplemental oxygen or intravenous fluids 2) Group 1: intravenous fluids or oxygen treatment or both for <12 hours 3) Group 2: oxygen for more than 12 hours without ventilatory support and intravenous fluids 4) Group 3: either mechanical ventilation or noninvasive respiratory support (mechanical ventilation was used primarily for infants who had severe respiratory failure not responding to nasal ventilation or with severe apnoea spells) Controls		Adjusted* odds ratio (95%CI) for pediatric intensive care unit admission for respiratory support compared with hospital admission to the short stay unit 1) Postnatal age <30 days: 8.382 (2.352 to 29.864), p=0.001, raw data not reported *Adjusted for, birth weight, RSV infection, lymphocytes, pulmonary consolidation and CRP	Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - No major limitations Indirectness Does study match review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information Setting PICU Sample size calculation Not reported, 310 were enrolled Outcome Paediatric intensive care unit admission Data sources Epidemiological, clinical and demographic data were obtained from parents with a structured questionnaire and from patients medical files Other From 1 to 3 days after hospitalisation, all infants underwent nasal washing: of

Study details	Participants	Factors	Results	Comments
for their first episode of bronchiolitis Source of funding Not reported	Subjects with hospital admission to the short stay unit n=294 Inclusion criteria - All consecutive term infants <12 months of age admitted to the Department of Emergency Paediatrics and PICU, University of Rome - During 5 epidemic seasons October to May of 2004/2005, 2005/2006, 2006/2007, 2007/2008 and 2008/2009, for their first episode of bronchiolitis* (5 year study period was chosen to collect an adequate number of infants while minimizing the effect of changing standards of care) *Bronchiolitis was diagnosed clinically according to the presence of a history of upper respiratory tract infection followed by acute onset of respiratory distress with cough, tachypnea, retractions and bilateral crackles on auscultation, having wheezing alone was not considered sufficient for inclusion in the study Exclusion criteria			310 specimens tested, 172 tested positive for 14 respiratory viruses; 73.6% were RSV positive

Study details	Participants	Factors	Results	Comments
	- Premature infants with a gestational age <37 weeks - Infants weighing <2000g at birth - Infants with underlying chronic diseases, cystic fibrosis or other chronic pulmonary diseases, congenital heart disease and immunodeficiency likely to increase the risk for severe bronchiolitis - Infants with previous wheezing episodes Statistical method - A one-way analysis of variance ANOVA and Student t-test were used to compare continuous variables - Multivariate analyses with logistic regression enter method were used to select variables independently associated with the severity of bronchiolitis Demographics Gender, % male 50.5 Age, % <6 months: 92.6 <3 months: 67.1 <1 month: 14.5 Gestational age in weeks,			

Study details	Participants	Factors	Results	Comments
	mean (SD), range 38.8 (1.3), 37 to 42 Birth weight in kg, mean (SD), range 3.1 (0.5), 2.040 to 4.840 Postnatal age on admission, median (interquartile range) 61 (33 to 99)			
Full citation Pezzotti,P., Mantovani,J., Benincori,N., Mucchino,E., Di Lallo,D., Incidence and risk factors of hospitalization for bronchiolitis in preterm children: a retrospective longitudinal study in Italy, BMC Pediatrics, 9, 56-, 2009 Ref Id 263684 Country/ies where the study was carried out Italy Study type Retrospective cohort Study dates 2002 to 2006 Aim of the study To evaluate the incidence and risk factors of	Cases First hospitalisation for bronchiolitis identified by ICD-9 code 466.11 or 466.19 within the first 18 months of life n=137 Diagnostic criteria - Identified by International Classification of Disease ninth revision (ICD-9) codes 466.11 or 466.19, reported as either the first or secondary diagnosis - Only code 166.11 refers to bronchiolitis due to RSV, also included codes for "other" or "unkown" etiologies because the etiology of bronchiolitis is very often not determined because it does not change the course of treatment in infants	Factors 1) Gender (male vs. female) 2) Age, months (<6 vs. ≥12) 3) Gestational age* (per 1 week less) 4) Broncho dysplasia (yes vs. no)** 5) CHD (yes vs. no)** *Study referes to <32 weeks and 32-36 weeks when described in the statistical analysis **Based on ICD-9 codes	Odds ratios Crude (CIRR) and adjusted* (AIRR) (95% CI) incidence rate ratios for hospitalisation for bronchiolitis in the first 18 months of age in premature infants from 2000 to 2006 1) Gender (male vs. female) Number hospitalised/Total male: 85/1282 Number hospitalised/Total female: 52/1125 CIRR: 1.47 (1.03 to 2.08), p=0.03 AIRR: 1.48 (1.04 to 2.10), p=0.03 2) Age, months <6 vs. ≥12 CIRR: 11.75 (5.44 to 25.35), p<0.01 AIRR: 14.54 (6.75 to 31.35), p<0.01	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: - Bronchiolitis hospitalisation based on ICD-9 codes (including codes for bronchioitis due to RSV and other or unknown etiologies) - Outcome of interest: Gestational age (per 1 week less) description for the incidence rate is unclear Indirectness Does the study match the review protocol in terms of: Population: All infants premature (<36 weeks gestation) Outcome: Yes Indirectness: Some

Study details	Participants	Factors	Results	Comments
hospitalisation for bronchiolitis in preterm infants and the use and impact of Palivizumab, a monolonal antibody Source of funding No competing interests to delcare	Controls Population of infants in Rome not hospitalised for bronchiolitis n=2270 Inclusion criteria - Preterm infants (<36 weeks gestation) - Born between 2000 and 2006 - Mothers at the time of delivery were living in the catchment area of two local health units Exclusion criteria Not reported Statistical method - The incidence rate was calculated as the ratio of hospitalisations for bronchiolitis within 18 months of age out of the person-time at risk - For each child, the person-time at risk was calculated from the date of discharge after delivery until the first hospitalisation from bronchiolitis, the date the child turned 18 months of		6 to 11 vs. ≥12 AIRR: 5.98 (2.68 to 13.35), p<0.01 3) Gestational age (per 1 week less) CIRR: 1.08 (1.02 to 1.14); p=0.01 AIRR: 0.97 (0.88 to 1.07), p=0.58 4) Broncho dysplasia (yes vs. no) Number hospitalised/Total with BPD: 6/61 Number hospitalised/Total without BPD: 131/2346 CIRR: 2.08 (0.91 to 4.75), p=0.08 AIRR: 1.70 (0.68 to 4.28), p=0.26 5) CHD (yes vs. no) Number hospitalised/Total with CHD: 3/34 Number hospitalised/Total without CHD: 134/2373 CIRR: 1.63 (0.51 to 5.18), p=0.41 AIRR: 1.64 (0.52 to 5.19), p=0.40 *Adjusted for all characteristics: age of mother, parity, years of education, birth	Other information Setting Two local health units in the Lazio region, central Italy, Rome Sample size calculation Not reported Outcome Bronchiolitis hospitalisation Data source Linked data from 4 health administrative databases in the Lazio region: the birth register, the hospital discharge register, the two ad-hoc databases that record the doses of Palivizumab administered at two local health units Other - Initally cases included hospitalisation for bronchiolitis before the age of three, but was then restricted to the first 18 months, since only 6 cases had >1 hospitalisation for bronchiolitis and only 2 cases were hospitalised after 18 months of age - Also report the use of Palivizumab in preterm infants

Study details	Participants	Factors	Results	Comments
	age, and the first of January 2007 - Incidence rates of hospitalisation for bronchiolitis were also calculated stratifying for several of the infants' characteristics at birth and maternal characterisitcs, and also for the age of infants - Crude and adjusted incidence rate ratios of bronchiolitis hospitalisations for characteristics were estimated using univariate and multiple Poisson models Demographics Incidence rates N; person years; cases; rate per 100 person years (95% CI) Parity 0: 1457; 1773.2; 77; 4.34 (3.47 to 5.43) 1: 679; 807.77; 45; 5.57 (4.16 to 7.46) Gender Male: 1282; 1535.2; 85; 5.54 (4.48 to 6.85) Female: 1125; 1377.3; 52; 3.78 (2.88 to 4.95) Birth weight, g		country of mother, gender, calender year, age, epidemic period, birth weight, gestational age, apgar score, broncho-dysplasia and CHD	and adjusted odds ratios by several characteristics

Study details	Participants	Factors	Results	Comments
	<1000: 152; 161.96; 15; 9.26 (5.58 to 15.36) 1000 to 2000: 786; 911.71; 60; 6.58 (5.11 to 8.48) >2000: 1469; 1838.8; 62; 3.37 (2.63 to 4.32) Gestational age, weeks <32: 516; 585.24; 34; 5.81 (4.15 to 8.13) 32 to 35: 1891; 2327.3; 103; 4.43 (3.65 to 5.37) Palivizumab 324 (13.5%) infants received ≥1 dose of, median of 4 doses received per infant			
Full citation Ricart,S., Marcos,M.A., Sarda,M., Anton,A., Munoz-Almagro,C., Pumarola,T., Pons,M., Garcia-Garcia,J.J., Clinical risk factors are more relevant than respiratory viruses in predicting bronchiolitis severity, Pediatric Pulmonology, 48, 456-463, 2013 Ref Id 263778 Country/ies where the study was carried out	Cases Children with severe bronchiolitis: those who reached a maximum bronchiolitis clinical score (BCS) equal to or greater than 11 points at admission or during hospital stay n=82 Diagnostic criteria - The BCS is a modified Wood Downes score that assesses auscultation, transcutaneous haemoglobin saturation, respiratory effort and heart	Factors 1) BPD: defined by Jobe and Bancalari - criteria not reported 2) Hemodynamically significant CHD: defined either by the use of medication to control congestive heart failure, infants with moderate to severe pulmonary hypertension or with cyanotic heart disease 3) Gestational age <37 weeks	Odds ratios Univariate analysis assessing risk factors for severe bronchiolitis 1) BPD: non severe group - 4/328 (1.2%), severe group - 6/82 (7.3%) 2) CHD: non severe group - 7/328 (2.1%), severe group - 5/82 (6.1%) 3) Premature birth: non severe group - 41/328 (12.5%), severe group - 21/82 (25.6%) Adjusted** odds ratio for severe bronchiolitis (95%CI) 1) BPD: 7.2 (1.2 to 43.3),	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist - No major limitations Indirectness Does the study match the review protocol in terms of: Population: Yes Outcome: Yes Indirectness: None Other information

Study details	Participants	Factors	Results	Comments
Spain Study type Prospective cohort Study dates Children admitted between October 2007 and October 2008 Aim of the study To assess the clinical factors and the viruses involved in cases of severe bronchiolitis, defining severity according to the respiratory burden using a bronchiolitis clinical score (BCS). Also, to investigate the clinical factors and specific respiratory viruses that can be used to predict a severe outcome of the disease at admission. Source of funding Funded by a grant from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, the Fundació Sant Joan de Deu and the Agencia de Gestio d'Ajuts Universitaris i de Recerca	rate and respiratory rate according to age, with a score ranging between 0 to 16 points - BCS was assessed daily and the highest score observed during the hospitalisation was retained for determination of the severity of the disease (maximum BCS) - Patients were admitted to hospital if one of the following criteria was present: pulse oximetry less than 92% on room air persistently during the stay in emergency room (minimum 1 hour), poor feeding with risk of dehydration, apnea, moderate bronchiolitis defined as a BCS ≥6 points, known cardiorespiratory disease (CHD or BPD) or young age of the child (less than 4 weeks). - Criteria for PICU admission were acute respiratory failure with severe hypoxemia (pulse oximetry <90% with oxygen supplementation > 40%), sepsis (defined according to International Consensus Conference on Pediatric Sepsis 2005), frequent apnea requiring vigorous stimulation, severe		p=0.031 2) Hemodynamically significant CHD: 4.7 (1.1 to 19.9), p=0.038 3) Gestational age <37 weeks: 2.6 (1.3 to 5.1), p=0.005 **Adjusted for BPD, hemodynamically significant CHD, gestational age <37 weeks, temperature >38 degrees, age at admission, human rhinovirus (HRV), human respiratory syncytial virus (HRSV)	Setting Paediatric ward or PICU of a tertiary university hospital Sample size calculation Not reported, however, 563 admitted for bronchiolitis, 53 excluded for meeting at least one of the exclusion criteria 23 because of insufficient nasopharngeal aspirate sample and 3 for not meeting the standardised admission criteria (admitted for parental discomfort or lack of follow up). 484 hospitalised infants included. Outcome Severe bronchiolitis (see cases section for definition) Data sources - Demographic, epidemiologic, clinical and laboratory data were obtained using a standardised questionnaire. Recorded variables included age, sex, birth history (gestational age and birth weight), need for neonatal admission, use of palivizumab prophylaxis, personal history of atopy, family history of asthma or atopy in the first degree relatives, and presence of underlying chronic conditions. - In the emergency room, weight, vital signs, severity

Study details	Participants	Factors	Results	Comments
	bronchiolitis or pneumonia, acidosis (pH less than 7.1) or rapidly progressing disease. Controls Children with non-severe bronchiolitis: those with maximum bronchiolitis clinical score less than 11 points n= 328 Inclusion criteria - Infants <12 months with acute bronchiolitis* hospitalised from October 2007 to October 2008 in the pediatric ward or the PICU of a tertiary university hospital in Spain *Bronchiolitis was diagnosed according to the presence of the first acute respiratory tract infection characterised by respiratory distress (tachypnea, use of accessory muscles), cough, widespread crackles, wheezing or both, associated with signs of viral infection (coryza) Exclusion criteria - Underlying chronic pulmonary disease other			according to BCS, days of coryza and days of respiratory effort prior to admission and history of fever registered by the caretakers 48 hours prior to admission were recorded. - During inpatient management, various clinical, laboratory and microbiological measures were recorded. Other A nasopharyngeal aspirate was collected in the emergency room or within the first 24 hours of admission. The most common pathogen was HRSV (43.1%).

Study details	Participants	Factors	Results	Comments
	than pulmonary bronchodysplasia (in order to not exclude patients born prematurely, who are known to be at risk for severe bronchiolitis) - Recurrent wheezing episodes - Apnea secondary to a known disease (gastroesophageal reflux demonstrated by pH metry or esophago-gastroduodenal transit, metabolic or neurologic disease) - Respiratory symptoms due to bronchoaspiration Statistical method - Bivariate associations were assessed with Student's t-test for normally distributed variables and Mann-Whitney U test for non-normally distributions. P values <0.05 were considered significant. - Multivariate logistic regression analyses were used to evaluate the risk factors for severe disease - Univariate models were first performed and subsequently, the variables with a significant association (p<0.1) and variables known as potential confounders (palivizumab immunoprophylaxis and			

Study details	Participants	Factors	Results	Comments
	HRSV infection) were introduced into the multivariate models with a step-wise approach to eliminate the possibility of mutual confounding and interaction Demographics Gender, n (%) Male: 237 (57.8) Female: 173 (42.2) Age in months, median (interquartile range) 1.9 (1.1 to 3.9) Weight at admission in kg, median (interquartile range) 4.8 (3.9 to 6.2) Prematurity (gestational age <37 weeks), n (%) 67 (16.3) Underlying chronic conditions, n (%) CHD: 12 (35.3)* BPD: 10 (29.4)* Polymalformative syndrome or chromosomopathy: 8 (23.5)* Severe neurologic impairment: 4 (11.8)* *Numbers in parentheses represent the percentage calculated for patients with			

Study details	Participants	Factors	Results	Comments
	an underlying chronic illness Admission, n (%) PICU: 58 (14.1) Pediatric ward: 352 (85.9) BCS at admission, median (interquartile range) 7 (5 to 9)			
Full citation Rietveld,E., Vergouwe,Y., Steyerberg,E.W., Huysman,M.W., de Groot,R., Moll,H.A., RSV Study Group, Hospitalization for respiratory syncytial virus infection in young children: development of a clinical prediction rule, Pediatric Infectious Disease Journal, 25, 201-207, 2006 Ref Id 263783 Country/ies where the study was carried out The Netherlands Study type Retrospective cohort study Study dates Children born between January 1, 1996 and December 31, 1998	Cases Children hospitalised for proven RSV infection n= 2469 Diagnostic criteria RSV infection confirmed by a positive direct immunofluorescent assay or viral culture of nasopharyngeal aspirates. The decision to hospitalise for severe RSV disease was based on standard diagnostuc criteria - feeding problems, dyspnea or apnea. Controls Children not hospitalised for RSV infection n= not reported Inclusion criteria - Children hospitalised* for severe RSV disease who	Factors 1) Gestational age ≤28 weeks, 29 to 32 weeks, 33 to 34 weeks, 35 to 36 weeks versus ≥37 weeks 2) Presence of BPD: defined as the need for supplemental oxygen on day 28 after birth or at the postconceptional age of 36 weeks, in the presence of typical abnormalities on the chest roentgenogram 3) Gender	Odds ratios Adjusted*** odds ratios (95%CI) for hospitalisation for RSV infection* 1) Gender Male: 1.4 (1.3 to 1.5) Female**: 1 2) BPD Confidence intervals could be calculated and therefore this data has not been extracted 3) Gestational age in weeks ≤28: 3.2 (2.1 to 4.8) 29 to 32: 2.8 (2.1 to 3.8) 33 to 34: 2.3 (1.8 to 3.0) 35 to 36: 1.6 (1.3 to 1.9) ≥37**: 1 *Raw data not reported **Reference category ***The final prediction rule included gender, gestational age, birth weight, BPD, age (with and without BPD)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist - Number of controls not reported and unclear whether controls were tested for RSV Indirectness Does the study match the protocol in terms of: Population: no, bronchiolitis or pneumonia were diagnosed in 93% whereas most of the remaining hospitalised children were diagnosed with upper respiratory tract infection Outcome: yes Indirectness: some Other information Setting Southwestern part of the Netherlands – all hospitals with a pediatric ward in this region

Study details	Participants	Factors	Results	Comments
Aim of the study To develop a clinical prediction rule to estimate the monthly risk of hospitalisation for severe RSV disease in young children Source of funding Supported by The Health Care Insurance Council of the Netherlands	met the following criteria: 1) Born between January 1, 1996 and December 31, 1998 2) Age younger than 1 year at the beginning of the RSV season or younger than 2 years for children with BPD 3) Hospitalisation in one of the 29 hospitals in the region 4) Hospitalisation during 1 of 3 RSV seasons 1996/1997, 1997/1998, and 1998/1999 (October 1 until April 30) 5) RSV infection confirmed by a positive direct immunofluorescent assay or viral culture of nasopharyngeal aspirates *The decision to hospitalise for severe RSV disease was based on standard diagnostic criteria (feeding problems, dyspnea or apnea) Exclusion criteria - Children with nosocomial infections (defined by a positive RSV test >5 days after hospital admission for a cause other than RSV disease) - Infants who died within the first 4 weeks of live (neonatal mortality)			Sample size calculation Not reported, 2469 hospitalised for RSV disease Outcome RSV hospitalisation Data sources - Routinely documented information was collected from medical records, in standardised forms - The registry of virologic diagnostic assays was used to identify the children in each hospital

Study details	Participants	Factors	Results	Comments
	Statistical method - The monthly risk of hospitalisation for RSV infection was modelled with logistic regression analysis - Missing values: of all hospitalised children, 4.7% of the predictor values were missing (for gestational age, birth weight and BPD). - Missing values on gestational age and birth weight were reduced with a questionnaire sent to the parents. Remaining missing values on gestational age ad birth weight were either imputed according to their strong intercorrelation and the correlation with gender as found in the complete population with regression analysis. - If this was not possible because both gestational age and birth weight were missing, values were randomly drawn from the distributions as observed in the data that were collected with the questionnaires - Missing values on BPD were imputed as no BPD Demographics Gender, n Male: 1463			

Study details	Participants	Factors	Results	Comments
	Female: 1006 Gestational age in weeks, n ≤28: 35 29 to 30: 30 31 to 32: 48 33 to 34: 105 35 to 36: 164 ≥37: 2087 Birth weight in grams, n ≤2500: 394 2501 to 3000: 443 3001 to 3500: 770 3501 to 4000: 609 >4000: 253 BPD, n Yes: 35 No: 2434 Age in months, n 0: 120 1 to 3: 1120 4 to 6: 632 >6: 597 *The above characteristics are of the 2469 hospitalised children			
Full citation Rossi,G.A., Medici,M.C., Arcangeletti,M.C., Lanari,M., Merolla,R., Paparatti,U.D., Silvestri,M., Pistorio,A., Chezzi,C., Osservatorio RSV Study	Cases Over 4 consecutive RSV seasons (2000-2004), records from children ≤4 years of age admitted for RSV-induced LRTI	Factors 1) Chronological age at the beginning of RSV season, months (<3, 3-5, 6-11, ≥12)	Odds ratios Risk factors associated with a higher liklihood to aquire RSV-induced lower respiratory tract infection severe enough to lead to hospitalisation over four	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported

Study details	Participants	Factors	Results	Comments
Group., Risk factors for severe RSV-induced lower respiratory tract infection over four consecutive epidemics, European Journal of Pediatrics, 166, 1267-1272, 2007 Ref Id 243429 Country/ies where the study was carried out Italy Study type Prospective, case-control Study dates 4 consecutive winter epidemics (2000-2004) Aim of the study To use the data collected to identify, by means of logistic regression analysis, risk factors associated with higher likelihood to acquire RSV-induced lower respiratory tract infection in children with symptoms severe enough to lead to hospital admission Source of funding The study "Osservatorio VRS" was sponsored by Abbott S.p.A., Italy	n=145 Diagnostic criteria - All consecutive children, aged ≤4 years of age, referred to emergency departments for acute respiratory infection on one day of the week (Tuesday), between 8am and 2pm, during the expected epidemiological seasons (October to April) were enrolled and tested for RSV - Medical history and physical examination were recorded and evaluated and clinical assessment, including nasal secretion specimens for RSV detection, were obtained according to the usual protocol for each hospital - Nasal secretion samples were sent to the microbiology laboratory of each hospital to check for RSV by an immunoenzymatic test within 24 hours, other respiratory viruses were not tested Controls - Children ≤4 years of age with LRTI not due to RSV and not requiring hospitalisation		consecutive winter epidemics (2000-2004) Cases n(%); controls n(%); odds* ratio (95% CI); p value 1) Chronological age at the beginning of RSV season - ≥12 months: 6(4.1); 48(16.4); reference; p<0.0001 - 6-11 months: 31(21.4); 98(33.6); 2.467 (0.879 to 6.925), p<0.0001 - 3-5 months: 48(33.1); 85(29.1); 4.153 (1.506 to 11.451) - <3 months: 60(41.4); 61(20.9); 8.462 (3.088 to 23.185) *Adjusted for birth weight, birth order	Study sample: Restricted recruitment times (Tuesdays 8am-2pm) Indirectness Does the study match the review protocol in terms of: Population: No, included infants less than or equal to 4 years of age Outcome: Yes Indirectness: Some Other information Setting Pediatric centres scattered over the Italian national territory Sample size calculation Not reported Outcome RSV-induced LRTI hospitalisation Data sources Used previous "Osservatorio" study database

Study details	Participants	Factors	Results	Comments
	- All controls should have come from the same residence areas as case-patients n= 295 Inclusion criteria - During a given study year, children were considered eligible based on their first LRTI during that year - See cases and controls section above Exclusion criteria - Children who had received immunoprophylaxis with palivizumab (≤7, each year) - From the cases excluded patients with LRTI induced by agents other than RSV or RSV-positive but not severe enough to require hospitalisation - Since case patients ranged from 0-30 months, control patients aged ≥31 months were excluded - 3 infants excluded because of missing values Statistical method - Bivariate analysis was performed and the comparison of quantitative			

Study details	Participants	Factors	Results	Comments
	variables between two groups of subjects was made calculating the the LR test and reporting the bivarate OR and 95% CI, the comparison of frequency data was performed by the chi-squared test or Fisher's exact test - To evaluate the role of different predictors in the association with the outcome (hospitalisation for RSV), multiple logistic regression analysis (step-down) was performed - Variables that were statistically significant in the bivariate analysis or that were considered a priori important for the outcome were entered in the model - The models' predictive ability investigated by calculating the area under the ROC curve of the model Demographics Gender, n(%): males; females Cases: 61(42.1); 84(57.9) Controls: 124(42.5); 168(57.5) Median age, months Cases: 3.5 Controls: 5			

Study details	Participants	Factors	Results	Comments
	Median birth weight, grams Cases: 3050 Controls: 2175 <36 weeks gestation, n Cases: 17 Controls: 18 No previous RSV infections, n(%) Cases: 126(88.7) Controls: 30(81.0) Birth weight, n(%): ≥2500g; 1500-2499g; <1500g Cases: 113(80.1); 24(17.0); 4(2.8) Controls: 259(92.2); 28(7.2); 2(0.6) Chronic diseases Two case-patients had CHD and five case-patients had a previous history of CLD			
Full citation Semple,M.G., Taylor-Robinson,D.C., Lane,S., Smyth,R.L., Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective	Cases Infants who require oxygen supplementation n=241 Infants who require mechanical ventilation n=51	Factors 1) Prematurity (<37 weeks gestation) 2) Gender (male) 3) Household tobacco smoker (related to current behaviour by any member of the household, the relative	Odds ratios Adjusted* odds ratio (95% CI) for severe bronchiolitis (oxygen supplementation/mechanical ventilation) in 378 infants <2 years of age admitted to hospital during the study period Reference category: No supplemental oxygen needed	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported Study sample: Restricted recruitment times - infants both

Study details	Participants	Factors	Results	Comments
cohort study, PLoS ONE [Electronic Resource], 6, e22425-, 2011 Ref Id 208115 Country/ies where the study was carried out UK Study type Prospective cohort Study dates Three consecutive winter endemic winter seasons (2002/3 and 2003/4 November through February, 2004/5 October through January) Aim of the study To examine demographic, environmental and clinical factors associated with severe bronchiolitis in infants admitted to hospital and quantify the independent effects of these factors Source of funding Funded by a National Clinician Scientist Award to Malcolm G. Semple by the Department of Health	Diagnostic criteria - Diagnosed bronchiolitis when infants (<2 years of age) presented with tachypnea (>50 breaths/min), subcostal recession, and bilateral inspiratory crackles on auscultation - Admission criteria typically involved feeding difficulties, hypoxia in air, respiratory distress or respiratory failure - RSV status was established by a rapid antigen ELISA of nasopharyngeal aspirate sampled on admission Controls Infants who do not require oxygen supplementation n=86 Inclusion criteria - <2 years of age - Admitted to Alder Hey Hospital with bronchiolitis during the study period - See diagnostic criteria above Exclusion criteria	influence of paternal vs, maternal vs. both smoking was not studied, nor was maternal smoking during pregnancy)	1) Premature birth, n Oxygen supplementation - cases: 51/241(23%); controls: 18/86 (21%); OR: 1.01 (0.94 to 1.08), p=0.843 Mechanical ventilation - cases: 27/51 (53%); controls: 18/86 (21%); OR: 0.99 (0.89 to 1.11), p=0.868 2) Gender (male) Oxygen supplementation: cases: 140/241 (58%); controls: 44/86 (51%); OR: 0.77 (0.43 to 1.38), p=0.374 Mechanical ventilation: cases: 31/51 (61%); controls: 44/86 (51%); OR: 1.28 (0.52 to 3.13), p=0.592 3) Household tobacco smoker Oxygen supplementation - cases: 154/241 (64%); controls: 41/86 (48%); OR: 2.23 (1.21 to 4.10), p=0.010 Mechanical ventilation - cases: 32/51 (63%); controls: 41/86 (48%); OR: 7.19 (2.28 to 22.60), p=0.001 *Adjusted for gestation, corrected age on admission, sex, family history of atopy, birth weight, index of multiple deprivations 2004 and weight on admission, household tobacco smoker	admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed. Indirectness Does the study match the review protocol in terms of: Population: Yes Outome: Compared need for oxygen supplementation and mechanical ventilation (all infants are admitted to hospital) Indirectness: None Other information Setting Alder Hey Children's Hospital, Liverpool Sample size calculation - No prior calculation made, but 10 to 15 cases required for each explanatory variable included in a multivariate logistic regression model - HES data for the duration of the study showed that 595 infants admitted from the local community were discharged with a final diagnosis of bronchiolitis, if these 445 were admitted for >24 hours

Study details	Participants	Factors	Results	Comments
	- Infants both admitted and discharged on Saturdays and Sundays were not recruited due to restrictions on staff - Previoulsy diagnosed haemodynamically significant congenital heart disease (cyanotic, single ventricle physiology, or acyanotic disease requiring medical therapy) - Infants living outside Liverpool Statistical method - Characteristics of the participants were analysed for association across disease severity groups using Pearson chi-squared test and the Kruskal-Wallis one-way analysis of variance - Multivariate multinomial logistic regression models were constructed to identify associations, the reference category for the outcome variable was "no need for oxygen supplementation" - Variables were rejected in an iterative process (backwards stepwise) where the association with the outcome was not significant (p>0.1)			- Using HES data as a denominator, recuitment to this study included 64% of all admissions and 85% of admission episodes >24 hours Outcome Need for oxygen supplementation or mechanical ventilation Data source - Measured on admission or parents/carers given structured history form at recruitment - Birth to one-year-old sex ratio data for England was derived from the 2001 census - Hospital episode summary (HES) provided an estimate of the total number of infants avaliable for recruitment

Study details	Participants	Factors	Results	Comments
	- All variables were also sequentially included and excluded and rejected where the OR for that variable was between 0.9 and 1.1 - Goodness of fit for each model was tested using Pearson's Chi-square and Deviance Demographics No oxygen supplementation; oxygen supplementation; mechanical ventilation n(%) or mean (95% CI) Gender, male 44(51); 140(58); 31(61) p=0.035 Premature birth (<37 weeks gestation) 18(21); 54(23); 27(53) p<0.001 Gestation, weeks 38.3 (37.6 to 39.0); 38.1 (37.7 to 38.6); 35.8 (34.6 to 36.9) p<0.001 Birth weight, kg 3.04 (2.89 to 3.20); 3.04 (2.94 to 3.15); 2.65 (2.40 to 2.90)			

Study details	Participants	Factors	Results	Comments
	p=0.002 Corrected age on admission, weeks 19.0 (15.3 to 22.3); 18.8 (16.1 to 20.9); 7.6 (3.3 to 11.8) p<0.001 Duration of illness prior to admission, days 4.2 (3.4 to 5.0); 3.6 (3.2 to 3.9); 3.1 (2.5 to 3.6) p=0.080 Atopic family history 44(52); 134(57); 21(45) p=0.608 Household tobacco smoker (Yes/No, %) 41/37 (53); 154/64 (71); 32/6 (84) p<0.001			
Full citation Simon,A., Ammann,R.A., Wilkesmann,A., Eis-Hubinger,A.M., Schildgen,O., Weimann,E., Peltner,H.U., Seiffert,P., Suss-Grafeo,A., Groothuis,J.R., Liese,J., Pallacks,R., Muller,A., DSM RSV Paed Study	Cases Inpatients treated for at least 24 hours with a virologically confirmed RSV infection with need for intensive care n=not reported Diagnostic criteria Positive RSV results by antigen detection, cell	Factors 1) Prematurity: birth before 37 weeks of gestation 2) Born before gestational age of 32 weeks 3) Congenital heart disease (not defined)	Odds ratios Adjusted* odds ratios (95%CI) for ICU admission in inpatients with RSV infection 1) Prematurity: 1.73 (1.08 to 2.72), p=0.0218 2) Born before gestational age of 32 weeks: 2.80 (1.58 to 5.00),	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist - Odds ratios for non-significant results not presented - Exclusion criteria not reported

Study details	Participants	Factors	Results	Comments
Group., Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database, European Journal of Pediatrics, 166, 1273-1283, 2007 Ref Id 263910 Country/ies where the study was carried out Germany Study type Prospective cohort study (multicentre) Study dates 6 consecutive RSV seasons (1 November to 30 April, 1999 to 2005) Aim of the study To facilitate the collection and analysis of detailed information on the population of hospitalised children with RSV infection in Germany Source of funding Partially supported by grants from the Else Kroner-Fresenius Foundation and the	culture methods, or PCR testing were reported within a few hours to the attending physicians. Controls Inpatients treated for at least 24 hours with a virologically confirmed RSV infection without the need for intensive care n=not reported Inclusion criteria - All inpatients treated for at least 24 hours with a virologically confirmed RSV infection, irrespective of age, underlying illness and other comorbidities Exclusion criteria Not reported Statistical method Exact logistic regression was used for both univariate and multivariate analysis. For multivariate analysis, the stepwise forward variable selection procedure was chosen, which starts with a model with only the variable most significantly associated in univariate analysis and resulting in a model incorporating all variables		p=0.0001 3) Congenital heart disease: 2.97 (1.81 to 4.82), p<0.001 *Adjusted for prematurity, born before gestational age of 32 weeks, CLD, congenital heart disease	Indirectness Does the study match the review protocol in terms of: Population: yes (but RSV) Outcome: yes Indirectness: none Other information Setting 14 pediatric hospitals in Germany Sample size calculation Not reported, 1568 prospectively documented RSV infections, 406 observed in preterms and 1162 in terms Outcome ICU admission Data source A standardised set of 85 clinical and laboratory items was extracted from files, controlled by a neonatologist and entered into a RSV Paed database

Study details	Participants	Factors	Results	Comments
BONFOR programme of the Medical Faculty of the University of Bonn. The development of the DSM RSV Paed software tool was supported by an educational grant from Abbott GmBH, Germany.	signficantly and independently associated with the respective outcome. Demographics Gender, male n/N (%) Terms: 683/1162 (58.8) Preterms: 229/406 (56.4) Age at diagnosis in days, median (interquartile range) Terms: 159 (64 to 340) Preterms: 142 (75 to 288) Gestational age in weeks, median (interquartile range) Terms: 39 (38 to 40) Preterms: 33 (30 to 35) Birthweight in grams, median (interquartile range) Terms: 3450 (3080 to 3650) Preterms: 1950 (1235 to 2490) Congenital heart disease, n/N (%) Terms: 61/1162 (5.2) Preterms: 70/406 (17.2)			
Full citation Wilkesmann,A., Ammann,R.A., Schildgen,O., Eis-Hubinger,A.M., Muller,A., Seidenberg,J., Stephan,V., Rieger,C., Herting,E., Wygold,T., Hornschuh,F.,	Cases Subjects with clinically relevant neuromuscular impairment (NMI)* hospitalised with RSV infection n=73 episodes in 70 patients	Factors 1) Prematurity - not defined 2) Born before gest. wk 32 3) CLDplus - chronic lung disease of prematurity and treatment within the last 6 months before diagnosis of the RSV infection	Odds ratios Results of multivariate logistic regression analysis Odds ratio* (95%CI) for intensive care 1) Prematurity: 1.73 (1.08 to 2.72); p=0.022	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported

Study details	Participants	Factors	Results	Comments
Groothuis,J.R., Simon,A., DSM RSV Ped Study Group., Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course, Pediatric Infectious Disease Journal, 26, 485-491, 2007 Ref Id 264193 Country/ies where the study was carried out Germany Study type Prospective cohort Study dates 6 consecutive RSV seasons: 1999 to 2005 Aim of the study To evaluate whether hospitalised RSV infected children with clinically relevant neuromuscular impairment (NMI) are at an increased risk for a complicated course of RSV infection Source of funding Supported by Abbott GmbH, Else Kroner-	*The NMI group included children with: - hydrocephalus n=3 - cerebral palsy and central hypoventilation syndromes n=41 - genetic defects/chromosomal abnormalities n=8 - neuromuscular disorders n=8 - severe developmental delay n=5 - peripheral nerve defects n=2 - other NMI as CNS neoplasia or epilepsy n=3 Diagnostic criteria All RSV infections were microbiologically confirmed but the study protocol did not stipulate the precise method of detection. The methods involved were antigen detection and cell culture using MS cells. In some participating centres, RSV infection was detected following in house PCR based diagnostic protocols. Controls Subjects without NMI but with RSV infection	4) Congenital heart disease - not defined 5) Neuromuscular impairment (NMI) - NMI was an item to be checked in the primary database by the local nurse and the attending physician. Information obtained from free text fields (admission note, discharge summary) was also used to identify all RSV-infected children with NMI.	2) Born before gest. wk 32: 2.80 (1.58 to 5.00); p<0.001 3) CLDplus: not signficant 4) Congenital heart disease: 2.97 (1.81 to 4.82); p<0.001 5) Neuromuscular impairment: 4.94 (2.69 to 8.94); p<0.001 Odds ratio* (95%CI) for respiratory failure 1) Prematurity: 4.73 (1.96 to 11.94). p=0.001 2) Born before gest. wk 32: not significant 3) CLDplus: 5.42 (2.00 to 14.17), p=0.0008 4) Congenital heart disease: not signficant 5) Neuromuscular impairment: 3.85 (1.28 to 10.22), p=0.017 Odds ratio* (95%CI) for death due to RSV 1) Prematurity: not significant 2) Born before gest. wk 32: not significant 3) CLDplus: not significant 4) Congenital heart disease: not	-Exclusion criteria not reported -Prematurity not defined Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Hospitals Sample size calculation Not reported Outcome Intensive care, respiratory failure, death due to RSV Data sources The DMS RSV Paed database was designed for the prospective multicenter documentation and analysis of all clinically relevant aspects of the management of inpatients with RSV infection. Patients with clinically relevant NMI were identified according to the specific comments of the attending physician.

Study details	Participants	Factors	Results	Comments
Fresenius Stiftung and the BONFOR program of the Medical Faculty of the University of Bonn	n=1495 RSV infections in 1471 patients without NMI Inclusion criteria - All pediatric inpatients with virologically confirmed RSV infection were included irrespective of age, underlying diseases, comorbidities and whether the infection had been acquired in the hospital or in outpatients Exclusion criteria Not reported Statistical method - Exact logistic regression was used for both univariate and multivariate analysis of associations - For multivariate analysis, the stepwise forward variable selection procedure was chosen, which starts with a model with only the variable most significantly associated in univariate analysis, and resulting in a model incorporating all variables signficantly and independently associated with the respective outcome Demographics		significant 5) Neuromuscular impairment: not significant *Adjusted for all other variables listed above plus nosocomial infection	

Study details	Participants	Factors	Results	Comments
	Gender - male, n(%) Neuromuscular impairment group: 43 (58.9) Controls: 869 (58.1) p=0.9 Age at diagnosis in days, median (IQR) Neuromuscular impairment group: 430 (183 to 1268) Controls: 145 (65 to 299) p<0.001 Gestational age in weeks, median (IQR) Neuromuscular impairment group: 38 (33 to 40) Controls: 39 (36 to 40)			
Full citation Zhang,T., Zhu,Q., Zhang,X., Ding,Y., Steinhoff,M., Black,S., Zhao,G., Clinical characteristics and direct medical cost of respiratory syncytial virus infection in children hospitalized in Suzhou, China, Pediatric Infectious Disease Journal, 33, 337-341, 2014 Ref Id 318710	Cases Subjects admitted to ICU for RSV infection n=49 (5.1%) Diagnostic criteria - Nasal aspirate specimen was collected within 24 hours of admission to assess presence of RSV Controls Subjects not admitted to ICU for RSV infection n=910	Factors 1) Sex 2) Age ≤ 6 months 3) Congenital heart disease - not defined 4) Prematurity <37 weeks	Odds ratios Adjusted* odds ratios (95%CI) for severe RSV disease - ICU admission 1) Sex: 1.45 (0.74 to 2.83); p=0.277 2) Age ≤ 6 months: 2.81 (1.36 to 5.80); p=0.005 3) Congenital heart disease: 8.20 (3.10 to 21.70); p<0.001 4) Prematurity: 2.46 (0.81 to 7.47); p=0.113 Adjusted for all other factors	Limitations Based on NICE guidelines manual 2012: Prognostic studies list Only limitations that arise in the study are reported - Although gender was examined, it is not reported whether this was male vs females or vice versa - therefore this data has not been graded - Exclusion criteria not reported

Study details	Participants	Factors	Results	Comments
Country/ies where the study was carried out China Study type Retrospective chart review Study dates January 2005 to December 2009 Aim of the study To describe the epidemiology, clinical features and direct medical cost of laboratory-proven RSV children hospitalised in China Source of funding Partly funded by SINO-US collaborative program on Emerging and Re-emerging Infectious Diseases, a grant from the US CDC influenza branch, a grant from the National Natural Science Foundation of China and Shanghai Leading Academic Discipline Project	Inclusion criteria - Of the total patients, 35.2% (959/2721) children with RSV infection were randomly selected for this chart review study Exclusion criteria Not reported Statistical method Multivariate analyses was conducted to calculate odds ratios along with 95%CIs Demographics Gender, n (%) Male: 644 (67.1) Female: 315 (32.9) Age in months, n (%) ≤6 months: 540 (56.3) 7 to 24 months: 309 (32.2) Over 25 months: 110 (11.4)			Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Tertiary children's hospital Sample size calculation Not reported Outcomes Severe RSV disease - ICU admission Data sources Data abstracted from medical charts by a structured medical record review
Full citation Moyes,J., Cohen,C., Pretorius,M., Groome,M., von,Gottberg A., Wolter,N.,	Cases HIV infected children hospitalised with RSV-	Factors 1) HIV: HIV status was derived from one of the following sources:	Odds ratios Adjusted* OR (95% CI) for the association between HIV and prolonged hospitalisation >5	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist

Study details	Participants	Factors	Results	Comments
Walaza,S., Haffejee,S., Chhagan,M., Naby,F., Cohen,A.L., Tempia,S., Kahn,K., Dawood,H., Venter,M., Madhi,S.A., South African Severe Acute Respiratory Illness Surveillance Group., Epidemiology of respiratory syncytial virus-associated acute lower respiratory tract infection hospitalizations among HIV-infected and HIV-uninfected South African children, 2010-2011, Journal of Infectious Diseases, 208 Suppl 3, S217-S226, 2013 Ref Id 318736 Country/ies where the study was carried out South Africa Study type Prospective cohort study Study dates January 2010 through December 2011 Aim of the study To describe the epidemiologic and clinical characteristics of RSV-associated ALRTI hospitalisation in HIV-	associated ALRTI n=49 Diagnostic criteria - A case of ALRTI was defined as illness fulfilling age-specific clinical inclusion criteria with onset within 7 days of hospitalisation in a child <5 years (see inclusion criteria section for further details) - Nasopharyngeal aspirates were collected within 24 hours of admission. Specimens were tested by real-time reverse transcriptase multiplex PCR assay - HIV status was derived from one of the following sources: 1) testing as part of the prevention of mother to child transmission program for children born to HIV infected mothers 2) hospital records when testing was performed at the discretion of the attending physician 3) and if the pervious 2 sources were not available, HIV testing performed on a dried blood spot specimen obtained through the surveillance program to determine HIV status	- testing as part of the prevention of mother to child transmission program for children born to HIV infected mothers - hospital records when testing was performed at the discretion of the attending physician - and if the pervious 2 sources were not available, HIV testing performed on a dried blood spot specimen obtained through the surveillance program to determine HIV status	days or death Prolonged hospitalisation >5 days 1) HIV infected - 23/49 (47%), HIV uninfected - 132/753 (18%); 4.0 (1.5 to 10.6), p<0.001 Death 1) HIV infected - 9/1153 (1%), HIV uninfected - 3/751 (<1%); 31.1 (5.4 to 179.8), p<0.001 *Unclear what factors were adjusted for	Only limitations that arise in the study are reported - Unclear what factors were adjusted for Indirectness Does the study match the protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Hospital-based Sample size calculation Not reported Outcomes Prolonged hospitalisation, death Data sources Medical records, structured interviews

Study details	Participants	Factors	Results	Comments
infected and HIV-uninfected children in South Africa Source of funding Funded through 2 grants from the Centers for Disease Control and Prevention	Controls HIV-uninfected children hospitalised with RSV-associated ALRTI n=753 Inclusion criteria - The inclusion criteria for infants aged 2 weeks to 3 months was neonatal sepsis as or ALRTI diagnosed by an attending physician in a patient who had been discharged from the hospital after birth - In children aged 3 to 59 months, the case definition was ALRTI diagnosed by the attending physician. The attending physician did not use any standardized criteria for diagnosing either neonatal sepsis or ALRTI Exclusion criteria - Infants aged <2 weeks because RSV infection may have been acquired in the hospital during the perinatal period Statistical method All enrolled children with an available RSV result were included in the univariate and multivariable analyses.			

Study details	Participants	Factors	Results	Comments
	Multivariable logistic regression models were evaluated, starting with variables that were significant at p<0.10 at univariate analysis, dropping nonsignficant factors with stepwise backward selection. Participants with missing data were dropped from the multivariable model. Demographics Age in months, median (IQR) RSV-associated ALRTI: 5.08 (2.36 to 12.30) Non-RSV associated ALRTI: 8.20 (3.15 to 18.36) p<0.001 Male sex, n/N (%) RSV-associated ALRTI: 656/1157 (57) Non-RSV associated ALRTI: 1828/3136 (58) p=0.35			
Full citation Paranjothy,S., Dunstan,F., Watkins,W.J., Hyatt,M., Demmler,J.C., Lyons,R.A., Fone,D., Gestational age, birth weight, and risk of respiratory hospital admission in childhood,	Cases Subjects with emergency admission for acute bronchiolitis Diagnostic criteria Based on ICD coding	Factors 1) Gestational age	Odds ratios Adjusted* hazard ratios (95%CI) for emergency admission for acute bronchiolitis Gestational age in weeks 40 to 42: 1 39: 1.16 (1.10 to 1.21) 38: 1.33 (1.26 to 1.40)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported

Study details	Participants	Factors	Results	Comments
Pediatrics, 132, e1562-e1569, 2013 Ref Id 318742 Country/ies where the study was carried out UK Study type Retrospective cohort Study dates May 1 1998 to December 31 2008 Aim of the study To investigate the risk of emergency respiratory hospital admission during childhood associated with gestational age at birth and growth restriction in utero Source of funding Not reported	Controls Subjects without emergency admission for acute bronchiolitis Inclusion criteria Not explicitly stated but children aged up to 5 years Exclusion criteria Not reported Statistical method Time to event Cox's regression analysis to obtain adjusted hazard ratios Demographics Age Upto 5 years		37: 1.59 (1.49 to 1.71) 35 to 36: 1.89 (1.75 to 2.03) 33 to 34: 2.45 (2.21 to 2.71) <33: 3.89 (3.55 to 4.25) *Adjusted for maternal age, parity, Townsend score quintile for social deprivation, geneder, major or minor congenital anomaly, multiple birth, breastfeeding, Apgar score at 5 min, neonatal admission to hospital and season of birth	- Inclusion and exclusion criteria not reported Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Hospital Sample size calculation Not reported Data sources The Wales Electronic Cohort for Children - includes Public Health Birth files from the Office for National Statistics (from 2003), National Community Child Health Database (from 1987), Public Health Mortality files from the Office for National Statistics (from 2002), Patient Episode Dataset for Wales (from 1998), All Wales Perinatal Survey (from 1983) and Congenital Anomaly Register and Information Service (from 1998) Outcomes Emergency admission

Study details	Participants	Factors	Results	Comments
Full citation Dotan,M., shkenazi-Hoffnung,L., Samra,Z., Livni,G., Yarden-Bilavsky,H., Amir,J., Bilavsky,E., Hospitalization for respiratory syncytial virus bronchiolitis and disease severity in twins, Israel Medical Association Journal, 15, 701-704, 2013 Ref Id 299469 Country/ies where the study was carried out Israel Study type Retrospective cohort study Study dates 1 January 2008 and 31 December 2010 Aim of the study To assess the impact of multiple births on the severity of RSV infection and define risk factors for acquiring RSV infection in infants of multiple birth Source of funding Not reported	Cases Subjects with severe RSV infection n=NR Diagnostic criteria Severe infection defined as one that required hospitalisation in the pediatric intensive care unit Controls Subjects without severe RSV infection Inclusion criteria All children hospitalised between 1 January 2008 and 31 December 2010 with a positive RSV antigen as tested by enzyme-linked immunoassay in nasopharyngeal aspirates Exclusion criteria There were no exclusion criteria Statistical method Univariate and multivariate logistic regression models were used to identify variables independently associated with the outcome	Factors 1) Young age <42 days 2) Early gestational age <32 weeks 3) Male gender	Odds ratios Adjusted* odds ratio (95%CI) for ICU admission 1) Young age <42 days: 3.39 (1.46 to 7.9) 2) Early gestational age <32 weeks: 10.58 (3.25 to 34.54) 3) Male gender: 1.97 (1.05 to 3.69) *Adjusted for each other and being a twin	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Odds ratios for non-significant factors (eg: being a twin) not reported - Data sources not reported - Retrospective study design Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Tertiary university-affiliated pediatric hospital Sample size calculation Not reported Outcome Severe RSV infection - hospitalisation in ICU Data sources Not reported

Study details	Participants	Factors	Results	Comments
	variable - the presence of severe RSV infection Demographics Male/female, % Singletons: 57.2/42.8 Twins: 53.1/46.9 p: 0.453 Age group in days, % Singletons: <42: 18.9, 42 to 69: 19.7, 70 to 150: 19.7, 151 to 299: 19.9, 300 to 3720: 21.9 Twins: <42: 25.8, 42 to 69: 27.3, 70 to 150: 28.8, 151 to 299: 9.1, 300 to 3720: 9.1 p: 0.02 Gestational age in weeks, % Singletons: <28: 1.3, 29 to 32: 1.8, 33 to 37: 17.1, >38: 79.8 Twins: <28: 3, 29 to 32: 6.1, 33 to 37: 77.3, >38: 13.6 p<0.001 Chronic disease (presence of pulmonary or cardiac dysfunction requiring medical therapy, or congenital/acquired immune deficiency), % Singletons: 9.4 Twins: 4.5 p=0.3			
Full citation	Cases	Factors	Odds ratios	Limitations

Study details	Participants	Factors	Results	Comments
Onoyama,S., Hoshina,T., Honjo,S., Ihara,K., Hara,T., Respiratory syncytial virus infection in children with severe motor and intellectual disabilities, European Journal of Clinical Microbiology and Infectious Diseases, 32, 1353-1357, 2013 Ref Id 318820 Country/ies where the study was carried out Japan Study type Retrospective case-control Study dates Five consecutive seasons from September 1 2006 to April 30, 2011 Aim of the study To investigate the severity of RSV-LRTI in children with severe motor intellectual disabilities (SMID) Source of funding Not reported	Children with SMID n=18 The underlying diseases of SMID were as follows: - malformation syndrome: n=3 - holoprosencephaly: n=2 - 21 trisomy: n=2 - sequelae of meningitis: n=2 - cerebral palsy: n=2 - 18 trisomy: n=1 - hydrocephalus: n=1 - colpocephaly: n=1 - lissencephaly: n=1 - Aicardi syndrome: n=1 - Zellweger syndrome: n=1 - Sub-acute sclerosing panencephalitis: n=1 Diagnostic criteria - SMID was diagnosed according to the classical criteria (Oshima's criteria) - Psychomotor development was evaluated by developmental quotients (DQ) using the Enjoji developmental test for those under 5 years of age and for those over 5 years of age by intelligence quotients (IQ) using the Wechsler Intelligence Scale for Children - All children with SMID were classified as grade 1 or 2	1) Severe motor intellectual disabilities (SMID): see diagnostic section for definition	Adjusted* OR (95%CI) between the severity of respiratory syncytial virus lower respiratory tract infections (RSVLRTI) and severe motor intellectual disabilities (SMID) Duration of hospitalisation >9 days: 2.544 (0.677 to 10.294), p=0.172 Mechanical ventilation: 5.100 (0.769 to 46.473), p=0.104 *Adjusted for duration of supplemental oxygen >7 days and each other	Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Retrospective study design - Exclusion criteria not reported Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Department of Pediatrics at Kyushu University Hospital Sample size calculation Not reported Outcomes Duration of hospitalisation >9 days, mechanical ventilation Data sources Not reported

Study details	Participants	Factors	Results	Comments
	who were bedridden or able to sit, crawl or walk with support, and had IQ or DQ lower than 20 - All patients were diagnosed as having RSV infection by a rapid antigen detection test using a nasopharyngeal aspirate or secretion suctioned through the tracheostomy orifice Controls Previously healthy children n=43 Inclusion criteria - Patients <16 years of age who were admitted to the Department of Pediatrics during 5 consecutive seasons from September 1 2006 to April 30, 2011 for RSV-LRTI Exclusion criteria Not reported Statistical method Multivariate logistic regression analysis was performed to estimate odds ratios for the association between the independent variables and outcomes, p value less than 0.05 was			

Study details	Participants	Factors	Results	Comments
	considered to be statistically significant. Demographics Age in months, median (range) Patients with SMID: 21 (2 to 33) Patients without SMID: 8 (0 to 31) p=0.002 Gender, % male Patients with SMID: 50 Patients without SMID: 53 p=0.804 Duration of supplemental oxygen in days, median (range) Patients with SMID: 10 (5 to 37) Patients without SMID: 8 (1 to 15) p=0.15 Pneumonia, % Patients with SMID: 44 Patients without SMID: 44 p=0.602 Duration of hospitalisation >9 days, % Patients with SMID: 56 Patients without SMID: 35 p=0.113 Mechanical ventilation, %			

Study details	Participants	Factors	Results	Comments
	Patients with SMID: 22 Patients without SMID: 5 p=0.057			
Full citation Ambrose,C.S., Anderson,E.J., Simoes,E.A., Wu,X., Elhefni,H., Park,C.L., Sifakis,F., Groothuis,J.R., Respiratory Syncytial Virus Disease in Preterm Infants in the US Born at 32-35 Weeks Gestation Not Receiving Immunoprophylaxis, Pediatric Infectious Disease Journal, 33, 576-582, 2014 Ref Id 318822 Country/ies where the study was carried out USA Study type Prospective cohort Study dates 2 RSV seasons: September to May 2009 to 2010 or 2010 to 2011 Aim of the study To determine the incidence of laboratory-confirmed, medically attended illness	Cases Subjects with RSV hospitalisation n=57 Diagnostic criteria For respiratory ED visits and hospitalisations without RSV testing, the event was considered RSV related if a sample collected by study personnel within 7 days of the ED visit or hospitalisation identified RSV. Controls Not reported Inclusion criteria - Preterm birth between 32 weeks 0 days and 35 weeks 6 days gestational age - Birth in May through February and chronologic age ≤6 months at enrollment Exclusion criteria - Chronic lung disease of prematurity - Hemodynamically significant congenital heart	Factors 1) Age at event: <3 vs ≥6 months; 3 to <6 months vs ≥6 months 2) Multiple birth: yes vs no	Odds ratios Adjusted* HR for RSV hospitalisation 1) Age at event <3 months vs ≥6 months: 2.82; p=0.004 3 to <6 months vs ≥6 months: 1.77; p=0.108 2) Multiple birth Yes vs no: 0.48; p=0.043 *Adjusted for preschool-aged non-multiple birth siblings, age, exposure to smoking and multiple birth	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Confidence intervals not reported Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting Outpatient clinics Sample size calculation Not reported Outcomes RSV hospitalisation Data sources Medical records

Study details	Participants	Factors	Results	Comments
and associated risk factors for RSV disease in a cohort of US infants 32 to 35 wGA <6 months and not receiving RSV prophylaxis Source of funding Sponsored by MedImmune	disease - A life expectancy of <6 months - Received or being considered for RSV prophylaxis Statistical method Risk factors for RSV events were identified using a Cox proportional hazard model with calendar time input to adjust for seasonality; the model also adjusted for subject differences in exposure time Demographics Age at enrollment in months, mean (SD) 2.3 (1.71) Male sex, n(%) 882 (54) Gestational age in weeks, n (%) 32: 142 (8.6) 33: 206 (13) 34: 405 (25) 35: 889 (54)			
Full citation Murray,J., Bottle,A., Sharland,M., Modi,N., Aylin,P., Majeed,A., Saxena,S., Medicines for	Cases Infants admitted as an emergency with a primary diagnosis of acute bronchiolitis* using ICD-10	Factors 1) Premature birth: gestational age at birth less than 37 weeks* 2) Cystic fibrosis**	Odds ratios Adjusted* relative risk for bronchiolitis hospital admission (95%CI)	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist

Study details	Participants	Factors	Results	Comments
Neonates Investigator Group., Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study, PLoS ONE [Electronic Resource], 9, e89186-, 2014 Ref Id 318831 Country/ies where the study was carried out England Study type Prospective cohort Study dates 1 April 2007 to 31st March 2008 Aim of the study To examine which infants are most at risk of an RSV bronchiolitis admission in England in term, preterm and high-risk infants and to determine the age at and duration of an RSV bronchiolitis admission Source of funding Funded through a National Institute for Health Research (NIHR) Programme Grant for	codes n=7189 admissions to hospital with a primary diagnosis of bronchiolitis, 2015 specifically coded as being due to RSV, remainder unspecified. 1529 admitted with bronchiolitis had more than one bronchiolitis admission during their first year of life. *Acute bronchiolitis due to RSV, acute bronchiolitis due to other specified organisms and acute bronchiolitis, unspecified Diagnostic criteria Bronchiolitis diagnosis based on ICD codes identified from a hospital episode statistics database Controls Not explicitly stated Inclusion criteria - Only live births - Infants under 1 year of age Exclusion criteria - Infants born in hospitals with poor recording (<90%	3) Congenital heart disease** 4) Chronic lung disease**: chronic respiratory disease originating in the perinatal period and other chronic respiratory diseases originating in the perinatal period 5) Immunodeficiency**: Immunity disorders which includes diagnoses such as hypogammaglobulinemia and severe combined immunodeficiency 6) Nervous system congenital anomalies**: incorporates conditions such as spina bifida, anencephaly, and other congenital malformations of the nervous system 7) Down's syndrome** 8) Cerebral Palsy** *If a birth record had no gestational age recorded, i.e. premature status was unknown, then they were assumed to be not premature (justified on the basis that infants in the unknown group had similarly low ICU admission rates and short length of stay at birth, to infants in the group known to be born at term) **Diagnoses obtained from individual birth records and	1) Premature birth: 1.89 (1.77 to 2.02) 2) Cystic fibrosis: 2.45 (1.36 to 4.43) 3) Congenital heart disease: 3.35 (2.92 to 3.84) 4) Chronic lung disease: 1.61 (1.42 to 1.82) 5) Immunodeficiency: 1.69 (0.80 to 3.58) 6) Nervous system congenital anomalies: 1.73 (1.26 to 2.36) 7) Down's syndrome: 2.53 (1.72 to 3.72) 8) Cerebral palsy: 2.43 (1.48 to 3.99) *Adjusted for all other factors	Only limitations that arise in the study are reported - Risk factor and bronchiolitis diagnoses based on reliability of coding systems Indirectness Does the study match the protocol in terms of: Population: yes Outcome: yes Indirectness: none Other information Setting NHS hospitals Sample size calculation Not reported Outcomes Bronchiolitis hospital admission Data sources Hospital Episode Statistics - a national administrative database

Study details	Participants	Factors	Results	Comments
Applied Research, support for data analysis was received from the Neonatal Data Analysis Unit, unrestricted support for the Neonatal Data Analysis Unit from Abbott International and Danone UK.	complete) of key indicators (birth weight and gestational age) - Bronchiolitis admissions in children over 1 year because of the uncertain nature of the clinical diagnosis in older infants Statistical method Adjusted relative risks for bronchiolitis admission with 95%CIs for infants in each individual risk group were calculated. Potential confounding was controlled for using Poisson regression models. Demographics Boys, % 51 Multiple births, % 1 Preterm, % 7.5 *The above characteristics are of the birth cohort not specifically those with bronchiolitis admission	any subsequent hospital admission records - based on ICD codes		
Full citation Lanari,M., Prinelli,F., Adorni,F., Di,SantoS,	Cases	Factors 1) Gender 2) Gestational age: 33 to 34	Odds ratios Adjusted hazard ratios (95%CI) for bronchiolitis hospitalisation	Limitations Based on NICE guidelines manual 2012: Prognostic

Study details	Participants	Factors	Results	Comments
Musicco,M., Risk factors of hospitalization for lower respiratory tract infections in infants with 33 weeks of gestational age or more: A prospective Italian cohort study on 2210 newborns, Early Human Development, 89, S88-S90, 2013 Ref Id 318833 Country/ies where the study was carried out Italy Study type Longitudinal multicenter cohort study Study dates Not reported Aim of the study To evaluate the role of prenatal, perinatal and postnatal/environmental conditions in determining the risk of hospitalisation for LRTI in a large cohort of preterm and full term newborns Source of funding Not reported	Subjects hospitalised for bronchiolitis n=120 Diagnostic criteria Based on presence of ICD-9 codes. Patients hospitalised for bronchiolitis underwent RSV laboratory confirmatory test whenever the test was foreseen as part of the routine diagnostic work-up. Controls Subjects not hospitalised for bronchiolitis n=2090 Inclusion criteria - Consecutive newborns of 33, 34, 35, 37 and 38 or more weeks of gestational age - For each 33 to 34 newborn enrolled, one of the 35 to 37 and one of the 38 or more weeks gestational age newborn of the same gender and with the closest date of birth were enrolled Exclusion criteria - Life expectancy shorter than 6 months - CHD and CLD - Participation in clinical studies on pharmacological	vs ≥38; 35 to 37 vs ≥38 3) Singleton delivery 4) Lack of breastfeeding 5) Passive cigarette smoke exposure	1) Gender (male) Hospitalised: 76/1150 (6.6%) Not hospitalised: 44/1060 (4.2%) HR*: 1.6 (1.1 to 2.4) 2) Gestational age in weeks 33 to 34 vs ≥38 - hospitalised: 54/737 (7.3%), not hospitalised: 25/706 (3.5%); HR**: 2.1 (1.3 to 3.4) 35 to 37 vs ≥38 - hospitalised: 41/767 (5.3%), not hospitalised: 25/706 (3.5%); HR**: 1.5 (0.9 to 2.5) 3) Singleton delivery Hospitalised: 97/1673 (5.8%) Not hospitalised: 23/537 (4.3%) HR*: 1.8 (1.1 to 2.9) 4) Lack of breastfeeding Hospitalised: 42/482 (8.7%) Not hospitalised: 78/1728 (4.5%) HR*: 1.8 (1.2 to 2.6) 5) Passive cigarette smoke exposure Hospitalised: 8/108 (7.4%) Not hospitalised: 112/2102 (5.3%) HR**: 1.5 (0.7 to 3.1) * Adjusted for gender, gestational age, treatment with corticosteroids, cigarette smoke exposure, singleton delivery,	studies checklist Only limitations that arise in the study are reported -Outcome (bronchiolitis hospitalisation) based on reliability of coding systems -Some risk factors not defined Indirectness Does the study match the review protocol in terms of: Population: yes Outcome: yes Indirectness: None Other information Setting 30 neonatology units Sample size calculation Not reported Outcomes Bronchiolitis hospitalisation Data sources Hospital unit information was collected by the coordinating investigator. After discharge, the child's parent participated to two follow-up phone interviews consisting in a semi-structured questionnaire administered by the same trained interviewers. The first interview took place at the end of the RSV epidemic season

Study details	Participants	Factors	Results	Comments
	or surgical interventions - Prophylaxis with palivizumab Statistical method The relative risks of exposed versus non-exposed children were estimated as hazard ratios (HR) with Cox proportional hazard method. Multivariable analysis was carried out considering only the variables signficantly associated with the outcome. Demographics Not reported		respiratory diseases, surfactant therapy, lack of breastfeeding, siblings, crowding, humidity, exposed to epidemic RSV season ** Adjusted for gender and gestational age	and the second interview at the 12th month after birth.

I.3 At the time of assessment, what clinical features predict deterioration?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Walsh,P., Rothenberg,S.J., O'Doherty,S., Hoey,H., Healy,R., A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis, European Journal of	Sample size Derivation phase: 118 episodes of bronchiolitis among 99 patients. Validation phase: 182 infants. Characteristics Ratio of male to female patients = 1.69:1	Interventions Vital signs were taken from nursing/triage notes. Tachycardia was defined as a heart rate > the 97th percentile for age. Adjusted ORs reported for:	Details In the first part of the study, the derivation phase, a severity of disease model was constructed using a retrospective chart review of patients at one hospital. In the second part, the validation phase, the performance of this model was tested on a	Results Outcomes Derivation phase: - Hospital LOS for admitted infants was diveded into stay up to and including the mean, and LOS greater than the mean in both groups, creating a three-category outcome: discharge, hospital	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Not clear which treatments were received by participants in the ED

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Emergency Medicine, 11, 265-272, 2004 Ref Id 208424 Country where the study was carried out Ireland Study type Retrospective review. Aim of the study To develop and validate a logistic regression model to predict need for admission and lenght of hospital stay in children presenting to the Emergency Department with bronchiolitis. Study dates Derivation: year 1999. Validation: year 2001. Source of funding Not reported.	Comparison between derivation and validation samples: - mean age, months: deriv = 6.1; valid = 5.8 - range of ages, months: deriv = 0.9-19; valid = 0.27-21.9 - number not requiring admission: deriv = 37 (31%); valid = 139 (76%) - mean LOS of those admitted: deriv = 3; valid = 3 - median LOS set: deriv = 4; valid = 3 - range of LOS: deriv = 2-19; valid = 2-24. Inclusion criteria - Children aged 2 years or under - Admitted and discharged in 1999 - With a primary diagnosis of bronchiolitis as determined by a consultant paediatrician Exclusion criteria Patients in the validation cohort who received treatments not used in the derivation cohort were excluded, as well as those with incomplete data.	- Tachycardia (HR > 97th percentile before treatment) The study doesn't present adjusted estimates for duration of symptoms, poor feeding, fever, tachypnoea, SaO2 <92% and subjective assessments.	cohort of infants from the other hospital. Statistical analysis The three-category LOS measure was used as dependent variable in a proportional odds ordinal logistic regression. This model was constructed using the derivation set by entering all variables that showed a significant relationship with LOS by univariate tests, then the authors trimmed the model to include only jointly significant predictor variables. The original model was validated by using the independent validation set with the variables in the original trimmed model. Model coefficients were compared between the two datasets by a likelihood-based Chow test to determine the significant differences in coefficients between the independent datasets. The Hosmer-Lemeshow goodness of fit test was performed.	stay less than or equal to the mean, hospital stay greater than the mean. - In the present healthcare system, disposition is decided by residents. This decision is reviewed within 24 h by a consultant paediatrician. A substancial number are discharged at this initial review. Authors therefore defined "need for admission" as a hospital stay of more than 24 hours, retrospectively categorizing those who were discharged on initial consultant review as fit for discharge for the initial derivation phase. Validation phase: The need for admission in the validation phase was determined as actual admission, or discharge with subsequent return visit requiring admission, or clearly inappropriate discharges. Derivation phase: Admitted n=81 Discharged n=37 Validation phase: Admitted n=43	- Demographic characteristics are based on the number of episodes of bronchiolitis instead of the number of patients - no significance level is reported for the statistical model - not clear definition given of "severe disease" (based on both admission and longer LOS) - retrospective study design Other information Indirectness Does the study match the review protocol in terms of: Population: Some (children aged up to 2 years) Outcome: Some (LOS) Indirectness: Yes Setting ED of the National Children's Hopital (derivation phase) and Our Lady's Hospital for Sick

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Researchers collapsed the three-category observed and model-predicted LOS to a two-category "admit or discharged" LOS to calculate model sensitivity and specificity on both datasets.	Discharged n=139 Raw Data ** 1) Duration of symptoms, mean in days: admitted = 4.96 discharged = 6.25 2) Poor feeding: admitted = 59/81 discharged = 11/37 3) Febrile on arrival: admitted = 21/81 discharged = 7/37 4) Tachypnoea before treatment: admitted = 8/81 discharged = 2/37 5) HR > 97th percentile before treatment: admitted = 15/81 discharged = 4/37 6) SaO2 <92% before treatment: admitted = 11/81 discharged = 4/37 * Categories "admitted for 2-3 days" and "4 or more days" were collated by NCC-WCH to get raw data for admitted infants.	Children (validation phase) in Dublin, Ireland. Other - The study was exempt from ethics committee review. - The authors reported that there were differences between paediatricians' prescribing of antibiotics, oxygen, steroids and bronchodilators, but these did not alter the outcomes. Also, no patients in the derivation set received epinephrine. Data Source Derivation phase: Hospital inpatient enquiry system. Validation phase: cases were identified by a hand search of ED logs and medical records. All cases were taken from a single bronchiolitis season 2 years after the derivation set.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				** Raw data reported for derivation phase. Adjusted ORs for variables indicating the need for admission Derivation model Tachycardia heart rate above 97th percentile for age (yes or no) : OR 3.78 (1.05-13.57) p=0.041 * adjusted (included in the model) for increased work of breathing, dehydration, and age. Validation model Tachycardia heart rate above 97th percentile for age (yes or no) : OR 5.58 (1.42-21.98) p=0.014 * adjusted (included in the model) for increased work of breathing, dehydration, and age.	
Full citation	Sample size 2156 children.	Interventions	Details Statistical analysis	Results Outcome	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Schroeder,A.R., Mansbach,J.M., Stevenson,M., Macias,C.G., Fisher,E.S., Barcega,B., Sullivan,A.F., Espinola,J.A., Piedra,P.A., Camargo,C.A.,Jr., Apnea in children hospitalized with bronchiolitis, Pediatrics, 132, e1194-e1201, 2013 Ref Id 293420 Country where the study was carried out United States Study type Prospective multicenter cohort study Aim of the study 1) To identify independent risk factors for the occurrence of apnoea during the bronchiolitis hospitalization, and 2) to compare virology results in infants with and without apnoea.	Characteristics - median age was 4 months - 59% were boys - 62% were white - 16% admitted in the ICU; 76% admitted in ward; 5% admitted in observation unit; 3% admitted in step-down unit Inclusion criteria - An attending physician's diagnosis of bronchiolitis - Age <2 years - The ability of the caretaker to give informed consent Exclusion criteria - Transfer to a participating hospital >48 hours after the original admission time - Previous enrolment (although data from the initial hospitalization for previously enrolled patients were still included)	Adjusted ORs reported for: 1) Respiratory rate at preadmission visit (categorical) 2) Lowest documented oxygen saturation over entire preadmission No adjusted estimates reported for: duration of illness, heart rate, fever, ability to feed, and subjective assessments.	All analyses were performed by using Stata 11.2. To examine potential risk factors for apnoea among children hospitalized for bronchiolitis, unadjusted analysis was initially performed by using chi-squared test, Fisher's exact test, and Kruskall-Wallis test, as appropriate. All p-values were 2-tailed, with $p<0.05$ considered statistically significant. Multivariable logistic regression was conducted to evaluate independent predictors of inpatient apnoea. Factors were tested for inclusion in the model if they were found to be associated with the outcome in unadjusted analysis ($p<0.20$), or were considered potentially clinically significant. To prevent the exclusion of children who were missing race data (9%) and to minimize the number of included factors that were unassociated with	Inpatients apnoea status: to examine inpatient apnoea among children admitted to the hospital with bronchiolitis, authors identified all children who experienced apnoea at any time during their hospitalization. Every day a child was in the hospital, site investigators examined the medical records of each participant for documentation of apnoea. The site investigators completed the daily chart reviews by reposnding to the question "has patient experienced apnoea?". Among the 2207 enrolled subjects, 2156 had inpatient apnoea status reported. Missing data were attributed to have no daily inpatient form available (1.4%), or no response to the inpatient apnoea question on any daily inpatient forms (0.9%). Raw Data No apnea (NA) n= 2048 Apnea (A) n = 108 1) Respiratory rate <30% : NA = 5%; A = 12% 30-39 : NA = 18%; A = 23%	Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - patients enrolled in academic medical centers, and therefore results maybe not generalizable to community medical centers - ED and daily hospital data (including clinical features of our interest) were obtined by chart review Other information Indirectness Does the study match the review protocol in term of Population: Some (age up to 2 years) Outcome: Yes Indirectness: Some Setting The present study is part of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 3 consecutive years during the 2007-2010 winter seasons. Source of funding The study is funded by the National Institute of Health (NIH).			inpatient apnoea, race was dichotomized as white versus nonwhite/missing. For all children born prematurely, age was corrected by subtracting the number of weeks the child was premature from the chronologic age. The final regression model accounts for potential clustering by site, which results reported as ORs with 95% CIs. Other - Patients were enrolled within 18 hours of admission. - The consent and data collection forms were translated into Spanish. - The institutional review board at all participating hospitals approved the study.	40-49 : NA = 31%; A = 22% 50-59 : NA = 17%; A = 15% 60-69 : NA = 19; A = 14% ≥70 : NA = 10%; A = 13% 2) Oxygenation - Initial oxygen saturation, median (IQR): NA = 96 (93-98); A = 97 (92-99) - Initial oxygen saturation <90% : NA = 11%; A = 20% - Lowest documented oxygen saturation, median (IQR) : NA = 93 (89-96); A = 92 (85-96) - Lowest documented oxygen saturation <90% : NA = 28%; A = 41% 3) Oral intake Adequate : NA = 44%; A = 28% Inadequate : NA = 42%; A = 56% Missing : NA = 14%; A = 17% Multivariable model of factors associated with inpatient apnoea among hospitalized children, adjusted * ORs (95% CI) and p-values a) Respiratory rate <30% : OR 4.05 (2.00-8.20) p<0.001 30-39% : OR 2.35 (1.52-3.64) p<0.001 40-49% : OR 1.00 reference	Multicenter Airway Research Collaboration, a program of the Emergency Medicine Network, and it involved 16 different sites. Data Collection Investigators conducted a structured interview that assessed patients' demographic characteristics, medical and environmental history, duration of symptoms, and details of the acute illness. ED and daily hospital data (including clinical features of our interest) were obtined by chart review.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				50-59% : OR 1.29 (0.66-2.51) p=0.46 60-69% : OR 1.06 (0.62-1.81) p=0.84 ≥70 %: OR 2.26 (1.03-4.95) p=0.04 b) Lowest documented oxygen saturation over entire preadmission visit <90% OR 1.60 (1.03-2.46) p=0.04 * model also contains: age, gender, race, birth weight, and reported apnoea.	
Full citation Corneli,H.M., Zorc,J.J., Holubkov,R., Bregstein,J.S., Brown,K.M., Mahajan,P., Kuppermann,N., Bronchiolitis Study Group for the Pediatric Emergency Care Applied Research Network., Bronchiolitis: clinical characteristics associated with hospitalization and length of stay,	Sample size Data were available for 598 patients. Characteristics - Mean age = 5 months - 62% were boys - mean RDAI score = 9 (minimum score set at enrollment was 6 and maximum possible RDAI score was 17) - Median SpO2 = 97% - 240 of 598 patients (40%) were hospitalized at the time of their study visit	Interventions Initial observations taken from the patient's assessment, recorded by a nurse The study presents adjusted estimates for: 1) Initial oximetry value <94% 2) Respiratory rate >60/min	Details Statistical analysis To identify the most important predictors of study outcomes, authors performed binary recursive partioning using classification and regression tree (CART) software. In identifying predictors of hospitalization, the staistical costs of incorretly predicting diascharge were set at twice those for incorrectly predicting	Results Outcomes 1) hospital admission 2) longer admission, defined as LOS of more than 1 night to exclude the patients who have succeeded in 24-hour observation care and those whose admission might have not been necessary in retrospect. Raw Data Admitted n = 240 Discharged n = 358	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - Population of interest and ability to generalize: the study excludes infants with risk factors, premature infants, infants with bronchiolitis complications (apnoea), and those

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatric Emergency Care, 28, 99-103, 2012 Ref Id 206633 Country/ies where the study was carried out United States Study type Secondary analysis of a multicenter randomized trial. Data were collected as a part of a RCT of dexamethasone for bronchiolitis conducted in 20 EDs of the Pediatric Emergency Care Applied Research Network. Aim of the study To identify objective variables noted during initial emergency department (ED) evaluation that best predicted hospital admission and longer lenght of stay (LOS). Study dates	Inclusion criteria Infants were eligible if - they were aged 2 to 12 months - with first-time bronchiolitis defined as wheezing with no history of any similar conditions - their disease was moderate to severe, defined as a RDAI score of 6 or greater Exclusion criteria Infants were excluded if they had - a previous adverse reaction to dexamethasone - a known heart disease or lung disease (eg cystic fibrosis) - premature birth with less than 36 weeks of gestation - immune suppression or immune deficiency - treatment with corticosteroids within the previous 14 days - active varicella, or exposure to varicella within 21 days - life-threatening complications of bronchiolitis, including apnoea, respiratory failure, or the clinical	The study doesn't report adjusted ORs for: day of illness, heart rate, temperature, ability to feed and subjective assessments.	admission. To quantify the relative stranght of association of the variables found in the CART analysis, the authors used multivariate logistic regression logistic regression to calculate odds ratios for the variabes and cutpoints identified in that analysis. - 22 patients were subsenquantly hospitalized during the 7 days after ED discharge; their data were not treated as admissions in these analyses. - all infants in the clinical trial underwent 4 hs of ED observation before a disposition decidion was reached. Authors didn't include the 4-hour data in the analysis of hospitalization per se; however, ongoing assessment is available for patients in observation care, so the model examining longer LOS among admitted patients also included the 4-hour variables for	Initial observations (mean values): 1) Day of illness discharged = 3.58 admitted = 3.64 2) Heart rate, beats per min discharged = 154.4 admitted = 161.8 3) SpO2, % discharged = 97.2 admitted = 95.7 4) Respiratory rate, breaths per min discharged = 51.5 admitted = 55.8 5) Temperature, ºC discharged = 37.6 admitted = 37.8 Results Mean difference (95% CI) and p-value 1) day of illness: -0.06 (-0.5 ; 0.3) p=0.76 2) heart rate, beats per min: -7.3 (-10.7 ; -4.0) p<0.001 3) SpO2, %: 1.6 (1.1 - 2.1) p<0.001 4) respiratory rate, breaths per min: -4.2 (-6.4 ; -2.1) p<0.001 5) Temperature, ºC: -0.1 (-0.3 ; 0.01) p=0.06	younger than 2 months. - unclear timing of baseline measurements - no significance level reported for statistical analysis - retrospective study design Other information Indirectness Does the study match the population in terms of: Population: Some (children younger than 2 months excluded) Outcome: Yes Indirectness: Some Data sources 20 EDs of the Pediatric Emergency Care Applied Research Network Setting Pediatric EDs Other

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
3 Bronchiolitis seasons (November through April) from January 2004 through April 2006. Source of funding The study was supported by a grant from th Maternal and Child Health Bureau Research Program . In addition, the Pediatric Emergency Care Applied Research Network is supported by cooperative agreements from the Emergency Medical Services for Children program of the Maternal and Child Health Bureau, Health Resources and Services Administration, US department of Health and Human Services.	appearance of sepsis or shock - inability of the parents to speak English or Spanish		SpO2, RDAI score and respiratory rate. - to avoid artifact, the SpO2 values from a single study center located at an altitude of approximately 1500 m were excluded from the analysis a priori; because CART can use surrogates from missing values, all the other variables from that center were retained in the data set (also sensitivity analysis didn't show altered decidions). The institutional review boards at all sites approved the study. Written informed consent was obtained from the parents of all included subjects.	Logistic regression for hospitalization, adjusted ORs: - Initial oximetry value <94%: OR 5.5 (2.9-10.2) p<0.0001 - Respiratory rate >60/min: OR 2.6 (1.7-4.1) p<0.0001 RDAI score >11: 2.5 (1.5-4.3) p=0.001	In the original trial, the patients were randomized to receive either oral dexamethasone or placebo. All other bronchiolitis treatments during study evaluation were administered according to clinical preference and local standards. No difference was found in the number of such treatments between dexamethasone and placebo groups. Although no treatment effect was demonstrated in the original trial, treatment group assignment was included as a potential variable in the current analyses.
Full citation Corrard,F., de La,Rocque F., Martin,E., Wollner,C., Elbez,A., Koskas,M., Wollner,A., Boucherat,M.,	Sample size 171 infants. Characteristics - mean age of 1.6 ±3.7 months	Interventions 1) 24h FI <50% The pediatrican noted the infant's usual type of feeding, the number of meals	Details Statistical analysis The sensitivity, specificity, PPV, NPP, positive and negative likelihood ratios were calculated with their	Results Outcomes Hospitalization : the doctor recorded the decision regarding immediate hospitalization. The hospital reports were recovered later	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cohen,R., Food intake during the previous 24 h as a percentage of usual intake: a marker of hypoxia in infants with bronchiolitis: an observational, prospective, multicenter study, BMC Pediatrics, 13, 6-, 2013 Ref Id 262567 Country/ies where the study was carried out France Study type Prospective multicenter observational study. Aim of the study To determine whether food intake in the previous 24 hs might serve as initial screening tool for hypoxia in infants with bronchiolitis, and to analyze the relation between both 24h FI and standard clinical signs and the decision to hospitalize the infant.	- infants were seen before the first and the sixth day after the onset of chest sounds (average 2 days, ±1.5 days) - during the previous 24hs, 22% had been febrile (≥38 º) - 24h FI: <50% in 14%, ≥50% to <70% in 26% of cases, and ≥70% in 60% of cases - respiratory frequency: ≥50/min in 43% of infants, and ≥60/min in 23% of infants - Mean oxygen saturation was 98% ±3%; 9% of infants had SpO2 <95% and 2 infants had SpO2 <90% - RSV was tested for in 104 infants, of whom 42% were positive. Inclusion criteria As reported in the definition of population of interest: - infants aged 0-6 months - diagnosed with bronchiolitis (rhinorrhea + cough + dyspnea + expiratory breath sounds) Exclusion criteria Infants were excluded if - they had risk factors (history of prematurity,	taken with a bottle or spoon, and the amount of formula-milk usually drunk, per meal, then calculated the total volume of milk taken over the past 24 hours. If the baby was partly spoon-fed, the pediatrician noted any change in the amount ingested during the previous 24 hour compared to normal. 2) SpO2 <95% Oxygen saturation was recorder only after collecting the other information (24h FI, reatractions and respiratory rate), in order not to interfere with the clinical examination. The pediatricians used a Hellcor pulse oximeter to measure SpO2. All results below 95% were verified by a second measurement, and	95% CIs, taking a SpO2 of <95% as the reference, and ROC curves were computed. Mean were compared between groups by using a t-test with an unequal variance option if necessary, and percentages were compared by using the chi-squared test or Fisher's exact test, as appropriate. Significance was assumed at p<0.05. Univariate and multivariate analyses (logistic regression) were used to identify factors associated with SpO2<95% after adjustment for age, and odds ratios were calculated with their 95%CIs. Stata SE 9.1 statistical software was used. Ethics A poster placed in the waiting room invited parents to participate to the study and informed that thay were free to refuse their	to determine whether the child had received specific hospital care (oxygen, infusion, or gastric gavage). Raw Data Hospitalized n = 17/171 non hospitalized n = 154/171 - 24h FI <50% hospitalized = 9/17 (53%) non hospitalized = 15/150 * (10%) - SpO2 < 95% hospitalized = 11/17 (65%) non hospitalized = 4/154 (3%) * missing data Results Multivariate analysis with SpO2, age<2 months, 24h FI<50%, intercostal retractions for Hospitalization - SpO2 <95%: p<0.0001 - 24h FI not significantly associated Multivariate analysis with age<2 months, 24h FI<50%, intercostal retractions for Hospitalization 24h FI < 50%: OR 10.6 (3.0-37.3)	Only limitations that arise in the study are reported - the study excluded patients with risk factors (i.e. prematurity) and breast-fed infants - statistical analysis: unclear how they constructed the regression model (significance level, all variables were initially considered?) - incomplete results (no OR for oxygen saturation and no p-value for food intake) - OR not adjusted for other relevant clinical signs reported in the study like respiratory rate and temperature Other information Indirectness Does the study match the review protocol in terms of Population: Some (0-6 months) Outcome: Yes Indirectness: Some

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Three winter periods (November to January), from late 2006 to early 2009. Source of funding All the authors declare no financial support for the submitted work from anyone other than their employer (Association Clinique et Therapeutique Infantile du Val de marne).	chronic heart or lung disease) - they were breast-fed (even partially) - they had previously received a treatment for a bronchial disorder (bronchodilators, corticosteroids, physiotherapy)	only the highest value was recorded. The study doesn't present adjusted ORs for: heart rate, respiratory rate, temperature, duration of illness, and subjective assessments.	participation. Before the enrolment, the investigators informed the parents about the purpose of the study and requested their oral consent. French legislation did not require ethical approval or other authorizations for research not involving unusual or additional procedures relative to usual practice.		Setting The infants were recruited by 18 community pediatricians in the Paris region. Data Source/Collection The pediatrician noted children's age, the duration of wheezing, type of feeding and all clinical measurements. Other Infants cared for outside the home by child minders could be enrolled, provided the parents knew the precise amount of food ingested in the previous 24hs.
Full citation Parker,M.J., Allen,U., Stephens,D., Lalani,A., Schuh,S., Predictors of major intervention in infants with bronchiolitis,	Sample size 312 children. Characteristics The study doesn't report population charcteristics.	Interventions The research nurses recorded historical information and measured relevant baseline clinical	Details Bronchiolitis was defined as coryza, cough, and the first episode of respiratory distress with wheeze or	Results Outcome MMI defined as oxygen administration for 30 min or more for saturation <90% in room air, IV fluid bolus of 20 ml/kg or more, any treatment	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatric Pulmonology, 44, 358-363, 2009 Ref Id 207826 Country/ies where the study was carried out Canada Study type Data from recent prospective cohort study (Schuh S. et al., Evaluation of the utility of radiography in acute bronchiolitis. J Pediatr 2007; 150:429-433). Aim of the study To identify predictors of the major medical intervention (MMI) in infants with bronchiolitis in the emergency department (ED) to recognize those in need of hospitalization versus the candidates for discharge. Study dates Not directly reported in the paper.	However, the two groups (children who required major medical intervention and those who did not) were similar in terms of duration of respiratory distress, family history of atopy, and temperature. Patients in the MMI groups were younger, and had greater tachypnea, retractions, and baseline hypoxia. Inclusion criteria Children aged between 2-23 months of age. Exclusion criteria - children with previous wheeze/bronchodilator therapy - children with previously diagnosed cardiopulmonary disease, aspiration, neuromuscolar disease, or chronic systemic disease - those with prematurity <35 weeks gestation, birth weight <2,500 g or neonatal vantilation for more than 24 hs	parameters, recorded patient disposition and telephoned all families on day 7 regarding subsequent hospitalizations. The study reports adjusted ORs for: 1) respiratory rate at baseline ≥60 2) oxygen saturation ≤92% at baseline The study doesn't present adjusted estimates for: heart rate, temperature, days from illness onset, subjective assessments and ability to feed.	crepitations in a non-toxic infant. The study utilized data from a recent prospective cohort study, and the convenience sample was collected consecutively whil one of three trained study nurses was on duty. A written consent was obtained from all participating famlies and the study was approved by the Research Ethics Board. Statistical analysis Potential a priori postulated predictors of the MMI were initially analyzed by univariate logistic regression to examine their individual association with the outcome, with significance determined at P<0.05. Predictors achieving statistical significance were then included in multivariate logistic regression analysis to examine their independent association with MMI.	for apnoea, or admission to the Critical care Unit (CCU). Criteria for admission to CCU included concern regarding potential need for intubation and mechanical ventilation for either recurrent apnoea with desaturations or for a possibility of impending respiratory failure. Raw Data MMI n = 52 no MMI n = 260 1) Temperature (ºC), mean ±s.d. MMI = 37.9 ±0.9 no MMI = 37.7 ±0.8 2) respiratory rate at baseline ≥60 MMI = 25/52 (48.1%) no MMI = 32/260 (12.4%) 3) oxygen saturation ≤92% at baseline MMI = 9/52 (17.3%) no MMI = 16/260 (6.2%) Results Adjusted odds ratios of major intervention for significant predictors (the statistical model includes: decreased dehydration, accessory muscle score ≥6/9, oxygen	Only limitations that arise in the study are reported - premature infants and those younger than 2 months were excluded - overall population characteristics not reported - while patients were enrolled as part of a prospective cohort study, some data utilized for this analysis was obtained through retrospective chart review Other information Indirectness Does the study match the review protocol in terms of: Population: Some (children aged up to 23 months) Outcome: Yes Indirectness: Some Setting The Hospital for Sick Children, a tertiary care center with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
From Schuh S. et al., Evaluation of the utility of radiography in acute bronchiolitis. J Pediatr 2007; 150:429-433. : November and April 2001 to 2005 from 8 AM to 9 PM,while the study nurses were on duty. Source of funding Not reported.				saturation and respiratory rate) a) oxygen saturation ≤92%: OR 2.41 (0.96-6.14) b) respiratory rate ≥60: OR 1.85 (0.97-3.54) Odds Ratios of MMI for Predictors Alone and in Combination (four predictors considered: severe retractions on arrival, baseline oxygen saturation of 92% or less, respiratory rate 60/min or more and history of poor fluid intake) - None n=148: OR=1 reference - Any one predictor n=100: OR=2.2 (2.4-13.1) - Any two predictors n=48: OR=5.7 (2.4-13.1) - Three or more predictors n=16: OR=12.9 (4.0-41.9)	54,000 ED patient visits annually. Data Collection See "Interventions" section, plus: supplemental information for this study regarding additional clinical data and details of the medical intervention and follow-up were obtained from a review of patient electronic charts. All charts were reviewed by a single investigator and data extraction form was used to systematically record data of interest. Other The usual bronchiolitis therapy in the ED consisted of supplemental oxygen given for saturation of <90%, intravenous fluids hydration in infants with dehydration or extreme respiratory distress and trial of nebulized

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					bronchodilators such as albuterol or epinephrine.
Full citation Damore,D., Mansbach,J.M., Clark,S., Ramundo,M., Camargo,C.A.,Jr., Prospective multicenter bronchiolitis study: predicting intensive care unit admissions, Academic Emergency Medicine, 15, 887-894, 2008 Ref Id 206669 Country/ies where the study was carried out United States Study type Prospective, multicenter, cohort study. Aim of the study To identify independent predictors of ICU admission. Study dates	Sample size Of 2129 eligible children, 1459 (68%) were enrolled. Characteristics - 583 (40%) were admitted to the hospital - among these 583 children, 533 were admitted to the regular floor and 50 to the ICU ICU patients were younger than floor patients; more than 80% of children admitted to either the regular floor or ICU were aged <12 months. No differences were observed in respect of gender, race/ethnicity, estimated median household income, or insurance status. The two groups were also similar in terms of medical factors: being breast-fed, history of wheezing, maternal smoking during pregnancy, prior hospitalization. ICU patients were less likely than those admitted to the regular floor to attend daycare, and more likely to have a ED visit in the past week. There were smaller numbers of patients	Interventions Adequacy of Oral Intake was determined by the ED attending as: adequate, inadequate and unknown. The study doesn't present adjusted ORs for: heart rate, respiratory rate, fever, duration of illness, SpO2, and subjective assessments.	Details As defined by the American Academy of Pediatrics, children with bronchiolitis were characterized by "rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring". In the data presented, 98% of the children met the AAP definition of bronchiolitis. Among the 2% (33) of children without any one of these factors, 15% had an oxygen saturation of <96% or air entry that was not normal. Using a standard protocol, investigators at 30 EDs in 15 U.S. states provided 18- to 24-hour-per-day coverage. 40% were EDs in children's hospitals, 47% pediatric EDs in general hospitals, and 13% general EDs in general hospitals. All patients were managed at the	Results Outcome The primary outcome of the current analysis was ICU admission. Children admitted to the ICU from the ED were compared to children admitted to the regular floor for >24 hours. Raw Data admission to regular floor n= 533 ICU admission n= 50 - Duration of symptoms ≥4 days (%) regular floor = 55 ICU = 40 - Respiratory rate, mean ±SD regular floor = 52 ±15 ICU = 51 ±15 - Oxygen saturation on room air, mean ±SD regular floor = 96 ±4 ICU = 94 ±6 - Oral intake (%) adequate oral intake: reg. floor = 64; ICU = 28	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - small sample size of patients admitted to ICU (n=50) - institutional variability in care and resource utilization for children with bronchiolitis not taken into account (children with similar severity of illness may be admitted to ICU in one hospital, but not in another) - no explanation given for not enrolled children, and the two groups were different in terms of admission (enrolled patients had a greater admission rate than non-enrolled patients)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2004 through 2006 winter seasons (December to March). Source of funding Funded by the Thrasher Research Fund (Salt Lake City, UT) and an unrestricted data analysis grant from Merck (Rahway, NJ).	with specific illnesses, low birth weight, premature birth and a history of intubation. Inclusion criteria - an attending physician diagnosis of bronchiolitis - patients age <2 years - the ability of the parent or guardian to give informed consent Exclusion criteria - previous enrollment		discretion of the treating physician. The institutional review board at each of the 30 partecipating hospitals approved the study and informed consent was obtianed for all participants. Statistical analysis All analyses were performed using Stata 9.0. The association of factors with ICU admission was examined using chi-square tests, Student's t tests, and Kruskal-Wallis rank test, as appropriate. All p-values are two-tailed, with p<0.05 considered statistically significant. Multivariate logistic regression was used to identify independent predictors of ICU admission compared to admission to the regular floor for ≥24hs. Factors associated with the ICU admission at p<0.20 were evaluated for inclusion in the multivariate analysis. Those that did not retain statistical	inadequate oral intake: reg. floor = 31; ICU = 53 unknown: reg. floor = 6; ICU = 19 Multivariate predictors of ICU Admission Compared to Hospital Admission to Regular Floor for ≥24hs (the model contains: age <2months, ED visit during past week, moderate/severe retractions) Oral Intake - Adequate: OR = 1 Reference - Inadequate: OR = 3.31 (1.55-7.07) p=0.002 - Unknown: OR = 8.44 (2.89-24.69) p<0.001	- authors don't provide explanation on how clinical measurements were taken (no definition given for “inadequate” oral intake) Other information Indirectness Does the study match the review protocol in terms of: Population: Some (age up to 2 years) Outcome: Yes Indirectness: Some Setting The study was part of the Multicenter Airway Research Collaboration (MARC), which is a division of the Emergency Medicine Network. The 30 partecipating sites were located across the United States: Northeast (37%), Midwest (27%), South (20%), and West (17%).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			significance on multivariate analysis were rmoved from the model. When the final model was identified, factors that had not been retained in the model were reevaluated for inclusion.		Data collection The standardized questionnaire consisted of an ED interview, ED chart review, and 2-week follow-up telephone interview. Physicians and researchers were trained in utilizing these forms. All forms were reviewed by site principal investigators, who are physicians, before submission to the EMNet Coordinating Center in Boston. At the Coordinating Center, the data were further reviewed by trained personnel and underwent double data entry.
Full citation Mansbach,J.M., Piedra,P.A., Stevenson,M.D., Sullivan,A.F., Forgey,T.F., Clark,S., Espinola,J.A., Camargo,C.A.,Jr., MARC-30 Investigators., Prospective	Sample size 2207 children. Characteristics - 17% were enrolled in the ICU - median age was 4 months - 61% were born in fall or winter months - 59% were male	Interventions ED and daily hospital clinical data were obtained by chart review. The study presents adjusted ORs for: 1) oxygen saturation by pulse	Details Statistical analysis All analyses were performed by using Stata 11.2. Univariate analyses were performed by using chi-squared test, Fisher exact test, and Kruskal-Wallis test, as	Results Outcomes Need for CPAP/intubation, interpreted as a sign of deterioration or more severe disease. Authors used this outcome as it has less variability than admission to the ICU.	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - patients enrolled in academic medical

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
multicenter study of children with bronchiolitis requiring mechanical ventilation, Pediatrics, 130, e492-e500, 2012 Ref Id 216255 Country/ies where the study was carried out United States Study type Prospective multicenter cohort study. Aim of the study To identify factors associated with continuous positive airway pressure (CPAP) and/or intubation for children with bronchiolitis. Study dates 3 consecutive years from November 1 until March 31, beginning in 2007. Source of funding This study was supported by two	- 76% were born term - 52% had birth weight ≥7 pounds. Inclusion criteria - an attending physician's diagnosis of bronchiolitis - age <2 years - the ability of the parent/guardian to give informed consent Exclusion criteria - previous enrollment - transfer to a participating hospital >48 hs after the original admission time	oximeter or ABG (5 categories) 2) oral intake (adequate, inadequate, missing) The study doesn't report adjusted ORs for temperature, heart rate, respiratory rate, duration of illness, and subjective assessments.	appropriate. All p-values were 2-tailed, with P<0.05 considered statistically significant. Multivariable logistic regression was conducted to evaluate independent predictors of CPAP/intubation, defined as any instance of patient requiring CPAP and/or intubation during the admission. Factors were tested for inclusion in the model if they were found to be associated to the outcome in unadjusted analyses (P<0.20) or were considered potentially clinically significant. An optimistic-corrected c-statistic was used to determine model discrimination, and the Hosmer-Lemershow test was used to determine model calibration. The final regression model accounts for potential clustering by site and was validated by using bootstrapping. The full model was bootstrapped 1000 times and bias-corrected and	Raw Data CPAP/intubation n= 161 No CPAP/intubation n= 1998 1) temperature (F), median (IQR) CPAP/intubation: 99.4 (98.2-100.7) No CPAP/intubation: 99.5 (98.6-100.6) 2) pulse (beats per min), median (IQR) CPAP/intubation: 173 (155-184) No CPAP/intubation: 160 (147-175) 3) respiratory rate (breaths per min), median (IQR) CPAP/intubation: 50 (40-60) No CPAP/intubation: 48 (40-60) 4) oxygen saturation by pulse oximeter or ABG (5 categories) - <85% CPAP/intubation: 17/161 No CPAP/intubation:3/1998 - 85-87.9% CPAP/intubation: 6/161 No CPAP/intubation: 3/1998 - 88-89.9% CPAP/intubation: 6/161	centers, and therefore results maybe not generalizable to community medical centers - variations in the use of CPAP/intubation by institution not explained or explored - ED and daily hospital data (including clinical features of our interest) were obtined by chart review, and adequate description of measurements is missing Other information Indirectness Does the study match the review protocol in term of Population: Some (age up to 2 years) Outcome: Yes - but must be specified that CPAP/intubation is considered as a level of disease severity Indirectness: Some

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
grants from the National Institute of Health (NIH).			accelerated 95% CIs were obtained.	No CPAP/intubation: 4/1998 - 90-93.9% CPAP/intubation: 16/161 No CPAP/intubation:17/1998 - ≥94% CPAP/intubation: 55/161 No CPAP/intubation:73/1998 5) oral intake - Adequate CPAP/intubation: 20/161 No CPAP/intubation: 45/1998 - Inadequate CPAP/intubation: 63/161 No CPAP/intubation: 41/1998 - Missing CPAP/intubation: 16/161 No CPAP/intubation: 14/1998 Results Independent associations with CPAP/intubation 1) temperature (F), median (IQR) p=0.17 2) pulse (beats per min), median (IQR) p<0.001 3) respiratory rate (breaths per min), median (IQR) p=0.17 4) oxygen saturation by pulse oximeter or ABG p<0.001 - <85 - 85-87.9 - 88-89.9	Setting The present study is part of the Multicenter Airway Research Collaboration, a program of the Emergency Medicine Network, and it involved 16 different sites. Data Collection Investigators conducted a structured interview that assessed patients' demographic characteristics, medical and environmental history, duration of symptoms, and details of the acute illness. ED and daily hospital data (including clinical features of our interest) were obtined by chart review. Other

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- 90-93.9 - ≥94 5) oral intake p<0.001 - Adequate - Inadequate - Missing Multivariable predictors of receiving inpatient CPAP and/or intubation * a) oxygen saturation by pulse oximeter or ABG - <85: OR 3.28 (2.02-4.82) - 85-87.9: OR 1.34 (0.57-3.43) - 88-89.9: OR 1.91 (0.79-3.80) - 90-93.9: OR 1.15 (0.70-1.52) - ≥94: 1.00 (reference) b) oral intake - Adequate: OR 1.00 (reference) - Inadequate: OR 2.51 (1.34-4.26) - Missing: OR 2.47 (1.34-5.07) * adjusted for age, gender, race, birth weight, mother smoked during pregnancy, difficulty breathing starting point, presence of apnoea, and retractions.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Yusuf,S., Caviness,A.C., kunle-Ojo,A.O., Risk factors for admission in children with bronchiolitis from pediatric emergency department observation unit, Pediatric Emergency Care, 28, 1132-1135, 2012 Ref Id 293602 Country/ies where the study was carried out United States Study type Retrospective cohort study Aim of the study To determine the predictors of subsequent hospital admission from the (Emergency department Observation Units	Sample size There were 325 patients in the study. Characteristics 85 (26%) were admitted to the hospital from EDOU; the average LOS in the EDOU was 15.4 hours; no other baseline characteristics reported. Among admitted infants (n=85): 53/85 were boys and 36 were aged less than 2 months. Inclusion criteria Patients younger than 2 years, with the diagnosis of bronchiolitis monitored in the EDOU (following their ED visit) were included. Exclusion criteria Patients with the same disgnosis admitted to other units were not included.	Interventions Clinical variables were considered based on the literature and clinical experience. The study reports adjusted ORs for: 1) Pulse oximetry <93% The study doesn't present adjusted estimates for fever, respiratory rate, duration of illness, heart rate, ability to feed and subjective assessments.	Details Statistical analysis The data were analyzed using SAS. Continuous variables were dichotomized. Pulse oximetry upon arrival in the ED were also dichotomized at the value most predictive of admission from the EDOU. Respiratory rates upon arrivale in the ED were also dichotomized but were not predictive of subsequent admission at any cutoff point. For this reason a cutoff point of 60 breaths per minute was used, because it represents the upper limit of normal for the patient age group. The frequency of patients demographics, historical characteristics, and vital signs, and ED treatments were	Results Outcomes The primary study end point was hospital admission from the EDOU, which was defined as the transfer of the patient from the EDOU to any inpatient hospital unit at any time in the EDOU stay. Patients who were not admitted to the hospital were discharged home from the EDOU. Raw Data admitted n = 85/325 discharged n = 240/325 1) Fever admitted = 48/85 * discharged =120/240 * 2) Difficulty feeding admitted = 39/85 * discharged = 80/240 * 3) Pulse oximetry <93% admitted = 8/85 * discharged = 5/240 * 4) Respiratory rate >60/min	Limitations Based on NICE guidelines manual 2012: Prognostic studies checklist Only limitations that arise in the study are reported - not reported how prognostic factors were measured - authors report that the primary reason for admission (outcome of interest) from the EDOU was sometimes absent from the chart - univariate associations table difficult to interpret because of the way results and raw data are reported - patients received treatments (i.e. oxygen supplementation) while in the ED, before disposition

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(EDOU) in infants and children with bronchiolitis, with the intent to identify patients in the ED who should not be admitted to the EDOU from the ED Study dates From April 1, 2003, to March 31, 2007. Source of funding Not reported.			compared between the two groups. Odds ratios and 95% confidence intervals were used to describe the univariate associations between patients demographic, clinical and medical intervention features, and hospitalization from the EDOU. Pearson chi-squared or Fisher exact test was performed to test the statistical significance of the associations were P<0.05 was considered statistically significant. Logistic regression was then used to determine the independent associations between patients features and hospital admission. If variables were highly correlated, the variable with the strongest association with admission was then included in the model. variables were retained in the logistic regression model if they were significant at the 0.05 level, and adjusted odds ratios were reported.	admitted = 31/85 * discharged = 65/240 * * Numerators calculated by NCC-WCH based on percentages reported in the paper Results Univariate associations, OR (95% CI) and p-values 1) Fever OR 1.29 (0.78-2.12) p=0.321 2) Difficulty feeding (reported by parents) OR 1.65 (1.00-2.74) p=0.050 3) Pulse oximetry <93% OR 4.78 (1.52-15.05) p=0.004 4) Respiratory rate >60/min OR 1.59 (0.94-2.70) p=0.081 Multivariable associations, adj OR (95% CI) and p-values Pulse oximetry <93%: OR 4.72 (1.47-15.18) p=0.009 IVF in ED: OR 2.51 (1.43-4.41) p=0.001	- retrospective study design Other information Indirectness Does the study match the review protocol in terms of Population: Some (children aged up to 2 years) Outcome: Yes Indirectness: Some Setting Texas Children's Hospital (TCH) EDOU, an urban tertiary-care free standing pediatric hospital. Data sources Study patients were identified from an electronic database of all patients cared for in the TCH EDOU. Patients medical records were reviewed and data were extracted by two researchers using a standardized data collection form.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- The diagnosis of bronchiolitis was made by the emergency room physician who admitted the patient to the EDOU. - The study was approved by the Baylor College of medicine Institutional Review Board with a waiver of patient consent.		Sample size calculation A sample size of 320 was estimated by the researchers, assuming a 25% admission frequency resulting in 80 admitted patients. The sample size was estimated to allow for the inclusion of at least 8 independent variables in a logistic regression model.

I.4 What are the indications for capillary blood gas testing?

No studies meeting the specified inclusion criteria were identified

I.5 What are the indications for fluids and nutritional support?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kugelman,A., Raibin,K., Dabbah,H., Chistyakov,I., Srugo,I., Even,L., Bzezinsky,N., Riskin,A., Intravenous fluids versus gastric-tube feeding in hospitalized infants with viral bronchiolitis:	Sample size 124 eligible infants, 73 not included due to technical constraints (mostly related to heavy work load in the emergency department during the RSV season) 31 assigned to gastric tube	Interventions IV fluids* Glucose 5%, NaCl 0.33% and potassium supplementation Nasogastric/orogastric tube (5F) feeding* Of breast milk or infant formula	Details Setting Hospitals Method of randomisation Not reported Blinding The mode of support	Results Outcomes as reported in protocol 1) Change in hydration (clinical hydration status/change in body	Limitations Based on NICE guidelines manual 2012: Randomised controlled trials checklist Only limitations that arise in the study are reported - Method of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
a randomized, prospective pilot study, Journal of Pediatrics, 162, 640-642, 2013 Ref Id 282282 Country/ies where the study was carried out Israel Study type Prospective, open randomised controlled clinical pilot study Aim of the study To compare the clinical outcomes associated with gastric tube feeding versus intravenous fluids among moderately ill infants hospitalised with acute viral bronchiolitis Study dates Not reported Source of funding Not reported	(GT) feeding, 20 assigned to intravenous fluids (IV) Characteristics Age in months, mean (SD) IV feeding: 2.6 (1.2) GT feeding: 2.1 (1.1) p=0.18 Weight in kg, mean (SD) IV feeding: 5.4 (1.4) GT feeding: 5.0 (1.2) p=0.30 Male/female, n IV feeding: 14/6 GT feeding: 24/7 p=0.79 Term/preterm (<37 weeks gestational age), n IV feeding: 18/2 GT feeding: 26/5 p=0.69 Background illness, n IV feeding: 1 (gastroesophageal reflux) GT feeding: 0 p=0.39 Known asthma or atopy in family, n IV feeding: 2 GT feeding: 2 p=0.64	*Both groups were allowed comfort non-nutritive sucking	assignment could not be blinded to the medical team - use of objective criteria and management protocols reduced the possibility of a bias related to nonblinding Allocation concealment Not reported Outcome measures Primary outcome measures were: - the duration of supplemental oxygen (criteria to stop oxygen were stable clinical situation for ≥4 hours with SpO2 >93% and tolerance of oral feeds) - length of stay (actual and theoretical [no or only mild retractions, able to tolerate oral feeds, no need for oxygen for ≥10 hours]) Statistical methods - Intention to treat analysis - Sample size calculation: estimated that there would be a >80% chance of detecting a 30%	weight/serum sodium concentration) Not reported 2) Change in oxygen saturation Not reported 3) Change in disease severity score Not reported 4) Length of hospital stay in hours, mean (SD) Actual IV feeding: 98 (48) GT feeding: 119 (55) p=0.12 Theoretical IV feeding: 81 (55) GT feeding: 92 (51) p=0.28 5) Change in respiratory rate Not reported 6) Need for high flow humidified	randomisation and allocation concealment not described - Small sample size (based on sample size calculation) Other information Crossover of treatments 3 infants were switched from GT feeding to IV fluids due to vomiting, and 2 infants were switched from IV to GT feedings, one because of failure to gain IV access and the other because of fluid extravasation into the tissue

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Smoking in close contacts, n IV feeding: 2 GT feeding: 1 p=0.55 RSV positive, n IV feeding: 15 GT feeding: 26 p=0.48 RSV negative, n IV feeding: 3 GT feeding: 4 p=1.00 Unknown RSV status, n IV feeding: 2 GT feeding: 1 p=0.55 Duration of illness before hospitalisation in days, mean (SD) IV feeding: 4.4 (2.7) GT feeding: 3.5 (2.7) p=0.04 Medications before admission, n IV feeding: 8 GT feeding: 7 p=0.21 Medications during hospitalisation, n IV feeding: 18		difference between the groups (α <0.05) with a sample size of 25 patients for each mode of treatment - Two sample unpaired t tests used for continuous variables with normal distribution and Wilcoxon rank sum test used where distribution was skewed - Differences for categorical variables tested by Chi-square analysis	oxygen, CPAP or mechanical ventilation Not reported 7) Adverse effects (including mortality), n No events of clinical aspiration were recorded	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	GT feeding: 26 p=0.69 Inclusion criteria - Age <6 months - Hospitalised with clinical diagnosis of moderate bronchiolitis* and unable to sustain oral feeding *Moderate bronchiolitis defined as infants who could not sustain oral feedings but had no signs of severe respiratory distress or of impending respiratory failure. Criteria for not sustaining oral feeding were respiratory rate >60 breaths/min, supplemental oxygen requirement and difficulties in eating. Supplemental oxygen was administered when the pulse oximetry oxygen saturation was <93% in room air, respiratory rate was >60 breaths/min or there were difficulties with breathing and feedings. Exclusion criteria - Severe respiratory distress and signs of impending respiratory failure defined by clinical				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	assessment (severe retractions, significant apnea or apathy), poor ventilation (single blood gas measurement with PCO2 >50mm Hg and pH <7.25 or evidence of CO2 retention with PCO2 >45mm Hg and pH <7.3 in repeat blood gas samples) or poor oxygenation (fraction of inspired O2 >0.4 with SpCO2 <91%)				
Full citation Oakley,E., Borland,M., Neutze,J., Acworth,J., Krieser,D., Dalziel,S., Davidson,A., Donath,S., Jachno,K., South,M., Theophilos,T., Babl,F.E., Paediatric Research in Emergency Department, Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial, The Lancet Respiratory Medicine, 1, 113-120, 2013 Ref Id 299761	Sample size 759 randomly allocated 381 allocated nasogastric hydration, 378 allocated intravenous hydration 336 from nasogastric group available at follow up, 342 from intravenous group available at follow up Characteristics Sex, male n (%) Nasogastric hydration: 228 (60) Intravenous hydration: 227 (60) Age in days, mean (SD) Nasogastric hydration: 177.6 (79.8)	Interventions - Nasogastric hydration: nasogastric fluids of continuous oral rehydration solution for the first 2 hours then their usual feed by bolus every 1 to 2 hours, with the total fluid volume of 80% of daily maintenance - Intravenous hydration: intravenous fluids of continuous 0.45% sodium chloride with 2.5%, 4% or 5% dextrose at 80% of daily maintenance *The initial route, rate and type of fluid administration at the time of randomisation were determined by the study protocol. Subsequent management decisions, including changes to the	Details Setting 7 hospitals in Australia and New Zealand - all hospital emergency departments that participated are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT) research network Method of randomisation Randomly allocated infants 1:1 by use of computer generated allocation sequence. Infants enrolled into the	Results Outcomes as reported in protocol 1) Change in hydration (clinical hydration status/change in body weight/serum sodium concentration) Not reported 2) Change in oxygen saturation Reported as oxygen saturation <90%, n (%)	Limitations Based on NICE guidelines manual 2012: Randomised controlled trials checklist Only limitations that arise in the study are reported - Includes subjects with history of previous wheeze and previous bronchiolitis Other information Crossover of treatments - 50 infants in the nasogastric hydration group and 95 infants in the intravenous

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia and New Zealand Study type Multicentre open randomised trial Aim of the study To compare the effectiveness and complications of nasogastric hydration and intravenous hydration in the management of previously healthy infants admitted with bronchiolitis who require fluid replacement. Study dates Bronchiolitis seasons (first week of April to the last week of October) of 2009 to 2011 Source of funding Australian National Health and Medical Research Council, Samuel Nissen Charitable Foundation, Murdoch Children's	Intravenous hydration: 186.3 (84.6) Age group, n (%) 2 to <6 months Nasogastric hydration: 201 (53) Intravenous hydration: 196 (52) 6 to 12 months Nasogastric hydration: 180 (47) Intravenous hydration: 182 (48) Previous medical history, n/N(%) History of previous wheeze Nasogastric hydration: 52/379 (14) Intravenous hydration: 50/375 (13) History of asthma Nasogastric hydration: 5/275 (1) Intravenous hydration: 2/375 (1) History of eczema Nasogastric hydration: 61/379 (16) Intravenous hydration: 52/375 (14) History of previous bronchiolitis	route, rate and type of fluid administration were at the discretion of the treating clinician.	study were not randomly allocated to treatment groups until treating clinicians deemed non-oral fluids to be necessary. Randomisation could occur at admission or at any time during hospital stay. Randomisation was stratified by hospital site and age group (2 to <6 months vs 6 to 12 months). Blinding The interventions were not masked for pragmatic reasons. The primary outcome measure (length of stay) was such that individual clinician preferences for one intervention over another were unlikely to have any effect. Allocation concealment Randomly allocated block sizes and opaque sealed envelopes Outcome measures Primary outcome measure was: - length of hospital	Nasogastric hydration: 19 (5) Intravenous hydration: 14 (4) Difference (95%CI): 1.3% (-1.6 to 4.2) p=0.39 3) Change in disease severity score Not reported 4) Length of hospital stay in hours, mean (SD) Nasogastric hydration: 86.6 (58.9) Intravenous hydration: 82.2 (58.8) Difference (95%CI): 4.5 (-3.9 to 12.9) p=0.30 Length of stay measured to time ready for discharge Nasogastric hydration: 84.1 (57.9) Intravenous hydration: 80.2	hydration group changed to the alternative hydration method The reasons for changing from nasogastric to intravenous therapy were: - admission to intensive care unit for 19 infants - required an intravenous bolus for 13 infants - intravenous drugs or blood tests required for 5 infants - increased work of breathing for 5 infants - cannot maintain oxygen saturation for 4 infants - abdominal distension or increased aspirate for 2 infants - parental request for one infant - other for 3 infants The reasons for changing from intravenous to nasogastric therapy were: - unable to place intravenous line for 56 infants

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Research Institute, Victorian Government	Nasogastric hydration: 108/379 (28) Intravenous hydration: 101/375 (27) Other medical disorder Nasogastric hydration: 55/380 (14) Intravenous hydration: 48/378 (13) Premature (<36 weeks) Nasogastric hydration: 39/381 (10) Intravenous hydration: 41/378 (11) Family environment, n (%) Family history of asthma Nasogastric hydration: 222/364 (61) Intravenous hydration: 207/366 (57) Smokers in home Nasogastric hydration: 168/369 (46) Intravenous hydration: 171/365 (47) Pet in home Nasogastric hydration: 135/362 (37) Intravenous hydration: 125/359 (35) Drugs used in week before emergency department		stay: determined from computerised hospital records (because length of stay might be affected by administrative and social factors unrelated to the clinical condition of the infant, the time that they were ready for discharge was also recorded prospectively with objective criteria - an infant was considered ready for discharge if he/she had not received supplemental oxygen for 12 hours, had stable respiratory status for 4 hours (including slight or no chest-wall recession) and was feeding adequately Secondary outcomes measures included: - incidence and type of complications of hydration therapy - local complications of the insertion methods - ease of insertion - need for replacement intravenous or nasogastric line - parental satisfaction	(58.3) Difference (95%CI): 3.9 (-4.3 to 12.2) p=0.35 5) Change in respiratory rate Not reported 6) Need for high flow humidified oxygen, CPAP or mechanical ventilation, n (%) Reported as need for CPAP Nasogastric hydration: 12 (3) Intravenous hydration: 13 (3) Difference (95%CI): -0.3% (-2.8 to 2.3) p=0.83 Reported as need for intubation and ventilation Nasogastric hydration: 5 (1) Intravenous hydration: 5 (1) Difference (95%CI): 0.01% (-1.6 to 1.6)	- intravenous fluid extravasation for 11 infants - hungry, crying and needing feeding for 9 infants - parental or medical staff request for 13 infants - gastric decompression required for 3 infants - other for 4 infants Additional treatment - 73 (19%) vs 95 (25%) of infants assigned nasogastric and intravenous hydration respectively received salbutamol at any time point - 9 (2%) vs 13 (3%) of infants assigned nasogastric and intravenous hydration respectively received nebulised adrenaline at any time point - 23 (6%) vs 23 (6%) of infants assigned nasogastric and intravenous hydration respectively received intravenous or oral steroids at any time point

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	visit, n/N (%) Bronchodilators Nasogastric hydration: 41/371 (11) Intravenous hydration: 43/374 (11) Inhaled steroids Nasogastric hydration: 6/365 (2) Intravenous hydration: 2/371 (1) Oral steroids Nasogastric hydration: 25/346 (7) Intravenous hydration: 27/375 (7.2) Antibiotics Nasogastric hydration: 54/370 (15) Intravenous hydration: 61/372 (16.4) RSV positive, n/N (%) Nasogastric hydration: 143/234 (61) Intravenous hydration: 130/233 (56) Inclusion criteria - Infants admitted with a clinical diagnosis of bronchiolitis* aged between 8 weeks (corrected for prematurity)		measured at end of hospital stay on 5 point Likert scale Statistical methods - Assessed differences between the 2 study groups with t tests (95%CI) of difference of means for continuous outcome variables, and chi-square (95%CI) of difference of percentages for categorical outcome variables - To reduce skew in the distribution of the primary outcome (length of stay), this outcome was capped at 2 weeks for infants with length of stay longer than 2 weeks* - Length of stay for infants who died before 2 weeks was also set to 2 weeks - Intention to treat analysis was used - Exact methods for all means (SD) - Sample size calculation: aimed to recruit 750 infants (375 per group) to have 80% power to detect a	p=0.99 7) Adverse effects (including mortality), n/N (%) Reported as numbers for nasogastric hydration vs intravenous hydration Intravenous line-site bruising: 3/336 (1) vs 33/342 (10) Sore nose: 9/336 (3) vs 1/342 (0.3) Intravenous line-site soreness: 0/336 (0) vs 9/342 (3) Epistaxis: 4/336 (1) vs 1/342 (0.3) Any sign nasal trauma: 3/336 (1) vs 0/342 (0) Intravenous line-site infection: 0/336 (0) vs 0/342 (0) Other (includes unspecified events 8 vs 7, vomiting 1 vs 2, worsened cough 1 vs 1, rash 1 vs	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and 12 months (chronological age) *Bronchiolitis defined as symptoms and signs of respiratory distress (tachypnoea, recessions, nasal flaring, or cyanosis) associated with symptoms of a viral respiratory tract infection Exclusion criteria - Chronic respiratory, cardiac or neurological illnesses - Oxygen saturations below 90% despite up to 3 L per min supplemental oxygen - Requirement of immediate ventilatory support - Requirement of intravenous fluid resuscitation for shock - Presentation to hospital with a nasogastric tube or intravenous line in situ - Requirement of intravenous or nasogastric access for another reason - Infants younger than 8 weeks of age because of concerns that nasogastric tube placement might impinge on the airway of smaller infants		difference of at least 0.2SD of length of stay between the 2 treatment groups with a two group t test with a 0.05 two-sided significance level. Therefore, expected to have sufficient power to detect a minimum difference in mean length of stay 10 to 14 hours. A difference in length of stay less than 10 to 14 hours was considered clinically insignificant. *4 infants in the nasogastric hydration group and 2 infants in the intravenous hydration group had a length of stay of 14 days or longer, none of which was regarded as related to study intervention.	0 and crying 0 vs 1): 11/336 (3) vs 11/342 (3) Intensive care unit admission: 21/381 (6%) vs 25/378 (7%), p=0.53	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

I.6 What are the criteria for a) referral to secondary care, b) hospital admission for observation or treatment, c) discharge from hospital?

Study details	Participants	Factors	Results	Comments
Full citation Corneli,H.M., Zorc,J.J., Holubkov,R., Bregstein,J.S., Brown,K.M., Mahajan,P., Kuppermann,N., Bronchiolitis Study Group for the Pediatric Emergency Care Applied Research Network., Bronchiolitis: clinical characteristics associated with hospitalization and length of stay, Pediatric Emergency Care, 28, 99-103, 2012 Ref Id 206633 Country/ies where the study was carried out USA Study type Secondary analysis of a RCT, multicentre Study dates January 2004 to April 2006 Consecutive recruitment Not reported Funding	Cases 240 infants admitted to hospital from the ED Diagnostic criteria Diagnosed by trained study physicians Controls 358 infants discharged from the ED Inclusion criteria - Aged 2 to 12 months - First-time bronchiolitis defined as: wheezing with no history of any similar condition - RDAI score ≥6 Exclusion criteria Original study excluded infants with the following: - Previous adverse reaction to dexamethasone - Known heart disease or lung disease - Premature birth with <36 weeks of gestation	Factors Admitted; discharged Mean oxygen saturation 95.7; 97.2 Mean difference (95% CI): 1.6 (1.1 to 2.1) p<0.001 Respiratory rate (breaths/min) 55.8; 51.5 Mean difference (95% CI): -4.2 (-6.4 to -2.1) p<0.001	Adjusted odds ratio Predictors of hospitalisation for bronchiolitis from a multivaraite logistic regression Adjusted* odds ratio (95% CI) Initial oximetry value <94% 5.5 (2.9 to 10.2) p<0.0001 Respiratory rate >60/min 2.6 (1.7 to 4.1) p<0.0001 * Adjusted for: initial oximetry value <94%, respiratory rate >60/min and RDAI score >11	Limitations The study sample represents the population of interest - The population is taken from a RCT for dexamethasone, therefore the original study exclusion and inclusion criteria applies. The prognostic factor of interest is adequately measured - Diagnosed by trained study physicians which appear to diagnose based on the inclusion criteria. The outcome of interest is adequately measured - All infants underwent 4 hours of ED observation before a disposition decision was reached. Do not predefine the criteria for admission to hospital. Important potential confounders are appropriately accounted for - Yes, treatment group assignment was

Study details	Participants	Factors	Results	Comments
Supported by a grant from the Maternal and Child Health Bureau Research Programme	- Immune suppression or immune deficiency - Treatment of corticosteriods within the previous 14 days - Active varicella - Known exposure to varicella within 21 days - Inability of parents/guardians to speak English or Spanish - Life threatening complications of bronchiolitis e.g. apnea, respitatory failure, sepsis Statistical method - In the original study patients were randomised to receive either oral dexamethasone or placebo, treatment group assignment was included as a potential variable in the current analysis - To identify the most important predictors performed binary recursive partitioning using CART software - In identifying predictors of hospitalisation, the statistical costs of incorrectly predicting discharge were set at twice those for incorrectly predicting admission - To quantify the relative strength of association of the variables found in the CART analysis, used multivariate logistic regression to calculate odds ratios and identify cut off points			included as a potential variable in the analysis. The statistical analysis is appropriate - It is unclear from the methods how measurements were timed and included in the model. Indirectness Population - Exclusion criteria from the original study applies to this study Outcome - Decision to admit based on trained study physician: do not predefine criteria for admission to hospital Other information Aim Identify the initial clinical characteristics of bronchiolitis associated with admission and with longer length of stay Setting 20 EDs Data collection Secondary analysis of a RCT Sample size - 598 infants enrolled

Study details	Participants	Factors	Results	Comments
	- Did not include the 4 hour data in the analysis of hospitalisation - Ongoing assessment is avaliable for patients in observation care, so the model examining longer LOS among admitted patients also included the 4 hour variables of oxygen saturation, RDAI score and respiratory rate - To avoid possible artifacts due to treatment, the 4 hour variables of heart rate and temperature were excluded a priori from analysis Demographics Admitted; discharged Mean age, months 4.8; 5.3 Mean difference (95% CI): 0.5 (0.03 to 0.9) p=0.03 Mean days of illness 3.64; 3.58 Mean difference (95% CI): -0.06 (-0.5 to 0.3) p=0.76 Gender 368 out of 598 (62%) were male			- 240 were admitted to hospital and 358 were discharged - 22 infants (3.7%) subsequently hospitalised during the 7 days after ED discharge were not treated as admissions Other - All infants underwent 4 hours of ED observation before a disposition decision was reached - Admission to observation or inpatient care was counted as hospitalisation

Study details	Participants	Factors	Results	Comments
	RSV 166 out of 269 (62%) tested positive RDAI score (RDAI based on retractions and wheezing on a scale of 0 to 17, increased severity indicated by higher values) 9.6; 8.7 Mean difference (95% CI): -0.9 (-1.2 to -0.5) p<0.001			
Full citation Mansbach,J.M., Clark,S., Christopher,N.C., LoVecchio,F., Kunz,S., Acholonu,U., Camargo,C.A.,Jr., Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department, Pediatrics, 121, 680-688, 2008 Ref Id 207528 Country/ies where the study was carried out USA Study type Prospective, multicentre, observational Study dates	Cases 837 infants discharged home from the ED Diagnostic criteria Attending physician diagnosis of bronchiolitis Controls 619 infants admitted to the OU, ward or ICU Inclusion criteria - AAP 2006 definition for infants with bronchiolitis "rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring" - Age <2 years - Ability of parent/guardian to give informed consent Exclusion criteria	Factors Admitted; discharged % or mean±SD Oxygen saturation in room air 95±4; 97±2 p<0.001 Lowest oxygen saturation in room air 93±6; 97±2 p<0.001 Respiratory rate 51±15; 44±14 p<0.001	Adjusted odds ratio Predictors of being discharged to home among infants treated in the ED for bronchiolitis from a multivariate model Adjusted* odds ratio (95% CI) Initial room air oxygen saturation ≥94% 2.28 (1.56 to 3.34) p<0.001 Respiratory rate less than normal for age 2.02 (1.46 to 2.80) p<0.001 Mild retractions	Limitations The study sample represents the population of interest - Median recuritment time of two weeks across the winter season appears restrictive. Only 68% of the eligible infants were enrolled, the remaining were missed by site personnel (89%) or other reasons such as refusal to participate. Loss to follow-up: 1012 out of 1456 infants had complete data. The prognostic factor of interest is adequately measured - Diagnosis appears to be based only on the physicians evaluation of the

Study details	Participants	Factors	Results	Comments
2004 to 2006 from December to March Consecutive recruitment 18 to 24 hour/day coverage for a median of 2 weeks Funding Supported by the Thrasher Research Fund (Salt Lake City, UT)	Previous enrollment Statistical method - Association of factors examined using chi-squared tests, student t-tests and Kriskal-Wallis - All p values are two sided - Multivariate logistic regressions were used to evaluate the association between the candidate predictors and the discharge decision - Factors associated with discharge in univariate analyses were assesed for inclusion in the multivariate model if p<0.20 - The 1456 enrolled patients were assignes randomly to 1 of 2 data sets (derivation and validation), the same factors were found to be significant when the derivation results were applied to the validation data set - The final model is presented for the 1012 infants with complete data on all factors in the model, creating dummy variables for missing responses and including them in the multivariate model to include children with complete data and those with missing data yielded similar results - the model which is presented is for children with complete data Demographics Admitted; discharged	Respiratory rate less than normal for age* 28; 46 p<0.001 Retractions - None/mild: 68; 90 - Moderate/severe: 32; 10 Oral intake - Adequare: 60; 84 - Inadequate: 32; 8 - Unknown: 8; 7 * Normal values for age: 0 to 1.9 months 45 breaths/min 2 to 5.9 months 43 breaths/min 6 to 23.9 months 40 breaths/min	2.78 (1.91 to 4.06) p<0.001 Oral intake (reference inadequate) Adequate: 6.02 (3.87 to 9.35) p<0.001 Unknown: 3.80 (1.89 to 7.63) p<0.001 * Adjusted for: no ED visit during the past week, age ≥2 months, female, nonwhite race/ethnicity, ≥1 parent with asthma, no history of intubation, eczema, duration of symptoms >7 days, number of β-receptor agonists and epinephrine treatments during the first hour	infant, diagnostic criteria are not reported. The outcome of interest is adequately measured - Do not predefine the criteria for admission to hospital. The final model includes 1012 infants but they do not report how many of those infants were admitted or discharged. Important potential confounders are appropriately accounted for - Yes. The statistical analysis is appropriate - Yes. Indirectness Population - Many infants covered by Medicaid insurance: admitted group 59%, discharged group 63%. Diagnostic criteria not reported Outcome - Admission decision made by the ED phycian: do not predefine the criteria for admission to hospital Other information Aim To identify factors associated with safe discharge home from the ED and then to develop a

Study details	Participants	Factors	Results	Comments
	% or median (IQR) Age, months 4.3 (1.9 to 8.5); 6.9 (4.2 to 11.3) p<0.001 Age <2 months 27; 6 p<0.001 <35 weeks gestation 12; 8 p=0.006 Male 59; 58 p=0.81 Nonwhie race/ethnicity 59; 68 p<0.001 Concomitant medical disorder 21; 16 p=0.02 History of wheezing 27; 33 p=0.008 Use of treatment during the past week			low risk model for children with bronchiolitis Setting 30 EDs in 14 US states Data collection - ED chart review provided clinical data - ED interview assessed patients demographic characteristics, medical and intervention history, details of acute illness and duration of symptoms - Follow-up data regarding relapse were collected in a telephone interview 2 weeks after the ED visit Sample size - 2129 eligible infants presented to the ED with bronchiolitis - 1456(68%) were enrolled - Among eligible infants not enrolled in the study, 89% were missed by the site personnel and 11% were missed for other reasons including refusal to participate

Study details	Participants	Factors	Results	Comments
	- Inhaled β-receptor agnoist: 36; 32; p=0.08 - Antibiotics: 18; 15; p=0.20 - Inhaled/nebulised corticosteriods: 10; 6; p=0.006 - Systemic corticosteriods: 11; 6; p=0.001 Of the 613 infants who were admitted: 96(7%) were admitted to an OU 479(3%) were admitted to a regular medical ward 44(3%) were admitted to the ICU Readmission - 722 of 837 (86%) infants presented for follow-up evaluation within 2 weeks - 49 of 722 (7%) had worsening bronchiolitis that led to hospital admission - 27 of 49 (55%) took place within 24 hours of ED discharge			
Full citation Walsh,P., Rothenberg,S.J., O'Doherty,S., Hoey,H., Healy,R., A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis, European Journal of Emergency Medicine, 11, 265-272, 2004 Ref Id	Cases See inclusion criteria Diagnostic criteria Diagnosed by attending paediatrician Controls See inclusion criteria Inclusion criteria Aged ≤2 years with a primary diagnosis of bronchiolitis as	Factors Results for the derivation phase Increased work of breathing* Fit for discharge: 10/37 (27%) LOS 2 to 3 days: 34/53 (64.2%)	Adjusted odds ratio Predictors of increased severity of disease* Odds ratio** (95% CI) Increased work of breathing*** (present or absent) Derivation model: 3.39 (1.29 to 8.92), p=0.013	Limitations The study sample represents the population of interest - Include infants who are readmitted in the 'need for admission' group. Return visits that did not lead to admission were also counted as discharges. Demographics only reported for the three categories (fit for discharge,

Study details	Participants	Factors	Results	Comments
208424 Country/ies where the study was carried out Ireland Study type Retrospective review Study dates 1999 Consecutive recruitment Retrospective review Funding Not reported	determined by a consultant (attending) paediatrician Defining cases and controls - Defined 'need for admission' as a hospital stay >24 hours (cases) - The need for admission in the validation phase was determined as actual admission, or discharge with subsequent return visit requiring readmission or clearly inappropriate discharges - Return visits that did not lead to admission were also counted as discharges (controls) Exclusion criteria Patients in the validation cohort who received treatments (i.e. epinephrine) not used in the derivation cohort Statistical method - Age was defined as the date of birth minus the date of entry and was not corrected for prematurity - Collapsed the three-category (fit for discharge, LOS 2 to 3 days, LOS ≥4 days) observed and model-predicted LOS to a two-category 'admit or discharge' to calculate the model - Verified the proportional odds assumption for the datasets by determining that the odds ratios calculated between adjacent	LOS ≥4 days: 18/28 (64.3%) Decreased air entry bilaterally Fir for discharge: 1/37 (2.7%) LOS 2 to 3 days: 5/53 (9.4%) LOS ≥4 days: 2/28 (7.1%) Poor feeding Fit for discharge: 11/37 (29.7%) LOS 2 to 3 days: 40/53 (75.5%) LOS ≥4 days: 19/28 (67.9%) Diarrhoea Fir for discharge: 3/37 (8.1%) LOS 2 to 3 days: 5/53 (9.4%) LOS ≥4 days: 8/28 (28.6%) * Determined by implicit review, but required at least more than one mild recession to be noted on the chart	Validation model: 6.94 (3.04 to 15.84), p<0.001 Dehydration**** (for each degree of severity, mild, moderate, severe) Dervation model: 2.54 (1.34 to 4.82), p=0.004 Validation model: 10.97 (4.00 to 30.08), p<0.001 * Table of results states predictors of increased severity of disease, unclear if this relates to hospital admission ** Odds ratios are not described as adjusted in the study, but the model in the appendix has coefficients for increased work of breathing, tachycardia, age and dehydration which implied the odds ratios are adjusted for these variables *** Determined by implicit review, but required at least more than one mild recession to be noted on the chart **** Determined either explicitly when documented or implicitly by the reviewer using the criteria described in Berhman & Orernstein 2000 and Baker & Ruddy 2000, classified on an	LOS 2 to 3 days, LOS ≥4 days) not the two-category model (discharged or admitted). Unclear how many analysed infants (n=76) in the derivation phase were admitted or discharged. The infants in the validation set have a larger mean age and larger number not requiring admission to hospital than infants in the derivation set. Loss to follow-up - In the derivation set 23 infants had missing data and were excluded from the analysis leaving 76 infants. The prognostic factor of interest is adequately measured - Diagnosed by attending paediatrician. Diagnostic criteria not reported. The outcome of interest is adequately measured - Unclear if diarrhoea and poor feeding relate to dehydration. Do not predefine the criteria for admission. Important potential confounders are appropriately accounted for - Unclear which treatments were received in the ED.

Study details	Participants	Factors	Results	Comments
	pairs of outcome categories in diagnostic multinomial logistic regressions were indistinguishable from each other - Constructed the original proportional odds logistic regression model using the derivation set by entering all variables that showed a significant relationship with LOS by univariate tests, then trimmed the variables - Validated the originial model by using the independent validation set with the variables in the original model Demographics Derivation sample; validation sample Mean age, months: 6.1; 8.5 Age range, months: 0.9 to 19; 0.27 to 21.9 Number not requiring admission: 37(31%); 139(76%) Mean LOS for admitted: 3; 3 Median LOS: 4; 3 LOS range: 2 to 19; 2 to 24 Fit for discharge; LOS 2 to 3 days; LOS ≥4 days Derivation phase patients demographics based on episodes of bronchiolitis, not the number of patients		ordinal scale as none, mild, moderate or severe	The statistical analysis is appropriate - Calculation for age unclear. Demographics are based on the number of episodes of bronchiolitis, not the number of patients. Unclear how the model was 'trimmed', no significance level is discussed. Indirectness Population - Diagnostic criteria not reported Outcome - Retrospective chart review where the admission decision made by the attending ED peadiatrician: do not predefine the criteria for admission to hospital Other information Aim To develop and validate a logistic regression model to predict the need for admission and length of hospital stay in infants presenting to the ED with bronchiolitis Setting - 2 children's hospitals in Dublin - The derivation phase used patients at one hospital (year

Study details	Participants	Factors	Results	Comments
	Male (83 episodes in 72 patients) 25(30%); 29(35%); 18(22%) Female (49 epidoes in 46 patients) 12(25%); 24(49%); 10(20%) Mean age (range) 7.0 (2.4 to 19.0); 6.7 (0.9 to 14.8); 3.7 (1.2 to 9.3) Mean duration of symptoms, days (range) 6.25 (1 to 60); 4.78 (1 to 42); 5.15 (1 to 35) Mean respiratory rate Before treatment: 48; 54; 52 After treatment: 39; 45; 47 Oxygen saturation <92% Before treatment: 4/37 (10.8%); 5/53 (9.4%); 6/28 (21.4%) After treatment: 0/37 (0%); 4/53 (7.5%); 3/28 (10.7%)			1999) and the validation phase used patients at the second hospital (2 years subsequent to the derivation season) - Reviewed infants presenting to the ED Data collection - A retrospective chart review was carried out by a single reviewer who extracted information on up to 170 variables using a standardised collection form - Cases for the validation phase were identified by a hand search of ED logs and medical records - All cases from the validation phase were taken from a single bronchiolitis season 2 years after the derivation set Sample size Derivation phase: - 132 episodes of bronchiolitis were identified - 3 excluded: one aged 4 years had a previous diagnosis of asthma, one was admitted solely for obtaining a computed tomogram of the head, and one had no admission record in the chart - Data avaliable on 99 patients (118 episodes)

Study details	Participants	Factors	Results	Comments
				- 37 infants discharged and 62 admitted - 23 infants had missing data and were excluded from the analysis leaving 76 infants Validation phase: - 225 episodes of bronchiolitis among 201 patients identified - 2 excluded for incomplete data - 17 excluded for use of treatments not employed at the derivation centre - Data on 182 patients remained - 139 infants discharged and 43 admitted
Full citation Yusuf,S., Caviness,A.C., kunle-Ojo,A.O., Risk factors for admission in children with bronchiolitis from pediatric emergency department observation unit, Pediatric Emergency Care, 28, 1132-1135, 2012 Ref Id 293602 Country/ies where the study was carried out Texas Study type Retrospective cohort Study dates	Cases 85 infants admitted to hospital from the EDOU Diagnostic criteria Diagnosis made by the emergency room physician Controls 240 infants discharged from the EDOU Inclusion criteria - <2 years of age with a diagnosis of bronchiolitis - Monitored in the EDOU following their ED visit Exclusion criteria	Factors Admitted freqency, n(%) Pulse oximetry <93% (hypoxia) 8(61.5) p=0.004 Respiratory rate >60 breaths/min 31(33.0) p=0.081 Increased work of breathing 52(34.2) p=0.002	Adjusted odds ratio Univariate associations between patient clinical features and hospital admission Unadjusted odds ratio (95% CI) Pulse oximetry <93% (hypoxia) 4.78 (1.52 to 15.05) Respiratory rate >60 breaths/min 1.59 (0.94 to 2.70) Increased work breathing	Limitations The study sample represents the population of interest - Demographics are reported as the admitted frequency. The prognostic factor of interest is adequately measured - Diagnosis made by the emergency room physician. Diagnostic criteria not reported. The outcome of interest is adequately measured - The primary reason for admission from the EDOU was sometimes absent from the chart (sometimes not

Study details	Participants	Factors	Results	Comments
April 1, 2003 to March 31, 2007 Consecutive recruitment Infants identified from electronic database Funding Authors declare no conflict of interest	Patients with the same diagnosis admitted to other units in the hospital were not included Statistical method - Pearson, chi-squared or Fisher exact tests were performed to test significance - Logistic regression was used to determine the independent association between patient features and hospital admission - Variables were retained in the model if they were significant at the 0.05 level - Pulse oximetry level <93% was included in the logistic regression model instead of the administration of supplemental oxygen in the ED and parental report of increased work of breathing or poor feeding because it was highly correlated with, but more predictive of, admission than the administration of supplmetal oxygen in the ED, increased work of breathing, and poor feeding Demographics Admitted freqency, n(%) Age, months 0 to 2: 36(26.9) 3 to 6: 21(25.3)	Difficulty feeding 39(32.8) p=0.050 Received intravenous fluids in the ED 30(41.1) p=0.001 Calculations by NCC-WCH based on percentages reported in the paper Pulse oximetry <93% Admitted (%) = 8/13 (61.5) Discharged (%) = 5/13 (38.5) 13 = number of infants with pulse oximetry <93% /325 Respiratory rate >60/min Admitted (%) = 31/94 (33.0) Discharged (%) = 63/94 (67.0) 94 = number of infants with RR>60 /325 Difficulty feeding	2.19 (1.32 to 3.65) Difficulty feeding 1.65 (1.00 to 2.74) Multivariate associations between patient clincal features and hospital admission (only pulse oximetry <93% and IVF in ED included in the model) Pulse oximetry <93% (hypoxia) Admitted from EDOU: 61.5% Adjusted OR: 4.72 (1.47 to 15.18) p=0.009 Intravenous fluids in ED Admitted from EDOU: 41.1% Adjusted OR: 2.51 (1.43 to 4.41) p=0.001	expanded on). Do not predefine the criteria for admission to hospital. Important potential confounders are appropriately accounted for - Unclear, demographics are reported as the admitted frequency. The statistical analysis is appropriate - Yes. Indirectness Population - Diagnostic criteria not reported Outcome - Infants received medical treatment in the ED before the decision was made to admit or discharge. Retrospective study design where the admission decision was made by the ED physician: do not predefine the criteria for admission to hospital Other information Aim To determine predictors of subsequent hospital admission from the EDOU in infants with bronchiolitis Setting Texas Children's Hospital EDOU

Study details	Participants	Factors	Results	Comments
	7 to 12: 17(30.4) 13 to 24: 11(21.2) p=0.741 Gender Male: 53(27.3) Female: 32(24.4) p=0.561 Premature birth 17(29.8) p=0.57 History congenital heart disease 4(40.0) p=0.301 History of wheezing 49(29.2) p=0.213 Medical interventions in the ED - Albuterol: 54(28.0), p=0.431 - Vaponephrine: 35(34.7), p=0.022 - Steriod: 21(29.6), p=0.470 - Deep suction: 69(28.4), p=0.126 - Supplemental oxygen: 29(43.3), p<0.0001 - Home medication of oral steriods: 12(33.3), p=0.512 There were 4 patients with combined hypoxemia and	Admitted (%) = 39/119 (32.8) Discharged (%) = 80/119 (67.2) 119 = number of infants with difficulty feeding /325 Increased work of breathing Admitted (%) = 52/152 (34.2) Discharged (%) = 100/152 (65.8) 152 = number of infants with difficulty breathing /325 Received intravenous fluids in the ED Admitted (%) = 30/73 Discharged (%) = 43/73 73 = number of infants who received intravenous fluids in the ED /325		Data collection - Patient medical records were reviewed, and data were extracted using a standardised data collection form - Patient demographic characteristics, historical features, physicial findings, medical interventions provided in the ED, duration of EDOU stay, and final disposition from the EDOU were extracted from the medical records Sample size A sample size of 320 was estimated, assuming a 25% admission frequency resulting in 80 admitted patients

Study details	Participants	Factors	Results	Comments
	treatment with intravenous fluids, and 2 of them were admitted to hospital from the EDOU			
Full citation Schuh,S., Freedman,S., Coates,A., Allen,U., Parkin,P.C., Stephens,D., Ungar,W., DaSilva,Z., Willan,A.R, Effect of oximetry on hospitalization in bronchiolitis: a randomized clinical trial, JAMA, 312, 712-718, 2014 Ref Id 323294 Country/ies where the study was carried out Canada Study type Randomized, double-blind, parallel-group trial. Study dates between March 2008 and May 2013. Consecutive recruitment Funding This study was supported by the Thrasher Research Fund and the Physicians' Services Incorporated Foundation. Masimo provided the oximeters used in the study.	Cases 105 Diagnostic criteria see inclusion criteria. Controls 108 Inclusion criteria Previously healthy infants aged 4 weeks to 12 months Diagnosed with bronchiolitis defines as the first episode of respiratory distress with coryza, cough, wheezing/crackles, and tachypnea and chest retractions Exclusion criteria - Children with cardiopulmonary, neuromuscular, hematologic, or congenital airway anormalities - those with true triage saturation levels below 88% - those transferred fron outside intitutions - those with severe respiratory distress defined by an initial retraction component of the RDAI score of 8 or 9 points. - children were also excluded if there was concern about impending respiratory failure	Factors - Oxygen saturation	Adjusted odds ratio Outcomes - primary outcome was hospitalization for bronchiolitis within 72 hours of enrollment - secondary outcomes included: supplemental O2 administration in the ED, hourly physician level of agreement with discharge home, lenght of stay in the emergency department, and unscheduled visits for bronchiolitis within 72 hours. Results for outcomes relevant to review protocol Hospitalized within 72 hours, No. (%) - True = 44 (41) - Altered = 26 (25) OR = 2.1 (1.2-3.8) Other results Lenght of ED stay, mean (SD) - True = 5.2 (5.6) - Altered = 5.0 (2.4) difference, % = 0.2 (-0.13 to 0.12) p=0.82	Limitations Based on NICE manual checklist for RCTs: - two groups were comparable at baseline although there was a limited number of patients presenting with low oxygen saturation levels which in the end did not allow to dermine a specif threshold for admisison. - high number of refusals (but 0 lost at follow-up or discontinued the intervention) Indirectness Indirectness Does the study match the review protocol in terms of: Population = Yes Intervention = Yes Control = No Outcome = Yes Indirectness = Some Setting tertiary-care pediatric emergency department. Sample size a sample size of 108 patients per group was estimated to provide 80% power to detect

Study details	Participants	Factors	Results	Comments
	Statistical method Study procedure All infants had their true O2 saturation measured by the triage nurse who notified a research nurse of patients with 88% or higher. Potential study candidates were screened for eligibility and approache for enrollment by two trained research nurses on duty between noon and midnight 6 days a week. Treatment allocation Participating infants were randomly allocated to either true saturation or altered saturation (saturation measurements displayed were 3 points higher, to a mazimum of 100%). The ED physicians were not told the primary hypothesis of the study. Prior to study commencement, 3 of the 6 study oximeters were altered by the manufacturer so that the saturation display was increased by 3 percentage points. Randomization and masking A random permuted randomization scheme with a block size of 6 was prepared by an independent Internet randomization service. prior to the study, the study nurses were unable to distinguish which oximeter		supplemental O2 in ED, No. (%) - True = 4 (3.7) - Altered = 4 (3.8) difference, % = -0.1 (-0.05 to 0.05) p=0.97	an absolute 15% difference in the primary outcome between groups, assuming an hospitalization rate of 30% in the true oximetry group. Other information None

Study details	Participants	Factors	Results	Comments
	belonged to each study group; the oximeters appeared identical. The treating ED physicians, nurses, families, and research nurses were blinded to group assignment. Follow-up The study nurses conducted telephone follow-up of all participants discharged home at the index visit 72 hours following enrollment to identify unscheduled visits for bronchiolitis and delayed hospitalization. Statistical analysis A statistician not otherwise involved in the study carried out the analysis using SAS version 9.3. The difference in the primary outcome was compared using the 1-sided unadjusted Fisher exact test. All other comparisons were 2-sided. As a sensitivity analysis, logistic regression analysis was used to examine the association between the primary outcome and study group, age, triage saturation, duration of distress, and initial RDAI score as independent variables. A multivariable model was then defined using backward stepwise elimination. Variables in the initial model with P>0.20 were			

Study details	Participants	Factors	Results	Comments
	removed from the multivariable regression model. To test if oxygen saturation was the main factor associated with hospitalizations, a sensitivity analysis was performed in which the saturation presented tot he treating ED physician was added to a logistic regression model as a covariate. Demographics Infants in the 2 groups had comparable disease severity, with a total of 13% of the participants presenting with triage saturations of less than 94%. The difference in the mean oxygen saturations between the two groups was 1.6%, less than the 3 percentage points expected, because the displayed oximetry reading of patients in the altered oximetry group with saturations of 98% or above could not exceed 100%. Age, mean (SD), mo True = 4.8 (3.0) Altered = 5.4 (3.0) Male sex, No. (%) True = 63 (58) Altered = 62 (62) Duration of respiratory distress, median (range), h True = 48 (7-672) Altered = 48 (7-360) Initial RDAI, mean (SD)			

Study details	Participants	Factors	Results	Comments
	True = 8.0 (2.9) Altered = 8.3 (2.9)			

I.7 When is pulse oximetry oxygen saturation (Sp_{O2}) monitoring indicated in bronchiolitis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Choi,J., Claudius,I., Decrease in emergency department length of stay as a result of triage pulse oximetry, Pediatric Emergency Care, 22, 412-414, 2006 Ref Id 210399 Country/ies where the study was carried out United States Study type Retrospective design studying patients pre- and post-intervention. Aim of the study To quantify the decrease in throughput time accomplished by initiating triage pulse oximetry.	Sample size Pre-intervention = 159 bronchiolitis patients Post-intervention = 89 severity-matched bronchiolitis patients Characteristics Mean age pre-intervetion group = 11.4 months post-intervetion group = 8.2 months, p<0.05 ED census (patients/month) pre-intervetion group = 4222 post-intervetion group = 5235, p=0.24 ED nurse : patient ratio	Interventions Before 2005, pulse oximetry was not measured in triage. In February of 2005, the ED initiated pulse oximetry in triage in al repsiratory and cardiac patients with a battery-powered Nellcore N20 pulse oximeter. No other interventions were made. By studying retrospectively the data before and after this interventions, the authors attemped to quantify the difference that the addition of pulse oximetry to the triage assessment made in overall throughput time for patients in whom assessment of oxygenation was indicated.	Details Diagnosis The ICD-9 code for bronchiolitis was used to identify 200 appropriate charts from March through May 2004, and charts were manually searched for a discharge diagnosis of bronchiolitis for February and March 2005. Data collection The researches recorded the traige to disposition time (either to home or to an inpatient bed), the age, and the percent admitted for both the pre- and post-intervention group. For the pre-intervention group, time from triage to initial pulse oximetry, drop in pulse oximetry after bronchodilator treatment, and nursing assessment of respirtaory distress was also recorded. In order to further assure equivalence between the	Results Triage to discharge time (LoS in ED) pre-int group = 299 minutes post-int group = 249 minutes, p=0.033 Admitted (%) pre-int group = 20 post-int group = 18, p=0.61 No data reported for: duration of admission, readmission rates, duration of oxygen supplementation, change in disease severity score, need for supplementation, need for high flow humidified oxygen, CPAP, or mechanical ventilation, and adverse effects. Additional results Of the 159 patients studied for 2004, the average time from triage to initial measurement of pulse oximetry was 64 minutes. Sixty-one of the 159 patients had a pulse oximetry reading at or below 93% either	Limitations Based on NICE appendix E checklist for case-control studies Only limitations that arise in the paper are reported: - cases and controls are takens from comparable populations: poorly addressed (population characteristics poorly reported) - participants and non-participants are compared to establish their similarities and differences: not reported - Main potential confounders are identified and taken into account: not addressed - Confidence intervals have not been reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates From March to May 2004 (pre-intervention group) and from February to March 2005 (post-intervention group). Source of funding Not reported.	pre-intervetion group = 1: 2.3 post-intervetion group = 1: 2.5, p=0.37 Time to inpatient bed (min) pre-intervetion group = 289 post-intervetion group = 286, p=0.82 Inclusion criteria Patients were included if - a timed pulse oximetry reading was recorded - a triage and discharge time were available on chart review Exclusion criteria Not reported.		2004 and 2005 study groups, ED census, nurse to patient ratio, and inpatient bed wait time were compared. Statistical analysis A 2-sample t test was used to compare total ED time between the pre- and post-intervention group. The P value was calculated as one sided as the throughput times were hypothesized to decrease. Illness severity was estimated by the number of admitted patients and the two groups were compared by chi-squared test in this regard. These were performed using Microsoft Excel. Sensitivity, specificity, and predictive values were calculated for nursing assessment of respiratory pathology and subsequent identification of hypoxia.	in triage or during their ED stay. For the hypoxic patients, the average time to pulse oximetry was 57 minutes. of the hypoxic patients, nurses in triage did not detect respiratory distress in 16 of 61 (26%). The triage nurses' clinical exam had a sensitivity of 74%, specificity of 44%, NPV of 72% and PPV of 46% for identifying hypoxia.	Other information Indirectness does the study match the protocol in terms of Population: Yes Intervention: Yes Outcome: Some Indirectness: Some Setting Children's Hospital Los Angeles, an urban tertiary are hospital with a dedicated ED (no ED observation unit). Other For patients who returned with a subsequent episode of wheezing also coded as bronchiolitis, each visit was included as a separate, unweighted encounter, as the analysis was of throughput time and not individual patient outcomes.

I.8 What are the indications for chest radiography in bronchiolitis?

Study details	Participants	Tests	Methods	Results	Limitations
Full citation Shaw,K.N., Bell,L.M.,	Sample size 228 infants with bronchiolitis who	Index test Chest X-ray findings: anteroposterior and	Methods Diagnostic criteria	Results Raw data	Limitations

Study details	Participants	Tests	Methods	Results	Limitations
Sherman,N.H., Outpatient assessment of infants with bronchiolitis, American Journal of Diseases of Children, 145, 151-155, 1991 Ref Id 208134 Source of funding Not reported. Country/ies where the study was carried out United States Aim of the study To identify the historical, physical, and laboratory clues at initial ED evaluation that would help to predict disease severity. Study type Cross-sectional study (prospective). Study dates From January to April 1987.	presented to the ED during the 1987 epidemic season for RSV bronchiolitis (January through April). Characteristics Of the 228 study infants with bronchiolitis who were evaluated in the ED, 213 had adequate follow-up to judge eventual outcome and severity of illness. Based on their total course of illness, the patients were divided in two groups - 139 patients with mild disease - 74 patients with more severe disease, of whom 59 received oxygen therapy, 13 were admitted to the intensive care unit, and 8 underwent mechanical ventilation. Demographic and Historical information The average ±s.d. age of the babies in the study was 5.6 ±3.1 months; 86% infants were black; 62% were	lateral chest roentgenograms were subsequently read by a staff radiologist who was blinded to the clinical presentation of the patient. Reference test Severity of illness: the study looked specifically at the presence of atelectasis and hyperaeration on chest films, comparing children with severe and mild disease.	Infants were considered having bronchiolitis if they had signs of lower airway disease such as tachypnea, rales, or wheezing. Mild disease defined as: infant remained alert and active and was well hydrated while he/she was taking fluids orally throughout the illness. Severe disease: all others without mild disease. Statistical method The chi-squared, Mann-Whitney, or t test was used to determine which individual components of the initial ED evaluation were associated with severity of the disease , and the relative risk (RR) of having severe disease is reported for each of these findings. Discriminant analysis was then used to determine a model of clinical and laboratory findings that would best predict illness severity.	Infants with mild disease - atelectasis on CXR: 3/139 * - hyperaeration on CXR: 72/139 * Infants with severe disease - atelectasis on CXR: 16/74 * - hyperaeration on CXR: 51/74 * Results Relative Risk (RR) for Atelectasis on chest x-ray infants with severe vs. mild disease: RR 2.70 p<0.001 (CI 1.97-3.70) RR for Hyperaeration on chest x-ray infants with severe vs. mild disease: RR 1.58 p<0.05 (1.03-2.42) Association with severity of illness chest roentgenogram with/without atelectasis: sensitivity 21% (0.12-0.30), specificity 98% (0.95-1.00), PPV 82% (0.68-1.00),	Based on NICE guideline manual 2012: Diagnostic studies checklist. Only limitations that arise in the study are reported 1) data collected retrospectively 2) no clinical exclusion criteria considered 3) the selection of patients could have introduced bias since the researchers included all patients with "bronchiolitis" without stating a clear method of diagnosis; only 42% with proven RSV infections; the severity of illness may have been lower than in other studies. 4) included patients and applicability: unclear ("history of previous upper tract respiratory infection" as inclusion criterion) 5) infants with severe disease are reported to be significantly different from those with mild disease in terms of historical information (history of cianosis or apnoea, gestetional age, age, decrease PO intake, perinatal complications, URI symptoms)

Study details	Participants	Tests	Methods	Results	Limitations
	male; 66% had history of exposure to a smoker in the family; 14% had been breastfed; 71% had family history of wheezing; 5% had history of cianosis or apnea; 5% had a gestational age in weeks <34; 41% experienced perinatal complications; 48% experienced URI symptoms. Inclusion criteria - infants younger than 13 months - had signs of lower airway disease such as tachypnea, rales, or wheezing - had history of a preceding upper respiratory tract infection Exclusion criteria Only study information with an 80% or greater response or completion rate was included in the data analysis.			NPV 70% (0.63-0.76), +LR10.47 (3.01-36.37), -LR (0.81 (0.71-0.91) **. The study doesn't report data on the following outcomes: antibiotic administration, admission rates, duration of admission, change in disease severity, need for high flow humidified oxygen, CPAP, or mechanical ventilation and on adverse effects. * Calculated by NCC-WCH based on data reported in the paper ** All CI and Likelihood Ratios were calculated by NCC-WCH based on data reported in the paper	6) no reference standard was used Other information Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: Yes Indirectness: None Outcome Detection of alternate diagnoses Setting Emergency Department of the Children's Hospital of Philadephia (Pa) Other - study protocol was approved by the hospital's Human Subjects Committee
Full citation	Sample size	Index test	Methods	Results	Limitations

Study details	Participants	Tests	Methods	Results	Limitations
Dawson,K.P., Long,A., Kennedy,J., Mogridge,N., The chest radiograph in acute bronchiolitis, Journal of Paediatrics and Child Health, 26, 209-211, 1990 Ref Id 212042 Source of funding Not reported. Country/ies where the study was carried out New Zealand Aim of the study To examine the relationship between the degree of change in the radiograph and parallel clinical assessment. Study type Cross-sectional study. Study dates Period 1986-1988.	153 children admitted to the Pediatrics Department of Christchurch Hospital with acute bronchiolitis during the period 1986-1988. Characteristics - 84 were male and 60 were female - their ages ranged from 28 days to 22 months with a mean age of 6 months Inclusion criteria Described in Dawson et al., "Acute Bronchiolitis: A Three Year Study", 1989: Children with a clinical diagnosis of bronchiolitis, with no previous history of a similar illness, as evidenced by a brief prodrome of upper respiratory symptoms following by rapid onset of cough, wheeze, tachypnea and poor feeding associated with hyperinflation,	A chest radiograph was taken as part of the management. Two radiologists independently examined the films for the presence of hyperinflation, atelectasis and infiltrates (radiological change). The severity of each finding was graded on a four-point scale: absent (0), minimal (1), moderate (2), severe (3), and very severe (4). Reference test Severity of the illness: the clinical aspects of the illness were graded using a clinical score, independently and blindly to the radiologists' assessment. The Clinical score criteria are reported in Dawson et al., "Acute Bronchiolitis: A Three Year Study", 1989: - mild (colour good, no additional oxygen required, no tube feeding or intravenous	Statistical method The Chi-square test was used to examined the relationship between the clinical and radiological groups. Diagnostic criteria Described in Dawson et al., "Acute Bronchiolitis: A Three Year Study", 1989: discharge diagnosis of acute bronchiolitis (described by the inclusion criteria) or with a respiratory tract infection. 77% of the children had a nasopharyngeal aspirate performed for respiratory virus identification and RSV was identified in 56% of them.	Raw Data 1) measure of hyperinflation - radiological change vs mild clinical assessment: absent 40/89; mild 28/89; moderate 19/89; severe 2/89; very severe 0/89. - radiological change vs moderate clinical assessment: absent 10/16; mild 1/16; moderate 4/16; severe 1/16; very severe 0/16. - radiological change vs severe clinical assessment: absent 13/36; mild 13/36; moderate 9/36; severe 1/36; very severe 0/36. - radiological change vs very severe clinical assessment: absent 4/11; mild 2/11; moderate 5/11; severe 0/11; very severe 0/11. 2) measure of infiltrates raw data not reported 3) sum of hyperinflation,	Based on NICE guideline manual 2012: Diagnostic studies checklist. Only limitations that arise in the study are reported - researchers enrolled a consecutive sample of patients - exclusion and inclusion criteria reported elsewhere - the study doesn't use an intervention and control group - no reference standard was used - the two radiologists were aware of the clinical diagnosis of acute bronchiolitis - data regarding one patient assessment is missing from the raw data about hyperinflation and clinical score (n=152) and no explanation is provided in the paper. Other information Indirectness Does the study match the review protocol in terms of: Population: Some (infants up to 22 months of age) *wait for the full text where they report inclusion and exclusion criteria

Study details	Participants	Tests	Methods	Results	Limitations
	recession, and fine crepitations. Exclusion criteria Not reported (see inclusion).	fluids given, chest retraction) - moderate (colour normal, retractions moderate, tachypnea greater than 50 per minute, air entry decreased, clinical hyperinflation) - severe (pale, dusky or cyanosed, additional oxygen required, marked retractions of chest noted with accessory muscle use, tachypnoea greater than 50 per minute, decreased air entry, intravenous and/or tube feeds necessary, +/- apnoea) - very severe (cyanosed or dusky, oxygen required, intensive care management, +/- ventilation, +/- heart failure).		infiltrates and atelectasis sum og radiological change: Low (0-2), Medium (3-4), and High (>5) - radiological change vs mild clinical assessment: low 58/81; medium 21/81; high 2/81. - radiological change vs moderate clinical assessment: low 13/27; medium 12/27; high 2/27. - radiological change vs severe clinical assessment: low 24/35; medium 9/35; high 2/35. - radiological change vs very severe clinical assessment: low 6/10; medium 3/10; high 1/10. Results 1) degree of hyperinflation and severity of the clinical illness chi-square = 9.92, d.f. 9, NS p<0.10 2) degree of infiltrates and	Intervention: Yes Indirectness: Some Outcomes detection of alternate diagnoses Setting Paediatric Department of Christchurch Hospital in NZ Other - the two radiologists were unaware of the clinical severity of the presentation and the previous radiological report, but aware of the clinical diagnosis of acute bronchiolitis - the clinical assessment score was incorporated the need of oxygen, tube feeding, intravenous fluid and measures of the degree of respiratory distress and the need for intensive care

Study details	Participants	Tests	Methods	Results	Limitations
				severity of the clinical illness chi-square = 4.56, d.f. 12, NS p<0.10 3) sum of grading and severity of the clinical illness chi-square = 6.55, d.f. 6, NS p<0.10 The study doesn't present data for the following outcomes: antibiotic administration, admission rates, duration of admission, change in disease severity, need for high flow humidified oxygen, CPAP, or mechanical ventilation and for adverse effects.	
Full citation Yong,J.H., Schuh,S., Rashidi,R., Vanderby,S., Lau,R., Laporte,A., Nauenberg,E., Ungar,W.J., A cost effectiveness analysis of omitting radiography in diagnosis of acute bronchiolitis,	Sample size 265 previously healthy infants 2-23 months of age who presented to the Emergency Department (ED) with typical bronchiolitis. Characteristics The mean age of enrolled patients was 7.7 ±5.5 months; 65%	Index test Pre-radiography scenario: after the initial patient assessment, the ED physician or fellow was asked by the research nurse about his/her suspicion regarding an associated diagnosis of pneumonia or of an alternate disease, as	Methods Diagnostic criteria - Typical bronchiolitis was defined as non-toxic appearance with coryza, cough and respiratory distress with wheezing for the first time. - Radiographs with alternate diagnosis inconsistent with bronchiolitis were those with lobar consolidation,	Results Raw Data Detection of alternate diagnoses Pre-radiography scenario: - cases of alternate diagnoses identified by ED physicians = 0 - cases of alternate diagnoses identified	Limitations Based on NICE guideline manual 2012: Diagnostic studies checklist. Only limitations that arise in the study are reported: - possibile risk of bias in patients selection: the researchers excluded premature infants - reference standard: the study radiologist knew the

Study details	Participants	Tests	Methods	Results	Limitations
Pediatric Pulmonology, 44, 122-127, 2009 Ref Id 208536 Source of funding Study supported by the Physicians' Services Incorporated Foundation of Ontario. Country/ies where the study was carried out Canada Aim of the study To carry out a cost-effectiveness analysis of omitting chest radiography in the diagnosis of infant bronchiolitis. Study type Economic evaluation. Study dates Not reported.	were boys. Other relevant data are described elsewhere. Inclusion criteria - non-toxic appearance with coryza, cough and respiratory distress with wheezing for the first time - written informed consent obtained from all participating families Exclusion criteria - infants with previous wheeze - infants with previous disgnosis of co-morbidities - premature infants - infants who had neonatal ventilation - infants with radiograph taken at other institutions	well as treatment plan, including disposition and antibiotic therapy. Post-radiography scenario: the chest radiograph was obtained on all infants and interpreted by the same ED physician. Reference test Gold standard: all radiographs were read at a later date by an expert radiologist, according to the same criteria as those employed in the ED.	cardiomegaly, congenital lung anomaly, pleural effusion and a mediastinal or parenchymal mass. - Bronchiolitis-associated pneumonia was defined as the presence of both airway disease and adjacent airspace disease without lobar consolidation. Statistical method The radiographs interpretations by the ED physicians were compared to those by the expert radiologist to determine the false-negative and false-positive rates of the ED alternate diagnoses and disgnoses of pneumonia. The study was approved by the institution's Reserach Etchics Board.	by expert radiologist = 2 (a secundum atrial septal defect and a lobar consolidation) Post-radiography scenario: - cases of alternate diagnoses identified by ED physicians = 0 - cases of alternate diagnoses identified by expert radiologist = 2 (a secundum atrial septal defect and a lobar consolidation) Detection of Pneumonia cases Pre-radiography scenario - cases of pneumonia identified by ED physicians = 2 - cases of pneuomia identified by expert radiologist = 17 Post-radiography scenario - cases of pneumonia identified by ED physicians = 7 - cases of pneumonia identified by expert radiologist = 17	patients were suspected of having bronchiolitis Other information Indirectness Does the study match the review protocol in terms of Population: Some (infants up to 23 months of age) Intervention: Yes Indirectness: Some Outcomes - detection of alternate diagnoses - antibiotic usage Setting Emergency Department of The Hospital for Sick Children, an urba tertiary peditric hospital. Other - this paper is linked to the study by Schuh et al., as they use the same population. - this study also reports that the interpretation of chest X-ray by ED physicians resulted in a fivefold increase in the rate of antibiotic therapy after radiography, from 2.6% to 14.7%. A study by Schuh et al., which uses the same study participants, presents the raw data for antibiotic

Study details	Participants	Tests	Methods	Results	Limitations
				Results Detection of alternate diagnoses Pre-radiography scenario - False-negative rates: 2/2 = 100% - False-positive rates: 9/263 = 3.4% Post-radiography scenario - False-negative rates: 2/2 = 100% - False-positive rates: 30/263 = 11.4% Detection of pneumonia Pre-radiography scenario - False-negative rates: 15/17 = 88.2% - False-positive rates: 26/248 = 10.5% Post-radiography scenario - False-negative rates: 7/17 = 41.2% - False-positive rates: 40/248 = 16.1% The false-positive rates of pneumonia resulted in a fivefold increase in the rate of antibiotic therapy after radiography,	administration: 7/265 pre-radiography vs. 39/265 post-radiography respectively. - the expert radiologist knew the patients were suspected of having bronchiolitis but were blinded to the details of the presentation, to the ED interpretations of the films, and to the interpretations by staff radiologists not participating in the study - when the study radiologist detected any alternate diagnosis inconsistent with bronchiolitis or a diagnosis of pneumonia, the patient was followed-up for treatment

Study details	Participants	Tests	Methods	Results	Limitations
				from 2.6% to 14.7% (no raw data). The study doesn't report data on the following outcomes: admission rates, duration of admission, change in disease severity, need for high flow humidified oxygen, CPAP, or mechanical ventilation, and on adverse effects.	
Full citation Christakis,D.A., Cowan,C.A., Garrison,M.M., Molteni,R., Marcuse,E., Zerr,D.M., Variation in inpatient diagnostic testing and management of bronchiolitis, Pediatrics, 115, 878-884, 2005 Ref Id 206575 Source of funding Not reported.	Sample size Infants younger than 1 year and hospitalized for bronchiolitis. Characteristics A total of 17397 patients were included in the analysis. The mean age was 3.96 ±2.92 months, and 59% were male. The mean LOS was 2.97 ±2.52 days; the readmission rate was of 1.3%; 72% received chest radiographs; 45% received antibiotics and 25% received	Index test Chest radiograph. Reference test No chest radiograph.	Methods Diagnostic method Diagnosis of bronchiolitis was made based on International Classification of Diseases, Ninth Revision (codes 466.11 or 466.19) and based on All-Patient Refined Diagnosis Realated Groups of bronchiolitis/asthma (code 141). Statistical method Chi-squared tests were used to compare categorical variables and t-tests were used to compare continuous ones.	Results Raw Data Chest radiograph Children < 3 months Yes: 5282/7336 No (baseline): 2054/7336 Children aged ≥ 3 months Yes: 7244/10061 No: 2817/10061 Results Linear regression of Lenght of Stay (LOS, days) *	Limitations Based on NICE guideline manual 2012: Diagnostic studies checklist. Only limitations that arise in the study are reported - selection bias: data were collected retrospectively and are cross-sectional; therefore, selection bias may be possible in the use of diagnostic testing (more severely affected patients may have been more likely to have chest radiograph performed) - differences between those who received x-ray and those who didn't

Study details	Participants	Tests	Methods	Results	Limitations
Country/ies where the study was carried out United States Aim of the study 1) to document variations in treatment and diagnostic approaches, lenght of stay (LOSs), and readmission rates 2) to determine which potentially modifiable process of care measures are associated with longer LOSs and antibiotic usage. Study type Retrospective descriptive study. Study dates Between October 1, 2001 and September 30, 2003.	systemic steroids. 7% were classified with a severe APR-DRG severity level. Inclusion criteria - discharge dates between October 1, 2001, and September 30, 2003 Exclusion criteria - the analysis is restricted to those patients for whom the expanded data were available on the Pediatric Health Information System database (30 hospitals out of 36).		Multivariate analysis of variance was used to determine whether hospital was a significant contributor to the variance in the outcomes after controlling for other covariates. A linear regression analysis was conducted to assess factors associated with lenght of stay (LoS); although the distribution of LoS is highly skewed, the large sample size made linear regression appropriate. A logistic regression analysis was carried out to examine the factors associated with the usage of antibiotics. Bothe regression analyses were clustered on hospital, to account for the decreased variability within hospitals as compared with between hospitals. regressions were stratified by age (<3 months vs 3-11 months), as treatments of very young infants with bronchiolitis can vary from that of older infants.	- chest radiograph (yes vs no): mean difference 0.34, p<0.001 (0.22 - 0.46) for children aged less than 3 months - chest radiograph (yes vs no): mean difference 0.30, p<0.001 (0.19 - 0.40) for children aged 3 months or more. Logistic regression for antibiotic use * - chest radiograph (yes vs no): OR 1.11 (0.96 - 1.28) for children aged less than 3 months - chest radiograph (yes vs no): OR 1.22, p<0.001 (1.10 - 1.36) for children aged 3 months or more. * Regression analyses adjusted for age (months), gender, Medicaid status, severity classification (derived from the APR-DRG Severity of Illness Guidelines), and month of admission (to adjust for seasonal trends).	receive x-ray are not reported - no specific (clinical) exclusion criteria stated - information on how the index test (X-ray) was performed are not reported - no reference standard Other information Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: Yes Indirectness: None Outcomes - LOSs - antibiotic usage Data Source Authors used the Pediatric Health Information System database developed by the Child Health Corporation of America, which includes demographic and diagnostic data of 36 children's hospitals.

Study details	Participants	Tests	Methods	Results	Limitations
				The study doesn't present data on the following outcomes: identification of additional or alternate diagnosis, admission rates, change in disease severity, need for high flow humidified oxygen, CPAP, or mechanical ventilation, and on adverse effects.	

I.9 What is the efficacy of chest physiotherapy in the management of bronchiolitis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Castro-Rodriguez,J.A., Silva,R., Tapia,P., Salinas,P., Tellez,A., Leisewitz,T., Sanchez,I., Chest physiotherapy is not clinically indicated for infants receiving outpatient care for acute wheezing episodes, Acta Paediatrica, 103, 518-523, 2014 Ref Id	Sample size 48 infants randomized as follows: 25 were assigned to the CP group and 23 to the without CP group. All patients completed the study and none were studied twice. Characteristics The two groups did not differ significantly in terms of age, birth weight, height, gestational age, age of their first wheezy episode or number of	Interventions CP group + salbutamol: the slow and long expiration flow techniques take place with the infant in the supine position. At the end of the spontaneus exhalation, slow manual pressure is exerted over the abdominal-thoracic region and continued until the	Details Four paediatric family medicine physicians consecutively selected the patients and recorded their initial Tal's clinical score and oxygen saturation using a pulse oximeter. The patient was then referred to one of the chest physiotherapists to receive the treatment defined by the randomization process. - after one hour of treatment, the patient was counter-referred to the same family physician, who did not know if	Results Outcomes Primary outcome was defined as the proportion of patients discharged after the first hour of treatment (clinical score ≤5/12 and SpO2 ≥93%). Secondary outcomes: number of admission to hospitals after the second hour of treatment and the need for oral corticosteroid bursts and admissions	Limitations Based on NICE 2012 guideline manual: RCT studies checklist - selection bias: low risk - performance bias: not reported if physiotherapists administering the intervention were aware of treatment allocation. - attrition bias: low risk - detection bias: investigators not kept

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
310400 Country/ies where the study was carried out Chile Study type Single-blind randomized clinical trial. Aim of the study To evaluate the effectiveness of chest physiotherapy (CP), which provides slow and long expiratory flow and assisted cough techniques, in infants receiving outpatient care for acute wheezing episodes. Study dates Not reported. Source of funding Research grants from the Comision Nacional de Investigation Cientifica y tecnologica - Fondo Nacional de Investigacion y Desarollo en Salud of	wheezy episodes in the past. In six of the 48 infants, it was their first wheezy episode and five of these belonged to the group without CP (p=0.06). The proportion of medications received previous to enrolment, such as salbutamol or ipratropium bromuro metered dose inhaler, oral steroid bursts and cough syrup, and the number of previous respiratory illnesses, including pneumonia, croup, pharyngitis and otis media, were also not different between the groups. There were also no differences in terms of baseline measurements of the duration of the acute wheezing exacerbation, temperature, respiratory and cardiac rate per minute, Tal's score, oxygen saturation and thoracic circumference. Inclusion criteria - infants with wheezing episodes	residual volume is reached with the main objective of clear the immediate and proximal airways. An assited cough consists of gently pushing the thumb over the trachea in the sternal notch, the thoracic outlet above the sternum, with the infant in the supine position, with the aim of clear the proximal airways. The CP was performed by chest physiotherapists. Salbutamol was administered in accordance with Chilean guidelines, using a facemask valve spacer, in a sequence of two puffs of 100 µg each every 10 minutes for 1 hour (1200 µg in total). Group 2 : just salbutamol without CP. Both groups received oxygen	the patient had received CP or not, for re-evaluation of his or her clinical status, Tal's score and SpO2 level. If the patient's clinical score was ≤5/12 and SpO2 was ≥93% at room temperature, he or she was discharged. However, if the patient's Tal's score ≥6/12 or SpO2 level ≤92%, a second hour of treatment, according to the original randomized group, was performed by the same chest physiotherapist. - after the second hour, the original family physician reassessed the patient, who was referred to the hospital for admission if the clinical score remained ≥6/12 or SpO2 level ≤92%. If at any time the patient suffered respiratory failure (SpO2≤90%), he or she was withdrawn from the study and referred for admission to the hospital. - all patients were seen again in the clinic on days 7 and 28 following treatment, and a questionnaire was completed about their need for hospital admission, emergency department consultations and oral steroid bursts after the original visit. Randomization	to hospital during the first 7 days after treatment. Raw Data Proportion of patients discharged after the first hour of treatment: - CP group = 92% - no CP group = 87% Clinical score after first hour of treatment, mean (95% CI): - CP group = 2.8 (2.2-3.3) - no CP group = 3.4 (2.8-4.1) Oxygen saturation after first hour of treatment, %SpO2: - CP group = 96.4 (95.7-97.1) - no CP group = 96.0 (94.9-96.5) Respiratory rate per min after first hour of treatment, mean± s.d.: - CP group = 43.0 ±11 - no CP group = 48.9 ±9 Results Proportion of patients discharged after the first hour of treatment: p= 0.66	blind to confounding and prognostic factors. Other information Indirectness Does the study match the protocol in terms of: Population: some ("most infants were under one year of age" and some of the participants had previous wheezy episodes) Intervention: yes Outcome: yes Indirectness: some Setting Outpatient clinic CESFAM, Pontificia Universidad Catolica de Chile, Santiago, Chile. Data collection A questionnaire to gather demographic data, including the patient's personal history with previous episodes of wheezing, acute respiratory illness and allergic diseases, as well as a family history of asthma, tobacco

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Chile and from the Pontificia Universidad Catolica de Chile.	- infants with modified tal's clinical score of >5/12 and ≤10/12 - infants whose parents signed the informed consent Exclusion criteria - prematury (not specified) - other chronic respiratory diseases - cardiovascular or neurological disease - gastroesophagical reflux - radiological pneumonia	and oral steroid bursts (oral prednisone 1 mg/kg), according to a validated modified Tal's clinical score.	A randomized computer programme was used to assign patients to receive either CPT or just salbutamol. Blinding Authors report that during the entire process, the family physicians (assessors) did not know to which group the patients have been assigned. Statistical analysis Univariate analyses for the infants with and without CP were conducted. A chi-squared test was performed for categorical data. The distribution of numerical variables was evaluated using the Shapiro-Wilk test; t-test and Wilcoxon analysis was used for the primary outcome. Logist regression analysis was used to test for significant associations between the primary outcome and those factors significantly associated in the univariate analysis and a priori list of confounding variables, including age, gender, days of wheezing exacerbation, previously use of inhaled corticosteroids, maternal education, identified virus, allergic history and parental history.	Clinical score after first hour of treatment, mean (95% CI): ns Oxygen saturation after first hour of treatment, %SpO2: ns Respiratory rate per min after first hour of treatment, mean± s.d.: ns - Secondary outcomes at day 7: ns - Secondary outcomes at day 28: ns * ns = non significant	consumption and maternal education, was completed by the parents at the time of the child's enrolment in the study. Sample size calculation Authors reported that a sample size of 32 patients in each group provided <80% power to detect a difference in the clinical score of 30%. This was based on the assumption that the use of CP plus a metered dose salbutamol inhaler had a 90% chance of success, according to previous studies. Other - On the day of enrolment in the study, nasopharyngeal aspirates were obtained to test for nine respiratory viruses. - The study was approved by the University's Etchics and Research Committee, and written informed consent permissions were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					obtained from the parents or the guardians. - No adverse effects, rib fractures, vomiting or desaturation, were reported in the whole population.
Full citation Gajdos,V., Katsahian,S., Beydon,N., Abadie,V., de,Pontual L., Larrar,S., Epaud,R., Chevallier,B., Bailleux,S., Mollet-Boudjemline,A., Bouyer,J., Chevret,S., Labrune,P., Effectiveness of chest physiotherapy in infants hospitalized with acute bronchiolitis: a multicenter, randomized, controlled trial, PLoS Medicine / Public Library of Science, 7, e1000345-, 2010 Ref Id 206898	Sample size 496 infants were included: 246 (49.6%) were assigned to the IET+AC group and 250 (50.4%) to the NS group. Characteristics At randomization, there were no marked differences between the two randomized groups for demographic variables, percentage of infants with hypoxemia or feeding difficulties, percentage of infants with nasal aspirate positive for RSV, and duration of respiratory symptoms before hospitalization. The proportion of cases of lung atelectasia diagnosis on X-ray was higher in the NS group (12.9% vs. 7.6%).	Interventions The treatment, either intervention or control, was performed by the physiotharpist staying alone with the infant, in a room with a covered window pane, to ensure that clinicians and parents could not observe the treatment. All infants received treatment three times daily. In each center, four to six physiotherapists, specially trained to carry out CPT in children, participated to the study. Intervention	Details Diagnosis of bronchiolitis bronchiolitis was diagnosed on the basis of a history of upper respiratory tract infection and clinical findins consistent with bronchiolitis, including wheezing or wheezing with crackles and respiratory distress. Clinical bronchiolitis was confirmed at the enrollment and clinicians determined the duration of symptoms before hospitalization, clinical respiratory score, and clinical variables (respiratory and heart rates, temperature, and oxygen saturation whilst breathing ambient air). Randomization Randomization involved the chest physiotherapist opening a sealed sequentially numbered envelope containing a random alocation computer generated with SAS software	Results Primary outcome The primary outcome was time from randomization to recovery. An infant was considered to be cured if no oxygen supplementation had been given for 8 hours and the child had minimal or no chest recession and was ingesting more than two-thirds of daily needs. The nursing staff recorded respiratory and heart rates, oxygen saturation, and signs of chest recession when the patient was quiet, at least once every 8 h. Evaluation was based on a clinical score that could be recorded reliably, every 8 h, by	Limitations Based on NICE guideline manual 2012: RCT studies checklist - selection bias: low risk - performance bias: low risk - attrition bias: low risk - detection bias: low risk Other information Indirectness Does the study match the review protocol in terms of Population: Some (children aged up to 24 months)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out France Study type Multicenter, randomized, controlled trial. Aim of the study To evaluate the efficacy of chest physiotherapy (increased exhalation technique and assisted cough (IET + AC)) in previously healthy infants hospitalized for a first episode of acute bronchiolitis. Study dates From October 2004 through January 2008. Source of funding The study was supported by a grant from French health Ministry (PHRC AOM 03/123) and by a grant from the Association des Reseaux Bronchiolites (ARB).	Before randomization, 14.4% infants in the NS group and 19.1% infants in the IET+AC group received bronchodilator inhalations (salbutamol). 13.6% infants in the NS group and 10.2% infants in the IET+AC group were treated with oral corticosteroids (betamethasone). Inclusion criteria - infants between the ages of 15 days and 24 months - hospitalized with a firts episode of wheezing diagnosed as bronchiolitis -infants were eligible within 24 h of hospitalization if they presented at least one of the following on admission: toxic aspect, history of apnoea or cyanosis, respiratory rate >60/min, pulse oximetry <95%, alimentary intake <2/3 of needs. - a maximum of two chest physiotherapy (CPT) procedures since admission was allowed Exclusion criteria	the intervention was defined as the IET followed by AC, with gentle nasal suction (NS). IET involved the generation of synchronized thoracic-abdominal movement by the hands of the physiotherapist ate the beginning of expiration with one hand on the thorax, meanwhile, with the other hand on the abdomen, centered on the umbilicus, the physiotherapist applied an abdominal counter-weight. The maneuver began at the end of the inspiratory plateau and was pursued until the end of expiration, according to the infant's thoraco-pulmonary compliance and up to his or her chest wall and lung resistence limits. The procedure was repeated until	packages in advance by the biostatistician. Randomization was stratified according to center and according to age (<2 mo, ≥2 mo) at each center, using permutation blocks with a block size of four that was not mentioned to the physicians involved in the patient recruitment. Randomization codes were kept secure until data entry was complete. Blinding All pediatric department staff, parents, guardians, were blind to treatment assignment. Those involved in the evaluation of primary outcome or in the decision of the cointerventions were blinded to group assignment. Statistical analysis Analysis was performed on an intent-to-treat basis and all patients included in the study were analyzed, including the two lost at follow-up (one in each group). The uthors first tested treatment by age group (<2 mo, ≥2 mo) interaction on the primary outcome by fitting Cox models in each age group, then testing for quantitative interaction with the gail and Simon test. No	any doctor, nurse, or physiotherapist. Secondary outcomes - physiotherapists reported side effects during procedures: bradycardia (<80/min) without desaturation, bradycardia with desaturation (SpO2<95%), vomiting, transient respiratory destabilization, or bouts of hypotonia requiring the interruption of the procedure. - upon discharge from the hospital, parents answered a questionnaire regarding their perception of their child's comfort and wree invited to give their opinion on the efficiency of physiotherapy for their own child. - secondary PICU admission and artificial ventilation, antibiotic treatment were recorded - the parents were contacted by phone within 30 d of	Intervention: yes Outcome: yes Indirectness: some Setting Seven French pediatrics department in the Parisian area. Data collection Medical history was obtained from parents or guardians, on a standardized data-collection form including questions about personal history of eczema, family history of asthma or eczema in parents and sibilings, and tobacco smoke in the home environment. Sample size calculation The authors reported that no accurate data for mean time to recovery were available from the literature, and therefore they used duration of hospitalization for bronchiolitis recorded in the study hospitals during previous years (6.5 d ±3.5 d). For

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The authors state that funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	- infants with severe respiratory distress necessitating immediate admission to PICU - infants with cardiac disease, with a previous significant respiratory condition, or premature (<34 weeks) - infants not included if they had controindications for the intervention (IET + AC): thrombocytopenia, prolonged corticosteroid treatment, rickets, bone diseases, known rib fracture.	meeting auscultation-efficacy criteria (decrease or disappearance of wheezing and/or increase of ronchi), but did not last for more than 10-15 min. The procedure was stopped in case of respiratory status aggravation. if no spontaneous coughing occured, coughing could be triggered by pressure on the suprasternal notch. Gentle NS with a flexible probe was used to remove mucous secretions at the end of the procedure. All patients were closely monitored by continuous pulse oxymetry during CPT. Control The control group spent 10-15 min in a room alone with the therapist three times daily. In this group ofinfants, the	treatment by age interaction was found (p=0.97), making it possible to perform the analysis on the pooled sample. Thus, survival curves for time to recovery were estimated on the whole cohort using the Kaplan-Meier method, then compared across randomized groups by using the log-rank test stratified by age group. Authors additionally adjusted survival analyses for prognostic baseline covariates (prsonal eczema or history of atopy, age in months, hypoxemia at randomization, durationof symptoms, atelectasia at randomization, need for IV fluids at randomization, use of mucolytics before randomization, RSV infection) using a Cox model. The center effect, was analyzed using frailty models. For secondary outcomes, adverse effects frequency was compared using the Fisher test. The need for PICU admission or ventilation, lung atelectasia, relapse, and the need for antibiotic treatment or secondary hospitalization were compared between the two groups using the chi square test and stratified on age.	discharge to identify cases of relapse and rehospitalization Raw Data Estimated effect of IET+AC, median time to recovery, d (95%CI): - Overall n=496 NS group: 2.31 (1.97-2.73) IET+AC: 2.02 (1.96-2.34) - <2 mo n=238 NS: 2.64 (2.25-3.08) IET+AC: 2.47 (1.98-3.31) - ≥2 mo n=258 NS: 2.01 (1.65-2.44) IET+AC: 2.00 (1.51-2.25) Side effects reported by physiotherapists during procedures: - bradycardia with desaturation n(%) NS = 3/250 (1.2%) IET+AC = 3/246 (1.2%) - bradycardia without desaturation n(%) NS = 2/250 (0.8%) IET+AC = 7/246 (2.8%) - vomiting n(%) NS = 1/250 (0.4%)	detecting a 20% decrease in time to recovery in the IET+AC group, they needed to include 228 infants (114 in each group). The authors reported that one of the aims of this trial was to investigate possible interactions with age, and that they therefore set up two groups of 228 children (under and over 2 mo), giving 456 children in total. Other - The study was approved by the Saint German en Laye ethics committee - The parents were informed about the stausy, its aims, and design. In particular, they were informed that they could not stay with their children during treatment. Both parents gave written informed consent. - For 153 additional infants whose parents were invited to participate, the parents refused participation;

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		physiotherapists preformed only gentle NS to remove mucous secretions for few minutes and stayed inside the room for the remaining time without performing any maneuver on the infants. Other treatments - Oxygen supplementation was administered if oxygen saturation was below 95% when awake and 92% when asleep. It was stopped when oxygen saturation was consistently above 95% when awake and 92% when asleep. Nurses interrupted oxygen supplementation three times per day to assess saturtion in room air. - Enteral feeding was administered when possible, with orogastric feeding offered to infants spontaneously	Data from analogical visual scales were compared using Wilcoxon test. Ttreatment was tested by covariate interactions on the primary outcome with personal eczema or history of atopy, hypoxemia at randomization, ans RSV infection. These were identified by post hoc analysis and all quantitative interactions were tested with the gail and Simon test. Measures of treatment effect were either hazard ratio (HR) for survival data, relative risk (RR) for binary data, mean differences for continuous data, all given with 95% CIs. Statistical analysies were carried out with R version 2.10.11 and SAS version 9.2.	IET+AC = 10/246 (4.1%) - respiratory destabilization n(%) NS = 3/250 (1.2%) IET+AC = 16/246 (6.5%) - hypotonia n(%) NS = 0/250 (0.0%) IET+AC = 2/246 (0.8%) - Need for ventilation, n(%) NS = 2/250 (0.8) IET+AC = 5/246 (2.0%) Results Estimated effect of IET+AC, HR (95%CI) and p-value: - Overall n=496: HR=1.09 (0.91-1.31), p=0.33 - <2 mo n=238: HR=1.09 (0.84-1.41), p=0.51 - ≥2 mo n=258: HR=1.09 (0.85-1.40), p=0.48 * after controlling for prognostic baseline covariates: HR= 1.21 (0.97-1.49), p=0.09. Side effects reported by physiotherapists	the resons for their refusal were the desire to stay with their infant, and the desire for their children to receive IET+AC tretment. - Just before the start of the study, a senior physiotherapist presented the IET+AC technique at each center, and all physiotherapists received formal training in these techniques. During the study, a referent physiotherapist at each center ensured that CPT was consistent and standardized.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		ingesting less than two-thirds of their dauly needs or with significant signs of chest recession, tachypnea or hypoxemia, or a worsening of respiratory signs during feeding. Intravenous fluids were preferred over oral feeding if respiratory conditions did not improve with orogastric feeding or oral feeding was insufficient. - Data concerning deviations from the clinical treatment pathway, including drug treatments, were recorded.		during procedures, RR (95%CI), p-value: - bradycardia with desaturation: RR= 1.0 (0.2-5.0), p=1.00 - bradycardia without desaturation: RR= 3.6 (0.7-16.9), p=0.10 - vomiting: RR= 10.2 (1.3-78.8), p=0.005 - respiratory destabilization: RR= 5.4 (1.6-18.4), p=0.002 - hypotonia: RR= NA, p=0.24 Need for ventilation, RR (95%CI), p-value RR = 2.5 (0.5-13.0) p=0.29	
Full citation Gomes,E.L.F.D., Postiaux,G., Medeiros,D.R.L., Monteiro,K.K.D.S., Sampaio,L.M.M., Costa,D., Chest physical therapy is effective in reducing the clinical score in bronchiolitis:	Sample size 30 infants were randomized as follows: 10 in Group 1, 10 in Group 2 and 10 in Group 3. Characteristics There were no between-group differences for the	Interventions Group 1- new CPT: Chest physical therapy with new techniques, prolonged slow expiration (PSE), which is a slow passive and progressive expiration from the	Details Randomization Children were randomized by using sealed opaque envelopes containing the instructions to be followed in each of three groups. Blinding Assessors were blinded to the treatment groups. These raters	Results Outcomes - Wang's Clinical score (CS): the score assigns a value between 0 and 3 to each variable, higher scores indicates a worst condition (max=12). - and its components: retractions, respiratory	Limitations Based on NICE 2012 guideline manual: RCT studies checklist - selection bias: method of randomization and concealment of allocation were not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomized controlled trialA fisioterapia respiratoria e eficaz na reducao de escore clinico na bronquiolite: Ensaio controlado randomizado, Revista Brasileira de Fisioterapia, 16, 241-247, 2012 Ref Id 284188 Country/ies where the study was carried out Brazil Study type Randomized controlled trial. Aim of the study To investigate the hypothesis that the appropriate CP techniques for infants may reduce bronchiolitis obstruction resulting from the pathological process of AVB and therefore reduce the signs and symptoms of respiratory distress and its repercussions.	variables age, weight, or clinical status at baseline. - Median of the clinical score at baseline: G1 = 7.0 (5.0-11), G2 = 7.5 (3.0-10), G3 = 7.5 (4.0-11). Medications taken in each group were also noted and no between-group differences were observed. The days of hospitalization were also similar between groups 1 and 2. Inclusion criteria - infants aged 28 days to 24 months - previously healthy - with a clinical diagnosis of AVB and positive outcome of RSV in nasopharyngeal aspirate detected by immunofluorence technique Exclusion criteria - infants without RSV - with a history of chronic lung disease - with a previous episode of hospitalization for wheezing,	Functional Residual capacity, and clearance rhinopharyngeal retrograde (CRR) which is a forced inspiratory maneuver that aims to clear the nasopharynx indicated for infants. Group 2- conventional CPT: Chest physical therapy with conventional techniques (vibrations, expiratory compression, modified postural drainage only in the lateral decubitis position and clapping). Group 3- Suction of the upper airways. The first two groups of infants received the same techniques during hospitalization. The third group could only be assessed on admission for	were trained specifically for this assessment. Also, the time spent caring for children was similar in all groups and parents were unaware of their child's group allocation. Statistical analysis To investigate the primary outcome measure (clinical score), the non parametric test Kruskal-wallis was used at the time of admission. Mann Whitney and Wilcoxon were calculated at 48 and 72 hours post admission. In the pre- and post-evaluation groups, the intra-Friedman test was used to assess within group evolution during the day. For variables with normal distribution such as age, weight and oxygen saturation, ANOVA and Student's t-test were used, depending on the time assessed. For nominal variables, Fisher's exact test was used.	rate, wheezing, and general condition. Raw Data Wang's clinical score (medians and range) post-treatment: G1 nCP: 4.0 (2-7) G2 cCP: 5.5 (1-7) G3 suction: 7.0 (4-10) Wheezing (medians and min-max) post-treatment expressed with score 0-3: G1 nCP: 0.0 (0-1) G2 cCP: 0.0 (0-1) G3 suction: 0.0 (0-2) Respiratory rate (medians and min-max) post-treatment expressed with score 0-3: G1 nCP: 2.0 (0-3) G2 cCP: 2.0 (1-2) G3 suction: 2.0 (1-3) Retractions (medians and min-max) post-treatment expressed with score 0-3: G1 nCP: 1.0 (0-2) G2 cCP: 1.0 (0-2) G3 suction: 1.0 (0-3) General condition (medians and min-	- performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described. - attrition bias: the third group did not receive assessment at follow up (low risk). - detection bias: low risk of bias. Other information Indirectness Does the study match the protocol in terms of : Population: Some (children aged up to 24 months, authors excluded infants without RSV) Intervention: Yes Outcome: Yes Indirectness: Some Setting Department of Pediatrics and the Pediatric ICU at Sirio Libanes Hospital and Menino Jesus

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates From march 2009 to April 2010. Source of funding Not reported.	- cardiac or neurological diseases - those whose parents or guardians refused to sign the waiver of informed consent.	the following ethical reasons: at the study hospitals, all children with AVB routinely receive care with CPT. Therefore, they could just receive upper airway suctioning during the hospitalization.		max) post-treatment expressed with score 0-3: G1 nCP: 3.0 (0-3) G2 cCP: 3.0 (0-3) G3 suction: 3.0 (0-3) SpO2 (%) expressed mean±s.d. post-treatment: G1 nCP: 89 ±4.47 G2 cCP: 93 ±4.05 G3 suction: 90.3 ±2.62 Results - Retractions: significant difference between G2 and G3 for retractions score post-treatment = p<0.05 - No other significant differences were found between G1 and G2, G2 and G3 and between G3 and G1.	Pediatric Hospital both in Sao Paolo, Brazil Data Collection Assessments were conducted by physical therapists and nurses from the hospitals where the data collections were performed before and after CP using the clinical score. Sample size calculation Sample size was calculated based upon previous studies. Assuming a beta error of 0.1, a power of 90% of the sample with an alpha error of 0.05 was calculated using a sample of 22 infants in total. Other The study has been carried out in two different hospitals, but authors didn't provide explanation for that. The research protocol was approved by the research and ethics committee at Sirio Libanes Hospital.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nicholas,K.J., Dhouieb,M.O., Marshall,T.G., Edmunds,A.T., Grant,M.B., An evaluation of chest physiotherapy in the management of acute bronchiolitis: Changing clinical practice, Physiotherapy, 85, 669-674, 1999 Ref Id 263563 Country/ies where the study was carried out United Kingdom Study type Randomized controlled trial. Aim of the study To test the hypothesis that chest physiotherapy (CPT) may be of benefit to those infants with acute viral bronchiolitis. Study dates	Sample size 50 infants. Characteristics Gender: 23 boys, 27 girls Mean age: 2.8 months (range 0.4-7.6) The two groups were similar in regard to age, sex, admission score, and the proportion who were RSV positive. Inclusion criteria Infants were identified for inclusion if: - they had been admitted to Royal Hospital for Sick Children, Edinburgh (RHSCE) with a clinical diagnosis of acute bronchiolitis - their respiratory distress was so severe that they required neasogastric tube feeding or intravenous fluids - parents signed informed consent Exclusion criteria Not reported.	Interventions Physiotherapy protocol Patient is treated on physiotherapist's knee; percussion and vibration in right side lying, left side lying and sitting; suction performed after each side if necessary until clear; no oxygen required during treatment. Two people to do physiotherapy and suction. Modifications possible on: general position (if unable to tolerate treatment on knee then on flat cot, if unable to tolerate this then on head-up tipped cot), postural drainage, techniques (if patient is unstable and unable to tolerate percussion then vibrations only), suction (if not tolerated until clear	Details Infants were randomly allocated to control and treatment groups using a random sequence number generated by the Medical Statistics Unit of the University of Edinburgh. Exit from the trial was automatic after 5 days; exit from the trial also occurred if there was linical deterioration to the point where the patient required admission to the intensive care unit (one infant came into this category). Statistical analysis The infants' clinical scores were subjected to the Student's t-test for matched subjects in order to compare differences between the two groups. The pulse oximetry data from the two groups were compared using the paired Student's t-test, and the Mann Whitney U-test was used to compare differences in lenght of hospital stay, provision of inspired oxygen and requirement for nasogastric feeding. There was a retrospective descriptive analysis of chest physiotherapy.	Results Outcomes - clinical score system (all components were scored individually, twice a day, so far as possible by a single observer) - lenght in hospital stay - provision of inspired oxygen and requirement for nasogastric feeding Raw Data - clinical score: not reported - lenght of stay (days): mean 6.6 in control group (2.3-11.5); mean 6.7 in intervention group (3-9.5) - nasogastric feeds: 92 h (mean) in control; 86 h (mean) in intervention group. Results - clinical score: the mean scores were higher in the intervention group than in the controls; however, differences	Limitations Based on Nice guideline manual 2012: RCT studies checklist - selection bias: allocation concealment not described - performance bias: blinding not reported - attrtion bias: not clear how data were treated (authors reported that 1 participant was excluded after been admitted to ICU) - detection bias: description of the outcomes (especially the clinical score) not appropriately reported, blinding not described. also: results, standard deviations and confidence intervals not fully reported. Other information Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: Yes Outcome: Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Three years 1986 to 1989, October to April inclusive. Source of funding The study was supported financially by Avenol Trust.		then as often as able), oxygen (an oxygen supply via mask or bag will be on hand during all treatment. If not tolerating treatment with no oxygen then it wil be given during treatment. If not tolerating this then infant will remain in headbox with extra oxygen during treatment). 'Not tolerating' is defined by respiratory distress, raised recession and respiratory rate, raised heart rate to unacceptable levels for that patient. Control group Infants in the control group were nursed in modified postural drained positions with suction performed by nurses as required.		were not statistically significant. - lenght of stay: reported to be very similar. - provision of oxygen and requirement for nasogastric or intravenous feeding: no significant differences.	Indirectness: None Setting Royal Hospital for Sick Children, Edinburgh. Data collection Authors reported that the effectiveness of CPT was evaluated using a set of specific parameters, ie clinical scoring system, lenght of stay, provision of oxygen and requirement for nasogastric feeding. Sample size calculation Not reported. Other The authors reported that the requirement for nasogastric feeding or intravenous fluids, as an inclusion criterion, defines a band of relative severity, as they are required when infants are too ill to tolerate breast or bottle feeding because of breathlessness, exhaustion, hypoxia, coughing or inability to absorb nasogastric feeds.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Postiaux,G., Louis,J., Labasse,H.C., Gerroldt,J., Kotik,A.C., Lemuhot,A., Patte,C., Evaluation of an alternative chest physiotherapy method in infants with respiratory syncytial virus bronchiolitis, Respiratory Care, 56, 989-994, 2011 Ref Id 207927 Country/ies where the study was carried out Belgium Study type Randomized controlled trial. Aim of the study To propose and evaluate the efficacy of a new chest physiotherapy (CPT) secretion clearance method to treat RSV bronchiolitis in infants.	Sample size 20 infants with bronchiolitis. Characteristics Control group = 8 infants Intervention group = 12 infants Age in months: 4.2±3.1 (controls) and 3.9±2.4 (interv.), p=0.80 Female/male: 4/4 (controls) and 2/10 (interv.) Baseline Wang clinical severity score: 6.0±3.2 (controls) and 5.5±2.9 (interv.), p=0.72 Stay (d): 6.3±2.0 (controls) and 5.3±1.8 (interv.), p=0.25 Inclusion criteria - first clinical episode of acute bronchiolitis - age <12 months - Wang score ≥3 - RSV in nasopharyngeal secretions, via immunochromatography Exclusion criteria	Interventions Intervention group The new CPT method includes prolonged slow expiration and provoked cough. The prolonged slow expiration slowly increases the intrathoracic pressure through an thoraco-abdominal compression by the clinician, to avoid the bronchial collapse and the flow interruption of forced expiration. Provoked cough is obtained with a brief pressure applied on the trachea above the sternal notch. The cough-induced secretions are swallowed, which obviated nasopharyngeal suctioning and thus avoids the risk of damaging the mucosal lining	Details Randomization The enrolled patients were randomly assigned to nebulization of hypertonic saline (control group), followed in the second group by the new CPT method, based on a stratified sampling for homogeneity. In fact, to ensure balance of illness severity and age across the groups, patients were grouped into 4 subgroups: Wang score between 3 and 5; Wang score above or equal to 6; age less than 2 months; and age between 2 and 12 months. Blinding Both pediatrician evaluators were blinded to the applied treatment and goals. The evaluations took place at the beginning of each session (T0), immediately after the 30-min treatment session (T30), and 2 hours after the treatment session (T150). During the study, 3 trained physiotherapists were in charge of administering the treatments, and they were instructed to ignore the results of each evaluation until the	Results Outcomes - Wang's clinical score: the score assigns values between 0 and 3 to each of 4 variables (respiratory rate, wheezing, retractions and general condition). The maximum Wang score is 12, and a higher Wang score indicates worse condition. - wheezing - respiratory rate - retractions - general condition - SpO2 % - heart rate Outcomes were evaluated at T0, T30, and T150. Raw Data control group = 8 infants underwent 27 nebulization sessions new CPT method group = 12 infants underwent 31 sessions Wang clinical severity score differences	Limitations Based on NICE guideline manual 2012: RCT studies checklist - selection bias: concealment of allocation not described, as well as the random sequence generation is not reported - performance bias: low risk - attrition bias: low risk - detection bias: low risk Other information Indirectness Does the study design match the protocol in terms of Population: yes Outcome: yes Intervention: yes Indirectness: none Setting Pediatric unit of the Gand Hôpital de Charleroi, Belgium.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Winter months (November to April) of 2004-2005, 2005-2006, and 2006-2007. Source of funding Not reported.	- Parents' refusal - no nasopharyngeal RSV - comorbidities such as cardiac or neurological disease - previous episode of wheezing - Wang score <3 - prescription of CPT on parents' request - chronic lung disease, such as bronchodysplasia - immunodeficiency - congenital anomaly - need for mechanical ventilatory support in the intensive care unit	and/or strong coughing bouts. Most RSV bronchiolitis patients have a high respiratory rate, so for optimal secretion clearance the thoracic pressure is applied during 2-3 consecutive expiratory phases. The infant is supine, with a head elevation of 35°, to prevent gastroesophageal reflux. The treatment was applied at least 2 hours after the last meal to avoid reflux vomiting during expectoration. The treatment was carried out once a day until the Wang score was normalized or until hospital discharge, based on the usual criteria: normal food intake and no need for supplemental oxygen.	end of the study. The patients' parents were unaware of the group in which their child was included. In both groups the periods of time spent in the room were identical, so outside observers were blinded to the applied treatment. Statistical analysis Student t test was used for paired values to assess the Wang-score changes within the groups, one-way analysis of variance to assess the Wang-score differences between the groups, one-way analysis of variance for independent sample to assess the Wang-score component changes expressed as the differences between the groups, one-way analysis of variance for repeated measures to compare the daily evolution of the Wang score in each group, and the Mann-Whitney U test to compare hospital stay between the groups. No adjustement for multiple comparisons was made.	between the groups, means ±SD: - Wang score control = 5.0±2.7 (T0), 5.1±2.6 (T30), 4.6±2.9 (T150) CPT = 4.3±2.7 (T0), 3.6±2.3 (T30), 3.7±2.7 (T150) - wheezing control = 1.2±0.9 (T0), 1.1±0.8 (T30), 1.1±0.9 (T150) CPT = 1.3±0.9 (T0), 0.8±0.8 (T30), 0.9±0.8 (T150) - respiratory rate control = 1.8±0.7 (T0), 2.0±0.7 (T30), 1.7±0.7 (T150) CPT = 1.4±0.8 (T0), 1.3±0.9 (T30), 1.3±0.8 (T150) - retractions control = 1.3±0.8 (T0), 1.2±0.8 (T30), 1.2±0.8 (T150) CPT = 1.1±0.7 (T0), 0.8±0.6 (T30), 1.0±0.7 (T150) - general condition control = 0.7±1.3 (T0), 0.7±1.3 (T30), 0.7±1.3 (T150)	Sample size calculation Not reported. Data collection Two pediatricians evaluated the Wang score variables, SpO2 and heart rate. Other Authors reported no adverse events. The RCT was approved by the institution's ethics committee, all the patients' parents or legal representative gave informed consent , and all research procedures were per the Helsinki declaration.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		The intervention group also received albuterol in 3 mL of hypertonic saline (3% NaCl), nebulized over 8-10 min with a Sidestream nebulizer at a flow of 8 L/min. Then they received the new CPT method for 10-15 min. Control group The control group received albuterol in 3 mL of hypertonic saline (3% NaCl), nebulized over 8-10 min with a Sidestream nebulizer at a flow of 8 L/min.		CPT = 0.6±1.2 (T0), 0.6±1.2 (T30), 0.5±1.2 (T150) - SpO2 % control = 96±3 (T0), 95±3 (T30), 96±2 (T150) CPT = 95±3 (T0), 95±3 (T30), 96±2 (T150) - heart rate, beats/min control = 146±18 (T0), 150±16 (T30), 144±16 (T150) CPT = 138±15 (T0), 135±14 (T30), 139±17 (T150) Results Wang clinical severity score differences between the groups, p-values: - Wang score p=0.37 (T0), p=0.02 (T30), p=0.21 (T150) - wheezing p=0.87 (T0), p=0.10 (T30), p=0.43 (T150) - respiratory rate p=0.05 (T0), p=0.001 (T30), p=0.06 (T150) - retractions p=0.33 (T0), p=0.05 (T30), p=0.35 (T150)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- general condition p=0.79 (T0), p=0.79 (T30), p=0.60 (T150) - SpO2 % p=0.61 (T0), p=0.61 (T30), p=0.83 (T150) - heart rate, beats/min p=0.52 (T0), p<0.001 (T30), p=0.34 (T150)	
Full citation Rochat,I., Leis,P., Bouchardy,M., Oberli,C., Sourial,H., Friedli-Burri,M., Perneger,T., Barazzone,Argiroffo C., Chest physiotherapy using passive expiratory techniques does not reduce bronchiolitis severity: a randomised controlled trial.[Erratum appears in Eur J Pediatr. 2012 Mar;171(3):603], European Journal of Pediatrics, 171, 457-462, 2012 Ref Id	Sample size 99 eligible children were evenly distributed between the CP arm (50) and the control arm (49). Characteristics The two groups were comparable at baseline, and there was no difference in clinical severity at admission as demonstrated by the initial clinical (mean 0.73 in both groups) and respiratory score (9.5 in CP group and 9.1 in controls). The administration of nebulised bronchodilators was similar between groups (38.0% vs. 40.8%, p=0.84) as was the	Interventions All infants were treated according to the national and international recomendations for the care of infants hospitalized with bronchiolitis. Rhinopharyngeal suctioning after installation of normal saline solution was applied to all patients if needed, as well as minimal handling, oxygen to achieve a saturation ≥92% and fractionated meals. Topical	Details Patients were recruited by the participating physiotherapists or by the study physician. Informed signed consent was obtained from at least one parent. Randomization Randomization was done by the attribution of a number contained in a sealed opaque envelope opened following the inclusion consent. Envelopes were prepared according to a randomization list in blocks of random lenght (8, 10 or 12) by the study epidemiologist, not involved in the clinical phase of the study. Statistical analysis	Results Outcomes Primary outcome: time to clinical stability, defined by feeding more than 50% of the required amount, the absence of vomiting, undisrupted sleep and SpO2 ≥92% for more than 10h. Secondary outcomes: change in clinical state, measured by a general score made of three well-being items (feeding, vomiting and quality of sleep); change in respiratory state, measured by a respiratory score made of seven items	Limitations Based on NICE clinical guideline manual 2012: RCT studies checklist - selection bias: low risk - performance bias: this was an open trial "all children underwent daily clinical evaluations performed by a physiotherapist who was different from the one administering the treatment". - attrition bias: low risk - detection bias: this was an open trial. Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
210605 Country/ies where the study was carried out Switzerland Study type Randomized controlled trial. Aim of the study The primary objective of this study was to evaluate the effectiveness of CP techniques using passive acceleration of expiratory flux in reducing the time to clinical stability in infants admitted for acute bronchiolitis. Study dates Two consecutive RSV seasons: 2005-2006 and 2006-2007. * The start and the end of the RSV season were defined when ≥2 admissions were due to RSv infection during two consecutive 7-day periods and when ≤1 such admission occurred during two	proportion of children receiving nasal decongestant or oral antibiotics (64.0% vs. 69.4% and 20.0% vs. 20.3%, p=1). Inclusion criteria - children aged ≤1 year - admitted with the diagnosis of bronchiolitis Exclusion criteria Patients with comorbidities such as cystic fibrosis, neuromuscular disease or congenital heart disease, or patients admitted directly to the intensive care unit, were excluded from the study.	bronchodilators and steroids were not routinely used as they are not recommended in Switzerland. Nasal drops such as xylometazoline were ofter employed to decrease nasal congestion. Finally, antibiotics were administered when concomitant bacterial infection was suspected (prolonged fever, otis media and increased white cell count). All children underwent daily clinical evaluations at a fixed time point prior to the physiotherapy sessions when allocated to the group with CP. Evaluations were performed by a study physiotherapist who was different from the physiotherapist	Authors first compared the groups at baseline for demographic and clinical characteristics. categorical and continuous variables were compared between the groups. Dichotomous outcome variables were compared using Fisher's exact tests. Time to clinical stability was compared using Kaplan-Meier curves and the log-rank test. This variable was also compared using a Student's t test. The study was designed to detect a difference of a half standard deviation in time to clinical stability (estimated SD was 2 days based on previous hospitalizations, difference to be detected 1 day). Changes in variables that were measured on a daily basis (general and respiratory score, SpO2, respiratory rate) were examined in mixed linear models where daily observations were nested within patients. The model included the treatment group, the day of hospitalization, and an interaction term of treatment by day as fixed predictors. It included a patient-specific intercept and slope as random predictors. The treatment by day	(respiratory rate, SpO2, presence and severity of retractions, adventitious respiratory sounds, presence of vesicular murmur, thoracic distension); occurrence of complications. Raw Data Time to clinical stability, mean ±SD CP group = 2.9 ±2.1 days control group = 3.2 ±2.8 days Clinical score, points/day measured as daily changes CP group = -0.12 (-0.08 to -0.15) control group = -0.09 (-0.06 to -0.13) Respiratory score, points/day measured as daily changes CP group = -1.6 (-1.4 to -1.8) control group = -1.3 (-1.1 to -1.5) Oxygen saturation, %/day measured as daily changes CP group = 1.0 (0.7-1.2)	Indirectness Does the study match the review protocol in terms of Population: Yes Intervention: yes Outcome: Yes Indirectness: None Setting The institution was not only a tertiary centre but also a primary care hospital as it is the only paediatric facility in the state of Geneva. Sample size calculation Authors reported that the calculated sample size was of 80 pateints in each arm. Other This study was approved by the institution's ethical committee on clinical research in children. Outcomes were assessed daily at a fixed time point, prior physiotherapy sessions.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
consecutive 7-day periods, respectively. Source of funding The study was partly funded with a research grant from the Research and Development Fund of the Hôpitaux Universitaires de Geneve.		administering the treatment. Intervention group Patients assigned to the intervention group had two daily physiotherapy sessions provided by a physiotherapist not participating in the study, at least 2h after feeds to avoid abdominal discomfort. The following techniques were used: - prolonged slow expiratory technique (PSET) obtained by bimanual pressure over the thoracic cage and the abdomen, exerted at the start of the expiratory phase down to the residual volume and maintained for two or three respiratory cycles. This technique allows complete expiration in the presence of	interaction captures the benefit of physiotherapy vs. control group in unit improvement per day. Analyses were performed using SPSS 17 software.	control group = 1.0 (0.8-1.2) Respiratory rate, rate/day measured as daily changes CP group = -1.1 (-0.6 to -1.7) control group = -0.7 (-0.2 to -1.2) Results time to clinical stability : p=0.45 clinical score : p=0.37 respiratory score : p=0.044 oxygen saturation : p=0.85 respiratory rate : p=0.24	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		bronchial obstruction anmd facilitates drainage of the sistal airways. - slow accelerated expiratory flow obtained by a manual pressure of variable strenght, speed and lenght exerted over the thoracic cage at different lung volumes to optimise bronchial clearance of the proximal airways - induced cough achieved after abrief manual pressure over the trachea at the level of the suprasternal notch at the end of the inspiration (rarely used).			
Full citation Webb,M.S., Martin,J.A., Cartlidge,P.H., Ng,Y.K., Wright,N.A., Chest physiotherapy in acute bronchiolitis, Archives of Disease	Sample size 90 children randomized as follows: 44 in the CPT group and 46 in the control group. Characteristics	Interventions Each child had an initial chest radiograph and nasopharyngeal aspirate for virological study. Other management decisions (for	Details Randomization Not described. Blinding Authors reported that "strictly speaking, this could not be 'blind' with respect to treatment status though in practice that	Results Outcomes Clinical assessment of illness severity was made at a fixed time each day by three medical doctors.	Limitations Based on NICE guideline manual 2012: RCT studies checklist - selection bias: randomization method was not described, concealment of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in Childhood, 60, 1078-1079, 1985 Ref Id 212241 Country/ies where the study was carried out United Kingdom Study type Randomized controlled trial. Aim of the study To determine objectively whether chest physiotherapy (CPT) is a helpful adjunct to treatment, in children with acute viral bronchiolitis. Study dates Not reported. Source of funding Not reported.	Mean age was 4.6 months. Authors reported that the two groups were similar with regard to age, sex, score on admission, proportion who were RSV positive (69% overall), proportion with a first degree family history of atopy (36% overall), and those with smokers in the household (66% overall). Inclusion criteria - a clinical diagnosis of acute viral bronchiolitis Exclusion criteria Not reported.	example supplementary oxygen, nasogastric feeding) were made irrespective of treatment group. Intervention group CPT comprised standard techniques applied by a trained paediatric physiotherapist: chest percussion with a cupped hand for three minutes in each of five postural drainage positions followed by assisted coughing or gentle oropharyngeal suction performed twice daily while in hospital. Control group No intervention.	status was not obvious at each assessment". Statistical analysis was perfomed using Mann-Whitney U test. Other At hospital discharge parents were asked to maintain a diary record of symptoms, and children were reviewed in outpatients after two weeks.	- clinical score: a score of 0 to 3 was allocated for each of ten clinical signs (heart rate, respiratory rate, hyperinflation, use of respiratory muscles, recession, rhinitis, wheeze, cough, crepitations, and ronchi). Clinical score has been reported on admission, every day and after 5 days. - lenght of hospital stay - total lenght of illness Raw Data Daily clinical scores (maximum = 30), median (range) - on admission control (n=46) = 12 (4-24) CPt (n=44) = 10 (4-22) - after 1 day control (n=45) = 10 (2-27) CPT (n=42) = 7 (2-24) - after 2 days control (n=39) = 8 (2-17) CPT (n=38) = 7 (2-21) - after 3 days	allocation was not reported. - performance bias: blinding was reported not to be possible. - attrition bias: a follow-up of two weeks has been described in the article, but data of such assessment are not reported. Also, 90 patients were analyzed, but not clear how many were randomized and if there was attrition of patients. - detection bias: unclear. Also: the study does not report means and standard deviations and exclusion criteria are not specified. Other information Indirectness Does the study match the review protocol in terms of Population: Some (children aged up to 15 months) Intervention: yes Outcome: yes Indirectness: some

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				control (n=31) = 6 (2-21) CPT (n=28) = 7 (3-28) - after 4 days control (n=21) = 6 (2-17) CPT (n=16) = 4 (2-18) - after 5 days control (n=18) = 5 (1-11) CPT (n=11) = 6 (3-10) Hospital stay (days), median (range) control group (n=46) = 4 (1-15) CPT (n=44) = 4 (2-11) Total lenght of illness (days), median (range) control group (n=46) = 14 (4-27) CPT (n=44) = 13 (7-26) Results Daily clinical scores (maximum = 30) - on admission = ns - after 1 day = ns - after 2 days = ns - after 3 days = ns - after 4 days = ns - after 5 days = ns Hospital stay (days) = ns	Setting Department of pediatrics and physiotherapy, City Hospital, Nottingham. Sample size calculation Not reported. Other Informed consent was obtained from parents before entry into the study. The authors reported that no child required immediate cessation of physiotherapy due to acute deterioration during a treatment session, although many children were noted to become more distressed during and immediately after treatment , albeit only temporarily.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Total lenght of illness (days) = ns * ns = non significant	

I.10 What is the efficacy of antibiotic treatment?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Field,C.M., Connolly,J.H., Murtagh,G., Slattery,C.M., Turkington,E.E., Antibiotic treatment of epidemic bronchiolitis--a double-blind trial, British Medical Journal, 1, 83-85, 1966 Ref Id 212299 Country/ies where the study was carried out Northern Ireland Study type Randomised double-blind trial. Aim of the study To assess the efficacy of ampicillin in the treatment of bronchiolitis.	Sample size Ampicillin: n = 28 Placebo: n = 24 Characteristics Age Ampicillin: Under 3 months - 12 3 month to under 6 months - 5 6 months and over - 8 Placebo: Under 3 months - 5 3 month to under 6 months - 10 6 months and over - 4 X2 = 5.15, 2 df, ns Illness Ampicillin: Mild - 2 Moderate - 19 Severe - 4	Interventions Ampicillin versus placebo.	Details Patients were admitted to the trial if they presented with bronchiolitis and matched the inclusion criteria and were categorised as mild, moderate or severe depending upon their symptoms. Patients were randomised using a code to receive either 125mg of ampicillin or placebo six-hourly. All patients also received 16mg of ephedrine three times per day. Most patients were also nursed in an oxygen tent with aerosol water vapour for one or two days.	Results Duration of symptoms and signs in hospital, mean Ampicillin: 6.36 days Placebo: 6.05 days Mean difference = 0.31 days t = 0.54, 42 df, ns Total duration of symptoms and signs, mean Ampicillin: 9.54 days Placebo: 9.7 days No significance tests carried out on these data.	Limitations - Method of randomisation was adequate - Allocation was concealed from patients but unclear for clinicians and investigators - study stated to be double-blind but blinding methods are not described. - Groups were comparable for attrition (ampicillin:3, placebo: 5) - Groups were comparable for age and severity of illness. No other confounders were investigated. - Length of follow-up was not reported - Statistical methods not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates October 30th to November 30th 1964. Source of funding Not fully reported. Ampicillin and placebo were supplied by Beechams Research Laboratories.	Placebo: Mild - 0 Moderate - 17 Severe - 2 Exact test combining mild and moderate p-value = 0.68. Inclusion criteria Coryza Paroxysmal cough Expiratory wheeze Increased respiratory rate Exclusion criteria Not reported.		Participants were removed from the trial if they became dangerously ill following a steady deterioration in their condition. Eight patients in total were removed. Analysis was based on 44 patients in total, 25 in the ampicillin arm, 19 in the placebo arm. Throat swabs were taken from 35 of 44 patients on admission for bacteriology. For virology, throat swabs were taken from 13 patients. Statistical analyses Not described		Indirectness: none Other information Bacteriological and virological swabs were not taken from all children Loss to follow-up based on removal of patients with severe deterioration in condition
Full citation Spurling,G.K., Doust,J., Del,MarC, Eriksson,L., Antibiotics for bronchiolitis in children, Cochrane Database of Systematic Reviews, 2011. Date of Publication, -, 2011 Ref Id	Sample size N = 5 trials N = 543 children Characteristics *additional information accessed from full text of trials because it was not reported in the systematic review	Interventions Oral, intravenous, intramuscular or inhaled antibiotics versus placebo	Details The Cochrane Central Register of Controlled Trials (CENTRAL, 2010 issue 4) was searched in December 2010, which includes: - the Cochrane Acute Respiratory Infection Group's specialised register	Results Oral antibiotics versus placebo 1. Duration of symptoms - days Mean difference 0.32 (95% CI -1.14 to 1.78) I^2=0% [Fixed effect; 2 trials: Field 1966; Kneyber 2008] *data from Kneyber 2008	Limitations Risk of bias of included studies, as assessed by review authors and indirectness assessed by NCC-WCH technical team Field 1966 - Adequate method of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
239003 Country/ies where the study was carried out Various Study type Systematic review of randomised controlled trials Aim of the study To evaluate clinical outcomes resulting from the use of antibiotics for bronchiolitis in children compared to placebo or other interventions Study dates The search was performed in December 2010; review content was assessed as up-to-date by the authors in December 2010 Source of funding University of Queensland, Australia	Field 1966 Inclusion criteria: *coryza, paroxysmal cough, expiratory wheeze, increased respiration Exclusion criteria: *not reported Sample size: *N=52 Intervention: ampicillin*(125 mg, 6-hourly) Comparator: placebo Age of children: *< 3 months = 17; ≥ 3 months, < 6 months = 15; ≥ 6 months = 12 Other details of care provided: *all children received ephedrine (16 mg) thrice daily and most were nursed for a day or two in an oxygen tent with aerosol water vapour Illness severity: mild = 2; moderate = 36; severe = 6 Country: *UK Kabir 2009 Inclusion criteria: *any child under 2 years hospitalised due to preceding or existing runny nose, cough, breathing difficulty, chest indrawing and rhonchi on auscultation		- the Database of Abstracts of Reviews of Effects (DARE, 2010 issue 4) - MEDLINE (Jan 1966 to Nov week 3 2010) - EMBASE (1990 to Dec 2010) - Current Contents (2001 to Dec 2010) No language restrictions were applied. References of all identified studies were handsearched and review authors contacted experts in the field looking for unpublished studies. Data collection and analysis Two review authors independently assessed all potentially eligible studies for inclusion. Two review authors independently extracted data from included studies using data extraction forms. Two review authors independently assessed methodological quality and resolved any disagreement by discussion. Data were	may be duration of symptoms at point of randomisation rather than outcome data and Field 1966 provide no SD so this study does not contribute to pooled estimate reported in Cochrane review 2. Duration of fever - days Mean difference 0.47 (95%CI -0.12 to 1.06) I^2=not applicable [Fixed effect; 1 trial: Kneyber 2008] *additional raw data supplied by study authors to review authors 3. Length of hospital stay - days Mean difference 0.34 (95% CI -0.71 to 1.38) I^2=69% [Random effects; Kabir 2009; Kneyber 2008; Tahan 2007] *Tahan 2007 provide no SD so this study does not contribute to pooled estimate reported in Cochrane review. Data from oral antibiotic arm of Kabir 2009 used 4. Bronchiodilator use and duration of use a. Use - n/N Antibiotic:17/32 Placebo: 23/39	randomisation - Allocation concelment not reported by review authors - Patients were blinded but not clinicians or outcome assessors - No intention-to-treat analysis but withdrawal rates were acceptable *8/52 (15%) children did not complete the trial due to severity of sign and symtpoms, diarrhoea and pyrexia or otitis media Indirectness: none Kabir 2009 - Adequate method of randomisation - Unclear allocation concealment - Blinding not reported - 32 participants dropped out (10%); 17 were referred to paediatric intensive care and 15 withdrew from the study or left the recruiting hospitals - High risk of reporting bias (selective reporting) Indirectness: none Kneyber 2008 - Adequate method of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria: *children with atopic conditions, congenital heart disease, possible immuno-deficiency, chronic lung problem, associated infection and receiving antibiotics previously Sample size: *N=327 Intervention: 1. IV ampicillin (parenteral ampicillin 50 mg/kg/6-hourly) plus supportive care; 2. Oral erythromycin (10 mg/kg/6-hourly) plus supportive care Comparator: no antibiotic (likely supportive care only) Other details of care provided: *antibiotic therapy continued for 7 days; supportive therapy followed Bangladeshi national guidelines with 6-hourly salbutamol at 0.15 mg/kg/6-8-hourly, oxygen inhalation, maintenance of nutrition with 10% i.v. dextrose in 0.255% saline, nasogastric tube feeding or breast feeding, oropharyngeal suction SOS and paracetamol suspension (if fever persisted)		analysed using Review Manager 5.1 Methodological quality was assessed under the headings of allocation, blinding, incomplete outcome data, selective reporting and other potential sources of bias. Continuous data were expressed as mean differences where there was one study or standardised mean differences where more than one study used different measurement scales. Dichotomous data were expressed as odds ratios. Data were pooled where multiple trial results for the same clinical presentation existed and heterogeneity did not preclude pooling of results.	OR 0.79 (95% CI 0.31 to 2.02) [Fixed effect: Kneyber 2008] b. Duration of use - days Mean difference -0.17 (95%CI -1.25 to 0.91) [Fixed effect: Kneyber 2008] 5. Oxygen use and duration of use a. Use - n/N Antibiotic: 20/32 Placebo: 23/39 OR 0.43 (95% CI 0.43 to 1.24) [Fixed effect: Kneyber 2008] b. Duration of use - days Mean difference 0.36 (95% CI -0.46 to 1.18) [Fixed effect: Kneyber 2008] 6. Naso-gastric feeding and duration of feeding a. Tube feeding - n/N Antibiotic: 16/32 Placebo: 16/39 OR 1.44 (95% CI 0.56 to 3.69) [Fixed effect: Kneyber 2008] b. Duration of feeding - days Mean difference 0.07 (95% CI -0.98 to 1.12)	randomisation and allocation concealment - Patients and doctors were blinded - No losses to follow up Indirectness: none Mazumder 2009 - Inadequate method of randomisation and unclear allocation concealment - Blinding not reported - Losses to follow up not reported by review authors Indirectness: unclear (original paper not accessed by NCC-WCH technical team) Tahan 2007 - Method of randomisation and allocation concealment unclear - Patients and investigators were blinded - 30 patients were randomised but 9 were later excluded as they received corticosteroid therapy Indirectness: none Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Illness severity: not clearly reported Country: Bangladesh Kneyber 2008 Inclusion criteria: *children < 24 months of age with a virologically confirmed clinical diagnosis of respiratory syncytial virus lower respiratory tract disease (RSV LRTD) Exclusion criteria: *lack of informed consent, symptoms restricted to upper respiratory tract infection, if only presented with apnea, nosocomial RSV LRTD, treated with antibiotics within 7 days prior to hospital admission Sample size: *N=71 Intervention: Azithromycin 10 mg/kg/day, once daily for 3 days Comparator: placebo Other details of care provided: *physicians were not allowed to prescribe antibiotics for 72 hours after randomisation; they were allowed to prescribe any other kind of drug Illness severity: no underlying diseases, 87% had impaired			[Fixed effect: Kneyber 2008] 7. Corticosteroid use - n/N Antibiotic: 1/32 Placebo: 7/39 OR 0.15 (95% CI 0.02 to 1.27) [Fixed effect: Kneyber 2008] 8. PICU admission - n/N Antibiotic: 0/32 Placebo: 1/39 OR 0.39 (95% CI 0.02 to 10.03) [Fixed effect: Kneyber 2008] 9. Re-admission - n/N Antibiotic: 1/12 Placebo: 4/9 OR 0.11 (95% CI 0.01 to 1.29) [Fixed effect: Tahan 2007] Oral or parenteral antibiotics versus placebo 1. Wheeze: on day 3 Antibiotic: 18/61 Placebo: 26/43 OR 0.27 (95% CI 0.12 to 0.62) [Fixed effect: Mazumder 2009] on day 5 Antibiotic: 13/61 Placebo: 2/43 OR 5.55 (95% CI 1.18 to 26.05)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	feeding Country: *The Netherlands Mazumder 2009 Inclusion criteria: 1 month to 2 years of age, preceding/existing runny nose, cough, breathing difficulty, lower chest in-drawing, wheeze and rhonchi on auscultation Exclusion criteria: atopic conditions, congenital heart disease, high fever >102°F. toxic appearance Sample size: N=104 Intervention: 1. Supportive management plus IV ampicillin *(100-200 mg/kg/dose every 6 hours); 2. Supportive management plus erythromycin *(30-50 mg/kg/day every 6 hours) Comparator: Supportive management Other details of care provided: *supportive care followed national guidelines, management with salbutamol nebulisation 6-8 hourly (0.15 mg/kg/dose), oxygen therapy (when oxygen saturation <90%) iv fluid 10% dextrose in 0.225% NaCl, nasogastric feeding for			[Fixed effect: Mazumder 2009] on day 7 Antibiotic: 17/198 Placebo: 4/97 OR 0.27 (95% CI 0.12 to 0.62) [Fixed effect: Kabir 2009] (Mazumder 2009: 100% children had wheeze on day 1; Kabir 2009: 92% children had wheeze on admission, group assignment unclear) 2. Shortness of breath: on day 3 Antibiotic: 34/61 Placebo: 27/43 OR 0.75 (95% CI 0.34 to 1.66) [Fixed effect: Mazumder 2009] on day 5 Antibiotic: 16/61 Placebo: 15/43 OR 0.66 (95% CI 0.28 to 1.55) [Fixed effect: Mazumder 2009] on day 7 Antibiotic: 17/198 Placebo: 2/97 OR 4.46 (95% CI 1.01 to 19.72) [Fixed effect: Kabir 2009] (Mazumder 2009: 100% children had shortness of	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	children unable to take milk by mouth, paracetamol for fever and oropharyngeal suction when needed Illness severity: not clearly reported Country: Bangladesh Tahan 2007 Inclusion criteria: Exclusion criteria: *cardiac disease, cystic fibrosis, chronic neonatal lung disease associated with prematurity, received corticosteroids within 24 hours or bronchiodilators within 4 hours before presentation Sample size: *N=30 Intervention: Clarithromycin 15 mg/kg/day, once daily for 3 weeks Comparator: placebo Other details of care provided: *supplemental oxygen was given to those cases with oxygen saturation levels <94% and was discontinued when levels were consistently >93% or when condition stable for 4 hours. Intravenous fluids were given when supplemental oxygen was required or oral			breath on day 1; Kabir 2009: 100% children had shortness of breath on day 1) 3. Oxygen saturation <96%: on day 3 Antibiotic: 15/61 Placebo: 5/43 OR 2.48 (95% CI 0.83 to 7.44) [Fixed effect: Mazumder 2009] on day 5 Antibiotic: 5/61 Placebo: 2/43 OR 1.83 (95% CI 0.34 to 9.91) [Fixed effect: Mazumder 2009] (Mazumder 2009: 54% children had oxygen saturation <96% on day 1; 33/61 (54%) in antibiotic group, 23/43 (53%) in control group) 4. Feeding difficulties: on day 3 Antibiotic: 6/61 Placebo: 5/43 OR 0.83 (95% CI 0.24 to 2.91) [Fixed effect: Mazumder 2009] on day 5 Antibiotic: 0/61 Placebo: 0/43	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	intake was inadequate. Children received β2-agonist treatment based on oxygen saturation, respiratory rate and respiratory effort Illness severity: mild = 4; moderate = 15; severe = 2 Country: Turkey Inclusion criteria Single or double-blind randomised controlled trials comparing antibiotics to placebo or control to treat bronchiolitis Children under 2 years of age Exclusion criteria Not reported			OR 0.00 (95% CI 0.00 to 0.00) [Fixed effect: Mazumder 2009] (Mazumder 2009: 48% children had feeding difficulties on day 1; 25/61 (42%) in antibiotic group, 25/43 (58%) in control group) 5. Fever: on day 2 Antibiotic: 11/198 Placebo: 4/97 OR 1.37 (95% CI 0.42 to 4.41) [Fixed effect: Kabir 2009] (Kabir 2009: 25% children had fever on admission, group assignment unclear)	
Full citation Kneyber,M.C., van Woensel,J.B., Uijtendaal,E., Uiterwaal,C.S., Kimpen,J.L., Dutch Antibiotics in RSV Trial (DART) Research Group., Azithromycin does not improve	Sample size Azithromycin: n = 32 Placebo: n = 39 Characteristics Mean age, months (±SE) Azithromycin: 3.0 (0.6) Placebo: 3.6 (0.5)	Interventions Azithromycin versus placebo.	Details Multicentre randomised double-blind placebo-controlled equivalence trial. Eligible participants were randomised to either oral azithromycin suspension	Results Mean duration of hospitalisation, hours (±SE) Azithromycin: 132.0 (10.8) Placebo: 139.6 (7.7) P-value = 0.328	Limitations - Method of randomisation was appropriate - Patients and clinicians were blinded to treatment allocation - Follow-up time was equal across groups - No loss to follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
disease course in hospitalized infants with respiratory syncytial virus (RSV) lower respiratory tract disease: a randomized equivalence trial, Pediatric Pulmonology, 43, 142-149, 2008 Ref Id 211698 Country/ies where the study was carried out Netherlands Study type Randomised double-blind placebo-controlled trial. Aim of the study To test the hypothesis that antibiotics would not lead to reduced duration of hospitalisation in mild to moderate RSV. Study dates Recruitment took placer between October to March in each of three separate RSV seasons: 2002 to 2004 and 2005 to 2006. Source of funding	Male/female sex Azithromycin: 19/13 Placebo: 24/14 Mean weight, kg (±SE) Azithromycin: 9.2 (2.5) Placebo: 6.4 (0.3) Duration of symptoms at baseline, days (±SE) Azithromycin: 4.9 (0.7) Placebo: 4.6 (0.3) Inclusion criteria Aged less than 24 months Virologically confirmed diagnosis of RSV LRTD Definition of RSV First attack of dyspnoea and one or more symptoms compatible with lower respiratory tract infection including: Body temperature > 37.5°C Coughing Wheezing Crackles on pulmonary auscultation RSV was confirmed using direct immunofluorescent		(10mg/kg/24 hr) or placebo in a single dose for three days. The first dose was given within 24 hours of hospital admission. Colour and taste of placebo were indistinguishable from azithromycin. Patients were randomised using block randomisation of ten patients per centre. Packaging was similar for both treatments. Physicians were not allowed to prescribe antibiotics for 72 hours following randomisation. Demographic data upon hospital admission were collected including age, sex, weight, gestational age, pre-existing comorbidities, breastfeeding, family history of atopy and day care attendance. The primary endpoint was duration of hospitalisation.	Mean difference in duration of hospitalisation, hours -7.58 for azithromycin versus placebo (95% CI: -33.5 to 18.3) Duration of bronchodilator use, days (±SE) Azithromycin: 2.8 (0.6) Placebo: 3.0 (0.4) P-value = 0.541 Duration of supplemental oxygen, days (±SE) Azithromycin: 3.8 (0.4) Placebo: 3.4 (0.3) P-value = 0.485	- Intention-to-treat analysis used Indirectness: none Other information No difference was observed in nasogastric feeding across groups (p-value 0.915)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported but not funded by any pharmaceutical company.	assay (DIFA) using FITC labelled monoclonal antibodies or enzyme-linked immunosorbent assay (EIA). Exclusion criteria Lack of informed consent Symptoms restricted to upper respiratory tract Patient only presented with apnoea Nosocomial RSV LRTD Treated with antibiotics within prior 7 days to admission		Discharge criteria were: No supplemental oxygen for at least 24 hours No nasogastric tube feeding Discharge criteria were assessed once a day. Secondary endpoints: Duration of oxygen supplementation Duration of use of brocnhodilators and/or corticosteroids Duration of nasogastric tube feeding Duration of tachypnoea (> 40 breaths per minute) Duration of elevated body temperature (> 37.5°C) Statistical analyses Intention-to-treat analysis was used. Continuous data were analysed using Mann-Whitney U test. Dichotomous data were analysed using X2 test with a continuity correction.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Threshold values for equivalence were between -49.37 and 49.37 hours. P-values less than 0.05 were statistically significant.		
Full citation Pinto,L.A., Pitrez,P.M., Luisi,F., de Mello,P.P., Gerhardt,M., Ferlini,R., Barbosa,D.C., Daros,I., Jones,M.H., Stein,R.T., Marostica,P.J., Azithromycin therapy in hospitalized infants with acute bronchiolitis is not associated with better clinical outcomes: a randomized, double-blinded, and placebo-controlled clinical trial, Journal of Pediatrics, 161, 1104-1108, 2012 Ref Id 239037 Country/ies where the study was carried out Brazil Study type	Sample size N=185 Azithromycin: 88 Placebo: 97 Characteristics Age - months (mean ± SD) Azithromycin: 3.08 ± 2.23 Placebo: 3.12 ± 2.29 Weight - kg (mean ± SD) Azithromycin: 5.63 ± 1.71 Placebo: 5.75 ± 1.72 Male - n/N (%) Azithromycin: 56/88 (63.6) Placebo: 55/96 (57.9) Antibiotic therapy - n/N (%) Azithromycin: 4/88 (4.5) Placebo: 6/96 (6.3)	Interventions Oral azithromycin (10 mg/kg/d) or equivalent volume of placebo, once daily for 7 days	Details Randomisation Not reported Care protocol Infants could receive additional therapies prescribed by attending paediatricians Statistical analyses To detect a reduction of length of stay of 1 day (SD 2 days), based on data from Tahan 2007, allowing for a 2-sided 5% significance level and a power of 80%, a sample dsize of 63 patients per group were required Primary outcomes were compared across groups using Mann-	Results Length of stay - days (median (interquartile range)) Azithromycin: 5.00 (3.00 – 7.00) Placebo: 5.00 (3.00 – 7.00)	Limitations - Unclear method of randomisation and allocation concealment - Authors state double-blinded trial but details not reported - 1 patient in the placebo group was lost to follow-up Indirectness: none Other information Subgroup analysis for age and specific viral diagnosis showed no significant differences

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial Aim of the study To test the hypothesis that 7-day course of azithromycin reduced the length of stay and oxygen requirement in infants with acute bronchiolitis Study dates 2009 – 2011 Source of funding Funded by Fundação de Amparo e Pesquisa do Estado do Rio Grande do Sul, which did not participate in the collection, analysis, or interpretation of data, nor in the writing or decision to submit the manuscript	Steroid therapy - n/N (%) Azithromycin: 4/88 (4.5) Placebo: 7/96 (7.3) Bronchiodilator therapy - n/N (%) Azithromycin: 18/88 (20.5) Placebo: 21/96 (21.8) Inclusion criteria 1. Aged 12 months or younger and admitted with a clinical diagnosis of acute bronchiolitis 2. Recruited within 48 hours of hospitalisation and had a maximum of 72 hours of a history of lower respiratory tract clinical manifestations Exclusion criteria 1. Any contraindication for oral macrolide therapy 2. Prescription of macrolide therapy by attending physician due to clinical and radiological features consistent with a diagnosis of of Chlamydia sp or Bordetella pertussis		Whitney. The effect of azithromycin on length of stay was assessed using Kaplan-Meier curves.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	respiratory infection 3. Chronic cardiopulmonary disorder, congenital or acquired immunodeficiency, or neuromuscular disease 4. History of prematurity or other neonatal complications				
Full citation Tahan,F., Ozcan,A., Koc,N., Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial, European Respiratory Journal, 29, 91-97, 2007 Ref Id 208280 Country/ies where the study was carried out Turkey Study type Randomised double-blind placebo-controlled trial. Aim of the study To investigate the efficacy of clarithromycin in	Sample size Clarithromycin: n = 15 Placebo: n = 15 Characteristics Median age, months (IQR) Clarithromycin: 2 (1 to 6) Placebo: 2 (1 to 7) P-value > 0.05 Male sex, n (%) Clarithromycin: 8 (66) Placebo: 4 (45) P-value > 0.05 Severity of disease at baseline, n (%) Clarithromycin: Mild - 2 (16) Moderate - 9 (72) Severe - 1 (12) Placebo:	Interventions Clarithromycin versus placebo.	Details All children admitted with bronchiolitis were treated using the same clinical pathway. Nasopharyngeal aspiration was used to detect RSV which was then diagnosed using DIFA staining. Discharge was allowed based on: No supplemental oxygen for 10 hours (oxygen discontinued when SpO2 consistently > 93%) Minimal or no chest retractions Feeding adequately without the need for IV fluids	Results Median length of stay in hospital, hours (IQR) Clarithromycin: 51 (48 to 68) Placebo: 88 (72 to 100) P-value < 0.05 Median duration of supplemental oxygen, hours (IQR) Clarithromycin: 31 (28 to 42) Placebo: 72 (52 to 80) P-value < 0.05	Limitations - Method of randomisation likely inadequate - described as simple randomisation with no explanation of methods - Patients and clinicians were blinded to treatment allocation - Follow-up and care were the same across groups - Loss to follow-up was not comparable (clarithromycin: 20%, placebo: 40%) Indirectness: none Other information Patients were excluded during the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treating RSV bronchiolitis. Study dates January to April 2005. Source of funding Not reported.	Mild - 2 (22) Moderate - 6 (66) Severe - 1 (11) P-value > 0.05 Inclusion criteria First episode of wheezing requiring hospitalisation Clinical diagnosis of bronchiolitis Definition of bronchiolitis Based on clinical findings including: Wheezing or wheezing with crackles Respiratory distress with retractions Exclusion criteria Presence of cardiac disease, cystic fibrosis or chronic neonatal lung disease associated with prematurity Received corticosteroids within 24 hours before presentation Received bronchodilators within 4 hours before presentation		Patients were randomised by a single nurse to either clarithromycin (15mg/kg) or placebo daily for three weeks using simple randomisation. Patients, parents and investigators were blinded until study completion. Primary outcome was length of stay in hospital. Secondary outcomes included: Changes in IL-4, IL-8, eotaxin and IFN-γ levels Readmission rate Wheezing after discharge Baseline characteristics collected included duration of symptoms before presentation, medical history, ability to feed, previous medication, parental smoking status		study if they were administered streroid treatments.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			and family history of atopy. Statistical analyses Chemokine levels were compared using either the Mann-Whitney U test or Wilcoxon tests. All other variables were compared using X2 tests. Results were significant for p-values below 0.05.		
Full citation Kabir,A.R., Mollah,A.H., Anwar,K.S., Rahman,A.K., Amin,R., Rahman,M.E., Management of bronchiolitis without antibiotics: a multicentre randomized control trial in Bangladesh, Acta Paediatrica, 98, 1593-1599, 2009 Ref Id 207224 Country/ies where the study was carried out Bangladesh	Sample size Parenteral ampicillin: n = 99 Oral erythromycin: n = 99 No antibiotic: n = 97 Characteristics Age in months, n Parenteral ampicillin: ≤3 - 38 4 to 6 - 33 7 to 12 - 23 13 to 18 - 4 19 to 24 - 1 Oral erythromycin: ≤3 - 36	Interventions Parenteral ampicillin, oral erythromycin and no antibiotic.	Details Randomisation was achieved using random number tables. Participants were randomised to receive either: Parenteral ampicillin at 50mg/kg/dose six hourly IV Oral erythromycin at 10mg/kg/dose six hourly No antibiotics Follow-up was undertaken by trained doctors every 8 hours	Results Mean length of stay in hospital, days (±SD) Parenteral ampicillin: 4.29 (1.89) Oral erythromycin: 4.44 (1.93) No antibiotics: 3.67 (1.45) P-value for no antibiotics versus parenteral ampicillin or oral erythromycin < 0.001	Limitations - Method of randomisation was adequate - Allocation to treatment was not blinded (no placebo and antibiotics administered in different preparations and via different routes). - Follow-up was similar across groups - Loss to follow-up not reported - methods state only that sample size was 327 initially

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Multicentre randomised controlled trial Aim of the study To determine whether antibiotics have a role in management of bronchiolitis. Study dates Not reported. One year in duration. Source of funding Bangladesh Medical Research Council (through a grant from the World Bank).	4 to 6 - 39 7 to 12 - 17 13 to 18 - 4 19 to 24 - 3 No antibiotics: ≤3 - 32 4 to 6 - 33 7 to 12 - 23 13 to 18 - 8 19 to 24 - 1 P-value = 0.66 Sex, male to female ratio Parenteral ampicillin: 2.96:1 Oral erythromycin: 3.30:1 No antibiotics: 1.93:1 P-value = 0.20 Inclusion criteria Aged under two years Hospitalised due to preceding or existing runny nose, cough, breathing difficulty, chest indrawing and rhonchi on auscultation Exclusion criteria Children with: Atopic conditions Congenital heart disease		over four to seven days using a structured sheet based on nine symptoms and nine signs. Antibiotics therapy was planned for seven days. In the case of early discharge parents were advised to continue therapy at home. Discharge criteria were based on national guidelines: Satisfactory feeding Return of social smile No hypoxia (SaO2 > 94%) in room air Statistical analyses Data were analysed using X2 tests or Fisher's exact test. Likelihood ratios, linear associations and correlations (Pearson's r and Spearman's ρ) were compared using Fisher's exact test. Continuous variables were analysed using		but only 295 were analysed. Indirectness: none Other information Improvement in clinical signs and symptoms were comparable across groups. A point-based system was used to measure this outcome (not validated).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Possible immunodeficiency Chronic lung problems Associated infection Previously received antibiotics		Student's t-test and ANOVA. P-values of <0.05 were deemed to be statistically significant.		
Full citation Rasul,C.H., Kabir,A.R.M.L., Rashid,A.K.M.M., Mahboob,A.A., Hassan,M.A., Role of antibiotic in the outcome of bronchiolitis, Pakistan Journal of Medical Sciences, 24, 707-711, 2008 Ref Id 239382 Country/ies where the study was carried out Bangladesh Study type Randomised controlled trial Aim of the study To estimate the outcome of bronchiolitis with supportive treatment and also to determine the difference with	Sample size N=60 Oral antibiotics = 22 Parenteral antibiotics = 23 No antibiotics = 15 Characteristics Under 6 months ofage - n/N (%) *48/60 (80) *n calculated by NCC-WCH from reported % Male - n/N (%) *43/60 (71.6) *n calculated by NCC-WCH from reported % Feeding difficulty at admission - n/N (%) 24/60 (40) Restlessness at admission - n/N (%) 16/60 (26.7) Inconsolable cry - n/N (%) 17/60 (28.3)	Interventions Arm 1: Oral erythromycin Arm 2: Parenteral amoxycillin Arm 3: No antibiotic	Details Randomisation Twenty five cards in each group were marked as no antibiotic, oral antibiotic or parenteral antibiotic. After repeated shuffling of all the cards each card was kept in a sealed envelope. Study cases were assigned the envelope as per their admission serial and the investigators were unaware of the treatment modalities before opening the envelope. Care protocol Supportive treatment was given according to national guidelines for the management of bronchiolitis. Oxygen and nebulisation were given immediately upon admission. Children were	Results Length of hospital stay - days (mean ± SD, N) Oral antibiotics: 6.7 ± 1.1 (22) Parenteral antibiotics: 6.3 ± 1.5 (23) No antibiotics: 6.2 ± 1.4 (15) Feeding difficulties on day 3 -n/N (%) Oral antibiotics: 3/9 (33.3) Parenteral antibiotics: 3/8 (33.3) No antibiotics: 2/7 (28.6) *24/60 (40%) had feeding difficulties on admission Fever on day 3 - n/N (%) Oral antibiotics: 2/9 (22.2) Parenteral antibiotics: 3/11 (27.3) No antibiotics: 2/8 (25) *28/60 (46.7%) had fever on admission Cough on day 3 - n/N (%) Oral antibiotics: 5/11 (45.5) Parenteral antibiotics: 5/13 (38.4)	Limitations - Adequate method of randomisation - Unclear whether patients, doctors or outcome assessors were blinded - Unclear whether any patients were withdrawn from the trial due to deterioration in condition Indirectness: none Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
additional antibiotic therapy Study dates October 2006 – March 2007 Source of funding Not reported	Sleeping difficulty - n/N (%) 18/60 (30) Cough - n/N (%) 34/60 (56.7) Fever - n/N (%) 28/60 (46.7) Inclusion criteria Age up to 2 years Lower chest indrawing Preceding runny nose/first attack of wheeze Not treated previously Exclusion criteria Atopic conditions Congenital heart disease Known immunodeficiency		withdrawn from the study only when their condition deteriorated and became life-threatening.	No antibiotics: 4/10 (40) *34/60 (56.7%) had cough on admission	
Full citation Mazumder,M., Hossain,M.M, Kabir,A., Management of Bronchiolitis with or without Antibiotics - A Randomized Control Trial, Journal of Bangladesh College of Physicians and Surgeons, 27, -, 2009 Ref Id 275960	Sample size Parenteral ampicillin: n = 30 Oral erythromycin: n = 33 No antibiotics: n = 63 Characteristics Age 92% of patients were in the first year of life Sex	Interventions Parenteral ampicillin, oral erythromycin and no antibiotics.	Details Convenience sample of 126 consecutive cases of bronchiolitis. Children identified at outpatient clinics were included if they met the inclusion criteria. Patients were randomised into three groups: Parenteral antibiotics (IV ampicillin 100 to	Results Change in respiratory rate Improvements in fast breathing were similar across groups Percentage of patients with fast breathing by day 5 of treatment: Parenteral ampicillin - 10.3 Oral erythromycin - 9.3 No antibiotics - 11.6 P-value = 0.05 (analysis method unclear)	Limitations - Inadequate method of randomisation - use of odd and even numbers and alternate allocation to antibiotics - No blinding to treatment allocation (antibiotics were given using different preparations and via different routes)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Bangladesh Study type Randomised controlled trial Aim of the study To evaluate bronchiolitis outcome with or without antibiotics in a hospital setting. Study dates January to July 2005 Source of funding Not reported	67.3% of patients were male, 32.7% were female Inclusion criteria Diagnosis of bronchiolitis based on: Aged between one month and two years Preceding or exisitng runny nose, cough, breathing difficulty, lower chest in-drawing, wheeze and rhonchi on auscultation Exclusion criteria Children with: Atopic conditions Congenital heart disease High fever (> 102°F) Toxic appearance		200mg/kg/dose six hourly and supportive management) Oral antibiotics (oral erythromycin syrup 30 to 50mg/kg/dose six hourly and supportive management) No antibiotics (supportive management only). Randomisation was carried out using odd numbers (oral and parental antibiotics alternately) and even numbers (no antibiotics). Hospitalised children were followed up three times in 24 hours, outpatients two times for up to seven days using a structured follow-up sheet. Outcome measures were: Breathing difficulties Feeding difficulties Social smile Fast breathing (> 50 breaths per minute)		- Very little baseline demographic information provided - Outpatient cases were followed up less frequently than hospitalised cases - Length of follow-up not clear - Groups were not comparable for attrition (parenteral ampicillin: 1, oral erythromycin: 1, no antibiotics: 20) - Statistical analysis methods unclear and likely inappropriate due to use of time series data Indirectness: none Other information Improvement in clinical signs and symptoms was comparable across groups.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Hypoxia (oxygen saturation < 95%) Wheeze Rhonchi Crepitation Statistical analyses X2 test and associated p-values used where appropriate No further description of analytical methods provided		

I.11 What is the efficacy of inhaled bronchodilator therapy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Plint,A.C., Johnson,D.W., Patel,H., Wiebe,N., Correll,R., Brant,R., Mitton,C., Gouin,S., Bhatt,M., Joubert,G., Black,K.J., Turner,T., Whitehouse,S., Klassen,T.P., Pediatric Emergency Research Canada (PERC), Epinephrine and dexamethasone in children with bronchiolitis, New	Sample size - 3556 assessed for eligibility. - 800 enrolled. - 3 lost to follow-up. - Included in analysis: 199 epinephrine-dexamethasone group. 198 epinephrine group. 199 dexamethasone group. 201 placebo group. Characteristics	Interventions - The pharmacy at each site prepared the study drugs in sequentially numbered, visually identical packets. - The active drugs and placebo were identical in appearance, volume, weight, odor and taste. 1. Epinephrine-dexamethasone group: Two treatments of nebulised epinephrine	Details Setting: Eight pediatric emergency departments. Randomisation: - Research nurse assigned treatment groups using a computer-generated randomisation sequence stratified by centre.	Results Protocol outcomes Epinephrine-dexamethasone group 1; epinephrine group 2; dexamethasone group 3; placebo group 4 Mean±SD 1. Hospital admission rate - At enrollment:	Limitations Based on the NICE checklist. Only limitations that arise in the study are reported. Selection bias: - 1841 did not meet criteria to enroll. - Recruitment up to 16 hours a day when the research nurse was present. Attrition bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
England Journal of Medicine, 360, 2079-2089, 2009 Ref Id 207913 Country/ies where the study was carried out Study type Multicentre, double-blinded, placebo-controlled trial. Aim of the study A clinical trial with a factorial design at multiple sites to determine whether treatment with nebulised epinephrine, a short course of oral dexamethasone, or both resulted in a clinically important decrease in hospital admissions among infants with bronchiolitis who were seen in the emergency department. Study dates Bronchiolitis season (December through April) from 2004 to 2007.	Characteristic: epinephrine-dexamethasone group 1; epinephrine group 2; dexamethasone group 3; placebo group 4 Median (IQR) or n(%) - Age, months: 5 (3-7); 5 (3-7); 5 (3-7); 5 (3-7) - Male, sex: 124 (62.0); 122 (61.3); 127(63.5); 120(59.7) - Oxygen saturation %: 97 (95-98); 97 (95-98); 97 (95-98); 97 (95-98) - Duration of symptoms before enrollment, days: 3 (2-5); 4 (3-6); 3 (2-5); 4 (2-6) - RSV positive: 128 (64.0); 129 (64.8); 127 (63.5); 136 (67.7) Previous treatment, no (%): - Bronchodilators 27 (13.5); 21 (10.6); 20 (10.0); 24 (11.9) - Antibiotics 24 (12.0); 20 (10.1); 21 (10.5); 17 (8.5) Inclusion criteria	and six oral doses of dexamethasone. 2. Epinephrine group: Nebulised epinephrine and oral placebo. 3. Dexamethasone group: Nebulised placebo and oral dexamethasone. 4. Placebo group: Nebulised placebo and oral placebo. Nebulised treatments: Administered 30 minutes apart, oxygen flow rate of 8l per minute, consisted of 3ml of generic epinephrine in a 1:1000 solution or an equivalent volume of saline. Oral treatments: - 1.0mg dexamethasone per kg of body weight (maximum dose 10mg) or placebo given after the first nebulised treatment in the emergency department,	- Randomised permuted blocks of 8 and 12. Outcome measures: - Hospital admission within 7 days after the day of enrollment. - Change in heart and respiratory rate. - RDAI score (based on wheezing and distress, 0 to 17 scale, used by Lowell et al.). - Oxygen saturation. - Length and severiy of symptoms. - Time to discharge. - Patient return to health care provider. Statistical methods: - Sample size calculation: 800 inflants required, power=80%, 5% type 1 error rate, to detect an absolute difference of 10 percentage points in admission rates resulting from	23(11.5%); 29(14.6%); 31(15.5%); 36(17.9%) - By seventh day: 34/199 (17.1%); 47/198 (23.7%); 51/199 (25.6%); 53/201 (26.4%) - The relative risk of admission by day 7 in group 1 as compared with group 4 was 0.65 (95% CI 0.45 to 0.95, unadjusted p=0.02, adjusted p=0.07). - 11 infants would need to be treated to prevent one hospital admission. - By day 22: 37(18.5%); 50(25.1%); 53(26.5%); 54(26.9) - Returned to health care provider: 95 (47.7%); 93 (47.0%); 106 (53.3%); 86 (42.8%) - Only difference between group 3 and group 4 significant, unadjusted p=0.04	No data were avaliable on the primary outcome for three patients, these patients were not included in the intention-to-treat analysis. Detection bias: Subjective clinical scoring system. Performance bias: - Blinding unclear. - Pharmacy error: 23 in group 1 and 23 in group 3 recieved a dexamethasone at 80% of the planned dose. - Care may vary across the 8 pediatric emergency departments and across infants treated at home or as inpatients. - Criteria for discharge not described. - At follow-up parents reported they stopped administering the study syrup so that a physician could prescribe oral corticosteriods: 19 in group 1, 13 in group 2, 20 in group 3 and 12 in group 4.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding - Supported by grants from the Canadian Institutes of Health Research and Alberta Children's Hospital Foundation. - Dr. Plint was supported in part by a salary award from the Canadian Institues of Health Research. - Dr. Johnson reports receiving grant support from Cumberland Pharmaceuticals. - No other potential conflict of interest relevant to this article was reported.	- Bronchiolitis defined as: the first episode of wheezing associated with signs of an upper respiratory tract infection during the peak RSV season. - 6 weeks to 12 months of age. - RDAI score 4 to 15. Exclusion criteria - Received oral or inhaled corticosteriods during the preceding 2 weeks. - Previous episode of wheezing. - Diagnosis of asthma. - Previous bronchodilator use. - Any chronic cardiopulmonary disease or immunodeficiency. - Infants in severe distress (pulse rate >80 breaths per min, RDAI score >15). - Profound lethargy. - Exposed to varicella within the preceding 3 weeks. - Born <37 weeks of gestation. - Insurmountable barriers to communication with the family.	followed by five once-daily doses of dexamethasone (0.6mg per kg; maximim daily dose, 10mg) or placebo. - Dexamethasone: generic dexamethasone phosphate injection solution mixed with Ora-Plus and Ora-Sweet (Paddock Laboratories). - Placebo: Ora-Plus and Ora-Sweet. Addiional treatment: - Oxygen saturation <92% while breathing ambient air recieved supplemental oxygen. - Fever (rectal temperature >38ºC) received acteminophen (15mg per kg body weight). - The treating physician in the emergency department was allowed to provide cointerventions after 90 minutes and independently determined whether to admit or discharge.	administration of each drug. - Intention-to-treat analysis. - Admission and return visits due to symptoms of bronchiolitis analysed with relative-risk regression for binary outcomes. - Time to discharge: Cox proportional-hazards model. - Time to symptom relief: parametric survival models with Weibull distributions. - Clinical characteristics: linear mixed-effects regression. Follow-up: By telephone performed daily by research nurse until day 7, then every 2 days until day 14, and then every 3 days until day 22.	2. Length of hospital stay Median hours (IQR), until discharge from the emergency department or hospital: 4.6 (3.5-7.0); 4.9 (3.7-9.6); 5.1 (3.6-17.0); 5.3 (3.8-21) P value unadjusted: 0.02; 0.78; 0.99; refenence P value adjusted: 0.94; 0.94; 1.00; reference 3. Change in respiratory rate: 30 min: -2.40±8.29; -1.35±8.53; -1.63±8.32; -0.59±8.34 60 min: -4.04±9.17; -3.68±8.89; -3.30±9.60; -2.88±10.20 P value unadjusted: 0.04; 0.44; 0.83; reference P value adjusted: 0.09; 0.66; 0.83; reference	Other information - Because of pharmacy error, a total of 23 patients in group 1 and 23 patients in group 3 received dexamethasone at 80% of the planned dose (0.8mg per kg of body weight in the emergency department and 0.48mg per kg of body weight at home), these patients were included in the analysis. - The additional use of bronchodilators 90 minutes after enrollment were similar across groups, with 18.4% of patients receiving albuterol and 20.6% receiving epinephrine. - The relative risk of admission, unadjusted and adjusted for multiple comparisons also reported (figure 2). - Median days to symptom resolution (normal feeding, normal sleeping, quiet breathing) also reported (figure 4).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				4. Change in disease severity score (RDAI): 30 min: -1.62±2.23; -1.44±1.94; -0.98±2.07; -1.06±2.16 60 min: -2.50±2.58; -2.45±2.32; -1.75±2.40; -1.65±2.42 P value unadjusted: <0.001; 0.003; 0.75; reference P value adjusted: <0.001; 0.005; 0.75; reference 5. Change in O2 saturation: 30 min: -0.35±2.61; 0.17±2.09; -0.52±2.45; -0.24±2.77 60 min: -0.73±2.56; 0.07±2.70; -1.02±2.57; -0.77±3.23 P value unadjusted: 0.59; 0.005; 0.22; reference P value adjusted: 0.59; 0.013; 0.36; reference	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported. 7. Need for/Use of feeding support Reported as time to return to normal feeding in days, median (IQR) Epinephrine: 0.5 (0.2 to 1.2) Placebo: 0.9 (0.3 to 2.1) Mean ratio (95%CI): 0.60 (0.47 to 0.76) 8. Adverse effects Observed in the emergency department by research nurse: - Tremor 4 (2.0); 4 (2.0); 5 (2.5); 2 (1.0) - Pallor 23 (11.5); 22 (11.1); 15 (7.5); 16 (8.0) - Vomiting 2 (1.0); 4 (2.0); 5 (2.5); 3 (1.5) Reported by families during the 22 day telephone follow-up:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- Varicella 0 (0); 0 (0); 0 (0); 0 (0) - Dark stools 17.5 (8.5); 14 (7.0); 12 (6.0); 16 (8.0) Observed in infants admitted to hospital: - Hypertension 0 (0); 1 (0.5); 1 (0.5); 0 (0) - Hyperkalemia 0 (0); 0 (0); 1 (0.5); 0 (0)	
Full citation Totapally,B.R., Demerci,C., Zureikat,G., Nolan,B., Tidal breathing flow-volume loops in bronchiolitis in infancy: the effect of albuterol [ISRCTN47364493], Critical Care (London, England), 6, 160-165, 2002 Ref Id 210423 Country/ies where the study was carried out USA Study type	Sample size - 20 enrolled, one patient excluded because flow-volume loops consistent with grunting. - Albuterol 10, placebo 9. Characteristics Characteristic: group A; group B - Male/female: 7/3; 2/7 - Mean age, months: 5.1; 5.8 - Mean weight, kg: 6.81; 7.1 - All 19 infants had a cough (3.6±2.8 days)	Interventions - Either 0.15mg/kg albuterol in 3ml saline (group A) or 3ml saline without albuterol (group B). - The same patients were crossed-over to receive the alternate saline or albuterol treatment 6 hours after the first aerosol administration. - Chloral hydrate (50mg/kg, orally) was administered 30 minutes before the	Details Setting: Pediatric unit of a community teaching hospital. Randomisation and concealment: - Observers were unable to distinguish between the two nebulizer solutions by any characteristics and both were dispensed by the pharamacy in identical syringes.	Results Protocol outcomes 1. Hospital admission rate Not reported 2. Length of hospital stay, days 3.9±1.1 (not reported separately for each treatment group) 3. Change in respiratory rate (bpm), mean (SD) Albuterol: before 42±9.4, after 42±10.7 Saline: before	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Characteristics not all reported per group. - Small sample size and power. Detection bias: - Blinding unclear. - Subjective wheeze score. Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised, double-blinded, placebo-controlled, crossover study. Aim of the study To evaluate the effect of nebulized albuterol on tidal breathing flow-volume loops in infants with bronchiolitis due to RSV. Study dates Not reported. Source of funding Not reported.	- 18 infants had symptoms of upper respiratory infection (2.94±0.9 days), wheezing (2.3±1.7 days), and breathing difficulties (1.7±0.9 days). - 17 infants had difficulties feeding (1.6±0.8 days) - 9 infants had fever (1.5±0.7 days) - A family history of wheezing or atopy was present in nine infants. - Exposure to passive smoking and household pets were present in 12 and 8 infants respectively. Inclusion criteria - <1 year old. - First episode of wheezing. - Clinical features of bronchiolitis (rhinorrhea, tachypnea, and wheezing, and/or rales). - Positive for RSV. Exclusion criteria - Preterm infants. - Underlying cardiopulmonary disease. - Bronchopulmonary dysplasia. - Previous history of wheezing.	measurements were taken. - An aerosol (albuterol or saline) treatment was given following baseline measurements, the same measurements were also repeated 15 minutes after the aerosol treatment. - The entire procedure was repeated in 6 hours, with the second aerosol (saline or albuterol) treatment. Additional treatment: - None of the patients received any other bronchodilators within 6 hours of the first aerosol treatment or between the first and second aerosol administration. - In those infants who were on supplemental oxygen, the amount of supplemental oxygen was kept constant during the study period. - Corticosteriods were not administered to any patients in the study.	- Block randomisation was performed by the pharmacy department and the records were concealed until the end of the study. Outcome measures: - Pulmonary function tests. - Respiratory rate. - Oxygen saturation. - Wheeze score (0-3 scale, also used by Schuh). Statistical methods: - Sample size calculation: to detect 40% improvement in the fraction of time to achieve peak tidal expiratory flow to total expiratory time (tPTEP/tE), α=0.05, two-tailed, power=90%, a sample size of 17-20 patients predicted. - Repeated-measures analysis of variance followed by Bonferroni correction for	41±9.8, after 41±10.8 4. Change in disease severity score, mean (SD) Wheeze score: Albuterol: before 0.79±0.71, after 0.95±0.71 Saline: before 0.53±0.70, after 0.58±0.77 5. Change in O2 saturation, mean (SD) Albuterol: before 95±3.3, after 95±3.1 Saline: before 95±2.7, after 94±2.4 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Five infants received oxygen supplementation and eight infants needed intravenous fluids for more than 1 day - not reported separately for each treatment group 7. Need for/Use of feeding support	- The 6 hour interval before cross-over measurments was used to exclude any carryover effect of nebulized albuterol or saline. - Group A received nebulized albuterol first followed by saline, group B received saline first followed by nebulized albuterol. - Pulmonary function tests also reported (table 3).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Needing admission to the pediatric intensive care unit.		multiple comparisons. - The wheeze scores compared with a non-parametric Friedman test followed by dunn's test. - Improvements from baseline compared with a paired t-test.	Sixteen infants had difficulties in feeding - not reported separately for each treatment group 8. Adverse effects Not reported	
Full citation Wainwright,C., Altamirano,L., Cheney,M., Cheney,J., Barber,S., Price,D., Moloney,S., Kimberley,A., Woolfield,N., Cadzow,S., Fiumara,F., Wilson,P., Mego,S., VandeVelde,D., Sanders,S., O'Rourke,P., Francis,P., A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis, New England Journal of Medicine, 349, 27-35, 2003 Ref Id 208418	Sample size 194 enrolled: 99 epinephrine, 95 placebo. Characteristics Characteristic: epinephrine; placebo; p value - Age months (Mean±SD): 4.52±3.01; 4.35±2.95; 0.70 - Male/female: 60/39; 61/34; 0.66 - Neither parents smoking: 47(47.5%); 50(52.6%); 0.50 - Premature birth: 13(13.1%); 15(15.8%); 0.68 - Duration of coryza at admission: p=0.35 No coryza 13(13.1%); 15(15.8%) <3 days 30(30.3%); 33(34.7%)	Interventions - Each infant assigned one amber bottle containing 15ml of clear colorless solution with an odor or chlorobutanol. - The contents were sufficient for three doses of 4ml, at 4 hour intervals with 24 hours after admission to hospital. - Epinephrine and placebo (normal saline) were administered by means of a standard hospital jet nebulizers through a firmly applied face mask with an oxygen flow of 6l per minute.	Details Setting: All children admitted to Royal Children's, Gold Coast, Caboolture and Redcliffe hospitals with bronchiolitis were treated according to the same clinical pathway to ensure consistent care and minimise the variability of the results. Randomisation and concealment: - Randomisation performed by the pharmacy at the Princess Margaret Hospital in Perth	Results Protocol outcomes Epinephrine; placebo ratio of means; p value Mean (95% CI) 1. Hospital admission rate: One patient in the epinephrine group and two in the placebo were readmitted to the hospital within one month after discharge. 2. Length of hospital stay, hours - Length of hospital stay, overall:	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Number of patients presented to hosptial with bronchiolitis who did not meet the inclusion criteria not reported. - Slightly more positive RSV patients in the epinephrine group than placebo, p=0.23. Performance bias: - Blinding unclear. - Additional treatments at physicians discretion. - Number of physicans/observers involved not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia Study type Multicentre, randomised, double-blinded, placebo-controlled trial. Aim of the study To examine if the effect of nebulized epinephrine on the length of hospital stay among infants with bronchiolitis. Study dates April 2000 and September 2001. Source of funding Supported by a grant from the Royal Children's Hospital Foundation, Brisbane, Australia.	3-6 days 44(44.4%); 37(38.9%) >6 days 12(12.1%); 10(10.5%) - Duration of wheezing at admission: p=0.16 No wheezing 41(41.4%); 42(44.2%) <3 days 31(31.3%); 42(44.2%) 3-6 days 21(21.2%); 7(7.4%) >6 days 6(6.1%); 4 (4.2%) - RSV positive: 70(70.7%); 59(62.3%); 0.23 - Supplementary oxygen and intravenous feeding: p=0.20 No oxygen 37(37.4%); 33(34.7%) Oxygen only 49(49.5%); 38(40.0%) Oxygen and intravenous feeding 13(13.1%); 24(25.3%) Inclusion criteria - <12 months of age (or <12 months of corrected age if premature).	Epinephrine: Epinephrine acid tartrate, 1%, with sodium metabisulfite and vehicle. Vechicle: Chlorobutanol, edetate disodium, sodium chloride, and purified water. Additional treatment: - The treating physicians were free to use suppletmental oxygen or intravenous fluids as they thought appropriate. - The criterion for supplemental oxygen was <94% oxygen saturation or any conbination of clincally significant respiratory distress, a respiratory rate above 60 per minute, and difficulty in feeding. The use of supplemental oxygen was terminated when the oxygen saturation was consistently above 93% or when the infant's condition had been stable for four hours and starting to tolerate oral feeding.	which manufactured the treatment packages. - Stratified according to centre in blocks of 50 numbers, so that each block comprised 25 patients randomly assigned to epinephrine and 25 to placebo. - Two of the smaller hospitals (Caboolture and Redcliffe) were regarded as one centre for the purpose of statification. - Each patient was assigned the next sequential number for the particular centre. - Except for interim analysis the allocation codes were not opened until the trial was completed. Outcome measures: - Length of hospitalisation and time until discharge	58.8 (49.4 to 70.0); 69.5 (59.3 to 81.4); 0.85 (0.67 to 1.07); 0.16 3. Change in Respiratory rate: 30 minutes after treatment was slightly higher (by about two breaths per minute) in the epinephrine group than in the placebo group, p=0.10 to p=0.68 - numbers not reported 4. Change in disease severity score: - No difference between the groups in the change in the respiratory-effort score from before to 60 minutes after each treatment (p=0.18 to p=0.76). - After 30 minutes after the first treatment the epinephrine group had a lower respiratory-effort score than the placebo group (p=0.04).	- Three different nebuliser systems used across the hospitals Detection bias: - Oxygen saturation and respiratory rates measured but the values are not reported separately. Other information - Calculation of severity score described in table 1. - Nebulizer brands/models used at each hospital reported. - 14 infants did not receive all three doses of nebulized epinephrine or placebo, 10 in the epinephrine group and 4 in the placebo group, p=0.11 - Three infants in the placebo group and one in the epinephrine group received antibiotics. - No infants received steriod therapy, and two in the placebo group were treated with bronchodilators other than epinephrine when their condition failed to improve.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- First episode of wheezing requiring hospitalisation. - Clinical diagnosis of bronchiolitis define as: a history of upper respiratory tract infection, wheezing or wheezing with crackles and respiratory distress with chest recession. (- Chronic neonatal lung disease associated with prematurity were included) Exclusion criteria - Cardiac disease, such as cystic fibrosis. - Received corticosteriods in any form within 24 hours before presentation. - Received bronchodilators within 4 hours before presentation. - Infants who required ventilatory support before their parents could give consent for their participation in the study.	- The clinical pathway guidelines suggested that infants should receive intravenous fluids rather than oral feeding if supplemental oxygen was required and the respiratory rate >60 per minute, or if oral feeding was deemed inadequate. The use of intravenous fluids was terminated when the infant was able to tolerate oral feeding. - Comfort feeding was allowed. Discharge criteria: Not received supplemental oxygen for 10 hours, had minimal or no chest recession, and was feeding adequately, without the need for intravenous fluids.	(both measured to acknowledge how administration and social factors may differ between the four centres). - Change in severity score (based on respiratory effort, oxygen saturation breathing ambient air, respiratory rate compared with that of healthy infants of the same age and overall severity score). - Time supplemental oxygen was required. - Heart rate, respiratory rate, oxygen saturation and blood pressure measured just before and 30 and 60 minutes after drug delivery. Statistical methods: - Sample size calculation: to detect a difference between the two groups of half a standard deviation in the length of hospital	- The epinephrine group had slightly lower respiratory-effort scores 60 minutes after the final nebulization than the placebo group (2.44 [95% CI 1.97 to 2.92] vs 3.35 [95% CI 2.78 to 3.91], p=0.02). 5. Change in O2 saturation: Not reported. 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: 49 infants (49.5%) in the epinephrine group and 38 infants (40.0%) in the placebo group required supplemental oxygen. Seven infants (3.6%) required admission to the intensive care unit, and three (1.5%) required ventilatory support. There were no significant differences between the groups in the	- Univariate analysis of the length of hospital stay and the time receiving supplemental oxygen showed no significant differences between the responses eo epinephrine at the various hospitals (p=0.31 and p=0.66, respectively).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			stay and the time until the infant was ready for discharge at the 1% significance level for a two-sided test with 85% power requires 100 infants in each group. - Intention-to-treat analysis. - Interim analysis was performed by the study statistician after the first 50 patients had undergone randomisation, the absence of a finding of superiority in the interim analysis was communicated solely to the principal investigator and the ethics committee. - Characteristics assessed by Fisher's exact test and Mann-Whitney test with exact probabilities. - Between group comparisons performed by analysis of variance after appropriate	proportions requiring intensive care (p=0.23) or ventilatory support (p=0.08) - numbers not reported 7. Need for/Use of feeding support 13 infants (13.1%) in the epinephrine group and 24 infants (25.3%) in the placebo group required oxygen and intravenous feeding. 8. Adverse effects: Not reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			logarithmic transformation to correct for skewness. - Time receiving oxygen analysed as a conditional variable. - One-way analysis of variance was used for a simple comparison between the groups. - Means, treatment differences and CIs back-transformed from log to linear scales, to adjust this comparison the effects of covariates were screened using general linear modelling. Follow-up: Data on readmission to the hospital in the month after discharge collected.		
Full citation Patel,H., Platt,R.W., Pekeles,G.S., Ducharme,F.M., A randomized, controlled	Sample size - 496 infants with bronchiolitis hospitalised.	Interventions Group 1: racemic epinephrine 0.03ml/kg/dose of a 2.25% solution.	Details Setting: Inpatient, admissions from	Results Protocol outcomes Mean±SD	Limitations Based on NICE checklist. Only limitations that arise in the study are reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis, Journal of Pediatrics, 141, 818-824, 2002 Ref Id 207830 Country/ies where the study was carried out Canada Study type Randomised, double-blinded, parallel-group, placebo-controlled trial. Aim of the study In previously well infants hospitalised with acute viral bronchiolitis, the effectiveness of repeated nebulized therapy with epinephrine was compared with treatment with albuterol or saline placebo. Study dates Two successive bronchiolitis winters (mid November to March; 1998-1999 and 1999-2000).	- 149 enrolled: epinephrine 50, albuterol 51, placebo 48. - 10 withdrawals during the study: epinephrine 1, albuterol 4, placebo 5, all were RSV positive. Characteristics Characteristic: Epinephrine, albuterol, placebo n (%) or mean±SD - Males: 28(56); 35(69); 25(52) - Age, months: 4.2±3.1; 3.9±2.9; 4.7±2.9 - Gestational age, weeks: 38.5±1.8; 38.9±1.8; 38.9±1.7 - Family history of asthma in first degree relatives: 16(32); 17(33); 21(44) - Mother smokes: 12(24); 13(25); 13(27) - Mean duration of illness pre-enrollment, days: 5.5±3.7; 4.9±2.6; 4.5±3.1 - RSV positive: 35(78); 40(87); 31(74) - Mean respiratory rate: 52±13; 56±14; 56±15	Group 2: albuterol 0.03ml/kg/dose of a 5mg/ml solution, (Ventolin, GlaxoSmithKline, Mississauga, Ont, Canada). Group 3: placebo 0.03ml/kg/dose of 0.9% sodium chloride. - All study solutions were identically clear, colorless, and odorless. - Equal volumes of medication, dispensed in opaque bottles, were prepared in advance with standard dosing units and were numerically coded. - Nebulizations were administered for 10 to 15 minutes with a small, tight-fitting plastic face mask with an updraft nebulizer with continous flow of 100% oxygen at 6 to 7l/min. - Infants received nebulizations every 1 to 6 hours, with frequency changes made at the discretion of the attending medical care team.	emergency department. Randomisation and conealment: - Computer-generated randomisation within blocks with 6 subjects. - Treatment was allocated in the emergency department by the Department of Pharmacy, with the code for medication allocation held by the study pharmacist who had not contact with the study participants. - All study personnel and participants were blinded to treatment assignment for the duration of the study. Outcome measues: - Assessed twice daily by research team. - Length of hospital stay.	Epinephrine n=50; albuterol n=51; placebo n=48; p value 1. Hospital admission rate: Not reported. 2. Length of hospital stay, hours - Primary analysis by intention-to-treat: 59.8±62; 61.4±54; 63.3±47; 0.95 - Secondary analysis using survivial curves p=0.89 - Secondary analysis with log transformations of the means: 3.75±0.78; 3.80±0.80; 3.86±0.82; 0.79 - Nonparametric comparson of medians (Kruskal-Wallis test): 36.0; 43.9; 51.2; 0.55 - Including only patients with complete follow up: 60.3±63; 53.5±41; 54.7±36; 0.77	Selection bias: - Reasons 149 out of 495 patients were eligible not reported but avaliable online. Attrition bias: - 10 withdrawn during the study (epinephrine=1, salbutamol=4, placebo=5), reasons not provided. - Number completing 7 day telephone follow-up not reported. Detection bias: - Subjective clinical scoring system. - Numbers for adverse effects not reported. - Number of investigators not reported. Other information - Blinded interim analysis between bronchiolitis seasons. - α levels adjusted according to O'Brien-Fleming stopping rules. - An independent data monitoring committee reviewed the blinded results of 149 infants after the second bronchiolitis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported.	- Mean % oxygen saturation in room air: 96±3; 95±3; 96±4 - Median RDAI score (range): 7(1 to 12); 6.5(0 to 16); 7(0 to 14) - Pneumonia on chest radiograph: 14(38); 16(42); 12(29) Inclusion criteria - Aged ≤12 months. - Previously well infants with a clinical diagnosis of acute viral bronchiolitis who were hospitalised because of hemoglobin oxygen saturation of <95% in room air, poor feeding with or without dehydration, lethargy, sustained tachypnea with a respiratory rate of ≥70 breaths/minute, or the gloabl impression of need for admission by the attending emergency department physician. - Bronchiolitis defined as: the first episode of wheezing in an infant and evidence of an acute respiratory infection (coryza or body temperature >38°C rectal or cough).	Additional treatment: - All infants with a hemoglobin oxygen saturation in room air of ≤95% received continuous supplemental humidified oxygen. - Oral or intravenous fluid supplementation was provided by using standard guidelines for the management of dehydration in infants. Discharge criteria: No need for supplmental fluids or oxygen, nebulisations not required more often than every 4 hours, and minimal respiratory distress.	- RDAI (0-17 scale, developed by Lowell et al.). - Time from admission until the infant had normal hydration, oxygenation, minimal respiratory distress and minimal requirement of nebulized medications. Statistical methods: - Sample size calculation: to detect a mean decrease of 24 hours in length of stay between the three treatment groups, α=0.05, power=80%, required 59 patients per group. - Primary analysis according to intention-to-treat. - Mean group difference in continuous vaiables analysed using one-way analysis of vaiance techniques.	3. Change in Respiratory rate: Not reported. 4. Change in disease severity score - Mean time to RDAI≤4, hours: 34.6±34; 45.7±55; 36.8±44; 0.4 - Clinical score after treatment, taken from Gadomski cochrane review: Placebo n=48, 6.17±3 Albuterol n=51, 5.33±2.86 Std mean difference (IV, random) -0.28, 95% CI -0.68 to 0.11 5. Change in O2 saturation - Mean time to normal oxygenation in hours (hemoglobin oxygen saturation of ≥95% in room air): 25.0±37; 33.0±55; 36.6±56; 0.5	season and recommended no further patient recruitment. - Figure 1 provides reasons for excluding patients and patient allocation by treatment group, figure 1 and additional data avaliable by logging onto The Journal of Pediatrics Online www.mosby.com/ipeds Pre-enrollment emergency department therapy: - Received oxygen: 13(26); 12(24); 12(25) - Antibiotic therapy: 9(18); 14(27); 14(29) - Received nebulized albuterol: 35(70); 40(78); 40(83) - Mean number of albuterol nebulizations: 2.9±2.0; 2.6±1.8; 2.6±1.5 - Received nebulized epinephrine: 18(36); 21(41); 18(38) - Mean number epinephrine nebulization: 1.5±0.7; 1.5±0.9; 1.3±0.5 - The mean number of study nebulizations was similar in each treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria - >12 months of age. - Previous history of wheezing or home bronchodilator use. - Directly transferred to an intensive care unit. - Gestational age at birth <34 weeks. - Underlying chronic cardiac or pulmonary disease eg bronchopulmonary dysplasia. - Immunocompromise. - History of immunoprophylaxis therapy (ie RSV immune globulin or RSV monoclonal antibody therapy). - Parents not fluent in either English or French.		- Secondary analysis used Kaplan-Meier survival curves. - Cox-proportional hazards regression to evaluate potential cofounders. - Twice daily measurements evaluated with repreated-measures analysis of variance. - Interobserver reliability for RDAI tested using weighted kappa, ≥0.8 satisfactory. Follow-up: Assessed by standardised telephone interview 7 days after hospital discharge.	- Oxygen saturation taken from Gadomski cochrane review: Placebo n=48, 96.22±3.3 Albuterol n=51, 95.76±4.1 Mean difference (IV, random) 0.46, 95% CI -1.00 to 1.92 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Need for/Use of feeding support Not reported 8. Adverse effects: - Asymptomatic transient (<1 hour) tachycardia, mild hypertension, and slight tremour; these were similar between treatment groups (numbers not reported). - One albuterol infant was transferred to the intensive care	group: epinephrine 12±10; albuterol 12±10; placebo 16±13, p=0.13 - No significant group differences in co-interventions including: concomitant antibiotic therapy, chest physiotherapy, and nasal suctioning. Medical visit in the week post discharge: - Epinephrine 32, albuterol 28, placebo 33. - Reasons: check-up 1, baby not better 5, baby worse 6, unrealted reason 15. - 8 out of 93 visits were to the emergency department: epinephrine 1, albuterol 3, placebo 4. - Three placebo patients re-admitted.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				unit for 48 hours but did not require intubation or mechanical ventilation.	
Full citation Tinsa,F., Ben,Rhouma A., Ghaffari,H., Boussetta,K., Zouari,B., Brini,I., Karboul,L., Souid,M., Bousnina,S., A randomized, controlled trial of nebulized terbutaline for the first acute bronchiolitis in infants less than 12-months-old, Tunisie Medicale, 87, 200-203, 2009 Ref Id 208321 Country/ies where the study was carried out Tunisia Study type Randomised, prospective, double-blinded, placebo-controlled trial. Aim of the study To evaluate the efficacy of nebulised tertbutaline in moderate severity	Sample size - 36 enrolled, one placebo patient excluded from the analysis because of worsening clinical status during the first 24 hours. - 16 terbutaline, 19 placebo. Characteristics Characteristic: terbutaline; placebo; p value Mean±SD or % - Male: 62.5; 47.4; 0.443 - Exposure to smokers: 60; 43.7; 0.253 - Family history of asthma: 37.5; 7.7; 0.369 - Age, months: 6.6±2.02; 5.9±2.3; 0.723 - Respiratory rate (breath/min): 63.5±14.2; 59.5±12.7; 0.275 - Oxygen saturation in room air: 95.8±1.58; 96.5±1.8; 0.884 - RDAI score: 7.5±0.96; 7.4±2.4	Interventions Nebulized terbutaline: 0.06ml/kg in normal saline to make a total volume of 4ml. Saline placebo: 4ml of normal saline solution. - Nebulizations were administered for 10 minutes with small, tight-fitting plastic face masks with an up draft nebulizer with continuous flow of 100% oxygen at 6 to 7l/min. - Infants received another nebulization 30 minutes after the start of the first treatment and every 4 hours during the study period. Additional treatment: All infants with oxygen saturation in room air ≤93% received supplemental oxygen	Details Setting: Pediatric B department of the Children's Hospital of Tunis. Randomisation and concealment: - Computer-generated table of random numbers. - Assessments made by a medical doctor blinded to the solution nebulized. Outcome measures: - Infants assessed when calm and breathing room air for at least 10 minutes, the clinical assessment was repeated 30, 60 and 120 minutes after the start of the first treatment.	Results Protocol outcomes Terbutaline; placebo; p value (Mean±SD) 1. Hospital admission rate: Not reported. 2. Length of hospital stay: - Mean time for discharge was 3.3 days (SD*:1.99) for terbutaline and 2.57 days (SD*: 1.95) for placebo, n=16 and 19 respectively *SD extracted from Gadomski cochrane review - No significant difference between the two groups for the median discharge time, p=0.253. 3. Change in respiratory rate:	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Attrition bias: - One infant excluded from analysis because of worsening clinical status. Performance bias: - Blinding unclear. Other information - Did not seek signed informed consent because nebulized terbutaline is widespread and routinely used in the management practise of acute bronchiolitis by paediatricians in Tunisia in outpatients and inpatients without side effects observed. - Moderate severe bronchiolitis chaacterised

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
bronchiolitis as evidence by improvement in clinical score, oxygen saturation or reduction in duration of hospitalisation. Study dates Two bronchiolitis seasons winters (December 2004 to March 2005 and October 2005 to April 2006). Source of funding Not reported.	Inclusion criteria - Previously well infants between 3 and 12 months of age. - Clinical diagnosis of first acute viral bronchiolitis who required hospitalisation. - Viral bronchiolitis defined as: an acute infection of the lower respiratory trac, preceeded by or accompanied by fever and/or rhinitis, and characterised by expiratory wheezing and increased respiratory effort. Exclusion criteria - Gestational age at birth <34 weeks. - Underlying chronic cardiac or pulmonary disease (eg bronchopulmonary dysplasia, cystic fibrosis). - Concurrent bronchodilator or corticosteriod. - Recurrent wheezing. - Severe respiratory distress as evidence by apnea, heart rate >200 beats per minute, RDAI score >15, respiratory rate >80 breath/minute, profound lethargy. - Duration of illness >15 days.	when not receiving nebulizations. Discharge criteria: No need for supplemental oxygen, RDAI score <4 and adequate fluid intake.	- RDAI score (based on wheezing and retractions, also used by Klassen). - Oxygen saturation. - Length of hospitalisation. Statistical methods: - Sample size calculation not reported. - Parametric t-test or nonparametric Mann and Withney test to compare two means from independent groups. - Wilcoxon test to compare two means from dependent groups. - Chi-squared or Fisher's exact test to compare two proportions from independent groups. - Rank correlation coefficient of Spearman (Rho) to test the correlation between quantitative variables.	- At 30 min 54.2±13.4; 59.8±15.5; 0.26 - At 60 min 54.3±13.5; 56.1±13.3; 0.7 - At 120 min 50.8±12.8; 50±9.6; 0.83 - Respiratory rate decreased significantly with time, placebo p=0.003, terbutaline p=0.049. 4. Change in disease severity score (RDAI): - At 30 min 6.73±2.5; 6.5±0.7; 0.78 - At 60 min 6.05±2.8; 5.5±1; 0.52 - At 120 min 4.7±2.4; 4.6±1.3; 0.94 5. Change in O2 saturation: - At 30 min 96.1±2.1; 95.5±1.8; 0.39 - At 60 min 96.8±1.9; 96±2.04; 0.26 - At 120 min 97.2±1.5; 97±1.3; 0.67	by and RDAI score between and 15.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- Oxygen saturation in room air increased significantly with time in the placebo group, p=0.023. - In the terbutaline group oxygen saturation increased but not significantly, p=0.13. 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Need for/Use of feeding support Not reported 8. Adverse effects: - One placebo patient excluded from analysis and transferred to intensive care. - Adverse effects including tachycardia, flushing and tremor did not occur in either group	
Full citation Khashabi,J., Salari,Lak S., Karamiyar,M., Mussavi,H., Comparison	Sample size - 72 infants with moderately severe bronchiolitis enrolled.	Interventions Epinephrine: Daroo-Pakhsh Tehran, Iran,	Details Setting: Pediatric emergency department of Imam	Results Protocol outcomes	Limitations Based on NICE checklist. Only limitations that arise in the study are reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of the efficacy of nebulized L-epinephrine, salbutamol and normal saline in acute bronchiolitis: A randomized clinical trial, Medical Journal of the Islamic Republic of Iran, 19, 119-125, 2005 Ref Id 261104 Country/ies where the study was carried out Iran Study type Prospective, randomised, double-blinded, placebo-controlled clinical trial. Aim of the study - To examine the efficacy of nebulized epinephrine, salbutamol and normal saline (as a placebo) on clinical scores and oxygenation of patients admitted in an emergency department. - To evaluate the safety and the clinical responses to nebulized L-eprinephrine and salbutamol in infants wit acute bronchiolitis.	- Einephrine 24, salbutamol 24, placebo 24. Characteristics Characteristic: epinephrine; salbutamol; placebo (%) Mean age, months: 8.9; 10.5; 7.9 1-6 months of age: 5; 8; 7 7-12 months of age: 10; 9; 9 13-18 months of age: 4; 3; 6 19-24 months of age: 5; 4; 2 Male: 19 (79.2); 18 (75); 15 (62.5) Female: 5 (20.8); 6 (25); 9 (37.5) Pretest clinical score: 12.4; 13.2; 10.6 Inclusion criteria - 2 to 24 months of age - Clinical diagnosis of virial bronchiolitis defined as: an acute infection of the lower respiratory tract, preceded or accompanied by fever and/or rhinitis and characterised by tachypnea, expiratory wheezing, and increased respiratory effort.	0.1ml/kg body weight of 1 in 10000 solution. Salbutamol: Ventolin, GlaxoWellcom Australia Ltd Boronia, Australia, 0.15mg/kg body weight. Placebo: Normal saline. - Drugs mixed with normal saline to make a total volume of 5ml. - Nebulized with oxygen flow of 8l/min. - All solutions identicaly clear and similar in appearance. - Three doses of each drug were given at 20-minute intervals. - No other drugs like antibiotics or steriods were administered during these periods. Discharge criteria: - Ten minutes after administration of the last dose of the study drugs, the clinical score was evaluated again to determine the response of therapy and decision for further management. - Children who showed a sustained decrease in	hospital, a tertiary medical care facility in Urumieh. Randomisation and concealment: All study personnel and participants were unaware of the treatment assignment. All solutions identically clear and similar appearance. Outcome measures: - Infants assessed before and 10 minutes after each treatment. - Clinical score combining RDAI and Yale observations scale (based on wheezing, retraction, state variation, color and hydration). - Oxygen saturation measured noninvasively by pulse oximetry at the start of the study and ten minutes after the first, second and third doses of the drug.	Epinephrine; salbutamol; placebo; between groups Mean±SD (p value) 1. Hospital admission rate: - 16 out of 24 in epinephrine group (66%), 12 out of 24 in salbutamol (50%) and 6 out of 24 in placebo (25%) showed significant improvement to a degree that they could be sent home. 2. Length of hospital stay: Not reported. 3. Change in Respiratory rate - Before treatment 55.5±9.9 (0.830); 56.4±9.4 (0.830); 53.0±8.5 (0.830); 54.9±9.3 (0.427) - After treatment 37.7±7.7 (<0.00); 44.6±10 (<0.00); 45.8±7.7 (<0.00); 42.7±9.2 (<0.00)	Selection bias: - Inclusion criteria based on subjective clincal scoring system. - Only age, sex and pretest clinical scores reported as patient characteristics. - Number of patient presented to hospital with acute or severe bronchiolitis not reported. - Randomisation method not explained. Performance bias: - One enrollment investigator, number of physicians not reported. - Blinding unclear. Detection bias: - Subjective clincal scoring system. - Statistical methods not explained other than sample size power. Other information - Clinical RDAI score described in table 1.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates October 2002 to May 2003. Source of funding Not reported.	- Moderate total clinical disease score 9-18. Exclusion criteria - Previous history of wheezing. - Bronchodilator therapy before current illness. - Underlying chronic cardiac, pulmonary disease and bronchopulmonary dysplasia. - Patients with mild (0-8) and severe (>19) total clinical scores were excluded and those with severe were admitted in the hospital.	tachypnea and respiratory distress and tolerated oral feeding, were sent home after an observation period of three hours on oral medication. - Children who did not improve or showed deterioration were admitted in the hospital for further management.	- Respiratiry rate. Statistical methods: Sample size calculation: to detect a difference of at least 5% in Sa02 and total clinical score between the 3 drugs, α=0.90, SD=4, requires a sample size of 24 in each arm.	4. Change in disease severity score - Before treatment 12.4±3.4 (0.813); 13.2±3.4 (0.813); 10.6±3.8 (0.813); 12.0±3.7 (0.35) - After treatment 4.9±4 (<0.00); 6.2±4.2 (<0.00); 7.9±5.2 (<0.01); 6.3±4.6 (<0.06) 5. Change in O2 saturation - Before treatment 86.4±4.2 (0.757); 84.3±3.4 (0.757); 86.3±3.3 (0.757); 85.7±3.5 (0.060) - After treatment 91.9±3.5 (<0.00); 90.5±4.4 (<0.00); 88.8±3.9 (<0.10); 89.4±4.2 (<0.28) Oxygen saturation recorded after the third dose of nebulisation showed significant improvement in all study groups, but in the epinephrine group mean oxygen saturation was significantly higher	- Patients were divided into mild, moderate and severe disease, based on the sum of the clinical scores. Children with total scores of 0-8, 9-18 and >19 were classified as having mild, moderate, and severe disease respectively.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				than salbutamol and placebo groups p=0.04 6. Need for high flow humidified oxygen, (CPAP) or mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: - No serious adverse clinical side effects like increased irritability, tremors, facial blanching, congestive heart failure, tachycardia and arrhythmia during the study.	
Full citation Chevallier,B., Aegerter,P., Parat,S., Bidat,E., Renaud,C., Lagardere,B., Controlled trial of nebulized salbutamol in children under 6 months of age with acute bronchiolitis, Archives de Pediatrie, 2, 11-17, 1995	Sample size Salbutamol 16, placebo 17. Characteristics Characteristic: salbutamol; placebo Mean±SD - Male/female: 11/5; 11/6 - Age: 90.3±9.8; 99.9±9.5	Interventions Nebulized salbutamol (0.15 mg/kg/dose) or saline placebo administered using oxygen propellant 3 times at intervals of 1 hour.	Details Setting: Inpatient. Outcome measures: Respiratory rate, oxygen saturation. Statistical methods:	Results Salbutamol; placebo (mean±SD) - Fréquence respiratoire (%) 30 min ↓10.4±1.6; ↓4.7±1.5; p=0.001 150 min ↓20.9±1.5; ↓12.1±1.4; p<0.001	Limitations Randomisation and allocation concealment not described Other information Paper written in French.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 261108 Country/ies where the study was carried out France Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study Study dates 1st November 1992 to 31st January 1993. Source of funding	- Respiratory rate (min): 65.4±8.3; 62.9±10.2 - Oxygen saturation 93.1±1.6; 94.1±1.4 - Isolement du VRS: 13(81%); 13(77%) Inclusion criteria - ≤12 months of age. - Hospitalised with first episode of bronchiolitis. - First time wheezing. Exclusion criteria		Chi-squared test, t-test, Mann-Whitney.	- Saturation en oxygène 30 min ↑1.3±0.2; ↓0.9±0.1; p=NS 150min ↑1.4±0.3; ↓1.1±0.2; p=NS - Oxygen saturation taken from Gadomski cochrane review: 94.4±0.4; 93.2±0.4 Mean difference (IV, random) -1.20, 95% CI -1.47 to -0.93	
Full citation Ho,L., Collis,G., Landau,L.I., Le Souef,P.N., Effect of salbutamol on oxygen saturation in bronchiolitis, Archives of Disease in Childhood, 66, 1061-1064, 1991 Ref Id 210660 Country/ies where the study was carried out Australia Study type	Sample size 21 enrolled: salbutamol 13, saline placebo 8. Characteristics - 11 boys and 10 girls. - Mean age of 3 months, range 3 weeks to 6 months. - Mean weight 5.6kg, range 3 to 6 kg. - 15 breat feed. - 14 had a histroy of parental smoking.	Interventions - Nebulised salbutamol (2.5mh/2ml) or placebo (2ml normal saline). - Continuous Sa02 measurements were made during 30 minutes baseline, 10 minutes of first nebulisation, 30 minutes observation, 10 minutes of second nebulisation, and 30 minutes obervation. - Nebulisations were given using an Airlife jet nebuliser run from a	Details Setting: Inpatient. Randomisation and concealment: Subjects studied using a double-blinded, random allocation, crossover design. Outcome measures: Sa02 measurements were made over 110 minutes before and	Results Protocol outcomes 1. Hospital admission rate Not reported 2. Length of hospital stay Not reported 3. Change in Respiratory rate Not reported 4. Change in disease severity score Not reported 5. Change in O2 saturation	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Characteristics not reported for each treatment group. - Unclear definition of bronchioloitis. - Unclear inclusion criteria. - Randomisation unclear. - Small sample size.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised, double-blinded, crossover trial. Aim of the study To determine the effect of inhaled salbutamol on Sa02. Study dates Not reported. Source of funding Not reported.	- None had a history of asthma in first degree relatives. - Thee of the children were receiving supplemental oxygen. Inclusion criteria - Children admitted with cough and wheeze dut to acute bronchiolitis were entered into the study within five days of admission. - All children had no prior history of respiratory symptoms, the clinical findings of hyperinflation with wheeze and crackles on auscultation, and respiratory syncitial virus isolated by immunoflouresence of a postnasal aspirate. Exclusion criteria Severly ill children and those with associated chronic disabilities.	compressed gas supply with a flow of 6l/minute. - For the three patients on oxygen, the concentration of oxygen was checked with an oxygen analyser, and maintained at the prestudy level using a Bird oxygen blender which could adjust the oxygen mixture and maintain a flow of 6l/minute.	after nebulised salbutamol or placebo. Statistical methods: - Sample size calculation not reported. - The average Sa02 for each minute was determined from the graph using area under the curves for each minute. - The mean Sa02 for baseline was obtained over the first 30 minutes. - The means of the 10 minute nebulisation period and mean of 5 minutes epochs after nebulisation for each patient were taken. - Readings beyond 25 minutes after the second nebulisation could not be analysed due to interference from excessive movement in the majority of patients. - The results of the patients first given	Mean (SD) extracted from Gadomski cochrane review Salbutamol: 95.4 (0.8), n=13 Placebo: 97.6 (0.7), n=8 - For the 13 patients receiving salutmaol first there was a desaturation from mean baseline Sa02 of 96.4 and 96.6 (during nebulisation) to 95.0, 95.0, 95.3, 95.4, and 95.4 at each five minute epoch after nebulisation. Signficant decrease occured five and 10 minutes after salbutamol nebulisation ($p<0.05$). - After saline at the second nebulisation, there was no further desaturation with an Sa02 of 96.1 during nebulisation to 96.2, 96.5, 96.4 and 96.8 after nebulisation. - The eight patients receiving saline first	Performance bias: Blinding unclear. Detection bias: Results presented in figures, not all Sa02 values are reported in the text. Other information Patients acted as their own control.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			salbutamol or saline were analysed with a two way analysis of variance and the significance of change in desaturation from bsaeline determined with Dunnett's q test. - The results of patients given salbutamol as the second nebulising solution were analysed with a one way repreated measure analysis of variance. - No further statistical analysis was performed on patients receiving saline second as there was some persistent effect of salbutamol used as the first nebulising solution. - The periods of maximum desaturation from baseline, the times to reach maximum desaturation and the times taken for recovery to baseline saturation for each	also showed desaturation from baseline Sa02 of 97.2 and 96.8 (during nebulisation) to 96.3, 97.6, 97.5, and 97.5 for each five minute epoch after nebulisation, a significant drop being recorded five minutes after saline nebulisation. - The drop in Sa02 was more noticeable after salbutamol given as the second nebulisation, with Sa02 of 97.4 during nebulisation and levels of 97.0, 95.9, 95.6, and 95.9 for each five minute epoch after nebulisation. Significant drop was seen 10 and 15 minutes after nebulisation ($p<0.05$). - 11 of the 13 patients given salbutamol had a desaturation from baseline after salbutamol. All eight given salbutamol	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			group of patients were studied using a Kruskal-Wallis test. - The difference between groups were analysed with chi-squared or Mann-Whitney non-parametric test where appropriate.	second desaturated after this nebulisation. - The maximum fall in Sa02 from baseline was greater in those who received salbutamol first and those who received salbutamol after saline than those who received saline first. - Although there was no significant difference between groups for the median maximum falls in Sa02 after the first nebulisation, nine of 13 had a maximum fall in Sa02 greater than 4% after salbutamol as the first nebulisation compared with two of eight after saline as the first nebulisation ($p<0.05$). - Four of the eight who had salbutamol as the second nebulisation showed a maximum fall in Sa02 >4%. - Median time ti reach maximal	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				desaturation after the first nebulisation was not significantly different between the salbutamol and saline groups (9-10 minutes and five minutes respectively). - The 11 patients given salbutamol who desaturated took a median of 12 minutes to recover while the other eight patients given saline who desaturated took five minutes to recover. The time taken for patients given salbutamol to recover was significantly longer ($p<0.05$). 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Need for/Use of feeding support Not reported 8. Adverse effects Not reported	
Full citation	Sample size	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Gadomski,A.M., Lichenstein,R., Horton,L., King,J., Keane,V., Permutt,T., Efficacy of albuterol in the management of bronchiolitis, Pediatrics, 93, 907-912, 1994 Ref Id 206894 Country/ies where the study was carried out USA Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study To examine the efficacy and safety of albuterol delivered by two different routes (inhalation and oral adminitstration) with two placebo groups: nebulised saline and oral placebo to aid in defining the effects of albuterol in infants with their first episode of wheezing. Study dates	- 93 enrolled. - 5 withdrawn before completion of the trial, two from the albuterol nebulization group and one from each of the other groups. Reasons for withdrawal (one infant per group) include loss of outcome data for three patients, and use of oxygen to drive nebulisation in one case. One infant from albuterol nebulisation withdrawn due to oxygen desaturation. - 88 completed, 13 were included in the pilot study in which they only received one treatment and were assessed at 30 minutes: 22 nebulized albuterol group, 23 nebulized saline group, 19 oral albuterol group, 24 oral placebo group. - 66 completed evaluations at 30 and 60 minutes after treatment: 21 nebulized albuterol group, 18 nebulized saline group, 15 oral albuterol group, 22 oral placebo group.	- Respiratory saline (0.9%, Addipak Co, Respiratory Care Inc, Arlington Heights, IL), the vechicle for albuterol nebulization, was the nebulized placebo. - 3ml saline added to the medication before nebulization, delivered using compressed air at 6l/min via Up-mist nebulizer with a pediatric face mask. - Oral placebo (oral rehydration solution, Ricelyte) was the same color as the oral bronchodilator. - Dosage was based on weight (0.15mg/kg per dose for nebulization and oral medicines), except for infants who weighed ≤7kg, who received a unit dose of 1mg of albuterol solution for inhalation (5mg/ml) to correct for lack of air entertainment during aerosol delivery, or an oral dose of 2.5ml (1mg). - Nebulized groups received two treatments 30 minutes apart, the	Setting: - Pediatric emeergency department (or the pediatric ambulatory clinic) and outpatient clinic at University of Mayland, Baltimore. - The same equipment, medications, and standardisation of clinical scoring were used at both sites. - Decision to hospitalise was made after the study was completed. Randomisation and concealment: - Randomisation list derived using the Moses-Oakford algorithm and a table of random numbers. - Block randomisation (blocks of 8) was used to ensure equal distribution of patients in the four groups. - Nursing staff prepared and	Protocol outcomes 1. Hospital admission rate (nebulized albuterol; nebulized saline; oral placebo): 3/21 (14%); 2/18 (11%); 4/22 (18%) 2. Length of hospital stay: Not reported. 3. Change in Respiratory rate (nebulized albuterol; nebulized saline; oral placebo): Mean±SD - Change at 30 min -11±10; -5±10; -9±11 - Change at 60 min -11±9; -6±13; -12±13 4. Change in disease severity score (nebulized albuterol; nebulized saline; oral placebo): Mean±SD - Change at 30 min -2±5; -4±3; -2±2 - Change at 60 min -5±5; -4±4; -3±3	Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: Number of patients presented to hospital with bronchiolitis who did not meet the inclusion criteria not reported. Attrition bias: - 75 (85%) patients had nasopharyngeal aspirate cultures performed. - 66 out of 75 patients completed assessment at 60 minutes. Performance bias: - 13 infants included from the pilot study only received one treatment. - Infants whose condition did not improve were given additional albuterol nebulization. - Number of nursing staff/investigators not reported. - Blinding unclear. Detection bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
February 1990 to December 1992. Source of funding Funded in part by Glaxo, Inc. Acknowledged the support of Nellcor, Inc who provided a pulse oximeter for this study.	Characteristics Characteristic: nebulized albuterol; nebulized saline; oral placebo - Mean age, months: 5.6; 5.8; 5.3 - Median age, months: 5.5; 5.0; 4.5 - Gestation age 32-37 week: 4; 5; 4 - Male (%): 45; 56; 62 - RSV positive, n (%=number positive/number tested): 11 (55); 10 (53); 8 (38) - Received acteminophen in triage or at home: 4; 6; 5 - Smoker at home, n (%): 19 (86); 13 (56); 9 (79) - Family history asthma, n (%): 8 (35); 10 (43); 14 (58) - Mean days wheezing before study: 2.4; 2.0; 2.1 Inclusion criteria - Infants included if they fit the clinical definition of bronchiolitis: an acute infection of the lower respiratory tract, preceded by or accompanied by fever and/or rhinitis, and characterised by tachypnea, expiratory wheezing, and increased respiratory effort.	oral treatment groups received one treatment. - If clinical condition worsened or did not improve after 60 minutes, they received an open label albuterol nebulization. - The decision to give additional treatment was made before the code was broken.	administered treatments indicated on the randomisation list behind closed doors so that the pediatricians remained unaware of the treatment as well as the route of administration. Outcome measures: - A checklist of potential adverse reactions was completed after the 30 and 60 minute assessments. - Clinical score (based on grunting, nasal flaring, supraclavicular retractions, intercostal retractions, air entry, air hunger, duration of wheeze in respiratory cycle, location of wheezes, general appearance). - Respiratory rate (RR). - State of child (asleep, feeding, awake and quiet, or	5. Change in O2 saturation (nebulized albuterol; nebulized saline; oral placebo): Mean±SD - Change at 30 min -0.2±2; -0.3±3; -0.1±3 - Change at 60 min 0.1±2; 0.1±2; 0.1±2 6. Need for CPAP/mechanical ventilation: Not reported 7. Need for/Use of feeding support (tube feeding, IV fluids): Not repoted. Need for additional treatment (nebulized albuterol; nebulized saline; oral placebo): 7/21 (33%); 8/18 (44%); 12/22 (54%) 8. Adverse effects: - A 1-month-old was withdrawn from the study due to oxygen desaturation both before (Sp02 88%) and after (Sp02 77%) receiving albuterol nebulization, this was the only withdrawn	- Subjective clincal scoring system. - 60 minutes may be too short a follow-up. - Decisions regarding hospital admissions not blinded. Other information - Severity of illness scoring system described in table 1. - Group means for all outcomes 30 and 60 minutes after treatment also reported (table 4). - 75 (85%) patients had nasopharyngeal aspirate cultures performed, 36 (48%) positive for RSV. - Oral albuterol group contained one child positive for cytomegalovirus. - Nebulized albuterol group contained two children positive for adenovirus. - Stratifying analysis of variance by age <6 months versus age ≥6 months does not reveal any significant differences in change in RR, scoring, or Sp02.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- 0 to 15 months of age. - First episode of wheezing. Exclusion criteria - Previously used a bronchodilator. - Been incubated and received mechanical ventilation. - Chronic diseases of the cardiorespiratory system(congenital heart disease, cystic fibrosis, bronchopulmonary dysplasia, etc.). - Severly ill infants (heart rate >200 beats per minute, repiratory rate >100 breaths per minute, and apathy/lethargy or otherwise depressed sensorium suggestive of incipient respiratory failure or sepsis were also excluded).		awake and active) for each RR assessment. - Oxygen saturation (Sp02). Statistical methods: - Pilot study results included in the analysis because no major design changes made. - ANOVA. - Variances checked for homogeneity using Cochran's C, Bartlett-Box F tests. - Pearson correlation coefficients for potential covariates and outcomes were calculated. Sample size calculation: - Clinically significant decrease in RR of 10 breaths per minute: albuterol groups: power=96% at 30 minutes power=89% at 60 minutes	infant who required hospitalisation. - Flushing of the face at 60 minutes nebulized albuterol group (3/19), none in the other groups - Hyperactivity nebulized albuterol group 2/19, - More coughing nebulized saline group 1/18 at 30 minutes oral placebo group 1/22 at 60 minutes - Tremor oral placebo group 1/22 at 60 minutes	- Clinical score powers also reported. - Requiring additional nebulization: nebulized albuterol 32%, nebulized saline 35%, oral placebo 50%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			α=0.05, SD=10, n=19 - Clinically significant change in Sp02 of 2%: power=86% at 30 minutes power=75% at 60 minutes α=0.05, SD=2.4, n=19		
Full citation Goh,A., Chay,O.M., Foo,A.L., Ong,E.K., Efficacy of bronchodilators in the treatment of bronchiolitis, Singapore Medical Journal, 38, 326-328, 1997 Ref Id 210658 Country/ies where the study was carried out Singapore Study type Randomised controlled trial. Aim of the study	Sample size - 99 admitted for bronchiolitis. - 89 analysed, 10 excluded (4 past history of wheeze, 2 misdiagnosed, 4 incomplete data). - Normal saline 29, salbutamol 30, ipratropium bromide 30, humidified oxygen 31 completed at a later date. Characteristics Characteristic: normal saline; salbutamol; ipratropium bromide; humidified oxygen (Mean±SD) - Male/female: 20/9; 24/6; 20/10; 22/8	Interventions Group 1 - salbutamol (2.5mg/ml). Group 2 - ipratropium bromide (250µg/ml). Group 3 - normal saline as placebo. Group 4 - humidified oxygen. - All treatments administered over 10 to 15 minutes by face mask driven by oxygen at a flow rate of 6-8l/min. - ≤6 months of age given 0.6ml of the solution made up of 2mls with normal saline for nebulisation.	Details Setting: Paediatric Department, Tan Tock Seng Hospital Randomisation and concealment: - Randomisation method not described. - Physicians unaware of the contents of the nebulising solutions. - The patients were assessed by selected study personnel who were blinded to the treatment allocation.	Results Protocol outcomes Normal saline; salbutamol; ipratropium bromide; humidified oxygen 1. Hospital admission rate: Not reported. 2. Length of hospital stay, days (mean): - age >6 months 4.4; 4.3; 3.9; 4.1 - age <6 months 4.7; 4.3; 3.9; 4.3 SDs or summary measure not reported	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: Number of patients presented to the hospital with bronchiolitis who did not meet the inclusion criteria not reported. Randomisation and concealment of allocation not described Performance bias: - Only attending physician making clinical observations blinded. - Humidified oxygen group completed at a later date.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine the efficacy of inhaled bronchodilators in children admitted with bronchiolitis. Study dates August 1992 to July 1993. Source of funding Not reported.	- Age, months: 7.4±0.89; 5.7±0.77; 5.2±0.67; 5.9±0.71 - Family history of asthma: 6; 4; 7; 8 - Family history of atopy: 6; 4; 7; 8 - Positive RSV isolation: 12; 15; 10; 14 - Oxygen saturation: 94.5±2.1; 94.2±2.8; 94.7±2.0; 94.5±2.2 Inclusion criteria - Admitted with signs/symptoms consistent with clinical diagnosis of bronchiolitis such as tachypnoea, crepitations and wheeze. - No past history of previous wheeze. - <2 years of age. Exclusion criteria - Congenital heart disease. - Immunocompromised patients. - Requiring mechanical ventilation.	- Nebulisations given at 4 to 6 hourly intervals. - Solutions dispensed to the ward by the pharmacy in 2mls aliquots.	Outcome measures: - Severity score (based on respiratory rate, presence of subcostal retractions, crepitations and wheeze, and the need for oxygen nebulisation or intravenous infusion). - Oxygen saturation. - Respiratory rate. - Duration of hospitalisation. Statistical methods: - Sample size calculation not reported. - Severity scores analysed using Kruskal-Wallis.	3. Change in Respiratory rate: Not reported. 4. Change in disease severity score (Mean±SD): - On arrival 7.0±1.8; 6.5±1.7; 6.4±1.7; 6.8±1.8 - Day 1 8.0±2.5; 7.5±2.1; 7.3±1.9; 7.6±2.2 - Day 2 4.4±2.4; 4.7±2.2; 4.6±1.9; 4.6±2.2 - Day 3 3.1±1.8; 3.0±1.5; 3.4±1.8; 3.2±1.6 5. Change in O2 saturation: Not reported. 6. Need for CPAP/mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects:	Detection bias: - Oxygen saturation and respiratory rates measured but values incorporated into the severity score and not reported separately. - Subjective clinical scoring system. - Oxygen saturation not included in the severity score due to shortage of oximeters. - Statistical methods unclear. - 10 subjects excluded for various reasons: unclear which group Other information - Clinical scoring system described in table 1. - Fourth study arm (humidified oxygen) from November 1993 to April 1994 included because nebulising normal saline may not be an adequate control group.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- Parainfluenzae virus was isolated in 4 patients.	
Full citation Lines,D.R., Kattampallil,J.S., Liston,P., Efficacy of nebulised salbutamol in bronchiolitis, Pediatric Reviews and Communications, 5, 121-129, 1990 Ref Id 261155 Country/ies where the study was carried out Australia Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study To see if there was an objective clinical improvement with nebulised salbutamol in children <18 months suffering bronchiolitis within hours of admission to hospital. Study dates March to July 1989.	Sample size - 50 enrolled, one excluded because of bronchopulmonary dysplasia. - 49 completed: 26 salbutamol, 23 saline. - Parents of a further 20 patients who met the inclusion criteria did not give consent. - Inspection of all admissions revealed another 11 potentially suitable patients who were not notified to the experimenters. Characteristics Characteristic: salbutamol; control Mean±SD - Male/female: 19/7; 17/6 - Age, months: 6.8±6; 5.5±6 - Respiratory rate: 54.0±11.9; 53.2±13.4 - Oxygen saturation: 96.5±1.9; 96.7±1.9 - 10 out of 15 salbutamol group patients and 10 of 17	Interventions - Each nebuliser contained either 0.2ml salbutamol (5mg/ml) or 0.2ml saline in 4ml of physicological saline given over 10 minutes with oxygen at 8l/minute through a Hudson mask. - A second mask of the same solution was given 2 hours later.	Details Setting: Flinders Medical centre. Randomisation and concealment: - Patients were randomly allocated to receive salbutamol or saline labelled solution A or B. - New solutions labelled X or Y were introduced halfway through the trial to avoid bias in the observes. - All statistics calculated blind with only knowledge which of A or B corresponded to X or Y. Outcomes measures: - Wheezing (0-8 scale described by Lowell et al.).	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay: Not reported. 3. Change in respiratory rate: - Respiratory rates for both groups, did not show differences at 30, 120, 150 and 240 minutes. - Percentage of baseline rate also did not show a significant difference at these times. - At 240 minutes the respiratory rate in the salbutamol group had decreased by 13.8% compared to 11.3% in the placebo group.	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Unclear inclusion criteria and definition of bronchiolitis. - Randomisation unclear. - 11 potentially eligible patients missed by experimenters. Attrition bias: 15 of 26 salbutamol group patients and 17 of 23 placebo patients had nasophatyngeal aspirates tested. Performance bias: Blinding unclear. Detection bias: - Results reported in figures, outcomes measures not reported seprately.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported.	placebo group patients were positive for RSV. Inclusion criteria - <18 months of age. - Admitted to hospital with bronchiolitis. Exclusion criteria - Pulse rate >200. - Respiratory rate >80. - ≥5% dehydration. - Anoxia requring continuous oxygen. - Bronchopulmonary dysplasia or other prior cardopulmonary disease.		- Retractions (0-9 scale described by Lowell et al.). - Pulse rate per minute. - Respiratory rate per minute. - Oxygen saturation. - RACS score (based on wheezing, retractions and respiratory rate, used by Lowell et al.). - Assessment immediately before the first nebuliser and then at 10 minute intervals for 1 hour. - Assessment immediately before the second nebulisation and at 10 minute intervals afterwards for an hour. - The observer for any one child remained constant. Statistical methods: - Sample size calculation not reported.	Numbers and overall summary measure not reported 4. Change in disease severity score: - No statstical difference was found at 30 or 150 minutes. - When improvers (≥4 RACS units) were compared to non-improvers (<4 units) at 30 and 150 minutes, the numbers in each group were not statistically different. - No improvement in clinical score, taken from Gadomski cochrance review Placebo 19 out of 23 Salbutamol 4 out of 26 Odds ratio (M-H, random) 0.04, 95% CI 0.01 to 0.17 5. Change in O2 saturation: - Lower values were obtained in the salbutamol group between 10 and 50 minutes after the salbutamol masks,	- Subjective clincal scoring system. Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- The wheezing change score and retraction change score calculated by subtracting the later assessment from baseline. - All variables were examined statistically 20 minutes after the end of the masks ie at 30 and 150 minutes. - Non parametric data: Fischers exact test. - Parametric: two tailed t-test.	this did not achieve significance. - Overall readings were simialr, over the four hours the placebo group had a mean of 96.06 and the salbutamol group had a mean of 95.63. - The Wilcoxon matched pairs rank test found the fall in oximetry for those patients given salbutamol was significant for all points (except 20 minutes) during the first hour. - No significant changes were found after the second mask except at 30 minutes when the oximetry fall was significant for those given salbutamol at the 5% level no significant falls in oximetry occured in the placebo group at any time. - Oxygen saturation, taken from Gadomski cochrane review Placebo 95.6±2 Salbutamol 95.8±1.9	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean difference (IV, random) -0.20, 95% CI -1.30 to 0.90 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: Not reported.	
Full citation Lines,D.R., Bates,M.L., Rechtman,A.R., Sammartino,L.P., Efficacy of nebulised ipratropium bromide in acute bronchiolitis, Pediatric Reviews and Communications, 6, 161-167, 1992 Ref Id 261156 Country/ies where the study was carried out Australia Study type	Sample size - 43 met inclusion criteria. - 12 out of 43 were not given consent to participate. - 31 enrolled: 17 ipratropium bromide, 14 saline. Characteristics Not reported. Inclusion criteria - <18 months of age. - Admitted with a clinical diagnosis of acute bronchiolitis.	Interventions - Patients received nebulised ipratropium bromide 1ml(250µg) in 4ml saline or 5ml of saline alone. - A second dose of the same solution was given at 2 hours. - Nebulisers driven with 100% oxygen.	Details Setting: Flinders Medical Centre. Randomisation and concealment: - The labelling of the active and placebo solution (A or B, C or D, E or F) was changed at intervals thoughout the study. Outcome measures: - Clinical assessment was	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay: Not reported. 3. Change in respiratory rate: - Decreases in respiratory rates were similar in both groups.	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Inspection of admissions revealed 3 potentially suitable patients who were not referred to the investogators and a further 8 patients who were not included since the investigators were unavaliable. - Patient characteristics not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised, double-blinded, placebo-controlled trial. Aim of the study To examine the effect of ipratropium bromide in the acutely ill bronchiolitic infants by double blind clinical assessment. Study dates 1990 autumn-winter epidemic. Source of funding Not reported.	Exclusion criteria - Pulse rate >200. - Respiratory rate ≥80. - Significant dehydration. - Anoxia requiring continuous oxygen. - Preexisting cardiopulmonary disease.		conducted immediately before the first nebulised solution and then every 10 minutes for 1 hour. Clinical assessments immedately before the second dose at 2 hours and at 10 minute intervals for the next hour. A finial assessment was conducted at 4 hours. - Wheezing on an 8 point scale by Lowell et al. - Retractions as described by Lowell et al. - Pulse rate. - Respiratory rate. - Arterial oxygen saturation measured by pulse oximetry. - RACS score (based on wheezing, retractions and respiratory rate, used by Lowell et al.). Statistical methods:	- Follow-up data obtained by the inspection of case notes showed that saline patients were slower to reach the respiratory rates for age, this did not achieve signficance which may be a type 2 error as the SDs were high. 4. Change in disease severity score - Both treatments were associated with an increase in the RACS score with those receiving ipratropum bromide making the cut off point of 4 units. - The saline treated patients only achieved a 3 point rise and this "natural" improvement was significantly less than in the treatment group. - No improvement in clinical score, taken from Gadomski cochrane review: Placebo 7 out of 14	- Unclear inclusion criteria and definition of bronchiolitis. - Randomisation unclear. Detection bias: - Length of follow-up for case notes not reported. - Subjective clinical scoring system. - Results presented in figures, the outcome measures are not reported separately. Performance bias: - Blinding unclear. - 4 hours appropriate length of follow-up? Attrition bias: Number of case notes analysed not reported. Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Sample size calculation not reported. - To assess change, scores obtained from a later assessment were subtracted from an earlier one. - All statistics calculated double blind with only the knowledge whcih of A or B corresponds to C or D etc. - Nonparametiric data: Mann-Whitney U test and Wilcoxon matched-pairs signed-ranks test. - Parametric data: two tailed t-test. - RACS improvement defined as >4 positive change units, no improvement defined as <4 positive change units.	Ipratropium bromide 5 out of 17 Odds ratio, (M-H random) 0.42, 95% CI 0.09 to 1.83 5. Change in O2 saturation: - Mean oxyggen saturation greater for infants treated with ipratropium bromide than saline, p<0.05. - Improvement over time in the ipratropium bromide patients was significantly greater, p<0.025. - Oxygen saturation (end-point mean±SD), taken from Gadomski cochrane review: Placebo 93±0.4, n=14 Ipratropium bromide 94±0.6, n=17 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				7. Need for/Use of feeding support: Not reported. 8. Adverse effects: None found.	
Full citation Karadag,B., Ceran,O., Guven,G., Dursun,E., Ipek,I.O., Karakoc,F., Ersu,R.H., Bozaykut,A., Inan,S., Dagli,E., Efficacy of salbutamol and ipratropium bromide in the management of acute bronchiolitis--a clinical trial, Respiration, 76, 283-287, 2008 Ref Id 211694 Country/ies where the study was carried out Turkey Study type Prospective, double-blinded, placebo-controlled trial. Aim of the study To investigate the efficacy of ipratropium bromide and salbutamol in the treatment of	Sample size - 70 infants hospitalised, 1 withdrawn from ipratropium bromide. - 69 completed: albutamol group 24, ipratropium bromide group 22, placebo group 23. Characteristics Characteristic: ipratropium group; salbutamol group; placebo group; p value Mean±SD or n(%) - Male: 13 (59); 14 (58.3); 13 (56.5); >0.05 - Family histroy of atopy: 8 (38); 8 (33.3); 10 (39.1); >0.05 - Age, months: 5.1±3.2; 5.8±1.8; 4.9±3.1; >0.05 - Duration of symptoms, days: 3.5±1.6; 3.1±2.0; 4.0±2.1; >0.05 Inclusion criteria	Interventions Salbutamol group: Nebulized salbutamol solution (Ventolin, Glaxo, Uxbridge, UK) 2.5ml (2.5mg) plus saline solution 90.9%) 2.5ml every 6 hours. Ipratropium bromide group: Ipratropium bromide (Atrovent, Boehringer Ingelheim, Germany) 250µg/2ml plus 3ml saline solution every 6 hours. Placebo group: 5ml normal saline every 6 hours. - Medications nebulized via a Portaneb compressor with oxygen flow of 6-7l/min with a tight fitting face mask.	Details Setting: Pediatric inpatient. Randomisation and concealment: - One of the investigators was in charge if randomisation which was applied according to a random number table. - Groups were coded and the allocation transferred to sequentially numbered envelopes. - No stratification was used. - The allocation was concealed from the physician of the patient who carried	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay, days (Mean±SD): Overall 2.5±1.4, range 1-7 Active treatment* 2.5±1.5 Placebo 2.4±1.2 p=0.85 *The study itself has reported results for this outcome for all active treatment arms (salbutamol and ipratropium bromide) together. The Gadomski cochrane review has reported data	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: Number of patients presented to hospital with bronchiolitis who did not meet the inclusion criteria not reported. Detection bias: - Outcome values not reported separatley for each treatment group. - The treatment groups (salbutamol and ipratropium) are combined and compared against placebo. - Subjective clinical scoring system. Attrition bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
patients with moderate-severe bronchiolitis. Study dates November 1998 to February 2000. Source of funding Supported by a research grant from the Marmara University.	- Bronchiolitis defined as: the first episode of wheezing associated with low-grade fever, rhinitis, cough, tachypnea and respiratory distress in a previously healthy infant during the winter months. - Based on clinical grounds and not dependent on viral etiology. - <1 year of age. - First episode of wheezing. - Acute onset of respiratory distress. - X-ray of the chest compatible with bronchiolitis. Exclusion criteria - Prematurity. - Chronic neurological or cardiopulmonary disease. - Previous treatment with bronchodilators or corticosteriods. - <4 weeks of age. - Ventilation during the neonatal period. - The presence of symptoms >7 days. - Presence of fever >38.5ºC - Mild bronchiolitis (a total clincal score <6).	- Patients discharged with a clinical score <4. - Investigators can withdraw patients from the study if any side effects or poor response to treatment (increase in clinical score of 2 points).	out the assessment throughout the study. - A nurse who was not responsible for the administration of medications to the patients assigned placebo or treatment medications to numbered containers. Outcome measures: - Changes in oxygen saturation. - Duration of hospitalisation. - Clinical score (based on respiratory rate, wheezing, accessory muscle use and general condition), also used by Wang et al. - Recorded at baseline, 0.5, 8 and 24 hours after admission and daily thereafter while the infant was quiet. Statistical methods: - Sample size calculation: to detect	separately for each treatment arm and so this data has been extracted. Ipratropium bromide: 2.91 ± 1.65, n=22; Placebo: 2.48 ±1.2, n=11, MD(95%CI): 0.43 (-0.56 to 1.42) Salbutamol: 2.17 ± 1.2, n=24, n=24; Placebo: 2.48 ± 1.2, n=12, MD(95%CI): -0.31 (-1.14 to 0.52) 3. Change in Respiratory rate: - Significant decreases in all groups p<0.001 - Significantly different changes between the groups at 24 hours, p=0.02 in each case. - Numbers not reported 4. Change in disease severity score: p values between treatments at 30 min	Patient withdrawn from ipratropium bromide group because of worsening condition. Other information - Figure 1 illustrates the clinical scores. - Figure 2 illustrates the oxygen saturation measurements.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			a clinical score difference of 2 points: power=90%, n=22, p<0.05 - To compare parameters: two tailet t-test, one-way ANOVA, chi-squared test. - To compare clinical scores: Kruskal-Wallis one-way ANOVA, Wilcoxon signed-rank test. - Non-parametric data: Pearson's chi-squared, Fisher's exact test or Mann-Whitney U test.	ipratropium V placebo p=0.001 salbutamol V placebo p=0.04 salbutamol V ipratropium p>0.05 treatment V placebo p<0.001] p values between treatments at 8 hours ipratropium V placebo p=0.001 salbutamol V placebo p=0.0001 salbutamol V ipratropium p>0.05 treatment V placebo p<0.0001 p values between treatments at 24 hours ipratropium V placebo p>0.05 salbutamol V placebo p=0.002 salbutamol V ipratropium p>0.05 treatment V placebo p=0.006 30 min (Mean±SD) - active treatment	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				7.5±0.8 95% CI 7.2 to 7.8 - placebo treatment 8.4±1.3 95% CI 8.0 to 8.9 8 hours (Mean±SD) - active treatment 5.9±1.1 95% CI 5.5 to 6.2 - placebo treatment 7.3±1.2 95% CI 7.0 to 7.9 24 hours (Mean±SD) - active treatment 4.5±1.6 95% CI 4.0 to 4.9 - placebo treatment 5.3±1.4 95% CI 5.0 to 6.2 *The above data presented for clinical score includes data for both active treatment arms together (as reported in the study itself). Data for each separate arm was available in the Gadomski cochrane review and so has been extracted from	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				here: Average clinical score after treatment, mean (SD) Ipratropium bromide: 4.9 (1.8), n=22 Placebo: 5.3 (1.4), n=11 SMD (95%CI): -0.23 (-0.96 to 0.49) Salbutamol: 4.1 (1.4), n=24 Placebo: 5.3 (1.4), n=12 SMD (95%CI): -0.84 (-1.56 to -0.12) 5. Change in O2 saturation: p values between treatments at 8 hours ipratropium V placebo p=0.005 salbutamol V placebo p=0.0001 salbutamol V ipratropium p>0.05 treatment V placebo p<0.0001 p values between treatments at 24 hours	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				ipratropium V placebo p=0.05 salbutamol V placebo p=0.001 salbutamol V ipratropium p>0.05 treatment V placebo p<0.0001 8 hours (Mean±SD) - active treatment 94.3±4.4 95% CI 93.0 to 95.6 - placebo treatment 89.6±2.4 95% CI 88.2 to 90.2 24 hours (Mean±SD) -active treatment 95.9±4.4 95% CI 94.6 to 97.2 p<0.0001 At 30 min no signifcant difference amongst the groups. *The study itself has reported results for this outcome for all active treatment arms (salbutamol and ipratropium bromide) together.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				The Gadomski cochrane review has reported data separately for each treatment arm and so this data has been extracted. Ipratropium bromide: 93.8 (4), n=22 Placebo: 92.2 (2.6), n=11 Salbutamol: 96.7 (4.1), n=24 Placebo: 92.2 (2.6), n=12 6. Need for CPAP/mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: - 1 patient in the ipratropium bromide group was withdrawn because of deteriorating clinical status. - No side effects found.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Anil,A.B., Anil,M., Saglam,A.B., Cetin,N., Bal,A., Aksu,N., High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis, Pediatric Pulmonology, 45, 41-47, 2010 Ref Id 206284 Country/ies where the study was carried out Turkey. Study type Prospective, randomised, double-blinded, placebo-controlled trial. Aim of the study To compare the effectiveness of nebulized albuterol, epinephrine, 3% hypertonic saline and high volume normal saline (0.9%NaCl) among children presenting to the emergency department with mild acute	Sample size - 190 assessed for eligibility. - 4 not enrolled: 2 protcol deviations and 2 parents refused consent. - 186 randomised: 38 group 1, 39 group 2, 36 group 3, 36 group 4, 36 group 4, 37 group 5. Characteristics Characterisitc: group 1; 2; 3; 4; 5; p value Mean±SD or n(%) - Age, months: 10.4±5.7; 9.4±5.0; 9.0±6.2; 9.7±6.2; 9.1±4.4; 0.86 - Male: 26(68.4); 29(74.3); 20(55.5); 23(63.8); 22(59.4); 0.06 - Family history of atopy: 17(44.7); 15(38.4); 12(33.3); 12(33.3); 13(35.1); 0.50 - Parental smoking: 21(55.2); 20(51.2); 17(47.2); 16(44.4); 12(32.4); 0.76 - Duration of illness, days: 2.2±0.1; 2.0±0.2; 2.6±0.1; 2.5±0.7; 2.2±0.4; 0.12 Inclusion criteria - Between 6 weeks and 24 months of age. - Presented to the emergency department with	Interventions Additional treatment: - Stabalised with antypyretics if necessary (temperature >38ºC) and/or nasal suction if the nose was blocked. - Facial oxygen was removed if Sa02 >90% in room air, if not, it was provided to maintain Sa02 at 90-92%. - This situation was maintained for at least 30 minutes before the patients received any study treatment and was unaltered throughout the study. Group 1: Inhalation of epinephrine, 1.5mg, diluted to 4ml with 0.9% saline solution. Group 2: Inhalation of epinephrine, 1.5mg, diluted to 4ml with 3% saline solution. Group 3: Inhalation of salbutamol (Ventolin® GlaxoSmithKline, Middlesex) 2.5mg diluted to 4ml with 0.9% saline solution.	Details Setting: Emergency department of the Tepecik Teaching and Research Hospital. Randomisation and concealment: - A random number table generated by a computer was used by the study coordinator to allocate patients to treatment groups. - The study coordinator was the only person with access to the randomisation. - The identity of the study solutions was blinded to all participants, care providers and investigators, identical in appearance and colour Outcome measure: - Assessments made prior to each drug administration	Results Protocol outcomes Group 1; 2; 3; 4; 5; p value Mean±SD (range) 1. Hospital admission rate: - One patient in group 2 and one patient from group 3 were admitted to hospital for further treatment, p=0.89. - Readmission in 2 days: 7 (18.4%); 5 (13.1%); 4 (11.4%); 6 (16.6%); 6 (16.2%); p>0.05. - Reasons for medical visit within 2 days post-discharge: child no better 12, child worse 16. - Six of the medical visits were to the emergency department: 2; 1; 1; 1; 1. - One child from group 5 was readmitted. 2. Length of hospital stay:	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Performance bias: - Discharge criteria not described. - Additional treatments. Detection bias: - Subjective clinical scoring system. - Respiratory rate measured but not reported separately. Other information Clinical severity score described in table 1.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
bronchiolitis, measured by the changes of clinical severity score and room air oxygen saturation. Study dates November 1, 2005 to March 31, 2006. Source of funding Not reported.	a first episode of bronchiolitis. - Bronchiolitis defined as: symptoms of upper respiratory infection and the presence of bilateral wheezing and/or crackles on auscultation. - Clincal severity score between 1 and 9. Exclusion criteria - Prematurity. - Any underlying disease (e.g. cystic fibrosis, bronchopulmonary dysplasia and cardiac or renal disease). - Proir history of wheezing. - Atopic dermatitis. - Allergic rhinitis or asthma. - Sa02 <85% in room air. - Clinical severity score >9. - Obtunded conciousness. - Progressive respiratory failure requiring mechanical ventilation. - Previous treatment with bronchioldilators. - Any steriod treatment within 2 weeks. - Patients were excluded from the study if the administration of the study	Group 4: Inhalation of salbutamol 2.5mg diluted to 4ml with 3% saline solution. Group 5: Inhalation of 4ml 0.9% saline solution. - Study solutions were identical in appearance and odor. - Administered at 0 and 30 min by Medic-Aid Sidestream nebulizer using a face mask with continuous flow of 100% oxygen at 6l/min. Discharge: - At the end of the period, the attending pediatrician determined the need for admission based on assessment of the children's condition. - Discharge medications and instructions were determined by the attending physician.	and at 60 and 120 minutes by three investigators. - Clinical severity score (based on respiratory rate, wheezing, retraction and general condition, also used by Wang et al.). - Readmission in 2 days. - Oxygen saturation. Statistical methods: - Sample size calculation: to detect a difference in 1 unit of the clinical severity score, α=0.05, power=80%, requires 150 patients (30 per group). - Interobserver agreeement for the clinical severity scores tested by using the kappa statistic, ≥0.8 satisfactory. - Continuous variables compared between groups using one-way	Not reported. 3. Change in respiratory rate: Not reported. 4. Change in disease severity score, mean ±SD (range): - 0 min: 4.1±1.2 (2-7); 3.8±1.1 (2-9); 3.5±0.9 (2-7); 4.1±0.8 (2-6); 3.6±1.0 (2-6); 0.24 - 30 min: 3.1±0.9 (1-5); 2.9±1.2 (1-8); 2.6±1.2 (1-5); 3.2±1.0 (1-6); 2.7±1.0 (1-5); 0.06 - 60 min: 2.3±1.1 (0-4); 2.3±1.4 (0-8); 2.2±1.1 (0-5); 2.4±1.0 (0-5); 2.1±1.2 (0-4); 0.84 - 120 min: 1.6±1.2 (0-4); 2.2±1.4 (0-8); 1.5±1.4 (0-5); 2.3±0.9 (1-4); 1.8±1.4 (0-4); 0.10 5. Change in O2 saturation, mean ±SD (range): - 0 min: 98.1±1.5 (94-100); 97.4±1.7 (92-100); 97.8±1.4 (92-100); 97.8±1.4 (92-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	drug was delayed by ≥10 minutes or if clinical deterioration mandated escalation of therapy and/or support.		analysis of variance (ANOVA). - Dichotomous events: chi-squared test. - Dependent variables: paired sample t-test. Follow-up: - The investigators contacted the parents or guardians of discharged study patients via telephone 2 days after their emergency department visit to determine their readmission rate. - Reassessed at 6th month by telephone to record wheezing attack rate.	100); 97.5±2.1 (91-100); 0.46 - 30 min: 98.0±2.3 (91-100); 97.8±1.8 (91-100); 98.5±1.6 (91-100); 98.3±1.4 (92-100); 97.9±1.6 (92-100); 0.41 - 60 min: 98.5±1.6 (94-100); 98.5±1.2 (95-100); 99.0±1.2 (94-100); 98.5±1.5 (95-100); 98.5±1.5 (92-100); 0.38 - 120 min: 98.7±2.8 (94-100); 98.5±1.2 (95-100); 99.1±1.9 (90-100); 98.8±1.1 (96-100); 98.7±1.2 (96-100); 0.79 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: - None encountered, no children were withdrawn from the trial due to side-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				effects or clinical deterioration. - All patients reassessed by telephone at 6 months: 10 (26.3%) from group 1, 14 (35.8%) group 2, 10 (27.7%) group 3, 12 (33.3%) group 4 and 13 (35.1%) group 5 showed recurrent wheezing attacks.	
Full citation Henry,R.L., Milner,A.D., Stokes,G.M., Ineffectiveness of ipratropium bromide in acute bronchiolitis, Archives of Disease in Childhood, 58, 925-926, 1983 Ref Id 211899 Country/ies where the study was carried out UK Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study	Sample size 66 enrolled: 34 ipratropium bromide, 32 normal saline as placebo Characteristics - RSV isolated from 45 (68%). - Average age 130 days, range 49 to 368 days . - 40 boys and 26 girls Inclusion criteria Admitted to hospital with bronchiolitis defined as: a tight, irritating cough, breathlessness, respiratory distress, hyperinflation, fine crepitations, and expiratry rhonci.	Interventions - 6 hourly nebulised solutions containing 250µg of ipratropium bromide in 2ml of saline or normal saline alone. - Treatment was stopped when the respiratory signs had resolved sufficiently for dischrage home.	Details Setting: Inpatient. Randomisation and concealment: Not described. Outcome measures: - One person made daily measurements of pulse and respiratory rate together with assessments of cough, rhinitis, nasal flaring, cyanosis, hyperinflation, tracheal tug, intercostal recession, subcostal recession,	Results Number of treatments received by the 66 children before respiratory signs had resolved sufficiently for discharge home: Number of treatments; ipratropium bromide; saline 4-7; 8; 10 8-11; 8; 6 12-15; 9; 10 16-19; 3; 3 ≥20; 6; 3 Total; 34; 32 8. Adverse effects:	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Characteristics not reported for each treatment group. - Number of patients presented to the hospital with bronchiolitis who did not meet inclusion criteria not reported. - Unclear inclusion and exclusion criteria. - Randomisation not described, allocation concealment not described

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the clinical benefit of ipratropium bromide in the treatment of acute viral bronchiolitis. Study dates Not reported. Source of funding Financial assistance provided by the Asthma Research Council, Boehringer Ingelheim, and Nestle Paediatric Fellowship (Australia).	Exclusion criteria Not reported.		respiratory distress, crepitations, and rhonchi, using a four point scale scoring system for each parameter. - Another person obtained detailed information from parents and nursing staff about whether there was an immediate response to each nebulised treatment. Statistical methods: Not reported.	Two children received ipratropium bromide developed a tachycardia and persistent coughing with treatment, and it seems likely that treatment prolonged their illness.	Detection bias: - Subjective length of follow-up. - Unclear discharge criteria. - Subjective scoring system and outcome measures. - Statistical methods unclear. (- Very short word count may limit the appeared quality of the study.) Performance bias: - Blinding unclear Attrition bias: - Incomplete data, 42 out of 66 parents avaliable to provide information on the immediate response to treatment. Other information - Table 2 presents the immediate response to nebulised treatment as judged by parents and nursing staff, for the 66 children. - Based on parental assessments, 11 of 24 children treated with ipratropium bromide were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					helped compared with only 3 out of 18 who received placebo, chi-squared=2.73, p<0.1.
Full citation Schuh,S., Canny,G., Reisman,J.J., Kerem,E., Bentur,L., Petric,M., Levison,H., Nebulized albuterol in acute bronchiolitis, Journal of Pediatrics, 117, 633-637, 1990 Ref Id 208094 Country/ies where the study was carried out USA Study type Randomsied, double-blinded, placebo-controlled trial. Aim of the study To evaluate the clinical response to nebulized albuterol in infants and young children with acute bronchiolitis who were seen in the emergency department. Study dates	Sample size 40 enrolled: 21 albuterol, 19 placebo. Characteristics Characteristic: albuterol; placebo (Mean±SD) - Age, months: 6.1±1.3; 5.3±1.2 - Duration of illness >96 hours: 4; 3 - Family history of atopy:11; 8 - Positive viral isolation: 14; 10 - Respiratory rate: 58.3±2.4; 56.4±3.0 - Oxygen saturation: 95.4±0.5; 96.4±0.5 Medication within 48 hours: - Orciprenaline: 4; 4 - Albuterol: 3; 1 - Antibiotics: 3; 4 - No medication: 11; 10 Inclusion criteria	Interventions Albuterol group: Three doses of 0.5% nebulized albuterol, 0.15mg/kg/dose, at 1-hour intervals. Placebo group: Two doses of nebulized saline solution, followed by one dose of 0.5% nebulized albuterol, 0.15mg/kg/dose, 1 hour apart. - Standard therapy includes nebulized albuterol, so the third dose in group 2 included the drug for ethical reasons. - Solutions provided by the pharmacy looked identical (clear, colorless and odorless). - All doses were suspended in 3ml of 0.9% saline solution and delivered for 15 minutes by face mask and nebulizer, driven by	Details Setting: Emergency department. Randomisation and concealment: - Research pharmacist randomly assigned according to a predetermined scheme. - Random numbers system was computed for groups of 10 to promote balance. - The investigators and families were unaware of treatment assignments. Outcome measures: - Evaluated by one of five investigators whilst awake in a quiet mood at 0, 60, and 120 minutes before each dose	Results Protocol outcomes Albuterol; placebo; p value (Mean±SEM) 1. Hospital admission rate: Albuterol 4/21 Placebo 2/19 2. Length of hospital stay: Not reported. 3. Change in Respiratory rate (%↓): - After dose 1: 16.2±3.3; 15.5±3.5 ; p=NS - After dose 2: 19.6±3.4; 8.0±3.0; p=0.015 - At <6 months after dose 2: 17.3±4.4; 2.4±6.2: n at <6 months unclear	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: Number of patients presented to the hospital with bronchiolitis who did not meet inclusion criteria not reported. Attrition bias: - Six sopharyngeal swabs were mislaid. - Four patients did not have chest radiographs. Detection bias: - Unclear definition of bronchiolitis. - Subjective scoring systems for wheeze and accessory muscle use. - Unclear if patients were assigned the same investigator throughout the study. Performance bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
December 1988 to April 1989. Source of funding Not reported.	- Enrollment between 8am and 12 midnight. - Between 6 weeks and 24 months of age. - History and clinical findings compatible with a diagnosis of acute bronchiolitis. Exclusion criteria - Prematurity or mechanical ventilation after birth. - History of lower respiratory tract disease, wheezing, or bronchodilator therapy. - History of suggestive chronic aspiration or cardiac disease. - Current episode that started more than 2 weeks before the present emergency department visit.	oxygen at a flow rate of 6 to 7l/min. - After the study was completed the child was either admitted or discharged by the attending pediatrician, who was not involved in the trial.	and 30 minutes after the last dose. - Respiratory rate. - Acccessory muscle score. - Wheeze score. - Oxygen saturation. - Heart rate. Statistical methods: - Sample size calculation: sample size per group of 21, power=90% to detect a difference of 1 SD in respiratory rate between the groups, α=0.05 - Two-tailed t test to compare mean changes and baseline clinical values. - Chi-squared statistic to compare baseline demographics. - Accessory muscle and wheeze score analysed using Mann-Whitney U test and two-tailed t test.	4. Change in disease severity score: Not reported. 5. Change in O2 saturation (from baseline): - After dose 1: 0.71±0.3; -0.47±0.3; 0.010 - After dose 2: 0.76±0.04; -0.79±0.5; 0.015 - At <6 months after dose 2: 1.09±0.37; -1.17±0.8 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: - Of the 34 swabs examined 21 positive for RSV, 1 for paramyxovirus, 1 for parainfluenza, and 1 for influenza.	- Some patients had to be sedated. - Four patients received albuterol before arrival at the emergency department. - Unclear if discharge was blinded, also no criteria for discharge described. Other information - All the discharged patients were treated with either orally administered orciprenaline or albuterol, none of these readmitted within 2 weeks of the initial visit. - Wheeze score and accessory muscle score also reported (table 2).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- 30 out of 36 chest radiographs before discharge showed hyperinflation.	
Full citation Gadomski,A.M., Aref,G.H., el Din,O.B., el,Sawy,I, Khallaf,N., Black,R.E., Oral versus nebulized albuterol in the management of bronchiolitis in Egypt, Journal of Pediatrics, 124, 131-138, 1994 Ref Id 206895 Country/ies where the study was carried out Egypt Study type Randomised, double-blinded, placebo-controlled trial Aim of the study To determine the efficacy of albuterol in reducing respiratory distress in infants with bronchiolitis and to assess which route of delivery (nebulisation vs oral) is more effective.	Sample size - 169 completed the study - 41 included in the recurrent wheezing group - 128 randomly assigned to four study groups - Nebulised albuterol 32, nebulised saline solution 32 Characteristics Characteristic: nebulised albuterol; nebulised saline solution - Median age, months: 4.0; 5.0 - Boys (%): 75; 72 - Days of cough preceding trial: 4.8; 3.8 - History of fever (%): 41; 56 - Exposed to smoke at home: (%): 75; 69 - Preterm (%): 6; 0 Patients (no.) receving medications before visit: - Antibiotics: 14; 16 - Theophylline: 5; 9 - Salbutamol: 3; 5	Interventions - Medications indistinguishable and clearly marked as to how they should be delivered - Isotonic saline solution (0.9%) (Addipak Respiratory Care Inc.) was the nebulised placebo - Albuterol 0.15mg/kg per dose administered as two nebulisation treatments 30 minutes apart, with room air and an Up-mist nebuliser and pediatric face mask - Nebulisation was completed within 10 to 12 minutes so that a flow rate of 4 to 6l/min could be delivered	Details Setting: - Both outpatient and emergency of the El Chatby Children's Hospital, Alexandria - The same equipment, personnel, and procedures were utilised at both clinical sites Randomisation and concealment: - Randomisation list by Moses-Oakford algorithm and a table of random numbers - Block period of eight - Nurses administered the medications to the infant in a room several rooms away from where the assessments were done by pediatricians	Results Protocol outcomes Nebulised albuterol; nebulised saline solution 1. Hospital admission rate: Not reported. 2. Length of hospital stay: Not reported. 3. Change in respiratory rate, mean ±SD: - Baseline 57; 60 - At 30 min 55; 57 - Change in RR at 30 min -2±10; -3±8 - At 60 min 53; 55 - Change in RR at 60 min -4±8; -4±10 4. Change in disease severity score: - Baseline 13.2; 14.2 - At 30 min 11.6; 11.3	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Only 2% of infants showed bronchiolitis in CXRs - RSV only tested in 118 out of 169, numbers not reported separately for each group only % - 6 preterm infants in the albuterol group compared to 0 in the saline group Performance bias: Number of outpatient and emergency patients not reported Detection bias: Subjective clinical scoring system Other information

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Study dates Not reported Source of funding Supported by the US Agency for International Development through the technical assistance contract of Clark Atlanta University with the Ministry of Health Child Survival Project in Cario	- The open-label control group (recurrent wheezers) included older infants (range 3 to 24 months of age) and received more theophylline and therapy with other bronchodilators - RSV positive in 51 of 118 infants tested (43%): nebulised albuterol 50%, nebulised saline solution 43%, recurrent wheezing group 17% - Hyperinflation noted in 27% of infants Inclusion criteria - <18 months - Seen with first time wheezing in the outpatient clinic and casualty department - Bronchiolitis defined as: an acute infection disease of the lower respiratory tract, preceded by fever, rhinitis, or both, and characterised by tachypnea, expiratory wheezing, hyperinflation, and increased respiratory effort in infants during the season when respiratory tract infections are most prevalent		- Caretaker was able to tell whether the infant had received oral or nebulised treatment but was not able to tell whether the substance was placebo or albuterol - Pediatricians could not hear the nebuliser and could not tell whether the patient had received nebulisation or oral treatment Outcome measures: - Clinical scoring performed by study investigator (0 to 3 scale, based on grunting, nasal flaring, supraclavicular retractions, intercostal retraction, chest indrawing, air entry, air hunger, wheezing and general appearance) - Respiratory rates - Oxygen saturation - Heart rates - State of the child (agitated, sleeping,	- Change in score at 30 min -2±2; -3±4 - At 60 min 8.6; 9.5 - Change in score at 60 min -5±4; -5±4 5. Change in O2 saturation: - Baseline 95; 94 - At 30 min 95; 93 - Change in Sp02 at 30 min -0.28±5; -0.91±4 - At 60 min 94; 94 - Change in Sp02 at 60 min -0.69±3; -0.27±4 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects Number of patients needing additional treatment: 24 (75%); 21 (87%)	- Infants with recurrent wheezing or with a diagnosis of asthma were recruited as open-label control subjects - After the 60 minute assessment, the pediatricans could opt for an albuterol nebulisation if they thought that the infant's condition had not improved during the trial, the final 90 minute assessment followed the administration of the open-label albuterol nebulisation - Open-label recurrent wheezing, oral albuterol and oral placebo groups reported in the study but not included in data extraction - CXRs obtained from 167 infants: normal 37%, bronchitis 22%, pneumonia 18%, obstuctive pneumopathy 8%, hilar inflammatory changes 6%, bonchiolitis 2% - Mean change in outcomes at 30 and 60 minutes after treatment in infants without state change as a confounding

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	Exclusion criteria - Chronic diseases of the cardiorespiratory system - Heart rate >200 beats/min - Cyanosis, apathy, lethargy, or an otherwise depressed sensorium suggestive of incipient respiratory failure or sepsis - Persistent vomitting - Refused feedings		quite alert, active alert) - All groups reassessed at 30, 60 and 90 minutes after treatment Statistical methods: - Sample size calculation: power=99.7% to detect decrease in RR of 10 breaths per minute in the albuterol groups, α=0.05, SD=10.6, n=32 power=86% to detect a score difference of at least 3 points among the four randomised groups, α=0.05, SD=4.7, n=32 - Analysis of variance - Physical examination findings and clinical scoring were standardised among pediatricans with the use of videotapes, conjoint examinations of infants, and periodic		variable also reported (table 4)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			tests of interrater variability		
Full citation Skjerven,H.O., Hunderi,J.O., Brugmann-Pieper,S.K., Brun,A.C., Engen,H., Eskedal,L., Haavaldsen,M., Kvenshagen,B., Lunde,J., Rolfsjord,L.B., Siva,C., Vikin,T., Mowinckel,P., Carlsen,K.H., Lodrup Carlsen,K.C., Racemic adrenaline and inhalation strategies in acute bronchiolitis, New England Journal of Medicine, 368, 2286-2293, 2013 Ref Id 261318 Country/ies where the study was carried out Norway Study type Randomised, double-blinded, multi-centre Aim of the study Tested the hypothesis that inhaled racemic adrenaline is superior to	Sample size - 404 randomised - 203 received inhaled RA: 102 RA on demand, 101 RA fixed schedule - 201 received inhaled saline: 98 saline on demand, 103 saline fixed schedule - 167 completed inhaled RA: 85 RA on demand, 82 RA fixed schedule - 154 completed inhaled saline: 78 saline on demand, 76 saline fixed schedule Characteristics Characteristic: RA on demand; RA fixed schedule; saline on demand; saline fixed schedule Mean±SD or N (%) - Number: 102; 101; 98; 103 - Male: 63(61.8); 60(59.4); 54(55.1); 63(61.2) - Age, days: 134.9±91.6; 116.9±87.8; 117.8±68.1; 136.0±97.0	Interventions - Pharmacy prepared doses of the two study medications: 10ml racemic adrenaline dissolved in 0.9% saline to form a solution of 20mg per ml or 0.9% saline alone - Medications in identical bottles, each labelled with a numerical code indicating the type of medication and timing of administration: on demand or fixed schedule - Dose administered based on infant's weight: 0.10ml for infants weighing <5kg, 0.15ml for 5 to 6.9kg, 0.20ml for 7 to 9.9kg and 0.25ml for ≥10kg - Medications diluted in 2ml saline before nebulisation and administered through a Sidestream Reusable Nebuliser with a Respironics Facemask driven by 100% oxygen	Details Setting: Pediatric departments of eight hospitals in southeastern Norway Randomisation and concealment: - 2-by-2 factorial design - Randomisation was performed centrally in blocks of eight, with assignment to one of the four study groups - Randomisation codes were communicated directly by the study statistician to the pharmacy - The study centres, which were not aware of the randomisation block size, were provided with a list of study numbers for use in the consecutive	Results Protocol outcomes RA (n=203); saline (n=201) Mean (range) 1. Hospital admission rate: Not reported 2. Length of hospital stay: 78.7 (69.2 to 88.1); 81.8 (72.6 to 91.0) p=0.43 3. Change in respiratory rate: Not reported 4. Change in disease severity score After 1 inhalation: -1.26 (-1.44 to -1.08); -1.08 (-1.23 to -0.92) 5. Change in O2 saturation: Not reported	Limitations Based on NICE checklist. Only limitations that arise in the study are reported Selection bias: - Respiratory viral assays performed in 123 out of 136 children admitted to Oslo Univerisity Hospital - Number of children presented with bronchiolitis who did not meet includion criteria not reported - Characteristics not avaliable for every infant Attrition bias: - 321 out of 404 completed the study - 17 discontinued from RA on demand: 11 treatment failure, 4 withdrawn by parent, 2 inappropriately withdrawn - 19 discontinued from RA fixed schedule: 12 treatment failure, 4 withdrawn by parent, 1 inappropriately withdrawn, 2 side effects

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inhaled saline in the treatment of acute bronchiolitis in infancy and that administration on a fixed schedule is superior to administration on demand Study dates January 2010 to May 2011 Source of funding Medicines for Children	- Allergies: 4 out of 87 (4.6); 0 out of 96 (0); 1 out of 90 (1.1); 2 out of 96 (2.1) - 1 previous wheeze: 24 out of 88 (27.3); 23 out of 91 (25.3); 20 out of 90 (22.2); 31 out of 93 (33.3) - Respiratory symptoms >1week: 8 out of 75 (10.7); 12 out of 90 (13.3); 10 out of 86 (11.6); 15 out of 89 (16.9) - Parental medical history of asthma: 17 out of 78 (21.8); 22 out of 83 (26.5); 23 out of 80 (28.8); 21 out of 84 (25.0) - Clinical score: 4.9±1.0; 5.0±1.0; 4.9±1.0; 4.9±1.0 - Oxygen saturation: 96.0±3.6; 96.0±3.3; 96.0±3.4; 96.1±2.8 - Respiratory rate (breaths/min): 53.1±11.8; 53.6±10.5; 53.8±11.3; 53.4±11.1 Inclusion criteria - Admitted to pediatric department with acute bronchiolitis - Bronchiolitis as defined by Court 1973 - <12 months old	at a rate of 6l per minute Additional treatment: - No other inhaled medications, with the exception of 0.9% inhaled saline administered at discretion of attending physician - Supportive therapy and any other treatments were provided in accordance with routine care - Glucorticoids and β2-adrenergic agonists were not administered	assignment of medication to enrolled children Outcomes measures: - Length of hospital stay - Change in clinical score 30 minutes after first inhalation - Use of nasogastric-tube feeding, oxygen supplementation or ventilatory support Statistical methods: - To detect a reduction in hospital stay of 5 hours in the group receiving inhaled RA, 176 patients in each group required, power=80%, two-sided α=0.05 - Categorical Pearson chi-squared test - Comparisons between groups assessed with two-sample t-test and Huber's M-estimator - Jonckheere-Terpstra test used to	6. Need for high flow humidified oxygen, CPAP or mechanical ventilation - Oxygen: 83 out of 192 (43.2); 83 out of 189 (43.9) - Ventilatory support: 15 out of 203 (7.4); 15 out of 201 (7.5) 7. Need for/Use of feeding support Nasogastric tube feeding: 57 out of 201 (28.4); 59 out of 199 (29.6) 8. Adverse effects: Three children, including one who was receiving inhlaed saline, discontinued treatment because of moderate tachycardia (denominators unclear)	- 20 discontinued from saline on demand: 15 treatment failure, 3 withdrawn by parent, 1 inappropriately withdrawn, 1 side effects - 27 discontinued from saline fixed schedule: 21 treatment failure, 5 withdrawn by parent, 1 inappropriately withdrawn Detection bias: - Subjective clinical scoring system Other information - Supplementary appendix avaliable NEJM.org, contains: biologic specimens gathered, number enrolled at each centre, interaction between the two treatment interventions, and influence of age, allergic disease and gender - Results for on demand and fixed schedule also reported (table 2)

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	- Clinical score ≥4 on a scale of 0 to 10 based on general condition, skin colour, findings on auscultation, respiratory rate and retractions Exclusion criteria - Presence of any serious cardiac, immunologic, neurologic, or oncologic disease - Any serious pulmonary disease other than bronchiolitis - >1 previous episode of obstructive airway disease - Symptoms of disease of the lower airway (eg coughing) for >4 weeks - Receipt of any glucocorticoid therapy in the preceding 4 weeks		assess interactions between age and interventions		
Full citation Klassen,T.P., Rowe,P.C., Sutcliffe,T., Ropp,L.J., McDowell,I.W., Li,M.M., Randomized trial of salbutamol in acute bronchiolitis.[Erratum appears in J Pediatr 1991 Dec;119(6):1010],	Sample size - 85 referred for inclusion. - One excluded because of a respiratory rate of 100 breaths/min, and another because of a prior history of chest tube placement during the neonatal period. - 83 completed: salbutamol 42, placebo 41.	Interventions Nebulized salbutamol: 0.10mg/kg (0.02ml/kg of the 5% respiratory solution, Ventolin). Placebo: 0.02ml/kg of 0.9% saline solution.	Details Setting: Emergency department at the Children's Hospital of Eastern Ontario. Randomisation and concealment:	Results Protocol outcomes Salbutamol; placebo; p value (Mean±SD) 1. Hospital admission rate: - Salbutamol 13 out of 42; placebo 11 out of 41.	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Number of patients presented to the hospital with bronchiolitis who did

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Pediatrics, 118, 807-811, 1991 Ref Id 207304 Country/ies where the study was carried out Canada Study type Randomised, double-blinded, placebo-controlled, clinical trial. Aim of the study To test the hypothesis that nebulized salbutamol would provide greater short-term improvement in respiratory status than a placebo in young children with acute bronchiolitis. Study dates November 1, 1988 and April 30, 1990. Source of funding Supported by grant No.01288N from the Emergency Services Division, Ministry of Health of Ontario, and by a Career Scientist Award (Dr. Rowe) from	Characteristics Characteristic: salbutamol; placebo; p value - Male: 22; 25; 0.57 - Age, months (Mean±SD): 7.3±4.2; 7.0±3.9; 0.71 - Age <12 months (%): 93; 85; 0.46 - Age <6 months (%): 50; 46; 0.91 - RSV positive: 24; 24; 0.93 - Family history of asthma: 30; 25; 0.44 - RDAI, median (range): 8.75 (4-11.5); 8 (4-14); 0.99 Inclusion criteria - <24 months of age. - Wheezing present on auscultation at inital presentation and at least 5 minutes later on examination by one of the investigators. - RDAI score >3. Exclusion criteria - History of previous bronchodilator therapy or chronic disease (including asthma).	- Either solution added to 2ml of 0.9% saline solution and administered for 5 to 8 minutes through an updraft nebulizer with continuous flow of oxygen for 5 to 6l/min. - All patients received a second dose of the drug or placeobo at 30 minutes after entry. - If by 60 minutes the patients had not experienced an improvement in RDAI by 3 points, they were given 0.10mg/kg of salbutamol with 2ml of 0.9% saline solution. - Patient admitted to hospital at discretion of physician. - One observer examined 84% of the patients, another examined 41%, weighted kappa 0.94.	- Computer-generated table of random numbers. - Investigators were unable to distinguish between the odors of nebulized saline solution and nebulized salbutamol. - Parents and investigators remained unaware of which drug the patient had received for the first two nebulizations. Outcome measures: - RDAI score (0 to 17 scale, based on wheezing and retractions, also used by Lowell et al.). - Respiratory rate. - Heart rate. - Pulse oximetry. - When the same patient was assessed by two observers, the mean of the two scores was calculated. Statistical methods:	2. Length of hospital stay: Not reported. 3. Change in Respiratory rate: - Basline 55±13; 52±11; 0.24 - 30 min 51±13; 52±11; 0.62 - 60 min 50±11; 50±11; 0.88 4. Change in disease severity score (RDAI): - Baseline 8.75; 8.00; 0.99 - 30 min 6.00; 7.75; 0.04 - 60 min 5.0; 6.25; 0.12 - SD or summary measure for the above not reported - When restricted to <1 year of age, at 30 min p=0.01, at 60 min p=0.08. Average clinical score after treatment, mean (SD) -	not meet the inclusion criteria not reported. Detection bias: - Unclear definition of bronchiolitis. - Subjective clinical scoring system. Other information - RDAI scoring system described in table 1. - One parent refused the third salbutamol nebulisation at 60 minutes. - Hospital admission rate disagreement from Gadomski cochrane review. Outcome after unblinded administration of salbutamoil at 60 minutes: - 50 patients qualified for salbutamol therapy because they had not achieved a RDAI 3 score change at the 60-minute assessment, 30 from placebo (RR 1.5 95% CI 1.06 to 2.22, p=0.03). - The 30 placebo patients had a greater improvement in their RDAI

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the Ministry of Health of Ontario.	- Severe respiratory disease (pulse rate >200 beats/min, respiratory rate >80 breaths/min, RDAI score >15 or profound lethargy).		- Categorical data: Yates corrected chi-squared statistic or Fisher Exact test. - RDAI score: Mann-Whitney U test. - Continuous data: two-tailed t test. - One observer examined 84% of patients and another examined 41%, Fleiss method to calculate weighted kappa statistic of 0.94. - Expected improvement of 20% in placebo, sample size of 44 in each group, power=90%, α=0.05 to detect a difference of 35% in improvement rates between the groups.	extracted from Gadomski cochrane review Salbutamol: 5 (2.9), n=42 Placebo: 6.2 (3.2), n=41 5. Change in O2 saturation: - Baseline 95±3; 95±4; 0.54 - 30 min 95±4; 95±3; 0.60 - 60 min 95±4; 95±4; 0.74 6. Need for CPAP/mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: Heart rate higher at 60 minutes in salbutamol group, p=0.03 but numbers not reported Oxygen saturation >85% in all patients	scores 30 minutes after receiving salbutamol than did the 20 in the treatment group who had already received two salbutamol nebulizations, p=0.005. Outcomes of RSV: - 58% positive for RSV. - After 30 minutes those in the salbutamol group had significantly better RDAI scores (p=0.04) than placebo. - After 60 minutes p=0.10

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ralston,S., Hartenberger,C., Anaya,T., Qualls,C., Kelly,H.W., Randomized, placebo-controlled trial of albuterol and epinephrine at equipotent beta-2 agonist doses in acute bronchiolitis, Pediatric Pulmonology, 40, 292-299, 2005 Ref Id 207953 Country/ies where the study was carried out USA Study type Randomised, double-blinded, placebo-controlled study. Aim of the study To determine if nebulized racemic epinephrine is more efficacious than nebulized albuterol or saline placebo in the treatment of bronchiolitis in the outpatient setting when dosing is	Sample size - Patients were only enrolled in the bronchiolitis season i.e., January, February and March pf each year, with enrollments of 17, 11, 14, 13, and 15 patients per season chronologically. - During the study months from 2000-2004, 199, 144, 191, 170, and 172 patients under 2 years were admitted to the study hospital from bronchiolitis. - The study enrollment as a percentage of admissions for bronchiolitis was 8.5%, 7.6%, 7.3%, 7.6% and 8.7%, respectively. - 155 patients screened. - 82 met criteria. - 17 refused participation. - 65 completed: epinephrine group 17, albuterol group 23, placebo group 25. - Eight (35%±9%) albuterol-treated patients, 8 (47%±10%) epinephrine-treated patients, and 11 (44%±10%) normal saline-treated patients were	Interventions Albuterol group: 5mg racemic albuterol sulfate. Epinephrine group: 5mg racemic epinephrine. Placebo group: 0.9% saline. - Medications delivered with an infant face mask and continuous flow of oxygen at 6l/min. - All in 3ml nebulized doses administered at 0 and 30 minutes. - Each solution colorless and odorless. - Study drug was prepared ahead of time by the research pharmacist and placed in a locked refrigerator, with sequential numbers corresponding to the next patient enrolled. - All drugs were stored in brown plastic envelopes to prevent light inactivation, and prepared for use in single-dose vials to limit the possibility of errors	Details Setting: Patients presented to urgent-care clinic of the University of New Mexico Department of Pediatrics. Randomisation and concealment: - Random number table generated by a computer was used by the research pharmacist to allocate patients to treatment groups. - The research pharmacist was the only person with access to the randomisation. - All study personnel remained blind to medication identity throghout the study period. Outcome measure: - Need for hospital admission or home oxygen.	Results Protocol outcomes 1. Hospital admission rate Poor reporting of data therefore not extracted (study uses the term x number of subjects admitted to each treatment group as opposed to admitted to hospital) 2. Length of hospital stay: Not reported. 3. Change in respiratory rate: Not reported. 4. Change in disease severity score Average clinical score after treatment, taken from Gadomski cochrance review, (Mean±SD): Placebo 7±2.84 Albuterol 6.39±2.43 Std mean difference (IV, random) -0.23, 95% CI -0.79 to 0.34	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - 73 out of 155 did not meet inclusion criteria. - Unbalanced sample sizes between groups. - Enrolled patients between 8am and 5pm. Performance bias: - Some patients received oxygen at home which is not standard care. Detection bias: - Outcome measures are presented in figure 2, the values are not reported separately. - Discharge criteria not described. - Poor reporting of data therefore not extracted (study uses the term x number of subjects admitted to each treatment group as opposed to admitted to hospital).

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equivalent in terms of beta-2 agonist potency. Study dates Over five bronchiolitis seasons (January, February and March), from 2000 to 2004. Source of funding Grant sponsor: Department of Health and Human Services/National Institutes of Health/National Centre for Research Resources/General Clinical Research Centre. American Academy of Pediatrics.	managed with home oxygen. Characteristics Characteristic: placebo; albuterol; epinephrine (Mean±SD) - Age, months:7.3±5.1; 7.7±6.0; 7.9±5.2 - Male (%): 60; 65; 35 - Medicaid (%): 92; 74; 65 - Duration of illness, days: 5.7±6.5; 4±2.9; 5.2±3.9 - Respiratory rate: 57±10; 57±11; 55±9 - Oxygen saturation: 90±5; 90±4; 90±4 - RDAI score: 8±2; 8±2; 8±2 Inclusion criteria - First episode of bronchiolitis defined as: wheezing associated with symptoms of upper respiratory infection and/or fever, temperature ≥38ºC. - Between 6 weeks and 24 months of age. - RDAI score ≥4. Exclusion criteria - Premature birth (<36 weeks gestation).	in dosage due to measurment by differing personnel at time of enrollment. - Therapies routinely performed during the study included nasal suctioning and provision of supplemental oxygen by nasal cannula or mask. - At 60 minutes, if RDAI >8 or oxygen saturation <90%, a third dose of study medication was administered with a final assessment at 90 minutes instead of 60. - After the final study assessment, the decision for admission was made by the responsible attending physician who was blind to all study interventions.	- RDAI score (0 to 17 scale, based on wheezing and retractions, also used by Lowell et al.). - Oxygen saturation. Statistical methods: - Sample size calculation: 21 patients per group to detect a difference in admission rates of 75% for placebo or albuterol and 33% for epinephrine, power=80%, α=0.05 - Intention-to-treat analysis. - Fisher's exact test. - Repeated-measures ANOVA. - Potential confounders considered as covariates. Follow-up: - Patient who received home oxygen (as an alternative to hospital admission) were considered with the admission	5. Change in O2 saturation: (Gadomski, Mean±SD) Placebo 89.32±6.75 Albuterol 88.52±5.06 Mean difference (IV, random) 0.80, 95% CI -2.56 to 4.16 6. Need for CPAP/mechanical ventilation: Not reported. 7. Need for/Use of feeding support: <10% received intravenous fluids. 8. Adverse effects: - Two albuterol group patients had a sustained heart rate >200 beats per minute for more than 30 minutes. - Both patients with tachycardia self-resolved on discontinuation of medication. One was admitted to the hospital for	Other information - Three protocol violations: Two patients had documentation of prior wheezing which would have excluded them from the study, but which neither their parents nor their physicians reported at the time of study enrollment. The third protocol violation had their fifth day of steriods at time of study enrollment, which was discovered only after hospital admission. All three protocol violations were in the normal saline group, and all three were admitted to hospital. - RDAI scoring system presented in table 1. - Univariate analysis showed that oxygen saturation alone predicted hospital admission. - Patients who received home oxygen were considered with the admission group for the primary outcome analysis. - 37 (57%) patients met criteria for all three doses of medication, the

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	- History of wheezing, asthma or significant chronic disease. - Use of systemic steroids for current illness. - Physiologically unstable at presentation (heart rate >200, respiratory rate >90, RDAI score >15, oxygen saturation <70%).		group for the primary outcome analysis. - Patient charts and emergency room logs and follow-up visits were examined for the week following the study.	respiratory problems for 48 hours and suffered no further complications. The other was discharged home on oxygen with two follow-up visits, without further complications. - Two patients were admitted to the hospital within 24 hours of study participation. One from the epinephrine group had a 32 hour hospitalisation and one from the albuterol group had a 92 hour hospitalisation in a general ward without complications.	remaining 28 completed the study after two doses. - Cochrane review contacted authors for data values. Figure 2 results: Admit n=13 (20%) Home 02 n=27 (42%) Home no 02 n=25 (38%) Admit or Home 02 n=40 (62%)
Full citation Can,D., Inan,G., Yendur,G., Oral,R., Gunay,I., Salbutamol or mist in acute bronchiolitis, Acta Paediatrica Japonica, 40, 252-255, 1998 Ref Id 206480 Country/ies where the study was carried out	Sample size - 158 enrolled. - Two patients excluded because of incomplete treatment. - 156 completed: 52 in each of the three groups. Characteristics Characteristic: group 1; group 2; group 3 Mean±SD or %	Interventions Group 1: nebulized salbutamol at a dose of 0.15mg/kg in 2ml saline. Group 2: nebulized saline. Group 3: mist in a tent. Additional treatment: - All patients received additional humidified	Details Setting: Emergency Department of Dr Behçet Uz Children's Hospital. Randomisation and concealment: Not described. Outcome measures:	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay: Not reported.	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Unclear definition of bronchiolitis. - Inclusion criteria based on Wohl et al. but not described in any further detail.

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Turkey Study type Prospective, randomised, single-blinded, placebo-controlled study. Aim of the study To evaluate the efficacy and safety of salbutamol in infants with acute bronchiolitis. Study dates 1 January 1994 to 1 January 1996. Source of funding Not reported.	- Female: 52; 24; 48 - Male: 48; 76; 51 - Atopy: 21; 26; 25 - Family atopy: 42; 41; 38 - Onset of clinical findings, day: 2.2±1.6; 2.4±1.3; 2.2±0.6 - Age, months: 7.2±4.2; 6.8±2.1; 7.4±5.3 - Weight, kg: 8.2±5.2; 8.3±4.3; 8.1±6.4 Inclusion criteria Derived from the study by Wohl et al (Gadomski cochrane review states this was outpatients with acute bronchiolitis) Exclusion criteria - Age >24 months. - History of premature delivery and mechanical ventilation during neonatal period. - Chronic cardiopulmonary disease. - Preceding bronchodilator and steriod administration during the admission attack. - Duration of symptoms for >1 week. - Heart rate >200 beats/min and/or respiratory rate >80 breaths/min.	oxygen at a rate of 5l/min. - A second dose of medication was given to patients with a RDS >5 at 30 min. - Did not administer any sedatives and did administer oxygen during salbutamol inhalation. - All three groups were administerred oxygen during the procedures	- Recorded before and after each treatment at 30 minutes and 60 minutes when the study was completed. - Heart rate. - Oxygen saturation. - Respiratory distress score (based on respiratory rate, cyanosis, wheezing, retractions and nasal flaring) modified from Klassen et al. Schuh et al. and Tal et al. Statistical methods: - Sample size calculation not reported. - Analysed using t-test, chi-squared and ANOVA.	3. Change in respiratory rate: Not reported. 4. Change in disease severity score - Initial mean RDS Group 1: 11.0±3.2 Group 2: 11.3±3.6 Group 3: 10.8±3.3 p>0.05 - % of patients with RDS >5 at 30 minutes: Group 1: 28 Group 2: 3 Group 3: 11 - Mean RDS of group 1 (7.0±3.1) at 30 minutes was significantly lower than the scores of the other two groups (p<0.001 for both). - Mean RDS at 30 minutes similar between group 2 (9.7±3.7) and group 3 (10.8±3.6), p>0.05. - Decrease in RDS of group 1 (5.2±1.8) was significantly more than that of the	- Number of patients presented to hospital with bronchiolitis who did not meet inclusion criteria not reported. - Randomisation unclear. Performance bias: - Single-blinded study, blinding unclear. - Number of physicians/investigators not reported. Detection bias: - Subjective clinical scoring system. - Results presented in figures, not all outcome measures are reported separately. - Respiratory rates measures but not reported. - Length of follow-up only 60 mintues. Other information - RDS scoring system descibed in table 2. - Typo error in initial mean RDS for group 3, reported SD of 33, assumed SD of 3.3.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Lethargy or stupor. - History of previous attack. - Respiratory distress score <5.			other two groups at 60 minutes of therapy, p<0.0001. - The third evaluation at 60 minutes revealed no significant difference between group 2 (10.2±3.5) and group 3 (9.6±3.4), p>0.05. - Subgroup 1a includes those <6 months of age, 1b includes those >6 months of age. - RDS at 30 minutes Group 1a: 7.1±4.4 Group 1b: 7.0±2.3 p>0.05 - RDS at 60 minutes Group 1a: 5.3±7.2 Group 1b: 5.1±3.8 p>0.05 5. Change in O2 saturation: - O2 saturation decreased in group 1 without reaching statistical significance. - 02 saturation increased slightly in groups 2 and 3, but	- Typo error in third evaluation at 60 minutes for group 3, reported SD of 34, assumed SD of 3.4. - Inclusion criteria by Wohl MEB. Bronchiolitis In: Chernick V, Kendig EL (eds). Disorders of the Respiratory Tract in Children. WB Sauders, Philadelphia, 1990; 360-70. X-ray findings consistent with acute bronchiolitis: - Group 1 88% - Group 2 69% - Group 3 73% - Presence significantly higher in group 1 compared with the other two groups (p<0.05) Laboratory findings of the patients: group 1; group 2; group 3 Mean±SD - Hemoglobin (g/dL): 10.0±1.3; 10.3±1.0; 10.6±9.4 - Hematocrit (%): 29.6±7.1; 31.1±5.8; 31.3±2.2

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				this increase was insigificant for both groups. - The final 02 saturation difference at 60 minutes between groups 1 and 3 was 93.9±16.3 versus 95.8±1.8, p>0.05. - Group 2 at 60 minutes 95.0±1.9 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation: Not reported. 7. Need for/Use of feeding support: Not reported. 8. Adverse effects: Tachycardia is reported frequently, but failed to reach statistical significance between the treatment groups.	- Leuocyte (/mm³): 13372±4960; 11269±2836; 12844±4325 - Neutrophils (%): 35.4±9.0; 34.5±15.2; 36.2±4.7 - Eosinophils (%): 1.5±2.7; 2.4±1.1; 2.3±5.4 - IgE (U/mL): 26.9±16.3; 29.4±12.8; 29.0±13.1
Full citation Ipek,I.O., Yalcin,E.U., Sezer,R.G.,	Sample size - 120 enrolled	Interventions - All patients given 4ml of a nebulised solution	Details Setting:	Results Protocol outcomes	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Bozaykut,A., The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis, Pulmonary Pharmacology and Therapeutics, 24, 633-637, 2011 Ref Id 210661 Country/ies where the study was carried out Turkey Study type Randomised, double-blinded Aim of the study Investigate the theraputic benefit of nebulised hypertonic 3% saline, by comparing four different nebulised regimens in the treatment of bronchiolitis in the emergency department Study dates October 2009 to March 2010	- Each of the four treatment groups contained 30 children Characteristics Characteristic: Group 1 salbutamol plus normal saline; Group 4 normal saline Mean±SD, n (%) - Age, months: 8.13±4.75; 7.40±3.08 - Female: 13 (43.3); 11 (36.7) - Male: 17 (56.7); 19 (63.3) - Exposure to tabacco smoke: 17 (56.7); 17 (56.7) - Family/individual history of atopy: 12 (40.0); 8 (26.7) Inclusion criteria - <2 years old - History of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation - Clinical bronchiolitis severity score 4 to 8 Exclusion criteria - Clinical bronchiolitis severity score <4 or >8 - Oxygen saturation <85% on room air	via a compressor nebuliser through a facemask with continued flow of oxygen at 4 to 5l/min - Group 1 received 0.15mg/kg salbutamol plus normal saline - Group 4 received only normal saline (placebo) - The nebulised solution was administered every 20 minutes until 3 doses had been administered (0, 20 and 40th minute) - Supportive care including oxygen supplementation, aspiration, and hydration when necessary provided to all patients - The decision of corticosteriod use and hospitalisation made when clinical score deteriorated and/or arterial oxygen saturation detected <85 on room air after treatment - Children necessitating hospitalisation were continued on nebulised	Short-stay unit of the pediatric emergency department Randomisation and concealment: - Randomly assigned to one of four groups according to the consecutive order of their admission to the unit - Study physician examining children blinded to the contents of all solutions Outcome measures: - Change in clinical bronchiolitis severity score (from Wang et al. based on respiratory rate, wheezing, retraction and genereal condition) - All children reexamined at 48 to 72 hours by the same physician - Oxygen saturation - Respiratory rate	Group 1; group 4 (mean±SD) 1. Hospital admission rate Required hospitalisation n(%): 3(10.0); 5(16.7) 2. Length of hospital stay: Not reported 3. Change in respiratory rate - Pretreament 45.53±6.43; 42.93±6.38 - Posttreatment 37.20±8.78; 39.20±8.21 - p value for pre vs posttreatment 0.0001; 0.005 4. Change in disease severity score - Pretreatment 4.87±1.01; 4.73±0.98 - Posttreatment 2.47±2.16; 3.10±2.43 - p value 0.0001; 0.0001	Based on NICE checklist. Only limitations that arise in the study are reported Selection bias: - Number of children presented with first time wheezing who did not meet inclusion criteria not reported - Poor randomisation method Performance bias: Blinding unclear Detection bias: Subjective clinical scoring system Other information - Clinical bronchiolitis severity score described in table 1 - Corticosteriod administration n(%): 8(26.7); 11(37.7) - Comparison of groups according to presence of atopy also reported (table 5) - Normal saline assumed as placebo

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	- Chronic cardiac illness - Premature birth - Birth weight <2500g - History of recurrent wheezing episodes - Proven immune deficiency - Severe neurological disease - Age <1 month or >2 years - Consolidation or atelectasis on a chest roentgenogram	treatment and the others were discharged without any treatment	Statistical methods: - Sample size calculation not reported - Categorical variables examined by x2 test - One-way analysis of variance (ANOVA) and Turkey's multiple comparison test used for continuous variables	Clinical assessment at 48 to 72 hours n(%) - Score lower than post-treatment values 27(90.0); 28(93.3) - Score same as post-treatment values 2(6.7); 2(6.7) - Score higher than post-treatment values 1(3.3); 0(0.0) 5. Change in O2 saturation - Pretreatment 95.57±2.22; 95.30±2.14 - Posttreatment 96.10±3.11; 96.33±3.35 - p value 0.330; 0.037 6. Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation: Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				7. Need for/Use of feeding support (tube feeding, IV fluids): Not reported 8. Adverse effects: Not reported	
Full citation Chowdhury,D., al,Howasi M., Khalil,M., al-Frayh,A.S., Chowdhury,S., Ramia,S., The role of bronchodilators in the management of bronchiolitis: a clinical trial, Annals of Tropical Paediatrics, 15, 77-84, 1995 Ref Id 206574 Country/ies where the study was carried out Saudi Arabi Study type Randomised clinical trial. Aim of the study To determine the efficacy of the bronchodilators salbutamol and ipratropium bromide,	Sample size - 278 admitted with bronchiolitis. - 102 eligible based on criteria. - 13 excluded (see adverse effects). - 89 completed. Group 1 - salbutamol 20. Group 2 - ipratropium bromide 23. Group 3 - salbutamol and ipratropium bromide 24. Group 4 - normal saline 22. Characteristics Characterisitc: salbutamol; ipratropium bromide; salbutamol and ipratropium bromide; normal saline - Male/female: 14/6; 16/7; 18/6; 17/5	Interventions Group 1 - salbutamol: Salbutamol respiratory solution (Ventolin, 5mg/ml, Allen & Hanbury Ltd, England), 0.15mg/kg (0.03ml/kg). Group 2 - ipratropium bromide: Altrovent 0.025% solution (Boehringer Ingelheim), 12.5µg/kg. Group 3 - salbutamol and ipratropium bromide: Combination of the drugs in groups 1 and 2 at doses given. Group 4 - normal saline: 0.3ml/kg normal saline. - All mixed with 2ml normal saline and delivered by 100% oxygen at a rate of 6-7l per minute using Aerosol Mist Nebulizer.	Details Setting: Patients admitted to the Respiratory Care Unit and two other general wards at Suleimania Children's Hospital under physicians who were not involved in the study. Randomisation and concealment: - Nurse randomly selects one of the four treatment groups using coded envelopes. - The investigator knew which drug had been used after 36 hours. Outcome measures:	Results Protocol outcomes group 1- salbutamol; group 2- ipratropium bromide; group 3- salbutamol and ipratropium bromide; group 4- normal saline 1. Hospital admission rate: Not reported. 2. Length of hospital stay, days (Mean±SD): 4.5±1.3; 4.4±1.4; 4.6±1.4; 4.3±1.1 F=0.3445 p=0.79 3. Change in Respiratory rate: Not reported.	Limitations Based on NICE checklist. Only those limitations that arise in the study are reported. Selection bias: - Coded envelopes are a poor method of randomisation. - Only 102 out of 278 considered eligible. - 13 excluded from analysis (adverse effects). - Not all tested for RSV. Performance bias: - Patients discharged at discretion of physician, discharge criteria not described. - Ability of physician to remove the patient from the study. - Not blinded.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
either as a single drug or in combination, given as a nebulized solution, compared with a normal saline placebo. Study dates 15 October 1992 to 30 January 1993 Source of funding Not reported.	- Age months (Mean±SD): 3.88±2.3; 4.16±2.4; 3.64±1.8; 3.72±2.27 - Patients >3 months: 11; 11; 11; 12 - Positive consanguinity: 9; 13; 9; 12 - Family histroy of atopy: 9; 12; 10; 9 - RSV positive: 12/16; 15/18; 14/21; 11/19 Inclusion criteria - Diagnosed with bronchiolitis based on a history of cough and/or wheeze, tachypnoea, intercostal retractions and, on auscultation, ronchi and râles. - <2 years of age. - Presence of wheezing, audible and/or ausultation - No previous history of wheezing or use of bronchodilator. - No chronic pulmonary disorder such as cystic fibrosis, bronchopulmonary dysplasia, immunodeficiency, etc. - No congenital heart disease.	- Medications administered 6-hourly for 36 hours. - After 36 hours all patients switched to a salbutamol nebulizer solution, 0.15mg/kg 6-hourly with 2ml normal saline, delivered by the same method. - Dicharge of patients was at the discretion of the treating physician. - If the admitting physician feld that the child required urgent attention and medication before the investigator could score the patient, treatment was started immediately and the patient was excluded from the study.	- Two investigators scored patients at 30 and 60 minutes after the first nebulisation, and after 60 minutes following completion of subsequent nebulisatins at 6, 12, 24 and 36 hours. - Modified RDAI from Lowell et al. (0 to 20 scale, based on wheezing, retraction and respiratory rate). - Length of hospitalisation. Statistical methods: - Sample size calculation not reported. - Chi-squared and Fisher exact tests to compare groups. - Analysis of variance to compare age and length of stay. - Clincal score analysed using Kruskal-Wallis.	4. Change in disease severity score (Modified RDAI score), median (quartiles): - 30 min: 3 (1.25-4.75); 2 (1-3); 2 (1-3); 2 (1-3); p=0.23 - 60 min: 2.5 (1-4); 3 (1-4); 2.5 (1.25-3.75); 2.5 (1-4); p=0.93 - 6 hours: 2.5 (1-4.75); 2 (2-5); 3 (1-5); 2.5 (2-3.25); p=0.92 - 12 hours: 3.5 (2-6); 2 (2-4); 4 (2-4.75); 2.5 (1.75-4.25); p=0.54 - 24 hours: 2.5 (1.25-4.5); 4 (1-6); 4 (2-4.75); 2.5 (1.75-4); p=0.58 - 36 hours: 4.5 (3-6); 5 (2-7); 4 (2.25-5.75); 3 (1.75-5); p=0.49 5. Change in O2 saturation: Not reported. 6. Need for CPAP/mechanical ventilation: Not reported.	Detection bias: Subjective clincal scoring system. Other information - Modified RDAI scoring system described in table 1. - Median change in the clinical score in the four treatment groups including only children >3 months also reported (table 4), at 36 hours p=0.35.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- No radiological evidence of significant pulmonary consolidation. - Judged by the admitting resident to be not sufficiently sick to require intensive monitoring or therapy. Exclusion criteria Previous history of wheezing or use of a bronchodilator to exclude cases of probable asthma.			7. Need for/Use of feeding support: Not reported. 8. Adverse effects: - 12 excluded from study because they developed pulmonary consolidation and received antibiotics. - 1 transferred to intensive care unit and excluded from study becaues of deterioration.	
Full citation Dobson,J.V., Stephens-Groff,S.M., McMahon,S.R., Stemmler,M.M., Brallier,S.L., Bay,C., The use of albuterol in hospitalized infants with bronchiolitis, Pediatrics, 101, 361-368, 1998 Ref Id 206722 Country/ies where the study was carried out Arizona Study type Prospective, double-blinded, placebo-controlled trial.	Sample size - 58 enrolled. - See limitations for incomplete follow-up. - 52 completed: albuterol 23, placebo 29. Characteristics Characteristic: albuterol; placebo Mean±SD or (%) - Age, months: 5.1±3.7; 6.1±5.4; p=0.491 - Male/female: 9/14; 16/13; p=0.278 - Weight, kg: 6.8±1.9; 7.2±2.4; p=0.546	Interventions Albuterol: - 1.25mg for patients <10kg - 2.5mg for patients >10kg - In normal saline to make a total volume of 3ml. Placebo: Saline placebo, 3ml of normal saline. - Prepared in the hospital pharmacy and supplied in individual identical containers.	Details Setting: Tertiary medical care facility in Phoenix, AZ. Randomisation and concealment: - Randomisation not described. - Both the study investigators and the pediatric inpatient team were blinded to the study drug. - Respiratory therapist who administered the	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay (percentage of patients discharged): 24 hours: albuterol 0; placebo 0 48 hours: albuterol 17.4; placebo 24.1 72 hours: albuterol 52.2; placebo 69 p=0.24	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Number of patients presented to hospital with bronchiolitis who did not meet inclusion criteria not reported. - Randomisation not described. Attrition bias: - 3 disenrolled during first 24 hours by parental request, they showed no signs of clinical

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine whether the use of albuterol by nebulisation enhances physiologic or clinical recovery in hospitalised infants with moderate bronchiolitis. Study dates December 1995 to March 1996. Source of funding Supported by funds from the Maricopa Pediatric Foundation.	- RSV: 17(24); 25(86); p=0.156 - Respiratory rate: 48±9; 50±13; p=0.518 - Sa02: 91.4±3.9; 91.9±2.5; p=0.61 - Exposure to smokers: 6(26); 12(41); p=0.379 Duration of: - Fever, days: 2.9±1.5; 2.6±1.5; p=0.612 - Cough, days: 3.6±1.6; 3.6±1.8; p=0.977 - Rhinorrhea, days: 3.5±1.5; 3.6±1.8; p=0.786 - Wheezing, days: 2.3±1.5; 2.9±1.9; p=0.292 - Pretreatment with nebulised albuterol, patients: 20(87); 26(90); p=1.0 - Pretreatment with nebulised albuterol, treatments: 2.1±1.8; 2.9±2.4; p=0.214 Inclusion criteria - Bronchiolitis defined as: an acute inflammatory respiratory illness in children that occurs in the first 2 years of life and is	- Administered viia a nebulised aerosol every 2 hours for the first 24 hours, then every 4 hours for the next 48 hours. Additional treatment: - Study patients were disenrolled at any time at parental request or if the pediatric inpatient team deemed it necessary to discontinue the study drug for clinical considerations. - Routine supportive care (oxygen administration to keep oxygen saturation ≥94%, intravenous hydration, nasopharygeal suctioning and chest physiotherapy) determined by pediatric inpatient team. - No study patient received steriod therapy or other respiratory medications. - To control for increased wheezing or accessory muscle use secondary to excessive secretions or agitation,	study drug was blinded to the identity of the study drug. Outcome measure: - Evaluated when asleep, awake, calm or content by one of five study investigators at 24 hour intervals for a maximum of 72 hours or until discharge. - Clinical score (based on general appearance, accessory muscle use and wheezing, adapted from Schuh et al.). - Improvement in oxygen saturation in room air during hospitalisation. - Time required to reach three separate preestablished discharge criteria (Sa02 in room air<94%, moderate to severe accessory muscle use, moderate to severe wheezing).	log rank=1.41 3. Change in respiratory rate: Not reported. 4. Change in disease severity score: Not reported. 5. Change in O2 saturation, mean (SD) - At 24 hours: albuterol 93.2 (7.83*), n=23; placebo 93.5 (6.04*), n=29; p=0.77 *SDs extracted from Gadomski cochrane review - Maximum Sa02 during study: albuterol 95.5; placebo 95.3; p=0.85 Improvement in % SaO2 on Room Air over time - Time 0 to 24 hours (95% CI): albuterol 1.8% (0.1% to 3.6%) placebo 1.6% (0.2% to 3.0%) p=0.86	deterioration and were excluded from the analysis. - 3 withdrawn by the pediatric inpatient team because of worsening clinical status, all 3 were randomised to receieve albuterol. Performance bias: - Routine care determined by pediatric team. Detection bias: - Results unclear based on figures. - Subjective clincal scoring system. Other information - Clinical score described in table 1. - Figure 3: Percentage of patients on albuterol and placebo with moderate to sevee retraction at baseline, 24, 48 and 72 hours of study. Log rank=0.02, p=0.90 - Figure 4: Percentage of patients on albuterol and placebo with moderate to severe wheezing at baseline, 24, 48 and 72

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	characterised by fever and/or rhinitis, tachypnea, expiratory wheezing, and increased respiratory effort. - <24 months of age. - Admitted to the general pediatric inpatient unit with a first episode of wheezing during bronchiolitis season. - Children meeting criteria for the diagnosis of viral bronchiolitis (an acute infection of the lower respiratory tract, preceded by or accompanied by fever and/orrhinitis, and characterised by tachypnea, expiratory wheezing, and increased respiratory effort). - Moderately severe acute bronchiolitis (at least one of the following: oxygen saturation in room air <94%, moderate to severe accessory muscle use [clinical score ≥2], moderate to severe wheezing [clinical score ≥2], clinical score adapted from Schuh et al.). - English or Spanish consent Exclusion criteria - Underlying chronic cardiac or pulonary disease.	all study patients received chest physiotherapy and nasal suction 5 to 10 minutes before clinical evaluation. Discharge: - Continued need for hospitalisation defined to be hypoxia (Sa02 <94%), moderate to severe accessory muscle use (clinical score ≥2), or moderate to severe wheezing (clinical score ≥2). - Decision to discharge a patient was made by the pediatric inpatient team independent of the study investigator's clinical evaluation of severity of illness.	- Length of hospital stay. - All clinical evaluations were made immediately before the next scheduled study drug treatment. Statistical methods: - 26 patients per group would be required to achieve a power of >80% in the primary outcome measure (improvement in Sa02). This would detect a difference in improvement of two percentage points in Sa02 between the groups with a p value <0.05. - Between group comparisons of baseline data using chi-squared tests for categorical and t-tests for continuous. - Repeated measures analysis of variance used to assess changes in Sa02 at each of the	- 24 hours to Max Sa02: albuterol 2.2% (1.3% to 3.1%) placebo 1.8% (0.9% to 2.8%) p=0.48 - Time 0 to Max Sa02: albuterol 4.0% (2.6% to 5.4%) placebo 3.4% (2.4% to 4.5%) p=0.55 - Figure 2: Percentage of patients on albuterol and placebo with oxygen saturation <94% in room air at baseline (albuterol; placebo) At 0 hours: 69.6; 79.3 At 24 hours: 43.5; 37.9 At 48 hours: 21.7; 21.1 At 72 hours: 17.4; 21.1 log rank=0.04 p=0.84	hours of study. Log rank=1.29, p=0.26 - Subgroup analysis of patients <12 months (45 of 52 study patients, 86%) found the same results and conclusions as the full sample.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Significant concurrent illness (sepsis, meningitis, pneumonia, urinary tract infections, gastroenteritis). - Current gestational age <38 weeks. - History of wheezing requiring hospitalisation or bronchodilators. - History of bronchodilator therapy before current illness. - Concurrent steriod treatment. - Severe bronchiolitis requiring intensive care (mechanical ventilation, documented apnea, heart rate >200 beats per minute, or hypercarbia).		24 hour observation periods. - The significance of change in Sa02 from baseline was determined using Dunnett's q test. - Survival analysis was used to assess the time required for patients to reach preestablished discharge criteria. - Cox proportional hazards model to compare groups and control for factors influencing recovery. - Log rank test to assess equality of distributions. - Analysis of the final data indicated a power of 90% had been achieved.	7. Need for/use of feeding support: Not reported. 6. Need for CPAP/mechanical ventilation: 8. Adverse effects: - 3 withdrawn from albuterol group because of deterioration in respiratory status (oxygen desaturation and increasing respiratory distress), none required mechanical ventilation and all recovered over time. - Comparison of adverse events for albuterol versus control groups p =0.10, numbers not reported - No patients in either group experienced clinically significant side effects (tachycardia or dysrhythmia)	

I.12 What is the efficacy of inhaled corticosteroid therapy?

	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bentur,L., Shoseyov,D., Feigenbaum,D., Gorichovsky,Y., Bibi,H., Dexamethasone inhalations in RSV bronchiolitis: a double-blind, placebo-controlled study, Acta Paediatrica, 94, 866-871, 2005 Ref Id 210130 Country/ies where the study was carried out Israel Study type Randomised, double-blinded, plaebo-controlled trial. Aim of the study To evaluate the effect of inhaled dexamethasone on hospitalisation for RSV bronchiolitis. Study dates	Sample size 61 enrolled: 0.9% saline 32, dexamethasone 29. Characteristics Characteristic: 0.9% saline group; dexamethasone group (Mean±SD) - Females/males: 18/14; 15/14 - Age months:3.8±2; 3.3±2.5 - Prematurely born (7; 6) 02 saturation at admission: 18.6±84.6; 85.7±25.2 - Full term infants (25;23) 02 saturation at admission: 88±15; 86±18 Inclusion criteria - Aged 3-12 months. - First episode of wheezing and dyspnea. - RSV antigen detected by ELISA. Exclusion criteria - Previous treatment with systemic steroids. - Administration of inhaled beta-2 agonists or inhaled steroids prior to admission.	Interventions Dexamethasone group: 0.25mg inhaled dexamethasone and 1ml epinephrine. 0.9% saline group: 0.5ml 0.9% saline and 1ml epinephrine (total volume 2ml completed with 0.9% saline). - The hospital pharmacist prepared the solutions, both in identical containers and indistinguishable to researchers - Solutions given via a face mask, every 6 hours throughout the hospitalisation period. - Nebulised solutions given with 100%	Details Setting: Inpatient, nebulisation therapy continued until patients discharged. Randomisation and concealment: In blocks of 10 (five saline/five dexamethasone). Outcome measures: - Respiratory rate, pulse, oxygen saturation and clinical status documented every 8 hours. - Clincal score based on respiratory rate, wheezing, retraction, general condition and oxygen saturation also used by Tal et al. - Length of hospitalisation. - Duration of oxygen and IV fluids. Statistical methods: - A sample size of 20 patients per group would be required to	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay, days, (Mean±SD): - Prematurely born (7; 6) Saline 9.1±1.9 Dexamthasone 6.5±1.7 - Full term infants (25;23) Saline 5.5±1.9 Dexamethasone 5.2±1.8 3. Change in disease severity score at 4 to 7 days after starting treatment (Mean±SD) - Clincal score at admission: Saline 8±1.1 Dexamethasone 8.2±1.1	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selction bias: - Number of patients presented to hospital with bronchiolitis who did not meet inclusion criteria not reported. Detection bias: - Subjective clincal scoring system. Attrition bias: -Unclear if all 61 patients had complete follow-up. Performance bias: - Blinding unclear. - Number of physicians/observers not reported. Other information Figure 1 shows the overall time-to-discharge curve. The cumulative proportion of in-hospital stay of patients was lower in the treatment group than in the placebo group, mainly

	Participants	Interventions	Methods	Outcomes and Results	Comments
September 2002 to March 2003. Source of funding The authors acknowledge the statistical contribution of Michael Huerta.	- Other chronic diseases, e.g. bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), and congenital heart disease.	oxygen at a flow of 5l/min. - Nebulisation therapy continued until discharge. Additional treatment: - Supplemental oxygen was provided in the interval for any patient with an initial oxygen saturation ≤92% in room air as measured by pulse oximetry. - If respiratory rate >60 breaths/min, oral feeding was stopped and intravenous fluids were started. Criteria for discharge: - Evaluated by a senior physician who was part of the study. - No dyspnea, at least 10 hours	detect a clincal score change of SD 1, α=0.05, two-tailed test, power=80%. - ANOVA measures and Spearman rank correlation test for evaluating the effects. - Differences between groups analysed using a proportionality test for chi-squared analysis of contingency tables for non-parametric variables and unpaired t-test for parametric. - For survival analysis, discharge rate expressed by the proportion of children in hospital was analysed using Kaplan-Meyer and log-rank test. Follow-up: Re-evaluated by a pediatric pulmonologist at 1 week, 1 month and 3 months post-discharge.	- Clinical score at discharge: Saline 2.2±0.4 Dexamethasone 2.1±0.5 4. Change in O2 saturation Duration of oxygen, hours (Mean±SD): Saline 100.6±37.6 Dexamethasone 93.84±45.4 5. Duration of cough: Not reported. 6. Readmission Patients with recurrent hospitalisations: Saline 14 Dexamethasone 12 7. Adverse effects: Not reported.	days 5 and 6 post-hospitalisation (p<0.038).

	Participants	Interventions	Methods	Outcomes and Results	Comments
		without the need for oxygen support and oral feeding without the need for IV fluids.			
Full citation Cade,A., Brownlee,K.G., Conway,S.P., Haigh,D., Short,A., Brown,J., Dassu,D., Mason,S.A., Phillips,A., Eglin,R., Graham,M., Chetcuti,A., Chatrath,M., Hudson,N., Thomas,A., Chetcuti,P.A., Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis, Archives of Disease in Childhood, 82, 126-130, 2000 Ref Id 206465 Country/ies where the study was carried out	Sample size - 165 randomised into the study: 83 budesonide, 82 placebo. - Excluded from analysis: 1 placebo transferrred to a non-participating centre before trial treatment, 2 placebo RSV negative, 1 budesonide previously exposed to systemic cortcosteriods. - 161 completed: 82 budesonide, 79 placebo. Characteristics Characteristic: budesonide; placebo - Age, days (Mean±SD): 130±85; 120±84 - Sex, male/female: 45/37; 47/32 - Median duration of symptoms, days (IQR): 4 (2-6); 4 (2-5) - Atopic history: 43; 38 - Smoker at home: 55; 53 Inclusion criteria - Acute viral bronchiolitis defined as: the most common lower	Interventions Budesonide: - 1mg nebulised budesonide (Astra Pharmaceuticals Limited, Kings Langley, Hertfordshire, UK). - Suspended in vehicle or nebulised vehicle (sodium chloride, polysorbate 80, citric acid, sodium citrate, and disodium edetate). - Twice daily. - Given immediately after randomisation and within 12 hours of adminission until 14 days	Details Setting: Inpatient, five West Yorkshire hospitals. Randomisation and concealment: - Stratified by sex and centre. - Trial solution and sidestream nebulisers manufactured and packaged to ensure double-blinding. Outcome measures: - Proportion of infants who experienced at least one episode of coughing or wheezing over the 12 months after admission. - Duration of hospital admission. - Time taken to become symptom free. - Re-admission rates.	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay Days from first nebulisation until discharge, median (IQR): Budesonide 2 (1 to 3) Placebo 2 (1 to 4) Hazard ratio 1.10 95% CI 0.80 to 1.51 3. Change in disease severity score at 4 to 7 days after starting treatment: Hazard ratio for time to become	Limitations Base on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Only included infants with acute viral bronchiolitis. - Randomisation unclear. - 200 patients required in each arm, only 161 enrolled. Attrition bias: - Parental diaries avaliable for 79 out of 82 in budesonide group and 76 out of 79 in the placebo group. Performance bias: - Care may differ across the five hospitals. - Placebo treatment unclear. - Blinding unclear. - All but one infant in both arms recieved additional prescribed medication while on the ward. These included ipratropium bromide, β2-agonists, antibiotics,

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England Study type Multicentre, randomised, double-blinded, placebo-controlled trial. Aim of the study To evaluate short and long term effects of giving nebulised budesonide early in RSV bronchiolitis. Study dates Winter 1995-1996. Source of funding Astra Foundation provided a full financial support grant to undertake this study.	respiratory tract illness of infancy and results in hospital admission in 1-2% of all children under the age of 1 year. - <12 months of age. - Confirmed RSV infection. - Randomisation within 12 hours of administration. Exclusion criteria - Previous hospital admissions with respiratory tract illness. - Chronic respiratory illness. - Congential heart disease. - Prematurity. - Pre-existing immunodeficiencies. - Recent exposure to varicella or tuberculosis. - Prolonged exposure to systemic steriods.	after being assessed as fit for hospital discharge, up to a maximum of 21 days. Budesonide and placebo solutions nebulised over a fixed 10 minute period, using a tightly applied face mask driven by 6.5l/min oxygen and a Medic-aid Portaneb CR60 compressor at home. Discharge criteria: At least 12 hours lapsed since administration of the trial solution, when they are feeding well, and when they no longer require supplemental oxygen.	- General practitioner consultation rates. - Use of antiwheeze medication during follow-up. Statistical methods: - To detect a reduction to 30% in the budesonide arm, at 5% significance level with 80% power, 100 infants were required in each arm. - Categorical data: chi-squared test. - Continuous variables: t-tests or Wilcoxon-Mann-Whitney U test. - Survival analysis with the proportional hazards model used to compare time from first nebulisation to resolution of symptoms and to discharge, summarised by hazard ratios. Follow-up: - Parents kept daily diaries for 4 weeks, after which they only noted symptoms and medications.	asymptomatic for 48 hours (day 1-28) = 1.41 p=0.07 95% CI 0.98 to 2.04 4. Change in O2 saturation: Not reported. 5. Duration of cough - Number of coughing/wheezing episodes, discharge to day 28 (Mean±SD): Budesonide 17.0±7.6 Placebo 17.1±8.5 p=0.91 95% CI -2.72 to 2.41 - At least one day with coughing/wheezing over the 12 month follow-up: Budesonide 78 out of 79 available diaries	and/or intravenous steriods. No differences between the two arms, but numbers not reported. - General practitioner prescriptions during 12 months after discharge. Detection bias: - Reliability of parent diaries. Other information Prescribed bronchodilators by general practitioners: Budesonide 60% Placebo 67% p=0.42 Prescribed steroids by general practitioners: Budesonide 50% Placebo 60% p=0.23 Post-discharge end points: - At the 14 day follow-up visit, 42 parents in budesonide and 48 parents in placebo told the research nurse that their child had been nebulised at home twice daily for 14 days after discharge. - Daily symotom diaries were complete and reliable for the first 28 days after discharge (96%

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			- After discharge a research nurse made home visits at 2 weeks, 4 weeks and then monthly for 12 months.	Placebo 75 out of 76 available diaries p=0.98 95% CI -3% to 3% 6. Readmission Number of infants re-admitted for respiratory morbidity over 12 months: Budesonide 13 Placebo 14 p=0.78 95% CI -14% to 10% - Number of general practitioner visits for respiratory morbidity relating to the year after discharge (available for review: budesonide 78, placebo 72), median (IQR): Budesonide 4 (2-6) Placebo 4.5 (2-9) p=0.29 95% CI -2 to 0	complete in budesonide and 98% complete in placebo; two and six diaries, respectively, were stopped before day 28). - Analysis of the time taken to become asymptomatic and the number of days with coughing or wheezing episodes was restricted to the first 28 days after discharge. This end point was censored on day 28 for infants still symptomatic on day 28. Time taken for half the infants to become asymptomatic for 48 hours: - Budesonide 10 days, 95% CI 10 to 13 - Placebo 12 days, 95% CI 10 to 16 - Difference not significant in survival analysis, p=0.07

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				7. Adverse effects: - Required intravenous fluids and/or nasogastric feed treatment Budesonide 35% Placebo 37% p=0.86 95% CI -17% to 13% - One infant in budesonide arm and two in placebo arm were transferred to intensive care units.	
Full citation Richter,H., Seddon,P., Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing, Journal of Pediatrics, 132, 849-853, 1998	Sample size Budesonide 21 Placebo 19 Characteristics Characteristic: budesonide; placebo - Male/female: 12/9; 10/9 - Age weeks, median (range): 16.3 (4.4-40.6); 10.8 (3.6-29.1)	Interventions Budesonide: - Budesonude suspension for nebulisation (Pulmicort respulse, Astra Pharmaceuticals Ltd., Kings Langley, UK, 250 and 500µg/ml).	Details Setting: - Royal Alexandra Children's Hospital, Brighton. - Trial medication started in hospital and continued at home after discharge.	Results Protocol outcomes 1. Hospital admission rate: Required hospitalisation for at least 2 days after trial entry Budesonide 15	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Randomisation method not described. - Number of infants presented with bronchiolitis who did not

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Ref Id 208003 Country/ies where the study was carried out England Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study To determine the effectiveness of nebulised budesonide in the treatment of acute bronchiolitis and in the prevention of postbronchiolitis wheezing. Study dates Not reported. Source of funding Not reported.	- Gestation weeks, median (range): 38 (34-41); 39 (36-42) - RSV positive: 16 (76%); 17 (89%) - Family history of atopy: 18 (86%); 12 (63%) - Smoker at home: 13 (62%); 13 (68%) Inclusion criteria - Bronchiolitis defined as: an infection of the lower respiratory tract, usually caused by the respiratory syncytical virus; up to 2% of all infants are hospitalised for this condition in the first year of life. - <12 months of age. - No previous wheezing episodes. - Hospitalised with the clincal features of bronchiolitis (tachypnea, recession, wheezing and crepitations). Exclusion criteria - Congenital abnormality. - Preexisting pulmonary disease. - Immune deficiency. - Need for assisted ventilation.	- Twice daily starting with 1mg in 2ml every 12 hours for the first 5 days. - Then 500µg in 2ml every 12 hours for the remainder of the 6-week treatment period. Placebo: 2ml nebulised placebo (0.9% saline) every 12 hours for 6 weeks. - The trial medication was started in the hospital and continued at home after discharge. - Both budesonide and placebo supplied in plastic respules prepared by Astra	Randomisation and concealment: - Randomisation method not described. - Details only held by hospital pharmacist. - Throughout the study, the investigators, nursing and medical staff, and parents were unaware to which treatment groups infants had been assigned. Outcome measures: - Single observer assessed each infant's respiratory symptoms twice daily until discharge. - Change in clincal score 48 hours after trial entry (based on respiratory rate, oxygen concentration required to keep Sa02 >92%, presence of wheeze, degree of recession, need for intravenous fluid or nasogastric tube feeding). - Number of days spent in oxygen.	Placebo 12 2. Length of hospital stay (days): Budesonide median 2.0, range 1 to 11 Placebo median 3.0, range 1 to 7 p=0.90 95% CI -1.0 to 1.0 3. Change in disease severity score at 4 to 7 days after starting treatment - Change in clinical score 48 hours after trial entry, median (range): Budesonide -2.0 (-6 to 6) Placebo -1.0 (-9 to 2) p=0.92 95% CI -3.0 to 2.0 - Mean daily symptom scores during 6-week treatment period, median (range):	meet inclusion criteria not reported. Attrition bias: - One infant in budesonide group lost to follow-up after 6-week treatment course because of social problems. Performance bias: - Parents use of terbutaline respules (Astra) for nebulisation. - No restrictions were imposed on other drug therapies, either in hospital or during the follow-up period, to avoid interference with normal clincal practice - Discharge criteria not reported. - Reliability of parent diaries. Detection bias: - Two subjective clinical scoring systems, Noble et al. used by parents, Westley et al. used by observer. Other information Usuage during the 6-week treatment period: - Infants not given bronchodilators Budesonide 9 (45%) Placebo 8 (42%) p=1.0

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		Pharmaceuticals. - Side stream nebulisers (Medic-Aid, Pagham, UK) with face masks were used to administer the treatments with a flow of 6l/min provided by wall oxygen in the hospital and by Portaneb compressors (Medic-Aid) after discharge. - After discharge parents were given a supply of terbutaline respules (Astra) for nebulisation when their infants were discharged to use at their discretion for wheezing episodes during the remainder of the treatment period. - No restrictions were imposed on other drug	- Maximum oxygen requirements. - Number of days to discharge. - Length of infant. Statistical methods: - To detect a 50% reduction in wheezing episode incidence with 80% power and 0.05 significance level, 25 patients required in each group. - Categorical data: chi-squared or Fisher exact test. - Continuous variables: non-parametric by Mann Whitney U test. Follow-up: - Parents calculated clinical scores (also used by Noble et al. based on cough and wheeze on a 0 to 3 scale) and use of inhaled bronchodilators in diaries twice daily during the treatment period and noted when symptoms appeared after this period for 6 months.	Budesonide 2.7 (0.0 to 5.6) Placebo 1.5 (0.0 to 8.5) p=0.94 95% CI -1.7 to 1.1 4. Change in O2 saturation: Not reported. 5. Duration of cough - Prevalence of wheeze during the 6-month follow-up after completion of treatment: Budesonide 15 (75%) Placebo 15 (79%) p=1.0 95% CI -6.0 to 5.0 - Number of symptom-free days during the 6-week treatment period, median (range): Budesonide 8.5 (0 to 28) Placebo 12.0 (0 to 28)	- Infants given bronchodilators >5 occasions Budesonide 10 (50%) Placebo 4 (21%) During the 6-month follow-up period: - Infants given bronchodilators Budesonide 13 (65%) Placebo 10 (53%) p=0.52 - Infants given inhaled oral steriods Budesonide 3 (15%) Placebo 3 (16%) p=1.0 p=0.1 Scores for cough and wheeze and for wheeze only also reported (table 4).

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		therapies for infants in the study, either in hospital or during the follow-up period.	- Infants reviewed every 6 weeks for 6 months.	p=0.57 95% CI -6.0 to 7.0 6. Readmission For respiratory problems during 6-month follow-up: Budesonide 10 (50%) Placebo 2 (10.5%) p<0.05 7. Adverse effects: Not reported.	
Full citation Fernandes,R.M., Bialy,L.M., Vandermeer,B., Tjosvold,L., Plint,A.C., Patel,H., Johnson,D.W., Klassen,T.P., Hartling,L., Glucocorticoids for acute viral bronchiolitis in infants and young children.[Update of Cochrane Database Syst Rev. 2010;(10):CD004878; PMID: 20927740],	Sample size N=17 trials N=2596 children Characteristics *additional information accessed from full text of trials because it was not reported in the systematic review Barlas 1998 Inclusion criteria: age <24 months, first episode wheezing, clinical score between 4 and 10 (mild to moderate) Exclusion criteria: history of premature heart disease, chronic heart and lung problems, prior	Interventions Short-term inhaled or systemic glucocorticoids (any type, dosage, duration, and route of administration), alone or combined with co-interventions e.g. bronchodilators	Details The following databases were searched: - Cochrane Central Register of Controlled Trials (CENTRAL, 2012 issue 12, searched January 2013), which contains the Cochrane Acute Respiratory Infections Group's Specialist Register - MEDLINE (1950 to January week 2, 2013) - EMBASE (1980 to January 2013)	Results 1. Admissions day 1 (outpatient studies) a. All studies Intervention: 205/907 Control: 217/855 RR 0.92 (95% CI 0.78 to 1.08) I^2 = 0% [Random-effects; 10 trials: Barlas 1998 (prednisolone and budesonide arms vs mist tent placebo arm);	Limitations Risk of bias of included studies, as assessed by review authors and indirectness assessed by NCC-WCH technical team Barlas 1998 - Unclear method of randomisation and allocation concealment - No blinding of participants, care givers or outcome assessors - No missing outcome data reported Indirectness: review authors combined inhaled and systemic corticosteroid arms for analysis, also included corticosteroid+bronchodilator vs

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Cochrane Database of Systematic Reviews, 6, CD004878-, 2013 Ref Id 261181 Country/ies where the study was carried out Various Study type Systematic review of randomised controlled trials Aim of the study To review the efficacy and safety of systemic and inhaled glucocorticoids in children with acute viral bronchiolitis Study dates The search was performed in January 2013; review content was assessed as up-to-date by the authors in January 2013 Source of funding	diagnosis of bronchial asthma, used bronchodilators and anti-inflammatory medications Sample size: 90 Intervention: (a) Predisolone IV (2mg/kg, single dose); (b) Budenoside NEB (0.5 mg, single dose); (c) Prednisolone IV (2 mg/kg, single dose) plus Albuterol NEB (0.15 mg/kg, single dose) Comparator: (a) Mist tent; (b) Albuterol NEB Other care provided: not stated Age of children: mean ± SD; 8.52 ± 0.59 months Percentage of children with RSV: 33.3% Setting: Outpatient - emergency department/outpatient clinic Country: Turkey Bentur 2005 Inclusion criteria: age 3 to 12 months, first episode wheezing/dyspnoea, RSV present, parental consent Exclusion criteria: previous therapy with systemic glucocorticoids, inhaled beta-2-agonists prior to admission, other chronic diseases Sample size: 61 Intervention: Dexamethsone NEB (0.25 mg) plus epinephrine NEB (1 ml). Nebulised in 5 L/min pre-specified 100% oxygen, every 6 h until discharge Comparator: Placebo - 0.9% saline NEB (0.5 ml) plus		- LILACS (1982 to January 2013) - Scopus (1823 to January 2013) - IRAN MedEx (1998 to November 2009) - Clinicaltrials.gov - ICTRP Search Portal - World Health Organization - Conference proceedings of Pediatric Academic Societies (2003 to 2012), European Respiratory Society (2003 to 2011), American Thoracic Society (2006 to 2012) Additional published, unpublished or ongoing studies were identified by handsearching reference lists and the included and excluded studies lists of relevant reviews. Additional information was not obtained from trial authors. Data collection and analysis Five review authors independently screened titles, keywords and abstracts for inclusion.	Barlas 1998 (prednisolone plus albuterol arm vs albuterol arm); Berger 1998; Corneli 2007; Goebel 2000; Kuyucu 2004; Mesquita 2009; Plint 2009 (epinephrine plus dexamethasone arm vs epinephrine plus placebo arm); Plint 2009 (dexamethasone plus placebo arm vs placebo plus placebo arm); Schuh 2002] b. Studies with protocolised use of bronchodilator Intervention: 49/373 Control: 57/344 RR 0.85 (95% CI 0.56 to 1.29) I^2 = 16% [Random-effects; 7 trials: Barlas 1998 (prednisolone plus albuterol arm vs albuterol arm); Berger 1998; Goebel 2000;	placebo+bronchodilator in analysis (protocolised use of bronchodilator) Bentur 2005 - Adequate method of randomisation and allocation concealment - Adequate blinding - No missing outcome data reported Indirectness: combined corticosteroid+bronchodilator vs placebo+bronchodilator (protocolised use of bronchodilator) Berger 1998 - Unclear method of randomisation, adequate allocation concealment - Adequate blinding - 4/42 lost to follow up Indirectness: protocolised use of bronchodilator Cade 2000 - Unclear method of randomisation and allocation concealment - Unclear method of blinding - 3 post-randomisation exclusions, balanced between groups Indirectness: none Corneli 2007 - Adequate method of randomisation and allocation concealment - Adequate blinding

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Knowledge Synthesis Grant (FRN 91767), Canadian Institutes of Health Research, Canada Programme for Advanced Medical Education (Fundação Calouste Gulbenkian, Fundação Champalimaud, Ministério da Saúde and Fundação para a Ciência e Tecnologia), Portugal Cochrane Incentives Funding Scheme, UK	epinephrine NEB (1 ml). Nebulised in 5 L/min pre-specified 100% oxygen, every 6 h until discharge Other care provided: all groups received oxygen therapy if SaO2 <92%, IV fluids if respiratory rate >60 bpm Age of children: mean ± SD; intervention group: 3.3 ± 2.5 months; control group: 3.8 ± 2.0 months Percentage of children with RSV: 100% Setting: Inpatients Country: Israel Berger 1998 Inclusion criteria: ≤18 months of age, first episode wheezing associated with low grade fever, rhinitis, tachypnoea and increased respiratory effort, otherwise healthy infant Exclusion criteria: chronic cardiopulmonary disease, asthma, proven or suspected acute bacterial infection, previous therapy with glucocorticoids, symptoms > 7 days, fever >38.5°C, severe bronchiolitis (clinical score ≥ 7) Sample size: 42 Intervention: Prednisone ORAL (1mg/kg, twice daily, 3 days) Comparator: Placebo ORAL (1mg/kg, twice daily, 3 days) Other care provided: all groups received inhaled albuterol		Data were extracted by seven authors using a standardised form and three authors independently checked for accuracy. Disagreements and discrepancies were resolved by consensus or inconsultation with a third author. Data were analysed using RevMan 5 software. Methodological quality was assessed under the headings of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Dichotomous variables were pooled using risk ratios. For continuous variables measured on the same scale mean differences were pooled, for those measured on different scales standardised mean differences were pooled. Hetereogeneit y was measured using	Kuyucu 2004; Mesquita 2009; Plint 2009 (epinephrine plus dexamethasone arm vs epinephrine plus placebo arm); Schuh 2002] c. Studies with no protocolised use of bronchodilator Intervention: 156/534 Control: 160/511 RR 0.94 (95% CI 0.79 to 1.13) I^2 = 0% [Random-effects; 3 trials: Barlas 1998 (prednisolone and budesonide arms vs mist tent placebo arm); Corneli 2007; Plint 2009 (dexamethasone plus placebo arm vs placebo plus placebo arm)] 2. Length of stay (inpatient studies) a. All studies Intervention: N=322	- Intention-to-treat analysis; no missing data for primary outcomes, less than 10% follow up data lost for secondary outcomes Indirectness: none De Boeck 1997 - Unclear method of randomisation and allocation concealment - Double blind but no other details of blinding reported - 3/32 were lost to follow-up, unclear from which groups Indirectness: protocolised use of bronchodilator Goebel 2000 - Adequate method of randomisation and allocation concealment - Adequate blinding - 3 post randmisation exclusions, plus 16/51 participants had missing primary outcome data Indirectness: protocolosied used of bronchodilator Gomez 2007 - Adequate method of randomisation, unclear allocation concealment - Adequate blinding - No information about losses to follow up or exclusions Indirectness: no placebo comparison, review authors used corticosteroid+bronchodilat or vs placebo+bronchodilator in

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	solution 0.03 ml/kg/dose (0.15 mg/kg/dose) every 4 to 6 hours, oxygen and hydration as needed Age of children: mean ± SD; intervention group: 5.2 ± 0.7 months; control group: 4.8 ± 0.9 months Percentage of children with RSV: intervention group: 50%; control group: 50% Setting: Outpatients - emergency department Country: Israel Cade 2000 Inclusion criteria: <12 months of age, confirmed RSV, informed consent, randomised within 12 hours of admission Exclusion criteria: history of hospitalisation with respiratory tract illness, chronic respiratory tract illness, congenital heart disease, prematurity, pre-existing immunodeficiencies, recent exposure to varicella or tuberculosis, prolonged exposure to systemic glucocorticoids Sample size: 165 Intervention: Budesonide NEB (1 mg, twice daily for 10 min, 14 to 21 days) Comparator: Placebo NEB (dose not reported, twice daily for 10 mib, 14 to 21 days) Other care provided: all groups received 6.5 L/min oxygen therapy, reported use of ipratropium bromide, beta-2-		I^2 statistic. A random-effects model was used regardless of heterogeneity due to expected differences in interventions, outcomes and measurement instruments. Missing data Trials were classified as either intention-to-treat with all data, intention-to-treat with imputation of missing data, intention-to-treat with available case analysis, per protocol analysis or treatment received analysis. Review authors did not impute missing data for dropouts. Standard deviations were calculated, if missing, where possible. Where clinical scores were reported as dichotomous data, odds ratios were re-expressed as standardised mean differences using existing approaches. Where data were unavailable for time points of itnerest, the closest time point was	Control: N=311 MD -0.18 (95% CI -0.39 to 0.04) I^2 = 16% [Random-effects; 8 trials: Bentur 2005; Cade 2000; De Boeck 1997; Gomez 2007; Klassen 1997; Richter 1998; Teeratakulpisarn 2007; Zhang 2003] b. Studies with protocolised use of bronchodilator Intervention: N=102 Control: N=104 MD -0.12 (95% CI -0.23 to 0.00) I^2 = 0% [Random-effects; 4 trials: Bentur 2005; De Boeck 1997; Gomez 2007; Klassen 1997] c. Studies with no protocolised use of bronchodilator Intervention: N=220 Control: N=207 MD -0.31 (95%CI -0.83 to 0.20)	analysis (protocolised use of bronchodilator) Klassen 1997 - Adequate method of randomisation and allocation concealment - Adequate blinding - 5 postrandomisation exclusions and 1 child discharged with missing outcome data Indirectness: protocolised use of bronchodilator Kuyucu 2004 - Unclear method of randomisation and allocation concealment - Adequate blinding - 21/90 children had missing outcome data, imbalanced between groups, reasons for missing data not reported - Duration of illness before admission was longer in comparator group (a) than intervention group (a) Indirectness: review authors analysed epinephrine plus dexamethasone versus epinephrine plus placebo and salbutamol plus dexamethasone versus salbutamol plus placebo (protocolised use of bronchodilator in all four arms of the trial) Mesquita 2009 - Adequate method of randomistion and allocation

	Participants	Interventions	Methods	Outcomes and Results	Comments
	agonists, oral/IV glucocorticoids and antibiotics - no differences in prescribing practices between the two arms Age of children: mean ± SD; intervention group: 4.3 ± 2.8 months; control group: 4.0 ± 2.8 months Percentage of children with RSV: 100% Setting: Inpatients Country: UK Corneli 2007 Inclusion criteria: 2 to 12 months of age, first episode of bronchiolitis, within 7 days of onset, moderate to severe (RDAI ≥ 6) Exclusion criteria: wheezing, asthma, previous use of bronchodilators, prior adverse event to dexamethasone, heart or lung disease, premature birth (<36 weeks), immunosuppression or immunodeficiency, therapy with glucocorticoids in previous 14 days, active or recent exposure to varicella, critically ill, parent unable to speak English/Spanish Sample size: 600 Intervention: Dexamethasone ORAL (1 ml/kg, max 12 mg, single dose) Comparator: Placebo ORAL (1 ml/kg, max 12 mg, single dose) Other care provided: reported use of albuterol, epinephrine		used. Where there was more than one time point the one with the largest magnitude of change was used. Unit of analysis issues Some of the included studies were multi-arm or factorial studies in which more than two intervention groups were eligible to contribute to several comparisons to a single meta-analysis e.g glucocorticoid vs placebo in two arms and glucocorticoid +bronchodilator vs placebo + bronchodilator in two arms, with both contributing to the overal glucocorticoid vs placebo comparison. When comparisons were independent (no intervention group in common) data were included from these arms with no transformation. If needed and feasible, active groups were pooled to avoid double counting of the	I^2 = 38% [Random-effects; 4 trials: Cade 2000; Richter 1998; Teeratakulpisarn 2007; Zhang 2003] 3. Clinical scores (outpatient studies) a. At 60 minutes after treatment Intervention: N=512 Control: N=494 MD -0.04 (95% CI -0.16 to 0.09) I^2 = 0% [Random-effects; 6 trials: Barlas 1998 (prednisolone and budesonide arms vs mist tent placebo arm); Barlas 1998 (prednisolone plus albuterol arm vs albuterol arm); Mesquita 2009; Plint 2009 (epinephrine plus dexamethasone arm vs epinephrine plus placebo arm); Plint 2009	concealment - Adequate blinding - 15/80 children were excluded post-enrolment (reasons adequately reported) Indirectness: protocolised use of bronchodilator Plint 2009 - Adequate method of randomisation and allocation concealment - Adequate blinding - 3/800 with missing outcome data Indirectness: review authors analysed epinephrine plus dexamethasone versus epinephrine plus placebo and dexamethasone plus placebo versus placebo plus placebo (protocolised use of bronchodilator in all four arms of the trial Richter 1998 - Unclear method of randomisation and allocation concealment - Adequate blinding - 1/40 had missing outcome data - No differences in bronchodilator and oral corticosteroid use between groups Indirectness: none Roosevelt 1996 - Unclear method of randomisation, adequate allocation concealment

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	Percentage of children with RSV: intervention group: 66.9%; control group: 57% Age of children: mean ± SD; intervention group: 5.1 ± 2.6 months; control group: 5.1 ± 2.8 months Setting: Outpatients - emergency department Country: USA De Boeck 1997 Inclusion criteria: <24 months of age, detection of RSV, first episode of wheezing or shortness of breath, onset of illness within the previous 5 days, informed consent Exclusion criteria: heart, lung or immune disorder, premature infants born before 34 weeks Sample size: 32 Intervention: Dexamethasone IV (on day 1: 06.mg/kg, 2 doses; on days 2 and 3: 0.15 mg/kg, 2 doses) Comparator: Placebo IV Other care provided: all groups received 0.25 ml salbutamol (0.5%) and 0.5 ml ipratropium bromide (0.025%), both aerosolised ever 6 h, also reported use of antibiotics Age of children: median (interquartile range); intervention group: 6.2 months (3.7 to 7.5); control group: 7.1 months (4.4 to 8.9) Percentage of children with RSV:		comparator group when there was more than one active group (e.g. two glucocorticoid groups vs placebo). No treatment groups were included twice in the same meta-analysis. Review authors performed "within the table" analysis where data were included separately e.g. for the glucocorticoid vs placebo comparison, glucocorticioid + bronchodilator vs placebo +bronchodilator and glucocorticoid +placebo vs double placebo were included separately. Sensitivity analysis pooling all arms was also performed ("at the margins" analysis). Subgroup analysis Prespecified subgroups on primary outcomes: - studies with protocolised use of bronchodilators vs no/unclear protocolised use - studies with all	(dexamethasone plus placebo arm vs placebo plus placebo arm); Schuh 2002] b. At 3 to 10 days after treatment Intervention: N=125 Control: N=99 MD -0.20 (95% CI -0.61 to 0.21) I^2 = 55% [Random-effects; 5 trials: Berger 1998; Goebel 2000; Kuyucu 2004 (epinehprine plus dexamethasone arm vs epinephrine plus placebo arm); Kuyucu 2004 (epinehprine plus dexamethasone arm vs epinephrine plus placebo arm); Kuyucu 2004 (salbutamol plus dexamethasone arm vs salbutamol plus placebo arm); Schuh 2002]	- Investigators were unaware of treatment allocation - 29/122 had missing outcome data - More children in the dexamethasone group than the placebo group had oxygen saturation ≤95% at enrolment Indirectness: none Schuh 2002 - Adequate method of randomisation and allocation concealment - Adequate blinding - 3/71 had missing data - Significant difference in baseline for family history of atopy - 22% of children in the placebo group received corticosteroids - 9 protocol violations - did not pursue therapy at home Indirectness: protocolised use of bronchodilator Teeratakulpisarn 2007 - Adequate method of randomisation and allocation concealment - Adequate blinding - 5/179 had missing data Indirectness: none Zhang 2003 - Adequate method of randomisation and allocation concealment - No blinded placebo control although authors state study

	Participants	Interventions	Methods	Outcomes and Results	Comments
	100% Setting: Inpatients Country: Belgium Goebel 2000 Inclusion criteria: ≤23 months of age, viral respiratory tract infection, first time wheeze that did not completely clear after 1 dose of nebulised albuterol Exclusion criteria: history of immune defect, neurological disease with possible aspiration, gastroesophageal reflux, congenital or acquired chronic heart or lung disease; mechanical ventialtion, birth <36 weeks, temperature >38.5°C (rectal), antibiotic therapy < 1 week or antipyretic therapy <8 h before enrolment, concomitant bacterial infection, emesis precluding oral medication, inital bronchiolitis score <2 or > 9 Sample size: 51 Intervention: Prednisolone ORAL (2mg/kg/day, twice per day for 5 days) Comparator: Placebo ORAL (100 ml each of water and glycerin with 5 ml of cherry-flavoured Kool Aid and 10 mg of quinine, twice per day for 5 days) Other care provided: all groups received albuterol - 0.15 mg/kg first dose, subsequent doses 0.3mg/kg/d 3 times a day by mounth or 0.15 mg/kg/dose qid by nebuliser		participants exclusively respiratory syncytial virus (RSV)-positive vs RSV-negative/unspecified RSV status - studies with all participants exclusively less than 12 months of age vs some participants older than 12 months of age - studies with all participants exclusively atopic versus some participants not atopic/unspecified atopic status - type of glucocorticoid and high vs low daily and overall dose	4. Clinical scores (inpatient studies) a. 3 to 6 hours after treatment Intervention: N=89 Control: N=85 MD -1.03 (95% CI -1.87 to -0.19) I^2 = NC [Random-effects; 1 trial: Teeratakulpisarn 2007] b. 24 to 72 hours Intervention: N=141 Control: N=130 MD -0.53 (95% CI -1.14 to 0.08) I^2 = 41% [Random-effects; 4 trials: De Boeck 1997; Klassen 1997; Richter 1998; Teeratakulpisarn 2007] 5. Oxygen saturation (outpatients) a. At 60 minutes after treatment Intervention: N=476 Control: N=460 MD -0.27 (95% CI -0.73 to 0.19)	investigators were blinded to treatment assignment - 2/52 had missing long-term outcome data - 2/28 in the intervention group received additional corticosteroids - IV hydrocortisone Indirectness: bronchodilator part of standard care, unclear how many children in each group received nebulised fenterol (given at physician's discretion based on standard protocol) Other information Abbreviations: IV, intravenous, IM, intramuscular, NEB, nebulised, RSV, respiratory syncytial virus The review was first published in issue 1, 2001 of The Cochrane Library and searches were updated in November 2009 and January 2013 Review authors defined bronchiolitis as "first episode of acute wheezing, respiratory distress and clinical evidence of a viral infection (cough, coryza, fever)". Trials where bronchodilators were protocolised were distinguished from trials were bronchodilators were at the discretion of the physician.

	Participants	Interventions	Methods	Outcomes and Results	Comments
	Age of children: median (range): intervention group: 4.0 months (0 to 13); control group: 4.5 months (0 to 16) Percentage of children with RSV: 51% Setting: Outpatients - paediatric emergency department/children's clinic Country: USA Gomez 2007 Inclusion criteria: age 1 to 18 months, observed in the emergency department, clinical and radiological diagnosis of bronchiolitis, <72 h of evolution of symptoms, RDAI score >2, Silverman-Andersen score > 0, informed consent Exclusion criteria: previous bronchospasm/bronchiolitis, congenital heart disease, chronic lung disease, possible bronchopneumonia, children treated with salbutamol/dexamethasone in the previous 48 h Sample size: 49 Intervention: Dexamethasone NEB (0.5 ml/2mg, every 4 hours for 24 hours) plus Salbutamol NEB (0.3 ml/1.5 mg, every 4 hours for 24 hours) Comparator: Salbutamol NEB (0.3 ml/1.5mg, every 4 hours for 24 hours) Other care provided: not reported Age of children: mean ± SD;			I^2 = 37% [Random-effects; 5 trials: Barlas 1998 (prednisolone and budesonide arms vs mist tent placebo arm); Barlas 1998 (prednisolone plus albuterol arm vs albuterol arm); Mesquita 2009; Plint 2009 (epinephrine plus dexamethasone arm vs epinephrine plus placebo arm); Plint 2009 (dexamethasone plus placebo arm vs placebo plus placebo arm)] b. At 24 to 72 hours after treatment Intervention: N=20 Control: N=18 MD 0.20 (95% CI -1.01 to 1.41) I^2 = NC [Random-effects; 1 trial: Berger 1998] 6. Oxygen saturation	Studies with inhaled bronchodilator vs placebo comparison: Barlas 1998, Cade, Richter Studies with systemic bronchodilator vs placebo comparison: Cochrane review does not report the following outcomes which were of interest to the GDG: duration of cough, adverse effects and need for CPAP/mechanical ventilation (systemic corticosteroids only) Inpatient studies: Bentur, Cade, De Boeck, Gomez, Klassen, Richter, Roosevelt, Teeratakulpisarn, Zhang Outpatient studies: Barlas, Berger, Corneli, goebel, Kuyucu, Mesquita, Plint, Schuh Percentage of children admitted to hospital in outpatient studies: Berger: 7/42 (16%); Corneli: 242/600 (40%); Goebel: 6/51 (12%)

	Participants	Interventions	Methods	Outcomes and Results	Comments
	intervention group: 5.22 ± 1.6 months; control group: 5.7 ± 1.3 months Percentage of children with RSV: not reported Setting: Inpatients - emergency department and infant paediatric department Country: Mexico Klassen 1997 Inclusion criteria: >6 weeks <15 months of age, first time wheeze, evidence of viral infection (rhinorrhoea/temperature >37.5°C), admitted to inpatient ward, SaO2 <95%, RDAI score >6 Exclusion criteria: underlying disease that might affect cardiopulmonary status, asthma, wheezing/cough previously treated with bronchodilators, therapy with glucocorticoids within the past 2 weeks, history of adverse events with glucocorticoids Sample size: 72 Intervention: Dexamethasone ORAL (first dose: 0.5 mg/kg; second dose: 0.3 mg/kg; max 3 doses) Comparator: Placebo ORAL (70% sucrose solution, max 3 doses) Other care provided: all groups received nebulised salbutamol (0.15 mg/kg) every 4 hours for first 24 h, 35% oxygen in a plastic tent, reported use of additional bronchodilators and antibiotics			(inpatients) a. At 6 to 12 hours after treatment Intervention: N=35 Control: N=32 MD -0.70 (95% CI -1.98 to 0.58) I^2 = NC [Random-effects; 1 trial: Klassen 1997] b. At 24 to 72 hours after treatment Intervention: N=35 Control: N=32 MD 1.10 (95% CI -0.77 to 2.97) I^2 = NC [Random-effects; 1 trial: Klassen 1997] 7. Hospital readmissions (inpatient studies) a. At 2 to 10 days after treatment Intervention: N=35 Control: N=32 MD 3.66 (95% CI 0.43 to 31.03) I^2 = NC [Random-effects; 1 trial: Klassen 1997] b. At 10 to 30 days after	

	Participants	Interventions	Methods	Outcomes and Results	Comments
	(assume balanced) Age of children: mean: intervention group: 4.68 months; control group: 4.68 months Percentage of children with RSV: intervention group: 86%; control group: 88% Setting: Inpatients - inpatient wards, paediatric tertiary hospital Country: Canada Kuyucu 2004 Inclusion criteria: 2 to 21 months of age, admitted with first episode of wheezing, clinical findings compatible with acute bronchiolitis, RDAI ≥ 4 Exclusion criteria: history of wheezing, previous therapy with bronchodilators, previous diagnosis of asthma or allergic bronchitis, personal history of atopic dermatitis or allergic rhinitis, chronic cardiac or pulmonary disease, any glucocorticoid therapy in the previous 2 weeks, signs of severe respiratory disease, bacterial infection, parental history of asthma or atopic disease Sample size: 90 Intervention: (a) Epinephrine NEB (3ml of 1:1000 L-epinephrine, nebulised with oxygens, flow 5 to 6 min L/min for 10 min, second dose given if no improvement after 2h) plus Dexamethasone IM (0.6 mg/kg, single dose); (b) Salbutamol NEB (0.15 mg/kg of 1			treatment Intervention: N=154 Control: N=138 MD 0.41 (95% CI 0.11 to 1.53) I^2 = NC [Random-effects; 1 trial: Roosevelt 1996] 8. Adverse events (see Table 6 in Cochrane review for original data - meta-analysis performed by NCC-WCH) Vomiting Intervention: 23/70 (6.4%) Control: 21/694 (3%) RR 1.08 (0.60 to 1.94) I^2 = 0% Bleeding Intervention: 31/488 (6.4%) Control: 31/488 (6.4%) RR 1.00 (0.62 to 1.62) I^2 = 0% Hypertension Intervention: 1/398 (0.25%) Control: 1/399	

	Participants	Interventions	Methods	Outcomes and Results	Comments
	mg/L solution added to 0.9% saline to total 3 ml, flow 5 to 6 min L/min for 10 min, second dose given if no improvement after 2h) plus Dexamethasone IM (0.6 mg/kg, single dose) Comparator: (a) Epinephrine NEB (3ml of 1:1000 L-epinephrine, nebulised with oxygens, flow 5 to 6 min L/min for 10 min, second dose given if no improvement after 2h) plus Placebo IM (single dose, other details not reported); (b) Salbutamol NEB (0.15 mg/kg of 1 mg/L solution added to 0.9% saline to total 3 ml, flow 5 to 6 min L/min for 10 min, second dose given if no improvement after 2h) plus Placebo IM (single dose, other details not reported) Other care provided: not reported Age of children: mean ± SD; intervention group (a): 7.2 ± 0.8 months; intervention group (b): 7.9 ± 1.0 months; control group (a): 9.6 ± 1.3 months; control group (b): 9.9 ± 1.7 months Percentage of children with RSV: not reported Setting: Outpatients - paediatric outpatient clinics and emergency department Country: Turkey Mesquita 2009 Inclusion criteria: 2 to 24 months of age, first episode of bronchiolitis defined as			(0.25%) RR 1.00 (0.10 to 9.60) I^2 = 0% Pneumonia Intervention: 2/438 (0.46%) Control: 6/421 (1.4%) RR 0.43 (0.09 to 2.02) I^2 = 0% Tremor Intervention: 9/398 (2.3%) Control: 6/399 (1.5%) RR 1.46 (0.51 to 4.18) I^2 = 0% Pallor/flushing Intervention: 38/398 (9.5%) Control: 38/399 (9.5%) RR 1.00 (0.65 to 1.54) I^2 = 0%	

	Participants	Interventions	Methods	Outcomes and Results	Comments
	respiratory distress, respiratory rate 40 to 80/min and wheezing, <7 days after onset of a cold Exclusion criteria: clinical or radiological pneumonia, cardiopulmonary congenital malformations, bronchopulmonary dysplasia, cystic fibrosis, foreign body aspirations, neurological alteration, previous wheezing or asthma episode, inhaled or systemic glucocorticoid <15 days, beta-2-agonists <4 h, history of atopy in the child (dermatitis or allergic rhinitis) or parental asthma, severe wheezing attack (respiratory rate ≥100/min and/or heart rate ≥200/min and/or shock or lethargy) Sample size: 80 Intervention: Dexamethasone ORAL (0.5 mg/kg, single dose) Comparator: Placebo ORAL (1ml/kg, single dose) Other care provided: all children received 4 ml physiological solution during a 6 min nebulisation with oxygen flow of 6L/min, after 30 min a dose of 1ml L-adrenaline solution (1:1000, 1 ml = 1mg) was received by nebulisation Age of children: mean ± SD; intervention group: 7.3 ± 4 months; control group: 5.9 ± 3 months Percentage of children with RSV:				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	intervention group: 58.6%; control group: 82.6% Setting: Outpatients - paediatric emergency department Country: Paraguay Plint 2009 Inclusion criteria: 6 to 12 months of age, RDAI score 4 to 14, first episode wheezing associated with upper respiratory tract infection, presenting bronchiolitis Exclusion criteria: prior bronchodilator treatment in emergency department, oral or inhaled glucocorticoid during previous 2 weeks, previous episode of wheezing or history or asthma, previous bronchodilator use, chronic cardiopulmonary disease, immunodeficiency, serious distress (pulse rate > 200 bpm, respiratory rate >80/min or RDAI score > 15), lethargy, exposed to varicella < 3 weeks, <37 week gestation who had a corrected age <6 weeks at presentation, communication barriers with family Sample size: 800 Intervention: (a) Epinephrine NEB (3 ml 1:1000 solution plus 1mg/kg, max 10 mg, nebulised in oxygen flow 8 L/min, 2 doses 30 min apart) plus Dexamethasone ORAL (generic dexamethasone phosphate solution mixed with Ora-Plus and Ora-Sweet, Paddock Laboratories, 1.0 mg/kg				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	then 0.6mg/kg, max 10 mg, five once-daily doses after leaving emergency department); (b) Dexamethasone ORAL (1.0 mg/kg then 0.6mg/kg, max 10 mg, five once-daily doses after leaving emergency department) plus Placebo NEB (3 ml saline nebulised in oxygen flow 8 L/min, 2 doses 30 min apart) Comparator: (a) Epinephrine NEB (3 ml 1:1000 solution plus 1mg/kg, max 10 mg, nebulised in oxygen flow 8 L/min, 2 doses 30 min apart) plus Placebo ORAL (Ora-Plus and Ora-Sweet, five once-daily doses after leaving emergency department); (b) Placebo NEB (3 ml saline nebulised in oxygen flow 8 L/min, 2 doses 30 min apart) plus Placebo ORAL (Ora-Plus and Ora-Sweet, five once-daily doses after leaving emergency department) Other care provided: oxygen was provided if SaO2 <92%, acetaminophen (15 mg/kg) if fever, co-interventions by the treating emergency department physician were permitted after 90 min, reported use of other bronchodilators and antibiotics Age of children: median (interquartile range); intervention groups (a) and (b): 5 months (3 to 7); intervention groups (a) and (b): 5 months (3 to 7)				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	Percentage of children with RSV: 65% Setting: Outpatients - paediatric emergency deparment Country: Canada Richter 2008 Inclusion criteria: <12 months of age, no history of wheezing, hospitalised with clinical features of bronchiolitis (tachypnoea, recession, wheezing, crepitations) Exclusion criteria: congenital abnormality, pre-existing pulmonary disease, immune deficiency, need for assisted ventilation Sample size: 40 Intervention: Budenoside NEB (1 mg in 2 ml, twice daily for 5 days, then 0.5mg in 2 ml, twice daily for 6 weeks, nebulised with oxygen, flow 6 L/min) Comparator: Placebo NEB (2ml 0.9% saline, twice daily for 6 weeks, nebulised with oxygen, flow 6 L/min) Other care provided: no restrictions on use of other drug treatments Age of children: median (range); intervention group: 4.08 months (1.1 to 10.15); comparator group: 2.7 months (0.9 to 7.82) Percentage of children with RSV: intervention group: 76%; control group: 89%				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	Setting: Inpatients Country: UK Roosevelt 1996 Inclusion criteria: < 12 months of age, bronchiolitis (lower respiratory tract infection characterised by wheezing), first episode of wheezing, requiring inpatient management, examined in emergency department Exclusion criteria: <4 weeks of age, needing admission to ICU, history of congenital heart disease, history of intubation, ventilation or oxygen therapy Sample size: 122 Intervention: Dexamethasone IM (1 mg/kg, every 24h for max of 3 doses) Comparator: Placebo IM (equivalent volume of saline, every 24h for max of 3 doses) Other care provided: co-interventions were left at the discretion of the physician Age of children: mean ± SD; intervention group: 5.3 ± 3.7 months; control group: 5.0 ± 2.5 months Percentage of children with RSV: intervention group: 60%; control group: 76% Setting: Inpatients Country: USA Schuh 2002 Inclusion criteria: 8 weeks to 23 months of age, first wheezing				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	episode associated with respiratory distress and upper respiratory tract infection, RDAI ≥6 at baseline Exclusion criteria: history of wheezing or bronchodilator therapy, prematurity, neonatal ventilation, chronic lung/cardiac disease, aspiration, neurologic/neuromuscular problems, immunodeficiency, critically ill infants requiring immediate airway stabilisation, previous oral or inhaled glucocorticoids, exposed to varicella <21 days of arrival Sample size: 71 Intervention: Dexamethasone ORAL (first dose 1 mg/kg then 0.6 mg/kg/day if discharged - single dose if admitted, 5 days if discharged) Comparator: Placebo ORAL (identical colour, taste, texture, smell - single dose if admitted, 5 days if discharged) Other care provided: all children received nebulised albuterol 2.5 mg/dose in 3 ml normal saline with oxygen flow 6 to 7 min/L at 0, 30, 60 and 120 minutes during observation period; albuterol (1.5 mg to 0.3 ml) 4 times daily with the same nebuliser if discharged home. Further treatment decisions were made by physicians not involved in the study; they were requested not to				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	administer additional therapy unless the patient's condition deteriorated. Use of bronchodilators is reported. Hospitalised patients were given nebulised albuterol only and supportive treatment as indicated Age of children: mean ± SD; intervention group: 6.1 ± 3.5 months; control group: 6.9 ± 3.9 months Percentage of children with RSV: intervention group: 53.6%; control group: 50% Setting: Outpatients - paediatric emergency department Country: Canada Teeratakulpisarn 2007 Inclusion criteria: 4 weeks to 24 months of age, first episode of wheezing with tachypnoea, increased respiratory effort, upper respiratory tract infection. Criteria for hospitalisation: <3 months, respiratory rate >60 breaths/min (<12 months of age) or > 50 breaths/min (≥ 12 months of age), SaO2 < 95%, apathy/refusal to eat Exclusion criteria: symptoms > 7 days, admission to ICU with intubation, history of intubation, asthma, atopy with good response to first dose of beta-2-agonist, therapy with glucocorticoid < 2 weeks, contraindication to glucocorticoid therpay, premature birth				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	Sample size: 179 Intervention: Dexamethasone IM (0.6 mg/kg, single dose) Comparator: Placebo IM (equivalent volume of saline, single dose) Other care provided: use of epinephrine, beta-2-agonist nebulisation, and oxygen were permitted - both study groups treated similarly following National Treatment Guidelines for Acute Respiratory Infection in Children, Thailand Age of children: mean ± SD; intervention group: 10.2 ± 5.5 months; control group: 11.2 ± 5.9 months Percentage of children with RSV: not reported Setting: Inpatients Country: Thailand Zhang 2003 Inclusion criteria: <12 months of age, diagnosis of bronchiolitis, first episode of wheezing with respiratory distress, history of upper respiratory tract infection Exclusion criteria: <4 weeks of age, any chronic cardiac or pulmonary disease, congenital abnormality, immediate favourable response to administration of single dose nebulised fenoterol, received glucocorticoids <4 weeks, severe initial disease requiring intensive care				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	Sample size: 52 Intervention: Prednisolone ORAL (1mg/kg, first at enrolment then once daily at 8 am for 4 days - total 5 day treatment, if hospital stay < 5 days remaining doses were given at home) plus Standard care (judged by attending physician based on standard protocol: oxygen therapy, fluid replacement, nebulised fenoterol) Comparator: Standard care - judged by attending physician based on standard protocol: oxygen therapy, fluid replacement, nebulised fenoterol Other care provided: Attending paediatricians were advised against prescribing any glucocorticoid for recruited patients. Use of IV hydrocortisone was reported Age of children: mean ± SD; intervention group: 4.0 ± 2.5 months; control group: 3.4 ± 1.8 months Percentage of children with RSV: not reported Setting: Inpatients (30-bed paediatric inpatient ward) Country: Brazil Inclusion criteria Randomised controlled trials in infants and young children ≤24 months of age with acute viral				

	Participants	Interventions	Methods	Outcomes and Results	Comments
	bronchiolitis in ambulatory care and/or emergency department (inpatients and outpatients) Exclusion criteria Studies in which any child had a history of wheezing or respiratory distress (one or more previous episode), a formal diagnosis of asthma, or if reporting of these items was unclear Studies in an intensive care setting or with intubated and/or ventilated children Studies assessing the use of longer courses of corticosteroids started during the acute phase for prevention of post-bronchitis wheezing				

I.13 What is the efficacy of systemic corticosteroid therapy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Berger,I., Argaman,Z., Schwartz,S.B., Segal,E., Kiderman,A., Branski,D., Kerem,E., Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up, Pediatric Pulmonology, 26, 162-166, 1998	Sample size - 42 enrolled, 38 completed. - 20 prednisone, 18 placebo. Characteristics Characteristic: prednisone; placebo (Mean±SD) - Age, months: 5.2±0.7; 4.8±0.9	Interventions - Patients recieved either oral prednisone (1mg/kg body weight per dose) or placebo, twice a day for 3 days. - The solutions provided by the pharmacist appeared identical.	Details Setting: The study was performed at the Pediatric Emergency Room, Shaare Zedek Medical Centre, Jerusalem,	Results Protocol outcomes 1. Hospital admission rate 2. Length of hospital stay: - Five (25%) infants treated with prednisone were	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Method of randomisation not described. - Numbers of patients presented to hospital with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 206370 Country/ies where the study was carried out Israel Study type Randomised, double-blinded, placebo-contolled study. Aim of the study To assess the short-term and long-term effects of oral corticosteroids in infants suffering from mild to moderate bronchilolitis. Study dates Winter months 1993-1994. Source of funding Not reported.	- Duration of illness, days: 4.2±0.4; 3.4±0.4 - History of atopy: 1; 0 - Atopy in family: 3; 4 - History of irritability: 11; 9 - History of apnea: 0; 2 Pretrial medications: - Albuterol 7; 5 - Antibiotics 4; 3 Inclusion criteria - Presented in the emergency room with bronchiolitis defined as: the first episode of wheezing assoiated with low grade fever, rhinitis, tachypnea, and increased respiratory effort in a previously healthy infant during the winter months. - Aged 1-18 months. - All eligible infants were enrolled regardless of whether or not they required hospitalisation. Exclusion criteria - Chronic cardiopulmonary disease, including asthma.	Additional treatments: - All patients recieved inhaled albuterol solution 0.03 ml/kg/dose (0.15mg/kg/dose) every 4-6 hours. - Supportive treatment, such as oxygen supplementation and hydration, was given as necessary. - All infants recieved a standard therapeutic regimen (nebulized albuterol q.i.d) with an inhaled β2-agonist. Discharge: - Decision to hospitalise made within 4 hours after initating therapy. - Based soley on infant's condition. - An attending physician in the emergency room who was not involved in the study made the decision.	affiliated with the Hebew University Medical School. Randomisation and concealment: - Each patient was randomly assigned by a research pharmacist according to a standardised statistical method. - Neither the investigators nor the families were aware of treatment assignments. - The examiner was blind to what treatment the patient had received. Outcome measures: - The same examiner evaluated all patients after 3 days of treatment. - Clinical respiratory score (0 to 9	initially hospitalised for a mean of 5 days (range, 2-9 days) and required a mean of 3 days (range, 1-8 days) of supplemental oxygen. - Two (11%) patients from the placebo group were hospitalised for 6 and 10 days and required 1 and 3 days of supplemental oxygen, respectively. 3. Change in disease severity score at 1 to 7 days after starting treatment (Mean±SD): - Prednisone: Before 4.4±2 After 3 days 1.95±1.9 - Placebo: Before 4.5±2 After 3 days 2.05±2 - p value: Before 0.82 After 3 days 0.59 - Mean change Prednisone 2.45±0.12 Placebo 2.45±0.3	bronchiolitis who did not meet inclusion criteria not reported. Attrition bias: - 28 (73.7%) of the 38 infants enrolled in the study were avaliable for a telephone interview, 14 out of 20 for the prednisone group and 14 out of 18 for the placebo group. - Numbers not reported for those needing repeat evaluation in an emergency room or outpatient clinic. Performance bias: - Blinding for the decision to discharge unclear. - Infants treated at home or as inpatients. Detection bias: - The clincal scoring system and the parents impression of their child's well-being are subjective measures of outcome. - The parents recall 2 years after epidose of bronchiolitis may be inaccurate.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Proven or suspected acute bacterial infection. - Previous treatment with corticosteroids by any route. - The presence of fever higher than 38.5°C. - Severe bronchiolitis (respiratory distress, a total clinical score>7, or an infant requiring immediate medical care, including oxygen supplementation). - Children who vomitted the syrup or children who did not recieve the nine doses of medication or did not use the inhalations according to the parent's report were excluded from the study.		scale, similar to Tal et al. and Schuh et al. based on repiratory rate, degree of wheezing, and degree of accessory muscle use). - Oxygen saturation. Statistical methods: - t-test and Chi-square statistic were used to compare the parametric variables. - Mann-Whitney U test with a z-statistic was used to analyse the nonparametric variables. - Minimum of 15 patients in each group to detect a difference of 2 SD in the mean score between the groups at a significance level of <0.05, power =90%.	4. Change in O2 saturation (Mean±SD): - Prednisone: Before 92.3±2.8 After 3 days 93.3±2 - Placebo: Before 93±1.8 After 3 days 93.8±1.8 - p value: Before 0.74 After 3 days 0.79 - Mean change: Prednisone 1±0.5 Placebo 0.8±0.3 5. Duration of cough: Not reported. 6. Need for CPAP/mecanical ventilation: Not reported. 7. Adverse effects: Two years after the episode of bronchiolitis. nine infants (32%) continued to suffer from recurrent respiratory symptoms, five (35.7%) in the	Other information - Accessory muscle score and wheezing scores also reported (table 3). - Clinical scoring system described in table 1.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Follow-up: - One week after the initiation of therapy, symptoms were reassessed either in person (for children still hospitalised) or by the telephone by the same investigating physician. - Two years after the episode of bronchiolitis, a telephone interview was conducted by the same investigator.	prednisone group and four (28.6%) in the placebo group.	
Full citation Corneli,H.M., Zorc,J.J., Mahajan,P., Shaw,K.N., Holubkov,R., Reeves,S.D., Ruddy,R.M., Malik,B., Nelson,K.A., Bregstein,J.S., Brown,K.M., Denenberg,M.N., Lillis,K.A., Cimpello,L.B., Tsung,J.W., Borgialli,D.A., Baskin,M.N.,	Sample size - 8686 infants were assessed for eligibility. - 8086 were not enrolled because they did not meet inclusion criteria or because consent was not provided. - 600 infants underwent randomisation: 305 dexamethasone, 295 placebo. 299 received dexamethasone:	Interventions - Research pharmacies prepared oral dexamethasone solutions (1mg per ml of liquid) from generic dexamethasone phosphate injection solution and identical oral placebo solutions. - Preparations packaged in identical clear plastic vials labelled only with the	Details Setting: Conducted in 20 emergency departments of PECARN. Randomisation and concealment: - Performed computerised randomisation by telephone, using	Results Protocol outcomes 1. Hospital admission rate: Dexamethasone group 39.7% Placebo group 41.0% Absolute difference -1.3% 95% CI -9.2 to 6.5 p=0.74	Limitations Based on NICE checklist. Only items that arise in the study are reported. Selection bias: - 7352 did not meet inclusion criteria. - Oxygen saturation characteristic unequal across groups. - Not all patients tested for RSV.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Teshome,G., Goldstein,M.A., Monroe,D., Dean,J.M., Kuppermann,N., Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network (PECARN), A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis.[Erratum appears in N Engl J Med. 2008 Oct 30;359(18):1972. Note: Majahan, Prashant [corrected to Mahajan, Prashant]], New England Journal of Medicine, 357, 331-339, 2007 Ref Id 206632 Country/ies where the study was carried out USA Study type Multi centre, double-blinded, randomised placebo-controlled trial. Aim of the study To determine the effectiveness of a single dose of oral	hospitalisation data avaliable for 305, RACS avaliable for 283, follow-up data avaliable for 284. 293 received placebo: hospitalisation data avaliable for 295, RACS avaliable for 271, follow-up data avaliable for 265. Characteristics Characteristic: dexamethasone; placebo n(%) or mean±SD - Male: 190 (62.5); 178 (60.5) - Age, months: 5.1±2.6; 5.1±2.8 - Oxygen saturation %: 96±4; 69±4 - No. of days of illness: 3.7±2.5; 3.6±2.5 - RSV positive - number positive/number tested: 85/127(66.9); 81/142(57.0) - Family history of asthma or eczema: 187 (63.4); 196 (69.0) - Smoker in home: 117 (39.0); 103 (35.9) Inclusion criteria - Infants between 2 to 12 months of age who were brought with a first episode of bronchiolitis.	randomisation numbers. - A nurse orally administered 1ml of solution per kg in the dexamethasone group (maximum, 12mg). - Any episode of vomiting within 20 minutes after administration of the study medication was recorded, but the dose was not repeated. Additional treatment: - All other bronchiolitis treatments were provided according to the clinician's preference and local standards. - Any diagnositic testing was left to the clinician's discretion.	the keypad for data entry. - Infants were assigned in equal numbers to the dexamethasone and placebo groups with the use of random permuted blocks stratified by centre. - All emergency department staff, study personnel, and parents and guardians were unaware of the group assignments. - Follow-up research assitant was unaware of the group assignments. - Randomisation codes were secured until all data entry was complete. Outcome measures: - A study clinican repeated respiratory scoring	Neither was there a significant difference when admission was analysed in the prespecified subgroups with eczema or a family history or asthma. 2. Length of hospital stay, mean days: Dexamethasone 2.55 Placebo 2.27 p=0.10 3. Change in disease severity score at 1 to 7 days after starting treatment (Mean±SD): - RACS Dexamethasone -5.3±4.7 Placebo -4.8±4.6 Absolute difference -0.5 95% CI -1.3 to 0.3 p=0.21 - RDAI Dexamethasone -4.4±3.1 Placebo -3.9±3.2	- For dexamethasone group RACS data avaliable for 283 out of 299 and follow-up data avaliable for 284 out of 299. - For placebo group RACS data avaliable for 271 out of 293, and follow-up data avaliable for 265 out of 293. Performance bias: - Additional treatments provided according to the clinician's preferences. - 20 emergency departments may differ in the care they provide. Detection bias: - Subjective clincal scoring system. - Discharge criteria not described. Other information - RDAI clinical score described in table 1. - Figure 2 displays risk ratios for hospital admission - Two randomly assigned infants were hospitalised before adminsitration of the study drug, leaving 598 treated infants, five of these

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dexamthasone in infants with moderate-to-severe bronchiolitis. Study dates Over a 3 year period during bronchiolitis season from January 2, 2004 through to April 30, 2006. Source of funding - Supported by a grant from the Maternal and Child Health Research program and by cooperative agreements with the Emergency Medical Services for Children program of the Maternal and Child Health Bureau, Health Resources and Services Administration. - Dr. Zore reports receieving grant support from Sepracor; and Dr. Holubkov consulting fees from St. Jude Medical, Tyco Health Care, and Ucyclyd Pharma and grant support from St. Jude Medical and GlaxoSmithKline.	- Bronchiolitis defined as: wheezing (with no prior bronchiolitis, wheezing, or asthma and no bronchdilator use before the current illness), within 7 days after the onset of symptoms. - The episode had to be moderate or severe as defined by a score on the Respiratory Distress Assessment Instument (RDAI) of 6 or more (on a scale of 0 to 17, with higher scores indicating more severe respiratory problems). Exclusion criteria - Infants with a prior adverse reaction to dexamethasone - Known heart or lung disease. - Premature birth (<36 weeks gestation). - Immunosuppression or immunodeficiency. - Treatment with corticosteriods in the previous 14 days. - Active varicella or recent exposure to varicella.		1 hour and 4 hours after the administration of the study medication and assessed each child for discharge or admission after 4 hours. - The decision to hospitalise or discharge the infant 4 hours after the administration of the study medication. - RACS score (based on wheezing and retractions, used by Lowell et al.) at 4 hours. Statistical: - Assuming a 40% admission rate in the placebo group, they calculated the sample size that would be required to provide more than 80% power (with a two-sided alpha level of 0.05) to detect an	Absolute difference -0.5 95% CI -1.0 to -0.1 p=0.03 4. Change in 02 saturation (Mean±SD): Dexamethasone 0.3±3.3 Placebo 0.9±3.2 Absolute difference -0.6 95% CI -1.0 to -0.1 p=0.02 5. Duration of cough: Not reported. 6. Need for CPAP/mechanical ventilation: Not reported. 7. Adverse effects: - Vomitting within 20 minutes after administration of the study occurred in 5.5% of the dexamethasone group and 4.7% of the placebo group.	infants received the wrong medication because of errors in vial selection, and 1 received an insufficient dose of dexamethasone, leaving 592 patients in the per-protocol analysis. - Infants requiring admission to an intensive care unit before 4 hours of observation had been completed were included in the analysis of admissions. - RACS calculated as the sum of the change in the RDAI score and a standardised score for the change in the respiratory rate, with a reduction of 1 unit for a decrease of 5 to 12%, 2 units for a decrease of 16 to 25% etc., a negative RACS values signify improvement. - Simiailar proportions of infants received inhaled bronchodilator treatmet, either with albuterol (dexamethasone 77.0%; placebo 80.3%) or epinephrine (15.5%; 16.7%) at baseline.

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	- Inability of the parent or guardian to speak English or Spanish. - Critically ill infants.		absolute reduction in hospital admission rates of 12% or more in the dexamethasone group. - Intention-to-treat principal. - Hospital admission rates were compared with Pearson's chi-square test. - RACS compared by t-test. - RACS adjusted measures using logisitc regression. - RACS subgroup effects using linear regression. - Generalised estimating equations and linear mixed models were used to test for an interaction between treatment group and site in the admission and RACS outcomes respectively.	- Pneumonia was diagnosed in three infants; two were in the placebo group, and an empyema developed in one of these two infants.	

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			- Length-of-stay measures were compared by means of the two-sample Wilcoxon test. Follow-up: After 7 to 10 days a telephone interview was conducted with the infant's parent/guardian by a research assistant.		
Full citation Goebel,J., Estrada,B., Quinonez,J., Nagji,N., Sanford,D., Boerth,R.C., Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis, Clinical Pediatrics, 39, 213-220, 2000 Ref Id 206952 Country/ies where the study was carried out USA Study type	Sample size - 51 enrolled, 3 excluded from analysis: medical noncompliance, initally unrecognised history of reactive airway disease or prematurity. - 48 randomised: 24 prednisolone, 24 placebo. - Complete follow-up: 17 prednisolone, 15 placebo. Characteristics Inital patient characteristics for all 51 patients: prednisolone; placebo	Interventions - All patients received albuterol therapy continued at 0.3mg/kg/day divided t.i.d by mouth or, 0.15mg/kg/dose q.i.d by nebulizer. - Both treatments formulated by the hospital pharmacist: 100ml each of water and glycerin with 5ml of cherry-flavoured Kool-Aid and 100mg of quinine. Prednisolone:	Details Setting: Infants managed predominantly as outpatients. Randomisation and concealment: - Computer generated. - All study physicians, patients, and caregivers were blinded in regard to treatment.	Results Protocol outcomes 1. Hospital admission rate: - Four patients in the prednisolone group and two in the placebo group were hospitalised at enrollment for oxygen saturation in room air below 90% (three patients), young age with recent disease onset by history (two patients), and a	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Only included patients with mild or moderate bronchiolitis. - Sample predominantly out-patients with lower disease severity at enrollment. - Randomisation method not explained. Attrition bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Double-blinded, randomised controlled trial. Aim of the study To evaluate combination therapy of mild to moderate bronchiolitis with bronchiodilators and corticosteroids. Study dates Not reported. Source of funding Not reported.	- Median age, months: 4.0; 4.5 - Sex (female/male): 6/18; 8/16 - Nasopharyngeal positive for RSV: 11; 15 - Hospitalised at enrollment: 4; 2 - Bronchiolitis score (Mean±SD): 4.5±1.7; 4.9±1.4 Inclusion criteria - Bronchiolitis defined as: often caused by a respiratory syncytical virus (RSV), is a frequent infection in early childhood and produces significant morbidity. - ≤ 23 months of age brought to the Pediatric Emergency Department or Children's Clinic of the University of South Alabama. - Symptoms of viral repiratory tract infection (rhinorrhea, cough, or fever up to 38.5ºC rectally). - During the fall and winter of two consecutive years. - First time wheezing that did not clear completely after one dose of nebulized albuterol (0.15mg/kg body weight).	- 5 day oral course. - 2mg/kg/day divided b.i.d. Placebo: - Identical: course, volumes per kg body, apperance, taste and bottle to prednisolone.	Outcome measure: - Clinical status, using a modification of the bronchiolitis scoring system published by Tal et al. (based on respiratory rate, retractions, oxygen saturation and wheezing). - Hospitlaisation. Statistical methods: - Bronchiolitis scores on days 0, 2, 3 and 6 compared by one-way analysis of variance for repeated measures (Student-New-man- Keuls method). - Scores on days 0 and 2 analysed by analysis of variance in a three-way factorial design with RSV-positive versus RSV-negative status and	history of possible apnea (one patient). - Two patients in the prednisolone group and three in the placebo group were hospitalised later during the study, four for persistent or worsened respiratory symptoms and one patient in the placebo group because of the onset of fever 6 days after enrollment. 2. Length of hospital stay - Mean initial hospitalisation (hospitalised at the time of enrollment): prednisolone group 2.3 days, placebo group 2.5 days. - Mean late hospitalisation (later during the study): prednisolone group 2.0 days, placebo group 3.0 days. 3. Change in disease severity score at 1 to	- Nine patients in the placebo group and seven in the prednisolone group had incomplete follow-up. Performance bias: - Some patients were hospitalised at the time of enrollment or later during the study. - Discharge crieria not described. - Number of physicians not reported. Detection bias: - Subjective bronchiolitis scoring method. - Oxygen saturation measured for the bronchiolitis score but the values are not reported separately. Other information - Initial patient characteristics for patients with complete follow up (32) also reported (table 2). - Table 1 describes the bronchiolitis scoring system.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria - History of immune defect, neurologic disease with possible aspiration, gastroesophageal reflux, congenital or acquired chronic heart or lung disease, mechanical ventilation, or birth before 35 weeks gestational age. - Fever over 38.5°C rectally, antibiotic therapy within 1 week before enrollment or antipyretic therapy within 8 hours before enrollment. - Evidence of concomitant bacterial infection on physical examination or any lab or radiographic studies. - Emesis precluding the oral administration of medications. - Inital bronchiolitis score less than 2 or greater than 9.		treatment with predinsolone versus placebo of the patients as the other factors. Follow-up: - Visits with a study physician on days 2, 3 and 6. - Patients whose disease had not resolved by day 6 of the study were followed up until complete convalesence.	7 days after starting treatment - Bronchiolitis score from 51 patients: predinosolonel; placebo (Mean±SD): Day 0: 4.5±1.7 p<0.05; 4.9±1.4 p>0.05 Day 2: 2.7±1.4 p<0.05; 4.0±1.5 p >0.05 - Bronchiolitis score from 32 patients: Predinosolonel; placebo (Mean±SD): Day 0: 4.7±1.9 p<0.05; 4.9±1.4 p>0.05 Day 2: 2.6±1.5 p<0.05; 3.9±1.5 p >0.05 4. Need for CPAP/mechanical ventilation: Not reported. 5. Change in O2 saturation: Not reported. 6. Duration of cough: Not reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				7. Adverse effects: Only one patient appeared "jittery" by caretakers at times after enrollment, resolved after a decrease in the albuterol dose.	
Full citation Klassen,T.P., Sutcliffe,T., Watters,L.K., Wells,G.A., Allen,U.D., Li,M.M., Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized, controlled trial, Journal of Pediatrics, 130, 191-196, 1997 Ref Id 210267 Country/ies where the study was carried out Canada Study type Randomised, double-blind, placebo-controlled trial.	Sample size - 102 patients approached. - 30 did not participate because: parent refused consent, communication barrier or absent parent/guardian. - A further 5 were excluded based on the criteria. - Dexamethasone 35, placebo 32. - Terminated after the enrollment of 72 patients because funding for the project had lapsed, enrolled 97% of specified sample size. Sample size: dexamethasone; placebo Baseline 35; 32 12 hours 35; 31 24 hours 33; 28 36 hours 30; 25	Interventions - Prepared and packged by pharmacy with a study number. - All treatment decisions made by treating physician and recorded. - All patients recieved nebulized salbutamol at 0.15mg/kg every 4 hours for the first 24 hours and an oxygen concentration of 35% in a plastic tent. Dexamethasone: - 0.5mg/kg as the first dose and 0.3mg/kg for the next 2 mornings, or until the patient was discharged from hospital.	Details Setting: Inpatient wards of a pediatric tertiary care hospital: Children's Hospital of Eastern Ontario. Randomisation and concealment: - Computer generated random numbers. - Performed by pharmacy. - Stratification by age (younger or older than 6 months) performed by the pharmacy.	Results Protocol outcomes 1. Hospital admission rate Readmission to hospital: Dexmethasone 4 (11%) Placebo 1 (3%) p=0.36 2. Length of hospital stay (Median, 95% CI): Dexamethasone 57 (38 to 76) Placebo 48 (42 to 54) p=0.19 3. Change in disease severity score at 1 to	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Performance bias: - Patients receiving additional treatment (intravenous antibiotics, hydration and hydrocortisone). - One masked interim analysis was conducted in June 1994, after the enrollment of 37 patients, by a statistican who was not involved with the conduct of the trial, the decision was made to complete the trial because there was no evidence of efficacy based on the interim analysis. Attrition bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the clinical benefit of oral dexamethasone in children admitted to the hospital with bronchiolitis treated with nebulized salbutamol. Study dates - February 1, 1993 to April 30, 1005. - Patients enrolled only from November 1 to April 30 during peak RSV season. Source of funding Not reported.	48 hours 23; 20 60 hours 17; 11 Characteristics Characteristic: dexamethasone; placebo - Male (%): 63; 47 - Age years: 0.39; 0.39 - Asthma in family (%): 57; 44 - RSV infection (%): 86; 88 - Oxygen saturation with room air: 92.9; 93.0 - RDAI score: 6.6; 6.2 Inclusion criteria - Bronchiolitis defined as affecting children under 1. - Children aged 6 weeks to 15 months. - Admitted to the inpatient wards. - First time wheezing (short-term <7days). - Evidence of a viral infection (rhinorrhea or temperature >37.5ºC). - Oxygen saturation less than 95% on hospital admission. - RDAI score >6. Exclusion criteria	- Clear 70% sucrose solution and dexamethasone sodium phosphate intravenous solution. Placebo: - Equal volume and appearance to dexamethasone. - 70% sucrose solution.	- Concealed until the study was complete. - Research assistants, treating physicians, and parents were masked to treatment allocation. Outcome measures: - Recorded twice daily for 4 days and then once daily until the child was discharged. - Measurements taken at least 1 hour after the last salbutamol dose and after the child had been taken out of the oxygen tent for 10 minutes. - RDAI score (0 to 17 scale, based on: expiratory wheezing, inspiratory wheezing, location of wheeze, supraclavicular intercostal and	7 days after starting treatment Dexamethasone; placebo; p value (Mean±SD) The change in the RDAI score from baseline to: 12 hours: -1.3±2.0; -1.0±1.8; 0.51 24 hours: 1.4±2.0; 1.6±2.3; 0.74 36 hours: -1.7±2.6; -2.0±2.1; 0.64 48 hours: -1.4±2.7; -2.4±2.5; 0.23 60hours: -2.4±2.4; 2.0±2.3; 0.66 4. Need for CPAP/mechanical ventilation: Not reported. 5. Change in O2 saturation: Dexamethasone; placebo; p value (Mean±SD) 12 hours 0.7±2.5; 1.4±2.8; 0.29 24 hours 1.0±3.6; 1.9±3.1; 0.28 36 hours 1.7±3.3; 1.1±3.0; 0.43	- 2 in placebo group lost to 1 week follow-up, but neither readmitted. (- Sample sizes change due to discharge.) Detection bias: - Unclear definition of bronchiolitis. - Unclear dose of placebo. Other information - 13 patients in placebo and 10 in dexamethasone received antibiotics during their hospital say, p=0.30. - 5 patients in placebo and 3 in dexamethasone received intravenous hydration during their hospitalisation, p=0.46. - One patient in the placebo group received intravenously adminstered hydrocortisone, and one patient in the dexamethasone group received orally administered prednisone after the three doses of dexamethasone. - Medication at discharge (dexamethasone; placebo):

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	- An underlying disease that might affect cardiopulmonary status. - Asthma. - Wheeze or cough previously treated with bronchodilators (not including the current acute episode). - Recent treatment with steriods within 2 weeks. - History of adverse reactions to steriods.		subcostal indrawing) - Oxygen saturation. - Respiratory rate. - Heart rate. - Use of cointerventions. - Length of hospitalisation. - Readmission rate. Statistical methods: - Dichotomous events were analysed using chi-squared test or the Fisher Exact Test. - Kaplan-Meier survival analysis was applied to the length of hospital stay, and signifcant differences were analysed by the log rank test. - RDAI detection difference of 2 points, number required per group was 37 patients, power=90%,	48 hours 2.2±4.1; 1.4±3.0; 0.46 60 hours 2.3±3.8; 1.2±4.0; 0.47 6. Duration of cough: Not reported. 7. Adverse effects: - Pneumonia developed in one patient in each group. - One patient in the placebo group required oxygen supplementation at a concentration greater than 35%.	Salbutamol 6 (17%); 6 (19%) Orciprenaline 7 (20%); 2 (6%) Beclomethasone 1 (3%); 0 (0%)

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			(β=0.10), α=0.05, two sided test, SD 2.64. - Interrater agreement was measured by having the same patient independtly assessed by the three research assistants and calulated by the weighted kappa. Follow-up: - Parents contacted by research assitant 1 week after the discharge of their child from hospital.		
Full citation Kuyucu,S., Unal,S., Kuyucu,N., Yilgor,E., Additive effects of dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis, Pediatrics International, 46, 539-544, 2004	Sample size - 69 completed. - 21 did not come to control visits on either the 24th hour, or fifth day, not included in analysis. - Epinephrine and dexamethasone group 1, 23. - Salbutamol and dexamethasone group 2, 23.	Interventions Salbutamol: (Ventolin®), 0.15mg/kg of a 1-mg/ml solution of salbutamol added to a 0.9% saline solution to make a total of 3ml. Epinephrine: 3ml (3mg) of 1:1000 L-epinephrine solution.	Details Setting: - Pediatric Department of the Faculty of Medicine, Mersin University. - Patients were discharged and reassessed at 24 hours.	Results Protocol outcomes 1. Hospital admission rate 2. Length of hospital stay: No patients in any group required hospitalisation.	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Attrition bias: - 21 lost to follow up. - Small sample sizes. - During the subsequent two months only 17 from group

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Ref Id 207374 Country/ies where the study was carried out Turkey Study type Randomised, placebo-controlled, prospective trial study. Aim of the study To compare the early and late effects of nebulised L-epinephrine (EPI) and intramuscular dexamethasone (DEX) combination therapy with nebulised salbutamol (SAL) and dexamethasone combination and bronchodilators alone in outpatients with acute bronchiolitis. Study dates Winter months, dates not reported. Source of funding Not reported.	- Epinephrine and placebo group 3, 11. - Salbutamol and placebo group 4, 12. Characteristics Characteristic: epinephrine and dexamethasone group 1; salbutamol and dexamethasone group 2; epinephrine and placebo group 3; salbutamol and placebo group 4 (Mean±SD) Age, months: 7.2±0.8; 7.9±1.0; 9.6±1.3; 9.9±1.7 Duration of illness, days: 2.5±0.1; 3.5±0.3; 2.6±0.2; 2.6±0.2 RDAI score: 7.3±0.2; 7.2±0.2; 7.4±0.1; 7.7±0.1 Passive smoking: 18 (78.2%); 19 (82.6%); 8 (72.5%); 8 (66.7%) Inclusion criteria - Acute bronchiolitis defined as: acute onset wheezing with or without cough, tachypnea, and increased respiratory effort, accompanied by clinical evidence of a viral illness such as coryza and fever.	- Solutions were given through a compressed type nebuliser with continuous flow of oxygen 5-6l/min for 10 min. - Fiftteen minutes following the administration of both nebulised medications, dexamethasone 0.6mg/kg, or a placebo was given intramuscularly in a randomised fashion independent of the first randomisation. - Preparation and administration of nebulised solutions were performed by a trained emergency department nurse. Additional treatment: - If the patients had not experienced an improvement in RDAI by 4 point in 120 minutes, they were given the same medications in the same doses again, reassessment was performed 30 and 60	Randomisation and concealment: - Parents and investigators remined blinded to administered medications throughout the study period. Outcome measures: - Assessed by two investigators when the infants were relatively calm and had been breathing room air for at least 15 minutes. - Clinical assessment performed on admission and repeated 30, 60, 90 and 120 minutes after the first treatment. - Heart rate. - Respiratory rate. - RDAI score (based on wheezing and retraction, also	3. Change in disease severity score at 1 to 7 days after starting treatment RDAI (Mean±SD): 120 minutes 3.8±0.2; 4.0±0.3; 4.2±0.3; 4.4±0.4 24th hour 3.4±0.2; 3.9±0.3; 3.7±0.3; 3.8±0.3 5th day 2.3±0.1**; 2.5±0.1*; 2.9±0.2; 3.4±0.2 **significantly different from group 3, p=0.02 *significantly differene from group 4, p=0.01 4. Change in O2 saturation: Not reported. 5. Duration of cough: Not reported. 6. Need for CPAP/mechanical ventilation: Not reported. 7. Adverse effects:	1, 16 from group 2 and a total of 13 from groups 3 and 4 were followed-up. Selection bias: - Randomisation method not described. - Unequal sample sizes acorss the 4 groups. - Duration of illness characteristic for group 2 significantly different from group 1, p<0.01 - Enrollment period between 8am and 5pm. Peformance bias: Some patients received a second dose of the sane medication: Group 1: 5 (27%) Group 2: 8 (34.8%) Group 3: 5 (45.4%) Group 4: 4 (33.3%) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Aged between 2 and 21 months. - Admitted with first episode of wheezing. - Clinical findings compatible with acute bronchiolitis. - RDAI score ≥4 Exclusion criteria - History of prior wheezing. - Previous treatment with bronchiodilators. - Previous diagnosis of asthma or allergic bronchitis by a physician. - Personal history of atopic dermatitis or allergic rhinitis. - Any chronic cardiac or pulmonary disease. - Any steriod treatment within the previous 2 weeks. - Signs of severe respiratory disease (pulse rate ≥200 beats/min, a respiratory of ≥100 breaths/min, RDAI score ≥15 or profound lethargy. - Parental history of asthma or atopic disease.	minutes after the second dose.	used by Lowell et al.). Statistical methods: - The same patient was assessed by two independent observers and the mean of the two scores was used for data analysis. - Continuous variables: independent two-tailed t-test performed by using pooled or separate variance estimates. - Dichotomous events: chi-squared test. Follow-up: - Patients were discharged and reassessed at 24 hours, and 5 days later. - Regular hospital visits during the subsequent two months.	- During the subsequent two months four (23.5%) patients from group 1, three (18.8%) from group 2 and six (46.2%) from the placebo group showed respiratory complaints such as a exercise-induced cough and mild wheezing. - No side-effects suc as pallor, vomitting or tremor were encountered.	

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Full citation Mesquita,M., Castro-Rodriguez,J.A., Heinichen,L., Farina,E., Iramain,R., Single oral dose of dexamethasone in outpatients with bronchiolitis: a placebo controlled trial, Allergologia et Immunopathologia, 37, 63-67, 2009 Ref Id 210066 Country/ies where the study was carried out Paraguay Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study To compare the efficacy of a single dose of oral dexamethasone in infants with acute moderate-severe bronchiolitis treated in an emergency department in a developing country. Study dates - During 5 months.	Sample size - 240 infants with acute respiratory illness were attended in the emergency department. - 80 satisfied the inclusion criteria. - 5 excluded because of evidience of pneumonia. - 2 from dexamethasone and 1 from placebo excluded because of vomitting within 20 after administration of medication. - 5 declined to participate. - 65 completed: 33 dexamethasone, 32 placebo. Characteristics Dexamethasone; placebo: (Mean±SD) - Male (%): 58; 47; p=0.4 - Age, months: 7.3±4; 5.9±3; p=0.1 - Weight, kg: 8.098±2.530; 6.543±1.670; p=0.005 - Oxygen saturation %: 92±1.5; 92±2; p=1.0 - RDAI score: 10±2; 10±2; p=1.0 Inclusion criteria	Interventions - The research pharmacy prepared the active drug and the placebo in identical sweet syrups and their bottles were labelled only with the randomisation numbers. - Any episode of vomitting within 20 min after administration of the oral study medication was recorded, but the dose was not repeated. Dexamethasone: - Lab. Formula Magistral, Paraguay. - Single dose of 0.5mg/kg (1ml/kg). Placebo: Single dose of syrup placebo (1ml/kg). Additional treatment: - Immediately after the dose, children from both groups received two nebulisations with 4ml of physicological solution and 1ml of L-	Details Setting: Emergency department of the Hospital General Pediatrico "Ninos de Acosta Nu", Asunción, Paraguay. Randomisation and concealment: - Table of random numbers. - In the whole period of the trial, the investigatos were blinded of the treatment administered. Outcome meaures: - Change in RDAI score (0 to 17 scale used by Lowell et al.). - Respiratory rates and heart rates. - Decrease in the hospital admission rate. - Transcutaneous haemoglobin oxygen saturation	Results Protocol outcomes (Dexamethasone; placebo; p value) 1. Hospital admission rate: At fourth hour 24%; 22%; 0.8 2. Length of hospital stay: Not reported. 3. Change in disease severity score at 1 to 7 days after starting treatment: RDAI score (Mean±SD) - At first hour 8±2; 8±2; 1.0 - At fourth hour 7±3; 7±2; 1.0 4. Need for CPAP/mechanical ventilation: Not reported. 5. Change in O2 saturation (Mean±SD):	Limitations Based on NICE checklist. Only limitations that arise in the study are reported Sampling bias: - 52 out of 65 infants tested for respiratory virus sampling. - 80 out of 240 satisfied inclusion criteria. - Placebo group younger and weighed less than dexamethasone group. Detection bias: - Randomisation not explained. - No systematic follow-up after the fourth hour. Performance bias: - Additional treatments. Other information Characteristics between the two groups (17 dexamethasone; 19 placebo) with positive RSV (table 2) also reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
- No dates reported. Source of funding - No funding reported. - The authors have no conflicts of interest to declare.	- Bronchiolitis defined as: respiratory distress with respiratory rate between 40-80/min and wheezing; and within 7 days after onset of a cold. - Children 2-24 months of age who came to the emergency department with their first episode of bronchiolitis. Exclusion criteria - Clinical or radiological pneumonia. - Cardiopulmonary congenital malformations. - Bronchopulmonary dysplasia. - Cystic fibrosis. - Foreign body aspiration. - Neuological alteration. - Previous wheezing/asthma episode. - Inhaled or systemic corticosteroids used in the previous 15 days. - Beta-2 agonists used within the previous 4 hours. - Antecedents of atopy (dermatitis or allergic rhinitis) in the child or parental asthma. - Severe wheezing attack (respiratory rate ≥100/min	adrenaline solution (1:1000, 1ml = 1mg) separated by 30 min. - Aerosol was generated by jet nebuliser (Micro-nebuliser) powered by a continuous flow of oxygen (6L) for 7 min and delivered via a tight fitting face mask. - Additional oxygen was administered to the patient if Sp02 <90%. - Aspiration for cleaning the nose was carried out. - Antipyretic medication was provided when necessary. Discharge criteria: - Decided at the end of the fourth hour by the two physicians. - Child admitted to hospital if Sp02 ≤ 90% and/or respiratory rate above normal values for age.	(Sp02) at fourth hour. Statistical methods: - To evaluate differences between groups, the chi-square was used for categorical and the t-test for continuous variables. - To detect a RDAI 2 score change the number required per group was 27, with a statistical power of 80% (β=0.20), α=0.05, two-sided test, SD 2.6. - Two study physicians with an interclass correlation coefficient kappa og 0.65	- At first hour 94±1; 94±2; 1.0 - At fourth hour 94±3; 94±3; 1.0 6. Duration of cough: Not reported. 7. Adverse effects: - 52 (80%) infants tested 29; 23. - RSV: 17; 19 - Influenza A: 3; 0 - Influenza B: 1; 0 - Adenovirus: 3; 1	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and/or heart rate ≥200/min and/or shock or lathargy).				
Full citation Plint,A.C., Johnson,D.W., Patel,H., Wiebe,N., Correll,R., Brant,R., Mitton,C., Gouin,S., Bhatt,M., Joubert,G., Black,K.J., Turner,T., Whitehouse,S., Klassen,T.P., Pediatric Emergency Research Canada (PERC), Epinephrine and dexamethasone in children with bronchiolitis, New England Journal of Medicine, 360, 2079-2089, 2009 Ref Id 207913 Country/ies where the study was carried out Canada Study type Multicentre, double-blinded, placebo-controlled trial. Aim of the study A clinical trial with a factorial design at	Sample size - 3556 assessed for eligibility. - 800 enrolled. - 3 lost to follow-up. - Included in analysis: 199 epinephrine-dexamethasone group. 198 epinephrine group. 199 dexamethasone group. 201 placebo group. Characteristics Characteristic: epinephrine-dexamethasone group 1; epinephrine group 2; dexamethasone group 3; placebo group 4 Median (IQR) or n(%) - Age, months: 5 (3-7); 5 (3-7); 5 (3-7); 5 (3-7) - Male, sex: 124 (62.0); 122 (61.3); 127(63.5); 120(59.7) - Oxygen saturation %: 97 (95-98); 97 (95-98); 97 (95-98); 97 (95-98) - Duration of symptoms before enrollment, days:	Interventions - The pharmacy at each site prepared the study drugs in sequentially numbered, visually identical packets. - The active drugs and placebo were identical in appearance, volume, weight, odor and taste. 1. Epinephrine-dexamethasone group: Two treatments of nebulised epinephrine and six oral doses of dexamethasone. 2. Epinephrine group: Nebulised epinephrine and oral placebo. 3. Dexamethasone group: Nebulised placebo and oral dexamethasone.	Details Setting: Eight pediatric emergency departments. Randomisation: - Research nurse assigned treatment groups using a computer-generated randomisation sequence stratified by centre. - Randomised permuted blocks of 8 and 12. Outcome measures: - Hospital admission within 7 days after the day of enrollment. - Change in heart and respiratory rate. - RDAI score (based on wheezing and	Results Protocol outcomes Epinephrine-dexamethasone group 1; epinephrine group 2; dexamethasone group 3; placebo group 4 1. Hospital admission rate - At enrollment: 23(11.5%); 29(14.6%); 31(15.5%); 36(17.9%) - By seventh day: 34/199 (17.1%); 47/198 (23.7%); 51/199 (25.6%); 53/201 (26.4%) - The relative risk of admission by day 7 in group 1 as compared with group 4 was 0.65 (95% CI 0.45 to 0.95, unadjusted p=0.02, adjusted p=0.07). - 11 infants would need to be treated to prevent one hospital admission.	Limitations Based on the NICE checklist. Only limitations that arise in the study are reported. Selection bias: - 1841 did not meet criteria to enroll. - Recruitment up to 16 hours a day when the research nurse was present. Attrition bias: No data were avaliable on the primary outcome for three patients, these patients were not included in the intention-to-treat analysis. Detection bias: - Subjective clinical scoring system. Performance bias: - Blinding unclear. - Pharmacy error: 23 in group 1 and 23 in group 3 recieved a dexamethasone at 80% of the planned dose,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
multiple sites to determine whether treatment with nebulised epinephrine, a short course of oral dexamethasone, or both resulted in a clinically important decrease in hospital admissions among infants with bronchiolitis who were seen in the emergency department. Study dates Bronchiolitis season (December through April) from 2004 to 2007. Source of funding - Supported by grants from the Canadian Institutes of Health Research and Alberta Children's Hospital Foundation. - Dr. Plint was supported in part by a salary award from the Canadian Institues of Health Research. - Dr. Johnson reports receiving grant support from Cumberland Pharmaceuticals.	3 (2-5); 4 (3-6); 3 (2-5); 4 (2-6) - RSV positive: 128 (64.0); 129 (64.8); 127 (63.5); 136 (67.7) Previous treatment, no (%): - Bronchodilators 27 (13.5); 21 (10.6); 20 (10.0); 24 (11.9) - Antibiotics 24 (12.0); 20 (10.1); 21 (10.5); 17 (8.5) Inclusion criteria - Bronchiolitis defined as: the first episode of wheezing associated with signs of an upper respiratory tract infection during the peak RSV season. - 6 weeks to 12 months of age. - RDAI score 4 to 15. Exclusion criteria - Received oral or inhaled corticosteriods during the preceding 2 weeks. - Previous episode of wheezing. - Diagnosis of asthma.	4. Placebo group: Nebulised placebo and oral placebo. Nebulised treatments: Administered 30 minutes apart, oxygen flow rate of 8l per minute, consisted of 3ml of generic epinephrine in a 1:1000 solution or an equivalent volume of saline. Oral treatments: - 1.0mg dexamethasone per kg of body weight (maximum dose 10mg) or placebo given after the first nebulised treatment in the emergency department, followed by five once-daily doses of dexamethasone (0.6mg per kg; maximim daily dose, 10mg) or placebo. - Dexamethasone: generic dexamethasone phosphate injection solution mixed with	distress, 0 to 17 scale, used by Lowell et al.). - Oxygen saturation. - Length and severiy of symptoms. - Time to discharge. - Patient return to health care provider. Statistical methods: - Intention-to-treat. - Admission and return visits due to symptoms of bronchiolitis analysed with relative-risk regression for binary outcomes. - Time to discharge: Cox proportional-hazards model. - Time to symptom relief: parametric survival models with Weibull distributions.	- By day 22: 37(18.5%); 50(25.1%); 53(26.5%); 54(26.9) - Returned to health care provider: 95 (47.7%); 93 (47.0%); 106 (53.3%); 86 (42.8%) - Only difference between group 3 and group 4 significant, unadjusted p=0.04 2. Length of hospital stay - Median hours, until discharge from the emergency department or hospital: 4.6 (3.5-7.0); 4.9 (3.7-9.6); 5.1 (3.6-17.0); 5.3 (3.8-21) P value unadjusted: 0.02; 0.78; 0.99; refenence P value adjusted: 0.94; 0.94; 1.00; reference 3. Change in disease severity score at 1 to	these patients were included in the analysis. - Care may vary across the 8 pediatric emergency departments and across infants treated at home or as inpatients. - Criteria for discharge not described. - At follow-up parents reported they stopped administering the study syrup so that a physician could prescribe oral corticosteriods: 19 in group 1, 13 in group 2, 20 in group 3 and 12 in group 4. Other information - Because of pharmacy error, a total of 23 patients in group 1 and 23 patients in group 3 received dexamethasone at 80% of the planned dose (0.8mg per kg of body weight in the emergency department and 0.48mg per kg of body weight at home), these patients were included in the analysis. - The additional use of bronchodilators 90 minutes after enrollment were similar across groups, with 18.4% of patients receiving

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- No other potential conflict of interest relevant to this article was reported.	- Previous bronchodilator use. - Any chronic cardiopulmonary disease or immunodeficiency. - Infants in severe distress (pulse rate >80 breaths per min, RDAI score >15). - Profound lethargy. - Exposed to varicella within the preceding 3 weeks. - Born <37 weeks of gestation. - Insurmountable barriers to communication with the family.	Ora-Plus and Ora-Sweet (Paddock Laboratories). - Placebo: Ora-Plus and Ora-Sweet. Addiional treatment: - Oxygen saturation <92% while breathing ambient air recieved supplemental oxygen. - Fever (rectal temperature >38ºC) received acteminophen (15mg per kg body weight). - The treating physician in the emergency department was allowed to provide cointerventions after 90 minutes and independently determined whether to admit or discharge.	- Clinical characteristics: linear mixed-effects regression. - Sample size of 800 inflants, power=80%, 5% type 1 error rate, to detect an absolute difference of 10 percentage points in admission rates resulting from administration of each drug. Follow-up: - By telephone performed daily by research nurse until day 7, then every 2 days until day 14, and then every 3 days until day 22.	7 days after starting treatment RDAI (Mean±SD): 30 min: -1.62±2.23; -1.44±1.94; -0.98±2.07; -1.06±2.16 60 min: -2.50±2.58; -2.45±2.32; -1.75±2.40; -1.65±2.42 P value unadjusted: <0.001; 0.003; 0.75; reference P value adjusted: <0.001; 0.005; 0.75; reference 4. Change in O2 saturation: (Mean±SD) 30 min: -0.35±2.61; 0.17±2.09; -0.52±2.45; -0.24±2.77 60 min: -0.73±2.56; 0.07±2.70; -1.02±2.57; -0.77±3.23 P value unadjusted: 0.59; 0.005; 0.22; reference P value adjusted: 0.59; 0.013; 0.36; reference 5. Duration of cough:	albuterol and 20.6% receiving epinephrine. - The relative risk of admission, unadjusted and adjusted for multiple comparisons also reported (figure 2). - Median days to symptom resolution (normal feeding, normal sleeping, quiet breathing) also reported (figure 4). - Unadjusted and adjusted p values also reported for changes in clinical characteristics of patients and time to discharge (table 2).

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				No coughing, median no of days (interquartile range): 12.6 (7.8-18.5); 13.2 (8.1-19.3); 13.8 (8.5-20.2); 13.3 (8.2-19.5) 6. Need for CPAP/mechanical ventilation: Not reported. 7. Adverse effects Observed in the emergency department by research nurse: - Tremor 4 (2.0); 4 (2.0); 5 (2.5); 2 (1.0) - Pallor 23 (11.5); 22 (11.1); 15 (7.5); 16 (8.0) - Vomiting 2 (1.0); 4 (2.0); 5 (2.5); 3 (1.5) Reported by families during the 22 day telephone follow-up: - Varicella 0 (0); 0 (0); 0 (0); 0 (0) - Dark stools	

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				17.5 (8.5); 14 (7.0); 12 (6.0); 16 (8.0) Observed in infants admitted to hospital: - Hypertension 0 (0); 1 (0.5); 1 (0.5); 0 (0) - Hyperkalemia 0 (0); 0 (0); 1 (0.5); 0 (0)	
Full citation Roosevelt,G., Sheehan,K., Grupp-Phelan,J., Tanz,R.R., Listernick,R., Dexamethasone in bronchiolitis: a randomised controlled trial, Lancet, 348, 292-295, 1996 Ref Id 208028 Country/ies where the study was carried out USA Study type Randomised, double-blinded, prospective study. Aim of the study	Sample size - 454 met inclusion criteria presented at the emergency department. - 197 required inpatient management. - 122 patients enrolled. - 4 excluded (clinical deterioration, diagnosis of cystic fibrosis, previous intubation, did not recieve all study treatment). - Dexamethasone 65, placebo 53. Characteristics Dexamethasone; placebo: Mean±SD or n(%) - Age, months: 5.3±3.7; 5.0±2.5	Interventions - 1mg/kg dexamethasone or 1mg/kg saline (placebo) administered intramuscularly for a maximum of three doses every 24 hours. - The hospital pharmacy prepared and coded drug and placebo. Additional treatments: - All of treatment for example antibiotics, nebulised bronchodilators, tribavirin left to discretion of physician.	Details Setting: Inpatient care in the Children's Memorial Hospital (tertiary-care referral hospital). Randomisation and concealment: - Three investigators unaware of treatment allocation. Outcome measures: - Each patient assessed after every 12 hours by	Results Protocol outcomes 1. Hospital admission rate: 197 out of 454 required inpatient management. 2. Length of hospital stay - Dexamethasone time to resolution, hazard ratio (95% CI): 1.3 (0.9 to 1.3) p=0.22 - 9 dexamethasone and 9 placebo patients were discharged before the	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Out of 197 eligible: 31 refused consent, 28 not identified as eligible for enrollment and 16 transferred to other hospitals. - Randomisation method not explained. - More males in dexamethasone group than placebo group. Attrition bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the efficacy and safety of corticosteroids in the treatment of bronchiolitis while addressing the shortcomings of previous studies. Study dates Infants examined between December 1, 1993 and March 31, 1994. Or between December 1, 1994 and March 31, 1995. Source of funding Generous support by Green Bay Foundation-James P Gorter Family Fund.	- Weight, kg: 7.1±1.7; 6.8±1.5 - Sex male/female: 41(63%)/24(37%); 33(62%)/20(38%) - Duration of illness, days: 4.7±4.0; 5.0±3.7 - Exposure to tobacco smoke at home: 22(34); 26(49) - Atopic family history: 26(40); 23(43) - RSV: 39(60); 40(76) Inclusion criteria - Bronchiolitis defined as: an infection of the lower respiratory tract that occurs during the first 12 months of life and is characterised by wheezing. - <12 months old. - Required inpatient care. - First episode of wheezing documented by a physician. Exclusion criteria - <4 weeks old. - Required admission to the intensive care unit. - History of congenital heart disease. - Previously needed intubation, ventilation, or supplemental oxygen.		one of three investigators. - The time to the resolution of symptoms defined as (scoring system used by Schuh et al.): 1. The number of assessments needed to reach oxygen saturation of more than 95% while receiving no supplemental oxygen. 2. An accessory muscle score of 0. 3. A wheeze score of 0 or 1. 4. Resumption of normal feeding and duration of oxygen therapy. Statistical methods: - Continuous variables were analysed by a non-parametric median test. - Categorical data were analysed by chi-squared tests.	third dose of study treatment p=0.68 3. Change in disease severity score at 1 to 7 days after starting treatment: Not reported. 4. Change in O2 saturation - Oxygen saturation on admission, time to resolution, hazard ratio (95% CI): 0.7 (0.4 to 1.1) p=0.13 - Oxygen saturation on admission, duration of oxygen therapy, hazard ratio (95% CI): 0.5 (0.3 to 0.7) p=0.0009 - Dexamethasone, duration of oxygen therapy, hazard ratio (95% CI): 0.9 (0.6 to 1.4) p=0.74 5. Duration of cough:	- 45 (69%) dexamethasone and 42 (78%) parents contacted at follow-up. Performance bias: - Additional treatments given according to physicians discretion, but no patients received theophyline, racemic adrenaline, or tribavirin. - Blinding unclear. Other information - Effects of dexamethasone in selected patient sub-groups from time to resolution and duration of oxygen therapy reported (table 3). - No differences between the groups in the use of antibiotics or nebulised β-agonist drugs. - One dexamethasone group patient and two placebo group patients were prescribed corticosteriods by their treating physician after the completion of study treatment.

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			- Patients who were not given consent were compared with study patients by logistic regression and non-parametric median test. - Time to resolution and duration of oxygen therapy were analysed by survival analysis with a proportional-hazards model. - The hazard ratio for each variable in this study indicates the contribution made by that to the endpoint. - Sample size of 60 patients in each group to detect a 30% reduction in the time to resolution or duration of oxygen therapy, α=0.05, power=80% Follow-up:	Not reported. 6. Need for CPAP/mechanical ventilation 7. Adverse effects: - One placebo patient transferred to intensive care unit 15 hours after admission because of clinical deterioration, but she did not require mechanical ventilation. - Two dexamethasone and one placebo had occult blood in their stools. - No episodes of gross haematochezia were observed.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			10-14 days after discharge by telephone.		
Full citation Schuh,S., Coates,A.L., Binnie,R., Allin,T., Goia,C., Corey,M., Dick,P.T., Efficacy of oral dexamethasone in outpatients with acute bronchiolitis, Journal of Pediatrics, 140, 27-32, 2002 Ref Id 210201 Country/ies where the study was carried out Canada Study type Randomised, double-blinded, plaebo-controlled trial. Aim of the study - To examine the efficacy of oral dexamethasone in acute bronchiolitis. - To investigate in outpatients younger than 2 years with acute bronchiolitis the clinical benefits of oral dexamethasone within 4	Sample size - 1464 presented at emergency department with bronchiolitis. - 544 patients approached. - 46 declined to participate. - 70 participated: 36 dexamethasone, 34 placebo. - 48 were discharged home, of those 26 in dexamethasone group and 13 in the placebo group agreed to continue the experimental therapy at home. Characteristics Dexamethasone; placebo (Mean±SD) - Sex (male/female): 20/16; 23/11 - Age, months: 6.1±3.5; 6.9±3.9 - Eczema history: 9; 6 - Family history of atopy: 30; 18 - Oxygen saturation %: 96.8±2.3; 96.0±2.5 - RSV positive: 15/28; 15/30	Interventions - Both groups recieved the same dosage (1mg/kg) flavoured with wild cherry syrup. - Oral dexamethasone syrup: Merck Frosst, Canada % Co, Pointe-Claire, Dorval, Quebec, Canada. - Both treatments of identical colour, texture, taste and smell. - All decisions regarding the need for further hospitalisation were made by the attending physicians not involved in the study who were unaware of the research nurse's scoring as well as the patients' treatment assignment and requested not to administer addtional therapy (other than acetominophen for fever).	Details Setting: - Children seen between 8am and 9pm in the emergency department. - Continued treatment as outpatients. Randomisation and concealment: - Blocked randomisation code prepared by pharmacy from a computer generated list of random numbers. - Identity of the treatment assignment was completely masked to patients, family, clinicians, and research personnel with the exception of the research pharmacists.	Results Protocol outcomes 1. Hospital admission rate: Dexamethasone group 7/36 (19%) Placebo group 15/34 (44%) p=0.39 No child was hospitalised between day 7 and 28. 2. Length of hospital stay: Not reported. 3. Change in disease severity score at 1 to 7 days after starting treatment Dexamethasone; placebo Mean±SD, Median, (Range): Mean RACS - At 4 hours: -5.0±3.1, -5, (-13 to 4);	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Attrition bias: - 9 patients dropped out once discharged. - 67 out of 70 reevaluated on day 7. Selection bias: - 920 of 1464 children at the emergency department were not approached because the research nurse was not present. Detection bias: - More patients taking placebo than dexamethasone received corticosteriods after discharge. Performance bias: - 39 patients continued treatment at home as outpatients and 32 as inpatients.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hours of administration in the emergency department and after 5 days of continued therapy and discharge. Study dates November 1997 to April 2000. Source of funding - Supported by grants from the Medical Research Council of Canada and Merck Foseet, Canada. - The Paediatric Outcomes Research Team is supported by The Hospital for Sick Children Foundation. - Dr. Dick recieves financial support from the Onatario Ministry of Health and Long-Term Care through a Career Scientist Award. - No official endorsement by the Ministry is intended ot should be inferred.	Medications before arrival: - Inhaled albuterol: 8; 4 - Oral albuterol: 1; 3 - Orciprenaline: 2; 3 Inclusion criteria - Acute bronchiolitis defined as: the most frequent cause of infant hospitalisations during yearly winter outbreaks. - Between 8 weeks and 23 months of age. - First wheezing episode associated with respiratory distress. - An upper respiratory tract infection. - RDAI rating of ≥6. Exclusion criteria - Children with history of wheezing or bronchodilator therapy. - Prematurity. - Neonatal ventilation. - Chronic lung/cardiac disease. - Aspiration. - Neurologic/neuromuscular problems. - Immunodeficiency.	Additional treatments: - The dose was repeated once in cases of vomitting within 20 minutes of administration, and further vomitting necessitated withdrawal from the study. - Nebulised albuterol (Ventolin 5% solution, GlaxoWellcome, Inc Mississauga, Ontario, Canada) via a vented Pari LC STAR nebuliser 2.5mg per dose (0.5ml) in 3ml of normal saline solution with oxygen flow of 6 to 7 l/min with tight fitting face mask at times 0, 30, 60 and 120 minutes. Discharge: - Children with persistent signs of respiratory distress 240 minutes after experimental therapy were admitted to the hospital. - Children discharged home after the 4 hour observation period continued to recieve	- Randomisation code revealed only after all patients had completed the study. Outcome measures: - RACS (used by Lowell et al. assess changes in RDAI and respiratory rate). - Hospitalisation rates after the 240 minute observation period. - Oxygen saturation. Statistical methods: - Differences in mean values between the dexamethasone and placebo groups were tested with a t-test. - Proportions were compared with a Fisher exact test.	-3.2±3.7, -3, (-9 to 8) p=0.029 - At 7 days: -8.9±5.2, -9, (-18 to 8) -9.3±4.9, -10, (-20 to 0) p=0.750 Mean RDAI - At 4 hours: 5.4±2.1, 6, (1 to 10); 7.2±2.8, 7, (2 to 14) p=0.064 - At 7 days: 2.4±3.1, 2, (0 to 12); 2.6±3.0, 2, (0 to 11) p=0.754 4. Change in O2 saturation % (Mean±SD): At 4 hours: Dexamethasone 96.4±2.8 Placebo 95.7±3.0 p=0.944 5. Duration of cough: Not reported. 6. Need for CPAP/mechanical ventilation:	Other information - Respiratory rate and heart rate also reported (table 2). - 7 out of 32 infants in the placebo group received cointervention with corticosteriods from their primary care provider after discharge because of persistent symptoms, none in the dexamethasone group received additional corticosteriods p=0.004.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Critically ill infants who required immediate airway stabalisation. - Infants previously given oral or inhaled corticosteriods. - Infants exposed to varicella within 21 days before arrival.	either daily oral dexamethasone (0.6/mg/kg/dose) or placebo for 5 days, and albuterol (1.5/mg [0.3ml]) 4 times daily with the same nebuliser.	- The change in clinical scores over 4 hours evaluated by repeated measures regression analysis. - Logistic regression analysis used to assess the effects of covariates on risk of hospitalisation. - Intention-to-treat analysis. - α=0.05, β=0.20 the sample size required to detect a RACS score change of 2 was 71 patients. Follow-up: - Parents of all patients telephoned on day 28.	Not reported. 7. Adverse effects: - Five children received racemic epinephrine during the study because of persistent respiratory distress, one in the dexamethasone group and four in the placebo group. - 9 (25%) in the dexamethasone group needed medical visits for continuing symptoms between day 7 and day 28 and 14 infants (48%) in the placebo group required medical attention p=0.069.	
Full citation Teeratakulpisarn,J., Limwattananon,C., Tanupattarachai,S., Limwattananon,S., Teeratakulpisarn,S.,	Sample size - 261 hospitalised due to acute bronchiolitis. - 179 of 261 met criteria with parental consent.	Interventions Dexamethasone: Single intramuscular injection of 0.9mg/kg. Placebo: An equivalent volume of	Details Setting: Pediatric wards of a University hospital and its affiliated hospital.	Results Protocol outcomes 1. Hospital admission rate	Limitations Based on NICE checklist. Only limitations that arise in the study are reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kosalaraksa,P., Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: a randomized, double-blind, placebo-controlled trial, Pediatric Pulmonology, 42, 433-439, 2007 Ref Id 208297 Country/ies where the study was carried out Thailand Study type Randomised, double-blinded, placebo-controlled trial. Aim of the study To examine the efficacy of a single intramuscular injection of dexamethasone in children hospitalised with acute bronchiolitis and followed up for 1 month after discharge. Study dates 2002 to 2004 Source of funding	- 5 excluded from analysis: one from the dexamethasone group and one from placebo refused further hospitalisation and three from the placebo group did not have their clinical scores assessed until the endpoint. - 174 completed: 89 examethasone, 85 placebo. Characteristics Characteristic: Dexamethasone; placebo; p value: Mean±SD or n(%) - Age months: 10.2±5.5; 11.2±5.9; 0.232 - Age <6 months: 21 (24); 15 (18); 0.333 - Age <12 months: 60 (67); 51 (60); 0.309 - Male: 55 (62); 55 (65); 0.691 - Body weight, kg: 8.1±2.0; 8.5±1.8; 0.107 - Atopic parent: 26 (29); 24 (28); 0.887 - Passive smokers: 53 (60); 53 (62); 0.705 - Symptom before admission, days: 3.6±1.8; 3.6±1.8; 0.785 - 02 saturation <95% at enrollment: 44 (49); 44 (52); 0.759	saline solution in a container of identical appearance to dexamethasone. - The study vials were prepared, numbered and sealed by a pharmacist according to the randomisation numbers. - Both study groups were similary treated following the National Treatment Guidelines for Acute Respiratory Infection in Children, Thailand. - Possible co-interventions included epinephrine and/or β2-agonist nebulisation. - The investigators closely monitored the treatment regimens in order to avoid any additional form of corticosteriod being added to either group	Randomisation and concealment: - Mixed, permuted, block randomisation, using a computer generated number. - The treatment allocation was concealed from the investigators, the attending pediatricians and all of the health personnel involved in patient care. Outcome measures: - Assessments performed when the child was relatively calm and without administration of oxygen for at least 15 minutes. - The time from study entry to resolution of respiratory distress (total clinical score ≤3	Re-hospitalisation rates up to 1-month post-treatment: Dexamethasone 3 out of 89 Placebo 7 out of 85 p=0.168. 2. Length of hospital stay, hours (Mean±SD): Dexamethasone 54.2±29.9 Placebo 67.6±41.8 Mean difference (95% CI): 13.4 (2.6 to 24.2) p=0.02 3. Change in disease severity score at 1 to 7 days after starting treatment: Not reported. 4. Change in O2 saturation: Not reported. 5. Duration of cough: Not reported. Days from treatment to symptom-free (Mean±SD):	Selection bias: - 5 patients exluded from analysis. - 179 of 261 met criteria Performance bias: - Subjective clinical scoring system. - Many co-intervention treatments. - Oxygen saturation measured but not reported for end point. Attrition bias: - Patients discharged, but numbers and continued treatment not reported. Other information Duration of 02 administration after enrollment: Dexamethasone 22.0±25.2 Placebo 36.5±37.7 Mean difference (95% CI): 14.9 (5.3 to 24.4) p=0.003 Duration from enrollment to end of respiratory distress, hours (Mean±SD): Dexamethasone 27.2±18.1 Placebo 39.0±32.8

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Grant sponsor: The National Research Council of Thailand.	- Salbutamol use before enrollment: 44 (49); 40 (47); 0.754 Inclusion criteria - Bronchiolitis defined as: the first episode of wheezing associated with tachypnea, increased respiratory effort and an upper respiratory tract infection. - Presented to the pediatric outpatient clinic or emergency department with bronchiolitis requiring hospitalisation. Hospitalisation criteria: - Diagnosed with bronchiolitis. - <3 months of age. - <12 months of age with a respiratory rate of over 60 breaths/min. - ≥12 months of age with a respiratory rate over 50 breaths/min. - 02 saturation breathing room air <95%. - Apathy and/or refusal to eat. Exclusion criteria		and oxygen saturation ≥95%). - Clinical score for respiratory distress (modified from De Boeck et al. and Tal et al. based on repiratory rate, wheezing, accessory respiratory muscle retraction and oxygen saturation). - Oxygen saturation measured using pulse oximetry. - Duration of oxygen therapy. - Additional use of drugs. Statistical methods: - Time to resolution of respiratory distress submitted to a survival analysis using the Kaplan-Meier and the difference examined using a log-rank test.	Dexamethasone 7.0±5.9 Placebo 9.0±6.4 p=0.035 6. Need for CPAP/mechanical ventilation: Not reported. 7. Adverse effects: - After the study endpoint prescribed systemic corticosteriods because of re-wheezing: Dexamethasone 4 Placebo 3 - Occult blood in stools: Dexamethasone 2 Placebo 1 p= 0.588 - Diarrhea: Dexamethasone 3 Placebo 3 p= 0.954 - 3 in placebo had subsequent pneumonia with suspicious bacterial causes and required antibiotics.	Mean difference (95% CI) 11.8 (3.9 to 19.7) p=0.004 Additional treatment: After enrollment, n (%) Dexamethasone; placebo; pvalue: Epinephrine 38 (43); 38 (45); 0.789 Salbutamol 64 (72); 69 (81); 0.150 Intravenous fluid 49 (55); 44 (52); 0.663 Antimicrobial drugs 12 (14); 8 (9); 0.400 Oxygen 66 (74); 67 (79); 0.468 - At 6 hours, 12 out of 89 (13%) of the children in the dexamethasone and 2 out of 85 (2%) in the placebo groups had resolution of respiratory distress with a total clinical score ≤3. At 12 hours 25 out of 89 (28%) in the dexamethasone group and 9 out of 85 in the placebo group reached the same endpoint. - The respective cumulative percentage of children with resolution of respiratory distress by days 1, 2 and 2

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Presence of symptoms for more than 7 days. - Inital admission to the intensive care unit with endotracheal intubation. - A previous history of intubation. - History of asthma. - Personal history of atopy with a good response to a first dose of β2-agonist nebulisation. - Children receiving treatment with any form of corticosteroid within 2 weeks. - Contraindication to corticosteriod treatment. - Born prematurely.		- Cox proportional hazards regression used to estimate the hazard ratio. - Difference in mean values tested by an independent t-test. - Categorical data compared between groups using a chi-squared test and Fisher exact test. - Each group required 85 children in order to detect a 35% relative reduction in the time to resolution of respiratory distress, compared with the placebo group assumed to have a median time to resolution of 96 hours according to a two-sided test, α=0.05 and statistical power of 80%. - Each pediatrician	- Visited an emergency room or private clinic because of respiratory symptoms: Dexamethasone 17 (19%) Placebo 26 (31%) p=0.079	was 54 out of 89 (61%), 77 out of 89 (87%) and 88 out of 89 (99%) in the dexamethasone group versus 37 out of 85 (44%), 68 out of 85 (80%) and 77 out of 85 (91%) in the placebo group. - Subgroup analysis in children <12 months of age showed that dexamethasone, compared to the placebo, significantly reduced mean respiratory stress duration by 15.5 hours (95% CI 5.9 to 25.1, p=0.001), mean duration of oxygen therapy by 20.9 hours (95% CI 8.5 to 33.3, p=0.003), and mean length of stay by 15.9 hours (95% CI 2.0 to 29.7, p=0.012). - After the study end point but before discharge, the attending physicians rescribed systemic corticosteriods (oral or injected dexamethasone or oral prednisolone) because of re-wheezing. - None of the children received theophylline or ribavirin. - Clinical scoring system for respiratory distress described in table 1.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			examined 16 patients independently, the kappa statistic from the five pediatricians obtained from the clinical score was 0.7 (p<0.01). Follow-up: - Any child reaching a clinical score of ≤3 for a 6 hour period plus resumption of normal feeding was discharged and followed up at 2 week intervals for at least 1 month. - All followed up 1 month after discharge.		
Full citation Zhang,L., Ferruzzi,E., Bonfanti,T., Auler,M.I., D'avila,N.E., Faria,C.S., Costa,M.M., Long and short-term effect of prednisolone in hospitalized infants with acute bronchiolitis, Journal of Paediatrics	Sample size - 63 admitted to hospital with bronchiolitis. - 52 recurited: 28 prednisolone, 24 control. - 25 completed prednisolone course in hospital, 3 completed at home. - 2 from prednisolone group lost to follow-up.	Interventions - Recruited patients assigned to recieve prednisolone plus standard care or standard care alone. - Prednisolone 1mg/kg as a single dose for 5 days and standard care.	Details Setting: 30-bed paediatric inpatient ward, teaching hospital of the Federal University of Rio Grande.	Results Protocol outcomes Prednisolone; control; p value 1. Hospital admission rate: Not reported.	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Concealment of allocation unclear, only study investigators were blinded to treatment assignment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and Child Health, 39, 548-551, 2003 Ref Id 210169 Country/ies where the study was carried out Brazil Study type Randomised controlled trial Aim of the study To assess long and short-term effect of prednisolone in hospitalised infants with bronchiolitis, principally the potential benefit on reduction of post-bronchiolitis wheezing. Study dates During peak bronchiolitis season (June to October) in two consecutive years (1997 and 1998). Source of funding Project grant from the Research Support foundation of Rio Grande do Sul (FAPERGS).	Characteristics Characteristic: prednisolone; placebo Mean±SD or n (%): - Age, months: 4.0±2.5; 3.4±1.8 - Sex, male: 21 (75.0); 20 (83.3) - Atopic family history: 23(82.1); 21 (87.5) - Tobacco smoke at home: 22(78.6); 17 (70.8) - Prematurity, <37 weeks: 5(17.9); 3(12.5) - Chest retractions: 25 (89.3); 22 (91.7) - Oxygen saturation with room air: 92.7±2.5; 93.1±2.1 - Duration of illness before hospitlisation, days: 3.5±1.7; 3.7±1.6 Inclusion criteria - Bronchiolitis defined as: a worldwide common lower respiratory tract infection in infants. - First episode of wheezing with respiratory distress (defined as tachypnoea and/or chest retractions. - History of preceding upper respiratory tract infection	- First dose of prednisolone at enrollment, remaining doses given once daily at 08.00 hours during the following 4 days. - If a patient vomitted within 30 min after administration, the same dose was repeated immediately. - The inpatient nurses were responsible for the adminstration of prednisolone. - If hospital <5 days the remaining doses of prednisolone were administered by parents at home. - Standard care judged by attending paediatricians according to the inpatient treatment protocol of the hospital, including oxygen therapy, fluid replacement and nebulised fenoterol. - All Paediatricians advised against prescribing and corticosteriods for recruited patients. - The decision for hospital discharge was	Randomisation and concealment: - The independent pharmacy staff members were responsible for group assignment and distribution of prednisolone, according to a random-number table generated randomisation list. - The randomisation list was concealed until the study was complete. - All study investigators were blinded to treatment assignment throughout the study. Outcome measures: - During hospitalisation, each patient was assessed daily by one of two trained investigators. - Prevalence of post-bronchiolitis	2. Length of hospital stay, days (95% CI): 6.0 (5.3 to 8.3); 5.0 (4.8 to 7.5); 0.70 Duration of 02 therapy, hours (95% CI): 24.0 (21.6 to 66.7); 24.0 (15.2 to 71.6); 0.41 Time to clinical resolution, days (95% CI): 4.0 (3.5 to 6.1); 4.0 (3.3 to 6.0); 0.75 3. Change in disease severity score at 1 to 7 days after starting treatment: Not reported. 4. Change in O2 saturation: Not reported. 5. Duration of cough Wheezing n (%): - 1 month after discharge 19(73.1); 20(83.3); 0.50	- Sample size of low power to detect differences. Attrition bias: - 2 patients from prednisolone group lost to 12 month follow-up. Performance bias: - Not double-blinded, may expect favour towards prednisolone from parents. - 2 from prednisolone group received intravenous hydrocortisone prescribed by the same attending paediatrician during the first 24 hours after hospitalisation. - Not a placebo-contolled trial. Detection bias: - Wheezing episodes could be a subjective measure. - Discharge criteria not described. - Oxygen saturation measured but not reported. Other information - Two patients from the prednisolone group received intravenous hydrocortisone prescribed by the same

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(coryza and/or temperature >37.5ºC). - <12 months old. Exclusion criteria - <4 weeks old. - Had any chronic cardiac or pulmonary disease. - Congenital abnormality. - Immediate favourable response to the administration of a single dose of nebulised fenoterol. - Received corticosteriods within the preceeding 4 weeks. - Severe initial disease requiring intensive care.	made by the attending pediatricians.	wheezing at 1, 3, 6 and 12 months after hospital discharge (frequent if ≥2 days a week, infrequent if <2 days a week). - Length of hospital stay. - Duration of oxygen therapy mesured by pulse oximeter applied to the big toe after the child had been in room air for 10 minutes. - Time to clinical improvement during hospitalisation (pulse blood oxygen saturation >95% without supplemental oxygen [measuerd by pulse oximeter], absence of chest retractions and respiratory rate less than upper limits for age). Statistical methods:	- 3 months after discharge 19(73.1); 19(79.2); 0.74 - 6 months after discharge 17(65.4); 16(66.7); 0.92 - 12 months after discharge 13(50.0); 14(58.3); 0.55 Infrequent wheezing n (%) - 1 month after discharge 17(65.4); 17(70.8); 0.68 - 3 months after discharge 18(69.2); 19(79.2); 0.53 - 6 months after discharge 16(61.5); 16(66.7); 0.71 - 12 months after discharge 12(46.2); 14(58.3); 0.42 Frequent wheezing n (%)	attending physician during the first 24 hours after hospitalisation. - With respect to standard care there were no significant differences between the two groups in terms of oxygen therapy, fluid replacement and nebulised fenoterol. - Four patients in each group had protracted course defined as the time to clinical resolution longer than 7 days, 14.3% prednisolone, 16.7% control, p=1.0. - Effect of prednisolone on the prevalance of postbronchiolitis wheezing also reported (table 2).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Intention-to-treat analysis. - Continuous variables were compared by unpaired t-test or Mann-Whitney U-test. - Categorical data were compared using chi-squared or Fisher exact two-tailed test. -Calculated a sample size of 25 patients per group would be required to detect a 50% reduction in prevalence which was considered clinically relevant, α=0.05, power=0.80. Follow-up: - Parents received adequate training to observe wheezing breathing, after discharge parents instructed to record wheezy breathing at home.	- 1 month after discharge 2(7.7); 3(12.5) - 3 months after discharge 1(3.8); 0(0) - 6 months after dischare 1(3.8); 0(0) - 12 months after discharge 1(3.8); 0(0) 6. Need for CPAP/mechanical ventilation: Not reported. 7. Adverse effects: Not reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- At the outpatient clinic at 1, 3, 6 and 12 months after hospital discharge, if absent a home visit was made by one of the investigators.		
Full citation Fernandes,R.M., Bialy,L.M., Vandermeer,B., Tjosvold,L., Plint,A.C., Patel,H., Johnson,D.W., Klassen,T.P., Hartling,L., Glucocorticoids for acute viral bronchiolitis in infants and young children.[Update of Cochrane Database Syst Rev. 2010;(10):CD004878; PMID: 20927740], Cochrane Database of Systematic Reviews, 6, CD004878-, 2013 Ref Id 261181 Country/ies where the study was carried out Study type There is only one evidence table in STAR	Sample size Characteristics Inclusion criteria Exclusion criteria	Interventions	Details	Results	Limitations Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
– in the inhaled corticosteroid question. In the systemic corticosteroid question in STAR the Fernandes review has been included but data has not been extracted in to the evidence table (the evidence table is purposefully empty). Aim of the study Study dates Source of funding					
Full citation De,BoeckK, Van,derAaN, Van,LierdeS, Corbee,L., Eeckels,R., Respiratory syncytial virus bronchiolitis: A double-blind dexamethasone efficacy study, Journal of Pediatrics, 131, 919-921, 1997 Ref Id 261345 Country/ies where the study was carried out Belgium Study type	Sample size - 32 fulfilled entry criteria. - 3 excluded because of incomplete data. - 29 randomised: 14 dexamethasone, 15 placebo. Characteristics - Age days, median (interquartile range): dexamethasone 186 (111 to 224) placebo 213 (133 to 267) - "No differences in weight, proportion of males,	Interventions - Dexamethasone 0.6/mg/kg intravenously in two doses on day 1; 0015mg/kg on days 2 and 3. - "Or placebo in double-blinded fashion" Additional treatment: - Concomitant therapy was standardised. - Salbutamol (0.5%), 0.25ml, and ipratropium bromide	Details Setting: Inpatient. Randomisation: Not described. Outcome measures: - Evaluation completed by one of two investigators every 12 hours. - Clinical score by Tal et al modified to include oxygen	Results Protocol outcomes 1. Hospital admission rate: Not reported. 2. Length of hospital stay (days): dexamethasone 6.0 (SEM 0.7) placebo 6.6 (SEM 0.3) 3. Change in disease severity score at 1 to	Limitations Based on NICE checklist. Only limitations that arise in the study are reported. Selection bias: - Individual characteristics not reported other than age. - Randomisation methods not reported. - Number of patients presented to hospital with bronchiolitis who did not meet inclusion criteria not reported. Attrition bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Double-blinded, placebo-controlled trial. Aim of the study To reevaluate the efficacy of intravenous corticosteriods in previously health infants without underlying disease hospitalised with proven RSV primary infection. Study dates Epidemic of 1991-1992. Source of funding Not reported.	leukocyte count, temperature, eosinophilia, and serum." Inclusion criteria - Bronchiolitis defined as: an infectious disease of the lower respiratory tract occurring mainly in infants. - <24 months of age. - Signs of bronchiolitis: prodromal rhinorrhea, cough, or low-grade fever. - Followed by at least two of the following: chest retractions, tachypnea, wheezing, or rales. - Detection of RSV in nasal wash. - First episode of wheezing or shortness of breath. - Onset of illness within the previous 5 days. Exclusion criteria - Underlying heart, lung, or immune disorder. - Premature infants born before 34 weeks were treated with ribavirin.	(0.025%), 0.5ml, were aerosolised every 6 hours. - Oxygen given to maintain oxygen saturation >90%. - Toal fluid intake stabilised to 100 to 120ml/kg per day. - 12 patients were treated with antibiotics: 5 dexamethasone, 7 placebo. - If saturation dropped to <85%, the measurement was discontinued, supplemental oxygen resumed, and 84% was noted.	saturation (0 to 12 scale). - Respiratory rate. - Oxygen saturation measured by pulse oximeter. - Duration of hospitalisation. - Pulmonary funtion (minute ventilation, inspiratory pulmonary resistance, expiratory pulmonary resistance, dynamic pulmonary compliance) tests on third day of therapy after sedation with oral chloral hydrate (80mg/kg). Statistical methods: - Mann-Whitney U test. - Wilcoxon signed rank test for pulmonary variables.	7 days after starting treatment: Mean, (IQR) - Intial score: dexamethasone 8 (6 to 10), placebo 7 (6 to 8). - Over time the score significantly improved in each group (p<0.001), but the rate of improvement was similar (two-factor repeated measurements ANOVA p>0.05). 4. Change in O2 saturation: - Mean inital scoring: dexamethasone 90 (SEM 2), placebo 91 (SEM 1). - No significant difference was noted between the groups at any point in time. 5. Duration of cough: Not reported. 6. Need for CPAP/mechanical ventilation: Not reported.	- Not all patients completed pulmonary function tests. Before: 11 dexamethasone; 13 placebo After: 9; 11 Detection bias: - Comments on the results are made which are not always supported by values before and after administration. - Clinical score results illustrated in a figure, separate values not reported. - Subjective clinical score. Performance bias: - Blinding unclear. - Placebo treatment unclear. Other information Pulmonary function test results before and after adminisatration also reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Two-factor repeated measurements ANOVA for variables with normal distribution.	7. Adverse effects: Not reported.	

I.14 What is the efficacy of nebulised hypertonic saline?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Al Ansari,K., Sakran,M., Davidson,B.L., El Sayyed,R., Mahjoub,H., Ibrahim,K., Nebulized 5% or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants, Journal of Pediatrics, 157, 630-634, 2010 Ref Id 262222 Country/ies where the study was carried out Qatar Study type Randomised, double-blinded, controlled Aim of the study To compare the efficacy and safety of 5%, 3% and 0.9% saline solution for treating acute bronchiolitis in the prehospital setting Study dates Between September 2007 and December 2008 Source of funding - Supported by Hamad Medical Corporation which employs all of the	Sample size - 187 enrolled - 16 excluded from analysis (9 based on exclusion criteria, 1 infant was enrolled twice, 6 removed by parents) - 171 randomised: 56 0.9% saline group, 58 3% saline group, 57 5% saline group Characteristics Characteristic: 0.9% saline; 3% saline; 5% saline; p value Mean±SD or n(%) - Age, months: 3.30±2.43; 3.84±2.84; 4.02±2.56; 0.32 - Duration of symptoms before enrollment, days: 3.6±1.87; 4.7±4.34; 4.6±3.22; 0.14 - Male/female: 31/26; 39/19; 31/26; 0.35 - Baseline severity score: 5.77±1.37; 6.16±1.53; 5.65±1.14; 0.11 - RSV positive: 31(55.4); 34(58.6); 31(54.4); 0.89	Interventions - Patients received 5ml of the study nebulisation (5%, 3% or 0.9% saline) mixed with 1.5ml epinephrine on enrollment and every 4 hours thereafter until discharge - Inhaled medications delivered through a tight fitting face mask by pressurised oxygen with the flow meter set at 10l/min - Additional nebulised epinephrine 5ml delivered in the same way could be administered with blinded study solution at a maximum frequency of every hour, and additional treatment (eg supplementary oxygen, hydration) could be given at the discretion of the treating physician Discharge: - Discharged when the treating physician determined they did	Details Ethics: - Study approved by hospitals Institutional Review Board - Written informed consent sought by parent/guardian on admission Setting: Short stay unit of the Pediatric Emergency Centre of Hamad General Hospital Randomisation and concealment: - Computer generated list of random numbers used by enrolling physician in consecutive order to identify a sealed envelope containing 1 of 3 codes identifying 1 of 3 different 500ml bags of sterilely prepared blinded study solution - Solutions prepared by pharmacist blinded to patient assignment Outcome measures:	Results Protocol outcomes 1. Hospital admission rate 5% saline group; 3% saline group; 0.9% saline group - Revisits to the Pediatric Emergency Centre within 7 days of discharge: 35(61%); 35(59%); 35(63%) p=0.91 - Short-stay readmission: 10(18%); 8(14%); 7(13%) p=0.73 2. Length of hospital stay, days: 1.56±1.38; 1.4±1.41; 1.88±1.76 p=0.36 4. Change in disease severity score: - At 24 hours: (5%; 3%; 0.9%) 3.75±1.27; 4.00±0.98; 3.97±1.27	Limitations Based on NICE appendix C checklist Attrition bias: Three infants (1.6%) were lost to follow-up after discharge, two in the 5% saline group and one in the 0.9% saline group Detection bias: - Results presented in figures, not all outcomes reported separately - Subjective clinical scoring system Performance bias: - Discharge frequently determined by social factors, such as avaliablity and consensus of family members - Additional treatments at discretion of physician Other information - Additional epinephrine doses

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
physicians except B.D., who also worked at Hamad - The authors declare no conflicts of interest	Inclusion criteria - Aged ≤18 months - Presented to the emergency departement with moderate to severe viral bronchiolitis - Prodromal history consistent with viral upper respiratory tract infection followed by wheezing and/or crackles on auscultation - Wang clinical score ≥4 Exclusion criteria - Born at ≤34 weeks gestation - Previous history of wheezing - Steroid use within 48 hours of presentation - Obtundation and progressive respiratory failure requiring intensive care unit admission - History of apnea within 24 hours before presentation - Oxygen saturation ≤85% on room air	not need supplementary oxygen, was feeding adequately without intravenous fluids, and had minimal or absent wheezing, crackles and chest retractions, provided that oxygen saturation was ≥94% and severity score <4 - At discharge patients sent home with an albuterol metered-dose-inhaler with an appropriately sized Aerochamber and mask attachment - A patient could return to the Pediatric Emergency Centre earlier if desired or necessary	- Clinical severity score (used by Wang et al.) - Oxygen saturation - Number of patients requiring ICU admission, readmission to short-stay unit or revisit in the one week after discharge determined by telephone follow-up by study nurse Statistical methods: - 45 patients in each group to proivde 80% power to detect mean severity score improvement of 10% for 5% saline group versus the 0.9% saline group, assuming a SD of 1 for each mean severity score. To account for patients discharged before 48 hours requires 55 patients in each group - Chi-squared test for categorical variables - One-way analysis of variance with post hoc Bonferroni correction for continuous variables	- Change from 0 to 24 hours calculated by NCC-WCH: 1.9; 2.16; 1.8 - At 48 hours: 5% saline group 3.69±1.09 0.9% saline group 4.12±1.11 p=0.04, difference 0.43, 95% CI 0.02 to 0.88 3% saline group 4.00±1.22 8. Adverse effects: - None observed - No patients withdrawn because of apnea, cyanosis, or decreased oxygen saturation and no patients required hospital or ICU admission during their study visit for bronchiolitis - One 0.9% saline group infant required a 2 day stay in ICU during a hospital admission in the weeks after the study visit Outcomes not reported:	prescribed for three infants (5.3%) in the 5% saline group, one infant (1.7%) in the 3% saline group and three infants (5.4%) in the 0.9% saline group, p=0.53 - Anitbiotic usage 19% in 5% saline group, 22% in 3% saline group, 18% in 0.9% saline group - No subjects received corticosteriod therapy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- History of a diagnosis of chronic lung disease, congential heart disease or immunodeficiency - Patients were withdrawn from the study if oxygen room air or if clinical deterioration was deemed to warrrent hospital admission			3. Change in respiratory rate 5. Change in O2 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	
Full citation Anil,A.B., Anil,M., Saglam,A.B., Cetin,N., Bal,A., Aksu,N., High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis, Pediatric Pulmonology, 45, 41-47, 2010 Ref Id 206284 Country/ies where the study was carried out Turkey Study type Randomised, double-blinded, controlled	Sample size - 190 enrolled - 4 excluded (2 protocol deviations and 2 parents refused participation) - 186 randomised - group 1 n=38, group 2 n=39, group 3 n=36, group 4 n=36, group 5 n=37 Characteristics Characterisitc: group 1; 2; 3; 4; 5; p value Mean±SD or n(%) - Age, months: 10.4±5.7; 9.4±5.0; 9.0±6.2; 9.7±6.2; 9.1±4.4; 0.86 - Male: 26(68.4); 29(74.3); 20(55.5);	Interventions - Stabilised with antypyretics if neccessary (temperature >38ºC) and/or nasal suction if the nose was blocked - Facial oxygen was removed if Sa02 >90% in room air, if not provided to maintain 90-92% - This was maintained for at least 30 minutes before receiving study treatment and unaltered throughout the study - Preparation of study drug by emergency department nurse, solutions were	Details Ethics: - Study approved by Tepecik Teaching and Research Hospital Ethics Committee - Written informed consent obtained from parent or guardian Setting: Pediatric emergency department of the Tepecik Teaching and Research Hospital Randomisation and concealment: - Random number table generated by a computer used by study coordinator to allocate	Results Protocol outcomes Group 1; 2; 3; 4; 5; p value Mean±SD (range) 1. Hospital admission rate: - One patient in group 2 and one patient from group 3 were admitted to hospital for further treatment, p=0.89. - Had a medical visit within 2 days post-discharge: 7 (18.4%); 5 (13.1%); 4 (11.4%); 6 (16.6%); 6 (16.2%); p>0.05. - Reasons for medical visit: child no better 12, child worse 16.	Limitations Based on NICE appendix C checklist Selection bias: - Enrollment between 8am and 5pm - Randomisation unclear Performance bias: - Discharge criteria not described - Additional treatments Detection bias: Subjective clinical scoring system Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare the effectiveness of nebulised albuterol, epinephrine, 3% hypertonic saline and high volume normal saline (0.9% NaCl) among children presenting to the emergency department with mild acute bronchiolitis Study dates November 1 2005 to March 31 2006 Source of funding Not reported	23(63.8); 22(59.4); 0.06 - Family history of atopy: 17(44.7); 15(38.4); 12(33.3); 12(33.3); 13(35.1); 0.50 - Parental smoking: 21(55.2); 20(51.2); 17(47.2); 16(44.4); 12(32.4); 0.76 - Duration of illness, days: 2.2±0.1; 2.0±0.2; 2.6±0.1; 2.5±0.7; 2.2±0.4; 0.12 Inclusion criteria - 6 weeks to 24 months old - Presented to emergency department with first episode of bronchiolitis (defined by symptoms of upper respiratory infection and the presence of bilateral wheezing and/or crackles on auscultation - Clinical severity score (Wang et al.) between 1 and 9 Exclusion criteria - Prematurity	identical in appearance and odor - Administration by emergency department nurse or investigator at 0 and 30 minutes by Medic-Aid Sidestream nebuliser using a face mask with continuous flow of 100% oxygen at 6l/min - Attending pediatrician determined need for admission and discharge medications Group 1: Inhalation of epinephrine 1.5mg, diluted to 4ml with 0.9% saline solution Group 2: Inhalation of epinephrine 1.5mg, diluted to 4ml with 3% saline solution Group 3: Inhalation of salbutamol (Ventolin, GlaxoSmithKleine) 1.5mg, diluted to 4ml with 0.9% saline solution Group 4: Inhalation of salbutamol (Ventolin, GlaxoSmithKleine) 1.5mg, diluted to 4ml with 3% saline solution	- Study coordinator only person with access to randomisation - Identity of study solutions blinded to all participants, care providers and investigators Outcome measures: - Clinical severity score (used by Wang et al. based on respiratory rate, wheezing, retraction and general condition) - Oxygen saturation - Hospitalisation - Investigators contacted dischaged patients two days later to record readmission and at 6 months to record wheezing - Adverse events defined as heart rate >200, tremor, withdrawal from the study due to worsening clinical status, or discontinuation of study medication due to side effects Statistical methods: - Three investigators, kappa statistic ≥0.8 satisfactory	- Six of the medical visits were to the emergency department: 2; 1; 1; 1; 1. - One child from group 5 was readmitted. 4. Change in disease severity score: - 0 min: 4.1±1.2 (2-7); 3.8±1.1 (2-9); 3.5±0.9 (2-7); 4.1±0.8 (2-6); 3.6±1.0 (2-6); 0.24 - 30 min: 3.1±0.9 (1-5); 2.9±1.2 (1-8); 2.6±1.2 (1-5); 3.2±1.0 (1-6); 2.7±1.0 (1-5); 0.06 - 60 min: 2.3±1.1 (0-4); 2.3±1.4 (0-8); 2.2±1.1 (0-5); 2.4±1.0 (0-5); 2.1±1.2 (0-4); 0.84 - 120 min: 1.6±1.2 (0-4); 2.2±1.4 (0-8); 1.5±1.4 (0-5); 2.3±0.9 (1-4); 1.8±1.4 (0-4); 0.10 - Change from 0 to 120 minutes calculated by NCC-WCH: 2.5; 1.6; 2; 1.8 5. Change in O2 saturation: - 0 min: 98.1±1.5 (94-100); 97.4±1.7 (92-100); 97.8±1.4 (92-100); 97.8±1.4 (92-100); 97.5±2.1 (91-100); 0.46	Clinical severity score described in table 1.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Underlying disease (eg cystic fibrosis, bronchopulmonary dysplasia, and cardiac or renal disease) - Prior history of wheezing - Atopic dermatitis - Allergic rhinitis or asthma - Oxygen saturation <85% on room air - Clinical severity score >9 - Obtunded conciousness - Progressive respiratory failure requiring mechanical ventilation - Previous treatment with bronchodilators - Any steriod theray within 2 weeks - Patients excluded from the study if the administration of the study drug was delayed by ≥10 minutes or if clinical deterioration mandated escalation of therapy and/or support	Group 5: Inhalation of of 4ml 0.9% saline solution	- To detect a difference of 1 unit in clinical score, α=0.05, power=80%, requires 150 patients (30 per group) - ANOVA for continuous variables - Chi-squared for dichotomous events - Paired sample t-test for dependent variables	- 30 min: 98.0±2.3 (91-100); 97.8±1.8 (91-100); 98.5±1.6 (91-100); 98.3±1.4 (92-100); 97.9±1.6 (92-100); 0.41 - 60 min: 98.5±1.6 (94-100); 98.5±1.2 (95-100); 99.0±1.2 (94-100); 98.5±1.5 (95-100); 98.5±1.5 (92-100); 0.38 - 120 min: 98.7±2.8 (94-100); 98.5±1.2 (95-100); 99.1±1.9 (90-100); 98.8±1.1 (96-100); 98.7±1.2 (96-100); 0.79 - Change form 0 to 120 minutes calculated by NCC-WCH: 0.6; 1.1; 1.3; 1.3 8. Adverse effects: - None encountered, no children were withdrawn from the trial due to side-effects or clinical deterioration. - All patients reassessed by telephone at 6 months: 10 (26.3%) from group 1, 14 (35.8%) group 2, 10 (27.7%) group 3, 12 (33.3%) group 4 and 13 (35.1%) group 5 showed recurrent wheezing attacks.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Outcomes not reported: 2. Length of hospital stay 3. Change in respiratory rate 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	
Full citation Grewal,S., Ali,S., McConnell,D.W., Vandermeer,B., Klassen,T.P., A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department, Archives of Pediatrics and Adolescent Medicine, 163, 1007-1012, 2009 Ref Id 210367 Country/ies where the study was carried out Canada Study type Randomised, double-blinded, controlled Aim of the study	Sample size - 48 enrolled - 2 exluded from analysis (one from HS group >12 months old and one from NS group inadvertently discharged prior to completion of the study period) - 46 completed: 23 NS group, 23 HS group Characteristics Characteristic: HS group; NS group Mean±SD or n(%) - Male: 14(60.9); 14 (60.9) - Age, months: 5.6±4.0; 4.4±3.4	Interventions - Pharmacy prepared 2.5ml aliquots of 0.9% NS and 2.5ml aliquots of a second, indistinguishable solution of 3% HS - Solutions similar in appearance and smell, stored in identical syringes, labeled only with a code number - Emergency department nurse added 0.5ml of 2.25% racemic epinephrine to the randomisation solution, and the total mixture of 3ml was given to the patient by nebulisation with a continuous flow of oxygen at 6l/min	Details Ethics: - Granted by local ethics board and a clinical trial application approved by Health Canada -Informed consent obtained from (of) enrolled Setting: Tertiary care pediatric emergency department, Stollery Children's Hospital, Edomonton, Alberta Randomisation and concealment: - Randomised into blocks of 4 generated by the pharmacy using the website randomization.com	Results Protocol outcomes HS group; NS group; difference Mean (95% CI) 1. Hospital admission rate: - 8; 13; RR 0.61 (0.22 to 1.19) - Returns to emergency department: 3; 4; RR 0.74 (0.11 to 2.91) 4. Change in disease severity score: RACS 4.39 (2.64 to 6.13); 5.13 (3.71 to 6.55); 0.74 (-1.45 to 2.93) 5. Change in 02 saturation:	Limitations Based on NICE appendix C checklist Selection bias: - Number who did not meet inclusion criteria not reported - Restricted recruitment times, usually 4pm to 2am when research assitant avaliable Detection bias: - Subjective clinical scoring system - Discharge criteria not described Performance bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine whether nebulised 3% hypertonic saline with epinephrine is more effective than nebulised 0.9% saline with epinephrine in the treatment of bronchiolitis in the emergency department Study dates February 2004 to March 2005 Source of funding - Financial disclosure: not reported - Funding/support: Department of Pediatrics, University of Alberta; and the Alberta Research Centre for Child Health Evidence	- Family history of asthma: 15(65.2); 17(73.9) - Smoke exposure: 8(34.8); 3(13.0) - RSV positive: 19 out of 13 (82.6); 18 out of 22 (81.8) - RDAI score 9.2±3.3; 8.7±2.8 - Oxygen saturation: 92.0±3.0; 92.4±2.5 - Respiratory rate: 54.8±13.1; 53.5±14.5 Inclusion criteria - Aged 6 weeks to 12 months - Clinical diagnosis of mild to moderate bronchiolitis defined as: the first episode of wheezing and clinical symptoms of a viral respiratory infection - Oxygen saturation between 85% and 96% on arrival - Respiratory distress assessment score (RDAI, used by Lowell et al.) score ≥4 Exclusion criteria - Preexisting cardiac or pulmonary disease	- Both groups received inhalation solutions at 0 minutes -Two doses of the study drug were avaliable for each patient such that, if the physician felt that a second dose of racemic epinephrine was needed during the 120 minute study period, the patient received the same drug combination again - Emergency department physicians were free to withdraw patients from the study or to use other interventions if deemed clinically necessary	- Emergency physicians , house staff, nurses, study personnel, and patients remained blinded to treatment allocation throughout the study Outcome measures: - Measurements at 0, 30, 60, 90 and 120 minutes, recorded after the patient's oxygen had been removed for a total of 5 minutes - Change in RACS (based on RDAI and respiratory rate) from 0 to 120 minutes - Change in oxygen saturation from 0 to 120 minutes - Rate of admission to hospital and rate of return to emergency department - Family contacted by telephone within 1 week to determine if any futher treatment was sought after discharge Statistical methods: - To detect a difference of 3 in the RACS between the two groups, α=0.05,	-0.44(-2.11 to 1.23); 1.34 (-0.29 to 2.99); 1.78 (-0.50 to 4.06) 8. Adverse effects: HS group: 3 vomitting and 1 diarrhea Outcomes not reported: 2. Length of hospital stay 3. Change in respiratory rate 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/use of feeding support	Additional medications and second dose at physicians discretion Other information - RDAI scoring system described in table 1 - 24 patients received a second dose of the study drug: 13 HS group, 11 NS group - Regression outcomes (variables to have an effect on RACS) also reported (table 5)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Previous diagnosis of asthma - Previous use of bronchodilators (except for treatment of the current illness) - Severe disease requiring resuscitation room care - Inability to take medication using a nebuliser - Inability to obtain informed consent secondary to a language barrier, or no phone access for follow-up		power=90%, required a sample size of 46 - Intention-to-treat analysis - t-test for continuous variables - Fisher exact test for dichotomous data - Linear multivariable regression analysis		
Full citation Ipek,I.O., Yalcin,E.U., Sezer,R.G., Bozaykut,A., The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis, Pulmonary Pharmacology and Therapeutics, 24, 633-637, 2011 Ref Id 210661 Country/ies where the study was carried out Turkey	Sample size - 120 enrolled - Each of the four treatment groups contained 30 children Characteristics Characteristic: group 1; group 2; group 3; group 4 Mean±SD, n (%) - Age, months: 8.13±4.75; 7.90±3.57; 8.40±4.19; 7.40±3.08; p=0.791	Interventions - All patients given 4ml of a nebulised solution via a compressor nebuliser through a facemask with continued flow of oxygen at 4 to 5l/min - Group 1 received 0.15mg/kg salbutamol plus normal saline - Group 2 received 0.15mg/kg salbutamol plus hypertonic saline - Group 3 received only hypertonic saline	Details Ethics: - Signed informed consent was obtained from the parents of each infant - Study approved by the Ethics Committee of Zeynep Kamil Maternity and Children's Training and Research State Hospital Setting: Short-stay unit of the pediatric emergency department	Results Protocol outcomes Group 1; group 2; group 3; group 4 Mean±SD or n (%) 1. Hospital admission rate Required hospitalisation: 3(10.0%); 2(6.7%); 3 (10.0%); 5(16.7%) p=0.65 3. Change in respiratory rate - Pretreament 45.53±6.43; 42.33±7.61;	Limitations Based on NICE appendix C checklist Selection bias: - Number of children presented with first time wheezing who did not meet inclusion criteria not reported - Randomisation unclear Performance bias: Blinding unclear Detection bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised, double-blinded, controlled Aim of the study Investigate the theraputic benefit of nebulised hypertonic 3% saline, by comparing four different nebulised regimens in the treatment of bronchiolitis in the emergency department Study dates October 2009 to March 2010 Source of funding Not reported	- Female: 13 (43.3); 12 (40.0); 13 (43.3); 11 (36.7); p=0.940 - Male: 17 (56.7); 18 (60.0); 17 (56.7); 19 (63.3) - Exposure to tabacco smoke: 17 (56.7); 19 (63.3); 20 (66.7); 17 (56.7) - Family/individual history of atopy: 12 (40.0); 8 (26.7); 8 (26.7); 8 (26.7) Inclusion criteria - <2 years old - History of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation - Clinical bronchiolitis severity score 4 to 8 Exclusion criteria - Clinical bronchiolitis severity score <4 or >8 - Oxygen saturation <85% on room air - Chronic cardiac illness - Premature birth - Birth weight <2500g - History of recurrent wheezing episodes	- Group 4 received only normal saline - The nebulised solution was administered every 20 minutes until 3 doses had been administered (0, 20 and 40th minute) - Supportive care including oxygen supplementation, aspiration, and hydration when necessary provided to all patients - The decision of corticosteriod use and hospitalisation made when clinical score deteriorated and/or arterial oxygen saturation detected <85 on room air after treatment - Children necessitating hospitalisation were continued on nebulised treatment and the others were discharged without any treatment	Randomisation and concealment: - Randomly assigned to one of four groups according to the consecutive order of their admission to the unit - Study physician examining children blinded to the contents of all solutions Outcome measures: - Change in clinical bronchiolitis severity score (from Wang et al. based on respiratory rate, wheezing, retraction and genereal condition) - Oxygen saturation - Respiratory rate - Second assessment performed 20 minutes after the last nebulisation (60th minute) - All children reexamined at 48 to 72 hours by the same physician Statistical methods: - Sample size calculation not reported	42.60±6.71; 42.93±6.38; p=0.242 - Posttreatment 37.20±8.78; 38.0±9.23; 35.67±9.37; 39.20±8.21; p=0.480 - p value 0.0001; 0.004; 0.0001; 0.005 - Change calculated by NCC-WCH: 8.33; 4.33; 6.93; 3.73 4. Change in disease severity score - Pretreatment 4.87±1.01; 5.13±1.20; 5.03±1.27; 4.73±0.98; p=0.525 - Posttreatment 2.47±2.16; 2.47±1.93; 2.27±2.07; 3.10±2.43; p=0.469 - p value 0.0001; 0.0001; 0.0001; 0.0001 - Change calculated by NCC-WCH: 2.4; 2.66; 2.76; 1.63 Clinical assessment at 48 to 72 hours - Score lower than post-treatment values 27(90.0%); 27(90.0%); 27(90.0%); 28(93.3%) - Score same as post-treatment values	Subjective clinical scoring system Other information - Clinical bronchiolitis severity score described in table 1 - Corticosteriod administration n(%): 8(26.7); 7(23.3); 7(23.3); 11(37.7); p=0.61 - Comparison of groups according to presence of atopy also reported (table 5)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Proven immune deficiency - Severe neurological disease - Age <1 month or >2 years - Consolidation or atelectasis on a chest roentgenogram		- Categorical variables examined by chi-sqaured test - One-way analysis of variance (ANOVA) and Turkey's multiple comparison test used for continuous variables	2(6.7%); 2(6.7%); 2(6.7%); 2(6.7%) - Score higher than post-treatment values 1(3.3%); 1(3.3%); 1(3.3%); 0(0.0%) 5. Change in O2 saturation - Pretreatment 95.57±2.22; 95.10±2.62; 93.90±2.86; 95.30±2.14; p=0.052 - Posttreatment 96.10±3.11; 96.07±3.66; 96.37±3.33; 96.33±3.35; p=0.979 - p value 0.330; 0.065; 0.0001; 0.037 - Change calculated by NCC-WCH: 0.53; 0.97; 2.47; 1.03 Outcomes not reported: 2. Length of hospital stay 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support 8. Adverse effects	
Full citation Kuzik,B.A., Al Qadhi,S.A., Kent,S., Flavin,M.P.,	Sample size	Interventions	Details Ethics:	Results Protocol outcomes	Limitations Based on NICE appendix C checklist

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hopman,W., Hotte,S., Gander,S., Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants, Journal of Pediatrics, 151, 266-270, 2007 Ref Id 265706 Country/ies where the study was carried out United Arab Emirates and Canada Study type Randomised, double-blinded, multicenter Aim of the study To investigate the addition of frequently nebulised 3% hypertonic saline to standard therapy of moderately ill infants hospitalised with typical viral bronchiolitis Study dates Winter bronchiolitis seasons between December 2003 and April 2006 Source of funding Supported by the Queen Alexandr Foundation for Children, British	- 96 enrolled, 32 from the two Canadian sites and 64 from SKMC - 47 HS group, 49 NS group - 5 infants (2 HS group, 3 NS group) were withdrawn at parental request before study completion but were included in the final intention-to-treat analysis Characteristics Characteristic: HS group; NS group; p value Mean±SD or n(%) - Male, %: 57; 61; 0.84 - Age, months: 4.4±3.7; 4.6±4.7; 0.54 - Duration of illness before admission, days: 4.5±2.3; 4.0±2.4; 0.30 - RDAI score: 7.8±2.5; 8.1±3.3; 0.69 - Oxygen saturation in room air: 94.9±3.9; 95.2±3.4; 0.71 - RSV positive: 25(62%); 30(75%); 0.39	- 4ml of nebulised 3% HS or 4ml of nebulised NS - Administered every 2 hours for 3 doses, followed by every 4 hours for 5 doses, followed by every 6 hours until discharge - All inhaled therapies delivered to a settled infant from a standard oxygen-driven hospital nebuliser through a tight-fitting facemask or head box Additional treatments: - At discretion of attending physician blinded to study treatment - If additional treatments included nebulised medication, the medication was nebulised in 4ml of the assigned study solution Discharge: - Protocol defined criteria: RDAI score <4 and and oxygen saturation ≥95% in room air for 4 hours	- Informed written consent obtained from at least 1 parent of each infant before enrollment - Study approved by the ethics and human research committees of the three hospitals Setting: - Inpatient - Three regional tertiary care hospitals (SKMC, Abu Dhabi; Victoria General Hospital, Canada; Kingston General Hospital, Canada) Randomisation and concealment: - Randomised independently at each study using a computer-based randomisation program - Identity of the solution blinded to all participants, care providers, and investigators Outcome measures: - Clinical response determined by designated study physician using oxygen	2. Length of hospital stay: - Determined by protocol criteria (55%) or attending physician (45%) - Did not differ significantly between study sites for either the NS group (p=0.12) or the HS group (p=0.44) - NS group 3.5±2.9 days, HS group 2.6±1.9 days, p=0.05 8. Adverse effects: - No adverse effect encountered - One of the five infants withdrawn from the study from the HS group cried vigorously during his third inhalation (HS alone) and fifth inhalation (HS plus racemic epinephrine) and was withdrawn at that time, discharged on day 6 - Another one of the five infants withdrawn from the study was because of agitation after her second inhalation (HS plus albuterol), discharged on day 2 Outcomes not reported:	Selection bias: Number of patient who did not meet inclusion criteria not reported Performance bias: - Many additional treatments at discretion of physician - Treatment at SKMC was more likely to include antibiotics (p=0.002) as well as the addition of racemic epinephrine to the inhaled study solution (p=0.003) Detection bias: - RDAI and oxygen saturation measured but not reported - Intervention, 4ml of solution unclear Other information Treatments received during the study: HS group; NS group; p value Mean±SD or n(%) (nebulisations/day)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Columbia, Canada; Vancover Island Health Authority, Youth and Maternal Programme, British Columbia, Canada; and an Ontario Thoracic Society block term grant	Treatments before study entry: - Bronchodilator: 37(86%); 41(91%); 0.52 - Steriods: 1(2.5%); 1(2.4%); 1.0 - Antibiotics: 6(15%); 4(9.8%); 0.52 Inclusion criteria - ≤18 months of age Admitted to the hospital with severe viral bronchiolitis which required: - History of a preceding viral upper respirtory infection - Presence of wheezing or crackles on chest auscultation - Oxygen saturation of <94% in room air - Respiratory distress assessment instrument (RDAI, used by Lowell et al.) ≥4 Exclusion criteria - Previous episode of wheezing	- Protocol defined or on independent clinical grounds by the attending physician	saturation and RDAI score (6 separate assessment of retractions and auscultatory findings are made and assigned a numerical score, 0 to 17 scale with increasing scores indicating increasing respiratory distress) - Length of hospital stay Statistical methods: - To detect a reduction in length of hospital stay by 1 day requires 46 patients per arm, power=80%, p value ≤0.05 - Intention-to-treat analysis - Chi-squared test (Fisher's exact) for categorical variables - Independent sample t tests and Levene's test for equality of variance for numeric variables - ANOVA to compare data from the three sites	1. Hospital admission rate 3. Change in respiratory rate 4. Change in disease severity score 5. Change in O2 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	- Study solution alone: 3.2±3.0; 3.8±4.1; 0.46 (38% of treatments) - Albuterol plus study solution: 3.1±3.5; 3.6±3.6; 0.49 (37% of treatments) - Racemic epinephrine plus study solution 2.7±3.7; 1.6±2.4; 0.13 (23% of treatments) - Steriods plus study solution 0.39±0.83; 0.26±0.60; 0.42 (3%) - Total nebulisations/day 9.1±3.0; 9.2±4.5; 0.93 - Patients given any systemic steriods 8(17%); 7(14%); 0.78 - Patients given any antibiotic 5(11%); 10(20%); 0.26

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Chronic cardiopulmonary disease or immunodeficiency - Critical illness at presentation requiring admission to intensive care - Use of nebulised hypertonic saline within the previous 12 hours - Premature birth (gestational age ≤34 weeks)				
Full citation Kuzik,B.A., Flavin,M.P., Kent,S., Zielinski,D., Kwan,C.W., Adeleye,A., Vegsund,B.C., Rossi,C., Effect of inhaled hypertonic saline on hospital admission rate in children with viral bronchiolitis: a randomized trial, CJEM Canadian Journal of Emergency Medical Care, 12, 477-484, 2010 Ref Id 210563 Country/ies where the study was carried out Canada Study type	Sample size - 88 enrolled: 44 HS group, 44 NS group - Completed RDAI scoring and analysed for RACS: 40 HS group (1 withdrawn by parent, 3 missing data), 44 NS group Characteristics Characteristic: NS group; HS group; p value Mean±SD or n(%) - Age, months: 9.2±5.2; 8.6±5.6; 0.60 - Male (%): 82; 73; 0.31	Interventions - Nebulised solution containing 1mg salbutamol (albuterol) plus 4ml of 3% HS or 4ml of 0.9% normal saline - Received three consecutive 4ml doses of the assigned solution with salbutamol over a 1 hour period - All inhaled therapies delivered from a standard oxygen driven hospital nebuiliser through a tight fitting face mask or head box	Details Ethics: - Study approved by the ethics and human research committees of each of the participating hospitals - Informed written consent obtained from a parent before enrollment Setting: Assessed and treated in one of four emergency departments (Royal Victoria, Kingston General, Hotel Dieu and Victoria General)	Results Protocol outcomes NS group; HS group; p value 1. Hospital admission rate: Admitted at inital presentation only - All (n=88): 12 out of 44 (27%); 8 out of 44 (18%); 0.31 - Age ≤1 year (n=64): 7 out of 33 (23%); 7 out of 34 (21%); 0.79 - Age >1 year (n=24): 5 out of 14 (36%); 1 out of 10 (10%); 0.34 - Previous history of wheezing (n=38): 4 out	Limitations Based on NICE appendix C checklist Selection bias: - Longer duration of illness before presentation in NS group - More infants with a previous history of wheezing in NS group - Not all infants tested for RSV (NS group 21(48%) tested, HS group 24(55%) tested) - Number of patients who did not meet inclusion criteria not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised, double-blinded, multi centre, controlled Aim of the study To determine whether inhaled 3% hypertonic saline reduces admission to hospital in ambulatory children with moderately severe bronchiolitis Study dates November 1 2008 to March 31 2009 Source of funding - Funding provided by the Physicians' Services Incorporated Foundation, but they did not participate in preparation of this manuscript - Authors did not receive any direct payment for the preparation of this manuscript	- RDAI score: 8.7±2.7; 8.5±2.6; 0.66 - Oxygen saturation: 95.7±3.0; 95.9±2.2; 0.73 - Duration of illness before presentation, days: 4.6±3.9; 3.4±1.6; 0.06 - Previous history of wheezing: 23(52); 15(34); 0.09 - History of bronchodilator use: 18(41); 19(43); 0.83 - Received steriods for illness before study entry: 10(23); 5(11); 0.16 - RSV positive: 11 out of 21 tested (52); 10 out of 24 tested (42); 0.47 Inclusion criteria - Aged ≤24 months - Presented to emergency department with moderately severe viral bronchiolitis - History of a preceding upper respiratory tract infection	- Did not receive further therapy other than supplemental oxygen (if neccessay) during the observation period - Admission decision made by emergency physician who was unaware of treatment allocation and RDAI values - Solutions identical in appearance and odor, labelled with sequential numbers	Randomisation and concealment: - Study solutions prepared by research pharmacist at each study site, randomly placed in blocks of 6 using a Web-based programme - The investigator responsible for recruiting the patient and supervising the protocol obtained the next avaliable study solution - Identity of the study solution known only to research pharmacists, not revelaed until completion of the study - All health care providers were unaware of the treatment allocations and RDAI scores Outcome measures: - Respiratory distress assessment instrument (RDAI, used by Lowell et al.) score obtained after 1 hour observation period following third treatment - RACS score (a positive RACS is a numerical estimate of the	of 23 (17%); 3 out of 15 (20%); 0.84 - No previous history of wheezing (n=50): 8 out of 21 (38%); 5 out of 29 (17%); 0.10 - Admitted within 7 days after inital presentation (subset not initally admitted n=67): 4 out of 31 (13%); 3 out of 36 (8%); 0.70 - Unscheduled physician visits within 7 days of presentation (subset not initally admitted n=67): 13 out of 31 (42%); 13 out of 36 (36%); 0.63 4. Change in disease severity score RACS mean±SD - All (n=84): 3.7±4.0 (n=44); 4.7±3.5 (n=40); 0.24 - Age ≤1 year (n=60): 3.3±3.6 (n=30); 4.4±3.6 (n=30); 0.27 - Age >1 year (n=24): 4.6±4.8 (n=14); 5.7±2.9 (n=10); 0.53 - Previous history of wheezing (n=38): 3.5±4.3 (n=23); 4.8±3.7 (n=15); 0.35	Attrition bias: 4 infants from HS group did not complete RDAI scoring Detection bias: Subjective clinical scoring system Performance bias: - Admissions at discretion of physician - Care may differ across the four sites Other information - RDAI scoring system described in table 1 - Excluded from Cochrane because of previous wheezing

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Presence of wheezing or crackles on chest auscultation - Oxygen saturation ≤94% on room air - RDAI score ≥4 Exclusion criteria - Immunodeficiency - Down syndrome - Neurologic or metabolic disease - Chronic cardiopulmonary disease other than recurrent wheezing - Severe illness at presentation (respiratory rate >80 breaths/min, oxygen saturation <88% on room air or need for assisted ventilation) - Prematurity (gestation ≤34 weeks) - Inhaled HS within the previous 12 hours		improvement in respiratory distress between two points in time, whereas a negative RACS reflects a worsening. RACS is calculated by combining two values: the difference between the RDAI score obtained before and after treatment, plus a value of +1 for each 10% improvement (decrease) in the posttreatment respiratory rate or a value of -1 for each 10% worsening (increase) in respiratory rate) - Hosptial admissions - Telephone contact made by research assistant 7 days later to assess further medical visits Statistical methods: - Sample size calculation: admisson rate of 40%, 50% reduction with short term intensive treatment with HS, α=0.05, two-tailed test. sample size of 85 per arm - Intention-to-treat analysis	- No previous history of wheezing (n=46): 3.9±3.7 (n=21); 4.6±3.4 (n=25); 0.52 8. Adverse effects: - None observed - One 11 month old girl in HS group withdrawn by parents because of excessive crying Outcomes not reported: 2. Length of hospital stay 3. Change in respiratory rate 5. Change in O2 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Independent samples t-test for continuous - Fisher exact or Pearson chi-squared test for categorical - RDAI scores before and after treatment were normally distributed, as were the RACS, calculation of skewedness and kurtosis for the 3 scores indicated that all fell within the expected range of chance fluctuations, and as a result parametric statistics were used for all analyses		
Full citation Luo,Z., Liu,E., Luo,J., Li,S., Zeng,F., Yang,X., Fu,Z., Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis, Pediatrics International, 52, 199-202, 2010 Ref Id 207482 Country/ies where the study was carried out China Study type	Sample size 93 enrolled: 43 NS group, 50 HS group Characteristics Characteristic: NS group; HS group; p value Mean±SD or n(%) - Male/female: 26/17; 30/20; 0.96 - Age, months: 5.6±4.5; 6.0±4.3; 0.64	Interventions - 2.5mg(0.5ml) salbutamol dissolved in 4.0ml hypertonic 3% saline or normal 0.9% saline - Both groups received the same supportive and comprehensive treatments, including sputum aspiration and water-electrolyte balance maintenance - Air-compressed nebulisers	Details Ethics: Study approved by the ethics and human research committees of the Children's Hospital Setting: - Inpatient - Children's Hospital, Chongqing Medical University Randomisation and concealment:	Results Protocol outcomes HS group; NS group 2. Length of hospital stay: 6.0±1.2; 7.4±1.5 p<0.01 4. Change in disease severity score: - Day 1: 3.4±1.2; 4.9±1.7 - Day 2: 2.2±1.1; 3.8±1.5 - Day 3: 1.5±0.5; 2.9±0.7	Limitations Based on NICE appendix C checklist Selection bias: - Randomisation not described - Informed consent not described - Number who did not meet inclusion criteria not reported Detection bias: Subjective clinial scoring system and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised, double-blinded, controlled Aim of the study To determine the efficacy and safety of nebulised 3% hypertonic saline solution and salbutamol in the treatment of mild to moderate bronchiolitis Study dates Between November 2007 and February 2008 Source of funding Not reported	- Disease course when hospitalised, days: 3.1±1.5; 3.2±1.6; 0.80 - Clinical score: 5.7±1.3; 5.8±1.2; 0.63 - RSV: 30(69.7%); 35(70%); 0.98 - % of whole-body glucocorticoid usage before admission: 31(72.1%); 36(72%); 0.99 Inclusion criteria - Wheezing infants suffering from viral bronchiolitis for the first time - Mild to moderate bronchiolitis based on clinical score Exclusion criteria - Aged >24 months - Previous episode of wheezing - Chronic cardiac and pulmonary disease - Immunodeficiency - Accompanying respiratory failure - Requiring mechanical ventilation - Inhaling the nebulised 3% HS and	- Received three treatments every day, delivered at intervals of 8 hours until discharge - No detectable difference in colour, smell or other physical properties between the two solutions - Decision to discharge made during morning rounds by attending physicians when the patients had had no respiratory symptoms or signs during the past 12 hours	- Identities of the theraputic package were not avaliable to the investigators, nurses, parents and physicians - Infants recruited in the trial were assigned to a treatment group or a control group Outcome measures: - Clinical severity score used by Wang et al., based on respiratory rate, wheezing, retractions and general condition - Length of hospital stay - Day when cough, wheezing and pulmonary moist crackles disappeared - Evaluated patients every day at 8-9am, 4-5pm and 10-12pm Statistical methods: - Sample size calculation not reported - Chi-squared test to compare categorical variables	8. Adverse effects: None encountered Outcomes not reported: 1. Hospital admission rate 3. Change in respiratory rate 5. Change in O2 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	days until symptoms/signs disappeared Other information Day when cough, wheezing and pulmonary moist crackles disappeared also reported (table 2)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	salbutamol solution 12 hours before treatment - Premature (<34 weeks gestation)				
Full citation Luo,Z., Fu,Z., Liu,E., Xu,X., Fu,X., Peng,D., Liu,Y., Li,S., Zeng,F., Yang,X., Nebulized hypertonic saline treatment in hospitalized children with moderate to severe viral bronchiolitis, Clinical Microbiology and Infection, 17, 1829-1833, 2011 Ref Id 207483 Country/ies where the study was carried out China Study type Randomised, double-blinded, controlled Aim of the study To determine the efficacy and safety of frequently inhaled nebulised hypertonic saline in infants with moderate to severe bronchiolitis Study dates	Sample size - 135 enrolled - 9 parents refused participation - 126 randomised: 64 HS group; 62 NS group - 7 patients from each group discharged within 12 hours after enrollment - 112 completed: 57 HS group, 55 NS group Characteristics Characteristic: NS group; HS group; p value Mean±SD or n(%) - Males/females: 31/24; 32/25; 0.98 - Age, months: 5.8±4.3; 5.9±4.1; 0.71 - Duration of wheezing on admission, days: 3.2±1.4; 3.4±1.7; 0.77 - Clinical score on admission: 8.5±1.5; 8.8±1.1; 0.42	Interventions - Received either 4ml of a solution containing either 3% HS or 0.9% NS - Solution administered every 2 hours for three doses, followed by every 4 hours for five doses, followed by every 4 hours until discharge - Both groups received the same supportive and comprehensive treatments, including sputum aspiration, water-electrolyte balance maintenance and oxygen therapy - All inhaled treatments delivered from standard air-compressed nebulisers - No detectable differences in colour, smell or other physical properties existed between HS and NS - The decisions to discharge made by	Details Ethics: - Study approved by the ethics and human research committees of the Children's Hospital - Written informed consent obtained from at least one parent before enrollment Setting: - Inpatient - Children's Hospital, Chongqing Medical Univeristy Randomisation and conealment: - Random code generated by computer - Code was concealed in a sealed, opaque envelope until the child was recruited - Identities of the solution not avaliable to the investigators, nurses, parents or attending physician	Results Protocol outcomes HS group; NS group 2. Length of hospital stay: Days, mean±SD 4.8±1.2; 6.4±1.4 p value <0.01 4. Change in disease severity score - Day 1: 5.7±1.5; 7.3±1.7 - Day 2: 3.5±1.1; 5.9±1.5 - Day 3: 2.4±0.9; 4.1±1.1 - Day 4: 1.7±0.6; 3.1±0.7 8. Adverse effects: - No infants were withdrawn by the medical staff because of clinical deterioration or the need for intensive care support - Two HS group infants and three NS group infants had hoarse voices which diappeared after 3 to 4 days	Limitations Based on NICE appendix C checklist Selection bias: Randomisation unclear, envelopes reliable? Performance bias: Intervention, 4ml of solution unclear Attrition bias: 7 patients from each group discharged within 12 hours after enrollment Detection bias: Subjective clinical scoring system and days until symptoms/signs disappeared Other information - Clinical score: mild 0 to 4.9, moderate 5 to 8.9, severe 9 to 12

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
November 2008 to November 2009 Source of funding Not reported, declare no potential conflicts of interest	- RSV detection rate: 40(72.7%); 42(73.7%) - Systemic glucocoticoid use before admission: 35(77.8%); 43(75.4%) Inclusion criteria - Aged <24 months - First episode of wheezing - Admitted to hospital with moderate to severe bronchiolitis (determined by clinical score) Exclusion criteria - Aged >24 months - Previous episode of wheezing - Chronic cardiac and pulmonary disease - Immunodeficiency - Accompanying respiratory failure - Requiring mechanical ventilation - Inhaled the nebulised 3% HS solution 12 hours before treatment - Prematurity (gestation <34 weeks)	attending physicians when the patients had experienced no respiratory symptoms and signs during the past 12 hours	Outcome measures: - Length of hospital stay - Clinical severity score recorded every 12 hours (based on respiratory rate, wheezing, retractions and general condition) - Day when cough, wheezing and pulmonary moist crackles disappeared Statistical methods: - Sample size calculation not reported - Chi-squared test to compare categorical variables - ANOVA for continuous variables	Outcomes not reported: 1. Hospital admission rate 3. Change in respiratory rate 5. Change in O2 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	- Day when cough, wheezing and pulmonary moist crackles disappeared also reported (table 2)
Full citation	Sample size	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mandelberg,A., Tal,G., Witzling,M., Someck,E., Houri,S., Balin,A., Priel,I.E., Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis, Chest, 123, 481-487, 2003 Ref Id 207517 Country/ies where the study was carried out Israel Study type Randomised, double-blinded, controlled Aim of the study To determine the utility of inhaled hypertonic saline solution to treat infants hospitalised with viral bronchiolitis Study dates December 2000 to March 2001 Source of funding Not reported	- 53 enrolled, one NS group patient exluded from analysis because of deterioration immediately after the first treatment inhalation, which required mechanical ventilation - 52 included in analysis: 25 NS group, 27 HS group - 8 potentially eligible patients excluded because parent refused consent (3 HS group, 5 NS group) Characteristics Characteristic: NS group; HS group Mean±SD - Age, months: 2.6±1.9; 3±1.2 - Female/male: 9/15; 12/15 - Clinical score: 8.08±1.3; 8.29±1.35 - Days of illness at hospital admission: 3±1.6; 3.9±2.9 - Oxygen saturation: 94.7±3.3; 93.8±3.2 - RSV positive: 22(88%); 23(85%)	- Aeromist nebuliser connected to a source of pressurised oxygen set to a flow rate 5l/min - Inhalation of epinephrine 1.5mg in 4ml of 0.9% saline or 3% saline solution - Patients in each group received three treatments for every day of hospital stay delivered at intervals of 8 hours, until the patients was ready for discharge - Additional inhalations as needed of epinephrine in 0.9% saline solution were recorded and calculated as add-on therapy	Ethics: - Signed informed consent obtained from parents - Helsinki human ethics committee of the hospital approved the study Setting: Inpatient, Edith Wolfson Medical Centre Randomisation and concealment: - Patients recruited sequentially and randomised in a double-blind fashion - Combination of theraputic package not avaliable to investigator or medical personnel - Code deposited with the statistican - Attending physician making decision to discharge blinded to treatment Outcome measures: - Wang clinical severity score (based on respiratory rate, wheezing, retraction and general condition)	Protocol outcomes 2. Length of hospital stay, days: Mean±SD NS group 4±1.9 HS group 3±1.2 p<0.05 4. Change in disease severity score: - The percentage fall of the clinical severity score after inhalation therapy was not significant in the NS group First day of hospitalisation 3.5% Second 2% Third 4% - In the HS group significant differences were observed on each of the first three days First day of hospitalisation 7.3% Second 8.9% Third 10% p<0.001 Taken from Cochrance review, mean±SD: HS group; NS group - Day 1 (n=27) 7.7±1.54; (n=25) 7.81±1.49	Based on NICE appendix C checklist Selection bias: - Inclusion criteria unclear - Randomisation unclear - Number of patients who did not meet inclusion criteria not reported Detection bias: - Subjective clinical scoring system - Results presented in figures Performance bias: - Add-on treatments of epinephrine in 0.9% saline solution, but the combination of the theraputic package (0.9% [normal] saline solution vs 3% saline solution) was not avaliable to the investigator, physician or medical personnel - Discharge criteria not described Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Presented with viral bronchiolitis with temperatures >38ºC that lead to hospitalisation Exclusion criteria - Previous wheezing episode - Aged >12 months - Oxygen saturation <85% on room air - Obtunded consciousness - Progressive respiratory failure requiring mechanical ventilation		- Duration of hospitalisation Statistical methods: - Sample size calculation not reported - Age and hospitalisation days log transformed - Continuous variables paired or unpaired t-test - Noncontinuous variables chi-squared - Days of illness at hospital admission regressed against days of hospitalisation using least squares	- Day 2 (n=24) 6.41±1.4; (n=25) 6.92±1.62 - Day 3 (n=21) 5.81±1.68; (n=23) 6.08±2.03 6. Need for intravenous fluids, CPAP or mechanical ventilation: Intention-to-treat analysis showed that two NS group patients required mechanical ventilation (one of these patients was excluded from the analysis) 8. Adverse effects: None observed Outcomes not reported: 1. Hospital admission rate 3. Change in respiratory rate 5. Change in 02 saturation 7. Need for/use of feeding support	- Radiograph assessment scores also reported Cochrane contacted authors for additional information: - report clincal severity scores for days 1, 2 and 3 - report randomisation in blocks of 4 using online randomiser - report 14 patients withdrawn from the trial (7 in each group discharged within 12 hours of enrollment) Add-on inhalation therapy needed per day: NS group 1.2±0.9 HS group 0.9±0.7
Full citation Miraglia,Del Giudice, Saitta,F., Leonardi,S., Capasso,M., Niglio,B., Chinellato,I., Decimo,F., Maiello,N., Capristo,C.,	Sample size - 136 assessed for enrollment - 109 enrolled	Interventions - Received every 6 hours nebulised 0.9% saline or 3% HS in addition to aerosolised epinephrine 1.5mg and	Details Ethics: - Informed consent obtained from parents/caregivers	Results Protocol outcomes NS group; HS group Mean±SD	Limitations Based on NICE appendix C checklist Selection bias:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Perrone,L., Peroni,D., Effectiveness of nebulized hypertonic saline and epinephrine in hospitalized infants with bronchiolitis, International Journal of Immunopathology and Pharmacology, 25, 485-491, 2012 Ref Id 265721 Country/ies where the study was carried out Italy Study type Randomised, double-blinded, controlled Aim of the study To verify effects of nebulised 3% hypertonic saline solution in comparison to normal saline in addition to epinephrine in hospitalised children with bronchiolitis Study dates Between November and April of two consecutive years (2008-2009 and 2009-2010) Source of funding	- After randomisation 2 patients from NS group and 1 patient from HS group declined consent - 106 agreed to participate: NS group 54, HS group 52 Characteristics Characteristic: NS group; HS group Mean±SD or n(%) - Males: 35(64); 34(65) - Age, months: 4.2±1.6; 4.8±2.3 - Clinical score: 8.8±1.5; 8.5±1.4 - Days of illness at hospital admission: 3±1.8; 3.6±2.2 - Oxygen saturation: 92.7±3.9; 93.5±4.2 - RSV positive: 45(83.3); 42(80.7) Inclusion criteria - Aged <2 years - Admitted to hospital with bronchiolitis defined as: the first episode of wheezing and clinical symptoms of a viral respiratory infection, oxygen saturation <94% in	to the conventional treatment (oxygen, fluids) - Each treatment delivered by a nebuliser with continuous flow of oxygen at 6l/min through a tight-fitting face mask - Discharged on clinical grounds by attending physician	- Study protocol approved by local hospital committee Setting: Inpatient, Division of Pediatrics at the Saint Mary Hospital in Pozzuli, Naples Randomisation and concealment: - Randomised using a computer-based randomisation program - Study solutions prepared by the local hospital pharmacy, were blinded to participants and investigators Outcome measures: - Length of hospital stay - Wang clinical severity score (in the morning, before and 30 minutes after treatment) Statistical methods: - Sample size calculation not reported - Qualititive data analysed using chi-squared or Fisher's exact test	2. Length of hospital stay, days: 5.6±1.6; 4.9±1.3 4. Change in disease severity score Before inhalation: - Day 1: 8.8±1.5; 8.5±1.4; p value not significant - Day 2: 8.3±1.7; 7.4±1.6; p<0.005 - Day 3: 7.7±1.6; 6.5±1.6; p<0.005 - Significant decrease in severity score from the first through to the third day of treatment was present in the NS group but even more evident in the HS group 30 minutes after inhalation: - Day 1: 8.8±1.6; 8.0±1.3 - Day 2: 8.2±1.7; 6.8±1.4 - Day 3: 7.6±1.6; 5.8±1.4 - HS group produced significant decreases in the severity score after each inhalation from the first day of treatment and remained significant from the first to the third days of treatment (p<0.0001),	Randomisation unclear Detection bias: - Discharge criteria not described - Subjective clinical scoring system Other information Results before inhalation the same as results for each day which are reported here

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Authors report no conflict of interest	room air and significant respiratory distress measured by using a clinical severity score described by Wang et al (0 to 12 scale based on respiratory rate, wheezing, retraction and general condition) Exclusion criteria - Pre-existing cardiac or pulmonary diseases - Premature birth <36 weeks gestation - Oxygen saturation ≤85% - Respiratory distress severe enough to require resuscitation		- Quantitative paired ot unpaired t-test - Mann-Whitney test used as a nonparametric counterpart - Quantitative variables (clinical score) for paired data compared using Wilcoxon test - Anova Friedman test to compare clinical score data	this was not significant in the NS group Outcomes not reported: 1. Hospital admission rate 3. Change in respiratory rate 5. Change in 02 saturation 6. Need for intravenous fluids, CPAP or mechanical ventilation 7. Need for/use of feeding support	
Full citation Sarrell,E.M., Tal,G., Witzling,M., Someck,E., Houri,S., Cohen,H.A., Mandelberg,A., Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms, Chest, 122, 2015-2020, 2002 Ref Id 208071	Sample size - 70 enrolled - 5 hospitalised and excluded - 65 completed: 32 NS group, 33 HS group Characteristics Characteristic: NS group; HS group Mean±SD - Age, months: 12.3±1.1; 12.7±0.9	Interventions - NS group: inhalation of 0.5ml(5mg) terbutaline in 2ml of 0.9% saline solution as a wet nebulised aerosol - HS group: inhalation of 0.5ml(5mg) terbutaline in 2ml of % saline solution as a wet nebulised aerosol, the final concentration of NaCl was 2.6%	Details Ethics: - Signed informed consent obtained from parents - Human ethics committee of the hospital approved the study according to the Declaration of Helsinki Setting: - Outpatient	Results Protocol outcomes 1. Hospital admission rate: NS group 3, HS group 2 4. Change in disease severity score: NS group; HS group (mean±SD) Day 2: 5.2±1.9; 3.9±1.5 Day 3: 4.8±2.3; 2.1±2.2	Limitations Based on NICE appendix C checklist Selection bias: - Randomisation not described - Inclusion criteria unclear - Excluding infants with oxygen saturation <96% in room air appears restrictive

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Israel Study type Randomised, double-blinded, controlled Aim of the study To determine the utility of inhaled hypertonic saline solution to treat ambulatory infants with viral bronchiolitis Study dates December 2000 to March 2001 Source of funding Not reported	- Female/male: 14/18; 15/18 - Clinical score: 6.4±1.8; 6.6±1.5 - RSV positive: 25(78%); 27(82%) Inclusion criteria - Bronchiolitis obstructs flow in small airways, leading to hyperinflation, atelectasis and wheezing - Presented to hospital with mild to moderate viral bronchiolitis Exclusion criteria - Cardiac illness - Previous wheezing episode - Aged >24 months - Oxygen saturation <96% in room air - Need for hospitalisation	- Both groups received three treatments every day, delivered at intervals of 8 hours for 5 days - Patients returned to the clinic once every morning to be examined by one investigator - First inhaltion treatments administered by study nurse, the nurse gave the parents the theraputic package and instructed them on how to administer the other two inhalation treatments at home	- Recruited and examined at Pediatrics and Adolescent Ambulatory Community Clinic of Gerneral Health Services of Petach-Tikva Randomisation and concealment: - The combination of the theraputic package was not avaliable to the investigator, nor to the medical personnel or the parents - The code was deposited with the statistician - Randomisation not described Outcome measures: - Clinical scoring system (used by Wang et al., based on respiratory rate, wheezing, retraction and general condition) - Hospitalisation rate Statistical methods: - Sample size calculation not reported - Mann-Whitney U test - Two tailed t-test	Day 4: 3.8±2.5; 1.1±2.2 Day 5: 2.9±2.7; 0.9±2.2 p<0.005 8. Adverse effects: None observed Outcomes not reported: 2. Length of hospital stay 3. Change in respiratory rate 5. Change in O2 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/Use of feeding support	- Number of patients who did not meet inclusion criteria not reported Attrition bias: 5 patients withdrawn Detection bias: Subjective clinical scoring system Other information - Analysis of intention-to-treat provided the same results - Radiograph assessment score described by Nasr et al. also reported - Cochrane reports randomisation in blocks of 4, using an online randomiser

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Chi-squared test for noncontinuous variables		
Full citation Tal,G., Cesar,K., Oron,A., Houri,S., Ballin,A., Mandelberg,A., Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience, Israel Medical Association Journal: Imaj, 8, 169-173, 2006 Ref Id 210620 Country/ies where the study was carried out Israel Study type Randomised, double-blinded, controlled Aim of the study - A preliminary study conducted in 53 hospitalised infants with viral broncholitis demonstrated the effectiveness of hypertonic saline as a treatment agent	Sample size - 44 enrolled - 3 excluded from analysis (one from NS group because of deterioration immediately after the first treatment inhalation, another NS group patient refused to remain hospitalised and was readmitted the following day, one HS group required steriod treatment due to low cortisol levels showed a swift recovery - 41 completed: 20 NS group, 21 HS group - Pooling 2 years (2000 to 2002) 93 hospitalised infants recurited: 45 NS group, 48 HS group Characteristics Characteristic: NS group; HS group Mean±SD - Number: 20; 21	Interventions - The second study used an ultrasonic nebuliser - Inhalation of 1.5mg epinephrine in 4ml 0.9% NS or 4ml 3% HS - Each group received three treatments on each day of hospitalisation delivered at 8 hour intervals, until the patient was ready for discharge - Additional inhalations of epinephrine in 0.9% saline as needed were recorded and calculated as add-on therapy - Decision to discharge during each morning round by attending physician based on clinical grounds alone, such as not needing supplemental oxygen, minimal or no chest recession, and feeding adequately without the need for intravenous fluids	Details Ethics: - Signed informed consent obtained from parents - Helsinki Committee of the hospital approved study Setting: Inpatient, Department of Pediatrics, Wolfson Medical Centre Randomisation and concealment: - Treatment not disclosed to the investigator or to the medical personnel - Sight or smell could not distinguish the difference between 0.9% and 3% saline - Code deposited with the statistician - Attending physician discharging patients blinded Outcome measures: - Wang clinical score (based on respiratory	Results Protocol outcomes 2. Length of hospital stay, days: NS group (n=20) 3.5±1.7 HS group (n=21) 2.6±1.4 p=0.018 NS group (n=48) 3.6±1.7 HS group (n=45) 2.8±1.3 p<0.05 4. Change in disease severity score: - The fall in clinical scores during the first 2 days after the inhalation therapy NS group (n=20) 0.6±0.9 HS group (n=21) 1.15±0.7 p=0.046 - The post inhalation clinical scores on days 1 and 2 after inhalation Day 1 NS group (n=20) 7±1 Day 1 HS group (n=21) 6.25±1.1	Limitations Based on NICE appendix C checklist Selection bias: - Inclusion criteria unclear - Randomisation unclear - Number of patients who did not meet inclusion criteria not reported Detection bias: - Add-on inhalation treatments - Subjective clinical scoring system - Discharge criteria suggests supplementary oxygen and intravenous fluids may be provided - Results for clinical score presented in a figure (main values written in results section) - Jet nebuliser used in first study, ultrasonic nebuliser used in second study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
- This study described a follow-up second year study and a pooled analysis of 2 years experience with a total of 93 hospitalised infants Study dates - Previous study in the winter of 2000 to 2001 - Second year study winter of 2001 to 2002 Source of funding Not reported	- Age, months: 2.3±0.7; 2.8±1.2 - Female/male: 7/13; 11/10 - Clinical score: 7.6±0.7; 7.4±1.4 - Days of illness at admission: 4.5±2.2; 4.0±2.2 - Oxygen saturation: 92.9±2.9; 93±1.9 - RSV positive: 15(75%); 18(86%) Inclusion criteria Hospitalised with viral bronchiolitis Exclusion criteria - Cardiac disease - Chronic respiratory disease - Previous wheezing episode - Aged >12 months - Oxygen saturation <85% on room air - Obtunded consciousness and/or progressive resiratory failure requiring mechanical ventilation		rate, wheezing, retraction and general condition) - Duration of hospitalisation Statistical methods: - Sample size calculation not reported - Mann-Whitney non-parametric U test - Continuous variables paired or unpaired t-test - Non-continuous chi-squared test	p<0.05 Day 2 NS group (n=20) 6.45±1 Day 2 HS group (n=21) 5.35±1.3 p<0.05 8. Adverse effects: - None observed - Eight NS group patients and five HS group patients underwent a second chest X-ray due to lack of improvement, three NS group patients showed atelectasis Outcomes not reported: 1. Hospital admission rate 3. Change in respiratory rate 5. Change in 02 saturation 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 7. Need for/use of feeding support	Other information - Basline oxygen saturation characteristic for HS group reported as 9.3, assumed 93 - Cochrane report randomisation in block of 4 using online randomiser Number of add-on inhalations Mean±SD: NS group (n=20); HS group (n=21) First hospitalisation day 1.5±1.2; 1.4±0.82 Second 1.25±0.85; 1.1±0.47 Third 1.18±0.98; 0.93±0.25
Full citation	Sample size	Interventions	Details Searches:	Results Length of hospital stay:	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Zhang,Linjie, MendozaSassi,Raul A., Wainwright,Claire, Klassen,Terry P., Nebulised hypertonic saline solution for acute bronchiolitis in infants, Cochrane Database of Systematic Reviews, -, 2013 Ref Id 265762 Country/ies where the study was carried out UK Study type Systematic review Aim of the study To assess the effects of nebulised hypertonic (≥3%) salline solution in infants with acute viral bronchiolitis Study dates - Initial search 2007 - Latest update May 2013 Source of funding No declarations of interest	- 2013 updated search retrieved 158 citations from the electronic databases - Identified four new trials (Al-Ansari 2010; Giudice et al., 2012; Ipek et al., 2011; Luo et al., 2011) - 11 trials were included in this updated review (Al-Ansari et al., 2011; Anil 2010; Grewal et al., 2009; Guidice et al., 2012; Ipek et al., 2011; Kuzik et al., 2007; Luo et al., 2010; Luo et al., 2011; Mandelberg 2003; Sarrell et al., 2002; Tal et al., 2006) Characteristics - All 11 studies were randomised, double-blind, parallel-group, controlled trials - One trial recruited outpatient participants (Sarrell et al., 2002), four trials recruited emergency department participants (Al-Ansari et al., 2011; Anil 2010; Grewal et al., 2009; Ipek et al., 2011), and	1. Nebulised hypertonic saline alone versus nebulised 0.9% saline 2. Nebulised hypertonic saline plus bronchodilator versus nebulised 0.9% saline 3. Nebulised hypertonic saline plus bronchodilator versus nebulised 0.9% saline plus same bronchodilator 4. Nebulised hypertonic saline alone or plus bronchodilator versus no intervention (Hypertonic saline was defined as a concentration of saline greater than or equal to 3%) Interventions for each individual study are extracted in the evidence table	- For the 2013 update searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 4, part of The Cochrane Library (accessed 8 May 2013), which contains the Cochrane Acute Respiratory Infections Group Specialised Register,MEDLINE (May 2010 to April week 4, 2013), EMBASE (June 2010 to April 2013) and LILACS (June 2010 to May 2013). Also included two further databases and searched CINAHL (1981 to May 2013) and Web of Science (1955 to May 2013) - No language or publication restrictions - Two review authors (LZ, RAM) independently assessed the titles and abstracts of all studies identified by the searches.We obtained the full articles when they appeared to meet the inclusion criteria or there were insufficient data in the title and abstract to	- 6 trials (Guidice et al., 2012; Kuzik et al., 2007; Luo et al., 2010; Luo et al., 2011; Mandelberg 2003; Tal et al., 2006), 500 participants - Mean Difference (IV, Random, 95% CI), -1.15 [-1.49, -0.82] - Heterogeneity I^2=30% - Test for overall effect: Z = 6.83 (P < 0.00001) - This represents a 22.7% reduction from the mean length of hospital stay in the 0.9% saline group Rate of hospitalisation: - 4 trials (Anil 2010; Grewal et al., 2009; Ipek et al., 2011; Sarrell et al., 2002), 380 participants - Hypertonic saline 16 out of 151 hospitalised, normal saline 25 out of 189 hospitalised - Risk Ratio (M-H, Random, 95% CI) 0.63 [0.37, 1.07] - Heterogeneity I^2=0% - Test for overall effect: Z = 1.72 (P = 0.086) Clinical severity score at day 1 (post treatment):	Limitations for each individual study based on the NICE appendix C checklist are extracted in the evidence table Other information If trials recruited multiple groups, combined them into the hypertonic saline group and the normal saline group: - Al-Ansari et al., 2010 - combined the 5% saline group and the 3% saline group into the hypertonic saline group - Anil et al., 2011 - comined four groups (3% saline mixed with epinephrine, 3%saline mixed with salbutamol, 0.9%saline mixed with epinephrine and 0.9% saline mixed with salbutamol) into the hypertonic saline group and the normal saline group - Ipek et al., 2011 - combined four groups (3% saline plus salbutamol and 3% saline alone, 0.9% saline plus salbutamol

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	six trials recruited inpatients (Guidice et al., 2012; Kuzik et al., 2007; Luo et al., 2010; Luo et al., 2011; Mandelberg 2003; Tal et al., 2006) - The mean age of the participants varied from 2.6 to 12.5 months (range: 9 days to 24 months) Characteristics for each individual study are extracted in the evidence table Inclusion criteria - RCTs and quasi-RCTs (where there is alternate allocation to treatment and control groups) - Infants up to 24 months of age with the diagnosis of acute bronchiolitis - Acute bronchiolitis was defined as the first episode of acute wheezing associated with clinical evidence of a viral infection (cough, coryza or fever)		make a clear decision for their inclusion Statistical methods: - Contacted three principal investigators (Kuzik et al., 2007; Luo et al., 2010; Mandelberg et al., 2003) for additional data on clinical score and methodological aspects - Performed pre-planned subgroup analysis according to patient status (outpatient, emergency department patient and inpatient) - Assessed heterogeneity in results between studies using the Cochrane Q test (P < 0.1 considered significant) and I^2 (measures the degree of inconsistency across studies, with values of 25%, 50% and 75% corresponding to low, moderate and high heterogeneity, respectively) - Random-effects model fo rmeta-analyses - Whenever possible used intention-to-treat analysis data	- 7 trials, 640 participants - Mean Difference (IV, Random, 95% CI) -0.88 [-1.36, -0.39] - Heterogenity I^2=78% - Test for overall effect: Z = 3.56 (P = 0.00038) - Test for subgroup differences I^2=84% Outpatients - 1 trial, 65 participants - Mean Difference (IV, Random, 95% CI) -1.28 [-1.92, -0.64] - Test for overall effect: Z = 3.90 (P = 0.000095) Emergency department - 1 trial, 171 participants - Mean Difference (IV, Random, 95% CI) -0.09 [-0.51, 0.33] - Test for overall effect: Z = 0.42 (P = 0.68) Inpatients - 5 trials, 404 participants - Mean Difference (IV, Random, 95% CI) -0.99 [-1.48, -0.50] - Test for overall effect: Z = 3.94 (P = 0.000081) Rate of readmission: - 3 trials, 366 participants	and 0.9% saline alone) into the hypertonic saline group and the normal saline group Time to resolution of symtoms/signs, radiological assessment score and clinical severity scores on days 2 and 3 also reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Confirmation of viral aetiology was not necessary for study inclusion - Studies of inpatients, emergency department patients or outpatients Exclusion criteria Studies which included patients who had had recurrent wheezing or were intubated and ventilated, and studies which assessed pulmonary function alone			- Risk Ratio (M-H, Random, 95% CI) 1.05 [0.62, 1.76] - Heterogeneity I^2=0% - Test for overall effect: Z = 0.17 (P = 0.87) Trials found no significant difference in respiratory rate, heart rate and haemoglobin saturation (oximetry) between the hypertonic saline group and the 0.9% saline group	
Full citation Jacobs,J.D., Foster,M., Wan,J., Pershad,J., 7% hypertonic saline in acute bronchiolitis: a randomized controlled trial, Pediatrics, 133, e8-e13, 2014 Ref Id 299716 Country/ies where the study was carried out United States Study type	Sample size 101 patients were enrolled in the study. 52 in the experimental group, and 49 in the control group. Characteristics Age, mo, mean± SD - HS group = 6.0± 3.9 - NS group = 5.6± 3.3 Gender, male - HS group = 36/52 (69%) - NS group = 28/49 (57%)	Interventions The study group received 0.5 mL 2.25% racemic epinephrine with 3 mL 7% HS. The control group received an aerosol of 0.5 mL 2.25% racemic epinephrine with 3 mL 0.9% NS. After initial screening and assessment and after consent was obtained, the patient was administered the medication via nebulization driven by	Details Depending on the availability of the principal investigator (a pediatric emergency medicine fellow), a convenience sample was used to recruit patients. The ED physicians and staff were notified of the fellow's hours of availability by way of a call schedule that was posted in the ED. The treating physician in the ED contacted the	Results Change in BSS after first nebulized treatment in ED disposition (mean ±SD) HS group = 2.06 ±1.7 NS group = 2.0 ±1.9 Difference, p-value (95% CI) = 0.06, p=0.87 (-0.67 to 0.78) Change in BSS for admitted patients (mean ±SD) HS group = 3.1 ±2.5 NS group = 3.7 ±1.9	Limitations Based on Nice Manual Appendix C for randomised controlled trials Selection bias: groups statistically different at baseline in terms of "family history of atopy" Performance bias: the study reports that any cointerventions were at the discretion of the treating clinician, but no data are reported that specify different

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Prospective, double-blind, randomized controlled trial. Aim of the study To study the role of 7% hypertonic saline (HS) in the ED setting for treating bronchiolitis. Study dates Between October and March over a 2-year period (2010-2012). Source of funding No external funding. Also the authors have indicated they have no financial relationships relevant to this paper to disclose.	Duration of symptoms, d, mean± SD - HS group = 3.4± 1.7 - NS group = 3.4± 1.6 Baseline BBS score, mean± SD - HS group = 5.8± 1.5 - NS group = 5.7± 1.8 Family history of atopy * - HS group = 24/52 (46%) - NS group = 33/49 (67%) * significant difference between the two groups Inclusion criteria - Age between 6 weeks and 18 months - With bronchiolitis defined as viral respiratory illness and first episode of wheeze - A BSS score ≥ 4 Exclusion criteria - previous history of wheezing	6 L per minute O2 flow.	principal investigator who enrolled the participants within an hour of an eligible patients' arrival. Caregiver consent was obtained before administration of inhaled therapy. BSSs were recorded before, immediately after, and 4 hours after administering the aerosol. If the patient was admitted or discharged before 4 hours, the second posttreatment score was recorded at the time of disposition. The treating ED clinician determined the final diaposition of the patient. Authors stated that the protocol the've used didn't require any specific criteria for discharge. Randomization Eligible patients were randomized to 1 of 2 groups in blocks of 10. The pharmacy department maintained a box in the ED holding sequentially numbered, previously randomized concealed envelopes containing either the	Difference, p-value (95% CI) = -0.6, p=0.37 (-2.0 to 0.78) Lenght of stay in the ED, hours (mean ±SD) HS group = 4.1 ±0.9 NS group = 3.9 ±4.0 p-value = 0.80 Proportion of patients admitted HS group = 22/52 (42%) NS group = 3/23 (13%) OR = 0.76 (0.35-1.70) Proportion of patients discharged at 24 h HS group = 2/22 (14%) NS group = 3/23 (13%) OR = 1.10 (0.20-6.20)	treatments received by the two groups. Attrition bias: low risk of bias Detection bias: low risk of bias Other information Indirectness does the study match the review protocol in term sof Population: some (children aged up to 18 months, excluded those with risk factors) Intervention: yes Outcome: yes Indirectness: some Data collection A standardized data sheet was completed after enrollment and during each patient's stay in the ED or inpatient ward. Any cointerventions, such as additional bronchodilators, supplemental oxygen, intravenous fluids, or deep nasal suction, were at the discretion of the treating clinician. Setting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- any use of bronchodilators within 2 hours of presentation - gestetional age ≤34 weeks - history of congenital heart disease or chronic pulmonary or chronic renal disease - SpO2 ≤85% at the time of recruitment - severe disease requiring ICU admission - inability to obtain informed content		study (7% HS) or control (0.9% NS) medication. Blinding Research personnel, including the investigators, the treating physician, and staff who performed the BSS were kept blinded throughout the process. Outcomes Authors used a modified BSS score to assess the severity of illness in acute bronchiolitis (primary score). Secondary outcome measures included hospitalization rate, dicharge rate at 23 hours, and lenght of hospital state. Statistical analysis The sample size was calculated on the basis of an anticipated difference in BSS of 2 points between the study and control groups. Assuming power of 80%, alpha of 0.05, and a 2-tailed test, estimated sample size was 47 patients per study group. Continuous variables were examined by using Student t-test. Dichotomous variables		ED of an urban tertiary care center with an annual census of 70000 patient visits.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			were examined by using the chi-squared or Fisher exact test.		
Full citation Sharma,B.S., Gupta,M.K., Rafik,S.P., Hypertonic (3%) saline vs 0.93% saline nebulization for acute viral bronchiolitis: a randomized controlled trial, Indian Pediatrics, 50, 743-747, 2013 Ref Id 299796 Country/ies where the study was carried out India Study type Randomized, double-blind, controlled trial. Aim of the study To evaluate the efficacy of nebulized 3% hypertonic saline (HS) in children diagnosed with clinical bronchiolitis. Study dates From September 2009 to December 2010. Source of funding	Sample size 248 patients were enrolled. 123 were randomized to NS group, and 125 to HS group. Characteristics Age, mo (mean) HS group = 4.93 ±4.31 NS group = 4.18 ±4.24 Male/Female (n) HS group = 97/28 NS group = 92/31 Duration of symptoms (at enrollment), days HS group = 3.6 ±2.87 NS group = 3.8 ±2.34 Baseline O2 saturation, % HS group = 94.43 ±2.77 NS group = 95.23 ±2.45 Clinical score at admission, median HS group = 6 NS group = 6	Interventions intervention: 4 mL of 3% hypertonic saline (HS), plus 2.5 mg salbutamol control: 4 mL of 0.9% normal saline (NS), plus 2.5 mg salbutamol Medical staff used a conventional jet nebulizer with tight-fitting face mask connected to a source of pressurized oxygen set to a flow rate of 7 L/min through tight-fitting face mask. The nebulization was continued till the nebulization chamber was empty. Patients were examined by investigators at the study entry and every day. Monitoring parameters for improvement or worsening of the condition were measured and	Details All patients were enrolled within 24 hours of admission to the hospital. Randomization Computer generated random numbers were used for enrolment in consecutive manner and patients were randomly assigned to receive either HS or NS along with 2.5 mg of salbutamol at intervals of 4 hours, six times daily till the patient was ready for discharge. Blinding There was no detectable difference in color, smell, or other physical properties between 0.9% saline solution and 3% hypertonic saline solution. The combination code of the therapeutic package was not available to the investigator or treating medical staff. The code	Results Outcomes 1- lenght of hospital stay (from admission to time take to reach clinical severity score <3) 2- improvement in clinical severity scores in hospitalized children Results Lenght of hospital stay, mean hours ±SD HS group = 63.51 ±21.27 NS group = 63.93 ±22.43 p-value = 0.878 Clinical severity scores monitored 12 hourly till discharge (132 hours) did not show statistically significant differences between the two groups. however, the median clinical score at time 0 would be based on 125 subjects, whereas the data at 132 hours would	Limitations Based on NICE appendix C checklist for RCTs: Selection bias: low risk Attrition bias: 250 patients have been initailly randomized to the two groups, 125 analyzed in the HS group and 123 in the NS group, but no reason has been provided for the 2 missing patients. Detection bias: No mention of important confounding factors and relative blinding to them. Performance bias: No information provided for additional treatments. Other limitations: - The study excluded patients with risk factors - No specific figures an p-value

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None.	Inclusion criteria Children with clinical presentation of viral bronchiolitis and hospitalized with a clinical severity score 3-6 were included. Bronchiolitis was defined by first episode of wheezing along with prodrome of upper respiratory tract infection including rhinorrhea, cough, and sometimes low-grade fever, which may progress to dyspnoea. Exclusion criteria Children with: - obtunded consciousness - cardiac disease - chronic respiratory disease - previous wheezing episode - progressive respiratory distress requiring respiratory support other thansupplemental oxygen Those having received nebulized HS within	recorded at admission and then at 12 hourly intervals using the clinical score described by Wang et al. Discharge criteria included feeding well orally, no need for intravenous fluids and supplemental oxygen, clinical severity score ≤3, absence of accessory muscle use or tachypnea (respiratory rate <31 breaths/min) and oxygen saturation >92% on air.	was deposited with the statistician. Statistical analysis Reduction in lenght of hospital stay of 1 day was previously proposed as being clinically significant. It was anticipated that this woud require a sample size of 113 patients in each arm. This number was based on a pre study mean lenght of hospital stay of 3.5±2.9 days. Each variable was scanned for normalcy of distribution. Categorical variables were compared using the Chi-square test. All continuous variables were compared using the paired or unpaired t-test as appropriate. a p value <0.05 was considered statistically significant. To examine the clinical severity scores at 12-hourly intervals Mann-Whitney non-parametric U test was carried out in each treatment group separately. For this analysis, P value 0.005 was considered	be based on only 2 patients.	reported for secondary outcome (clinical severity) Other information Indirectness Does the study match the review protocol in terms of Population: some (children aged up to 24 months) Intervention: yes Outcome: yes Indirectness: some Setting Tertiary care teaching hospital

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	the previous 12 hours were also excluded.		significant due to multiple comparisons.		
Full citation Teunissen,J, Hochs,AHJ, Vaessen-Verberne,A, Boehmer,ALM, Smeets,CCJM, Brackel,H, van Gent,R, Wesseling,J, Logtens-Stevens,D, de Moor,R, Rosias,PPR, Potgieter,P, Faber,MR, Hendriks,HJE, Janssen-Heijnen,MLG, Loza,BF, The effect of 3% and 6% hypertonic saline in viral bronchiolitis: a randomised controlled trial, European Respiratory Journal, epub ahead of print, -, 2014 Ref Id 319750 Country/ies where the study was carried out The Netherlands Study type Double-blind, multicentre, randomised controlled trial. Aim of the study To investigate the efficacy of nebulised 3% and 6% hypertonic saline compared with 0.9%	Sample size 292 children were included in the study and randomized. In total, 247 patients completed the study and were analysed in the per protocol analysis. 84 received 3% HS, 83 received 6% HS, and 80 received NS. Characteristics Patient baseline characteristics did not significantly differ between the three groups. Age months (IQR) 3% HS = 3.6 (5.2) 6% HS = 3.4 (3.8) NS = 3.6 (5.0) Males 3% HS = 44 (52.4%) 6% HS = 48 (57.8%) NS = 49 (61.3%) Baseline clinical severity score 3% HS = 6.2 ±1.9 6% HS = 6.2 ±2.2	Interventions The intervention groups received inhalations with 3% or 6% HS, and the control group received inhalations with 0.9% sodiu chloride (normal saline NS). Study medications for all centres were prapared by an internationally certified research pharmacist. To prevent bronchial obstruction, 2.5 mg salbutamol was added to each dose. The saline concentrations were calculated so that the concentration of the definitive solution with salbutamol was 0.9%, 3%, or 6% sodium chloride and the total volume was 4 mL. The solutions were nebulised every 8 hours with a constant oxygen flow of 6-8 L*min froma wall outlet in combination with a HOT Top Plus Nebuliser, via a tight-	Details Enrolment On admission the clinical history of the patients was recorded, which included duration of symptoms, use of medications, and the patient and family history of atopy. A nasopharyngeal swab was obtained for viral analysis. If the child furfilled the inclusion criteria and parental informed consent was obtained, nebulisation with the study medication was started within 12 hours of admission. The diagnosis of bronchioitis was clinically defined by symptoms of an upper respiratory tract infection with wheezing, tachypnoea and dyspnoea. Randomization All selected patients were randomly assigned to one of the three groups (two intervention	Results Outcomes 1. duration of hospital stay, which was calculated as the number of hours between the first dose of study medication and the clinical decision to dicharge. Protocol-defined dicharge criteria included no need for supplemental oxygen, tube-feeding or intravenous fluids, according to the responsible paediatrician. 2. transfer to a PICU because of respiratory insufficiency, need and duration of supplemental oxygen or tube feeding. Supplemental oxygen was started in infants with a room air saturation of 93% or lower, during >10 min of deoxidisation of <85%. This was stopped when saturation was consistently >93%. The indication for starting and stopping tube feeding was a minimal intake	Limitations Based on Nice Manual Appendix C for randomised controlled trials Selection bias: unreported who prepared the randomization sequence. Unclear concealment of allocation. Performance bias: low risk of bias Attrition bias: low risk of bias Detection bias: low risk of bias Other information Indirectness Does the study match the review protocol in terms of population: some (aged up to 24 months) intervention: yes outcome: yes indirectness: some Setting This study was conducted in 11 general hospitals and

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normal saline in children hospitalized with viral bronchiolitis. Study dates November 2009 to May 2011, during the bronchiolitis season. Source of funding Not reported.	NS = 6.2 ±2.1 Baseline oxygen saturation on room air % 3% HS = 95.4 ±3.6 6% HS = 95.4 ±3.4 NS = 95.5 ±3.4 Positive family history of atopy 3% HS = 33 (39%) 6% HS = 31 (37%) NS = 29 (36%) Inclusion criteria Children aged 0-24 months if they were admitted to one of the participating hospitals because of mild-to-severe viral bronchiolitis and had a Wang score ≥3 at presentation. Exclusion criteria Children were excluded if the Wang score improved at least 2 points after inhalation. Further exclusion criteria were: haemodynamically important congenital heart disease, chronic pre-existent lung disease, T-cell	fitting face mask and were administered until empty. Nebulisations were continued until discharge. Additional treatments Besides the study medication, patients received: nasal-decongestants n = 161 (equally distributed among the study groups). paracetamol n = 30 antibiotics n = 11 salbutamol n =6 ibuprofen n = 1 nystatine n = 1 raniditine n =1	groups and one control). Randomization was done per centre and clustered in blocks of six patients. Each patient received a consecutively randomised number that corresponded to identical 20 mL vials, which contained the study medication. Blinding All participants, care givers and medical staff were blinded to the composition of the study solutions, which were identical in vial packaging, colour, smell and other physical characteristics. Evaluation All patients were evaluated twice a day, which was based on physical examination, the wang score, heart rate, saturation, respiratory rate, need for supplemental oxygen and tube feeding. These evaluations were done by two paediatricans on duty. Before the start of the study, all participating medical staff were trained how to evaluate the patients	calculated as 75% of normal intake. Furthermore, the safety of the treatment was measured by registration of adverse events. Results 3% HS n = 84 6% HS n =83 0.9% NS n = 80 Lenght of hospital stay in hours, median (IQR) 3% HS = 69 (57) 6% HS = 70 (69) 0.9% NS = 53 (52) p-value = 0.29 Oxygen supplementation, patients n (%) 3% HS = 50 (60) 6% HS = 53 (64) 0.9% NS = 51 (64) p-value = 0.81 Supplemental oxygen, duration in hours, median (IQR) 3% HS = 54 (48) 6% HS = 54 (61) 0.9% NS = 40 (41) p-value = 0.14 Tube feeding, patients n (%) 3% HS = 29 (35)	one tertiary medical centre in the Netherlands. Ethics The study was approved by the central medical ethics committee of the netherlands and the local ethics committees of all participating hospitals. On behalf of each child, at least one legal caregiver signed an informed consent form before study start. Sample size calculation Authors reported that previous studies showed a decrease in the lenght of stay in hospital from 4 days to 3 days, after the inhalation of 3% nebulised HS. base on this 25% reduction, a sample size of 65 patients per trial arm was required for this study to achieve a power of 90% with a p-value <0.05.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	immunodeficiency, treatments with corticosteroids, and previous wheezing, food allergy or eczema.		and classify the wang clinical severity scoring system in order to improve interobserver agreement. Statistical analysis Analyses were done according to the intention-to-treat and per protocol principles. Differences between included and excluded patients, with respect to patient characteristics, were evaluated by means of independent t-test (age) and Chi-squared test (sex and intervention). All continuous variables were tested for normality; in case of normal distribution, differences between the three groups were tested with ANOVA and in case of not-normal distribution, the Kruskal-Wallis test was used. For categorical variables differences in distribution between intervention groups were tested with the Chi-squared test. Univariate differences in time until hospital dischargebetween	6% HS = 31 (37) 0.9% NS = 22 (28) p-value = 0.39 Tube feeding, duration in hours, median (IQR) 3% HS = 62 (58) 6% HS = 52 (55) 0.9% NS = 54 (83) p-value = 0.87 Median Wang score at discharge 3% HS = 2.0 6% HS = 1.0 0.9% NS = 2.0 p-value = 0.53 Mean improvement of Wang score at discharge 3% HS = - 4.55 6% HS = - 4.54 0.9% NS = - 4.33 p-value = 0.80 A susbtantial number of adverse effects were noted in all treatment groups. Except for cough, which occurred significantly more often in the HS groups (p=0.03), no significant difference were found between groups for bronchial obstruction, agitation, rhinorrhea, dry mucosae, resistance, vomiting, saturation dips,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			groups were tested with the Log-rank test.	and tachycardia. Withdrawals because of adverse events did not differ between grousp (p=0.59).	
Full citation Wu,S, Baker,C, Lang,ME, Schrager,SM, Liley,FF, Papa,C, Mira,V, Balkian,A, Mason,WH, Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial, JAMA Pediatrics, 168, 657-663, 2014 Ref Id 320193 Country/ies where the study was carried out United States Study type Double-blind, randomized clinical trial. Aim of the study To compare the efficacy of inhaled hypertonic saline vs normal saline on admission rate, length of stay, and respiratory distress in infants and young children 24 months or younger with bronchiolitis.	Sample size A total of 408 patients were enrolled in the study and randomized as follows: - 197 allocated to NS group * - 211 allocated to HS group An additional 39 patients were enrolled after admission, and not included in the analysis (although they have been included in the descriptive analysis). Seven patients in each group left or were transferred before receiving any study medication. *One patient in the NS group received the HS group treatment and underwent analysis in the originally allocated group. Characteristics	Interventions Intervention group received 3% hypertonic saline (HS). Control group received 0.9% normal saline (NS). Study medication was identical in colour, odour, and labelling. Researchers reported that, because previous studies showed a potential risk for bronchospasm from hypertonic saline in patients with underlying asthma, all doses of study medication were pre-treated with albuterol. Additional treatments Patients enrolled in the ED received 2.5 mg of nebulized albuterol sulphate, followed by 4 mL of normal saline or hypertonic saline via a small-volume wall nebulizer. The ED	Details Enrolment Study personnel were available to enrol patients for 70 hours per week. Once a diagnosis of bronchiolitis was made by the treating physician, study staff screened patients for eligibility and obtained parental consent. Baseline demographics, vital signs, and laboratory results were obtained from the medical record. Additional patient history was recorded on standardized case report forms. Randomization Patients were allocated by simple randomization to HS or NS group by the investigational pharmacy, using a computer-generated random number table stratified by site.	Results Outcomes Admission rate:criteria for admission included a persistent oxygen saturation <92%, increased work of breathing, or inadequate oral intake. The ED attending physician determined whether the patient could be discharged or required admission. Length of stay RDAI score: it was assigned by a study investigator before and 30 minutes after each treatment in the ED and once each morning of hospitalization Results Admission rate NS group = 84/197 (42.6%) HS group = 61/211 (28.9%) Adjusted* OR = 0.49 (95% CI, 0.28-0.86)	Limitations Based on NICE appendix C checklist for RCTs: Selection bias: low risk Attrition bias: - authors applied intention-to-treat principles - 7 patients in each group left without receiving the treatment - An additional 39 patients were enrolled after admission and not included in the analysis. However, they have been included in the descriptive analysis and no reason or explanation has been given in the article. Detection bias: - Not reported whether investigators were kept blind to important confounding and prognostic factors. - The paper reported that this study did not

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Study dates Three consecutive bronchiolitis seasons from March 1, 2008, through April 30, 2011. Source of funding The study was supported by a grant from the Thrasher Research Fund and by a Mentored Junior Faculty Career Development of Paediatrics, University of Southern California Keck School of Medicine (Dr Wu).	Based on the following samples (including the 39 patients enrolled after admission): - NS group = 216 - HS group = 231 No significant differences were found between the two groups in terms of age, sex, duration of symptoms, tobacco exposure and positive findings for RSV. Subjects demographics were also similar by site of recruitment, although more Hispanic/Latino patients were recruited in Los Angeles (86.2%) than Oakland (46.9%, p<0.001), and more patients in Los Angeles had atopy (9.4% vs 3.7%; p=0.03). Inclusion criteria Patients were eligible if they were younger than 24 months with a primary diagnosis of viral bronchiolitis. Exclusion criteria	physicians could order two additional treatments every 20 minutes to a maximum of 3 inhaled doses. Authors reported that other care was provided per local clinical practise guidelines. Admitted patients continued receiving study medication at a dosage of 4 mL every 8 hours until discharge. All other treatments and testing were ordered at the discretion of the treating physician.	Blinding Families, clinical staff, and study personnel were blinded to treatment allocation. Statistical analysis Authors conducted a statistical analysis with intention to treat principles using SPSS. Logistic regression was used to investigate treatments effects on admission rate, and multiple linear regression analysis was used to model treatment effects on length of stay and RDAI score, controlling for demographic variables and potentially related clinical factors. For the post-treatment RDAI score, the pre-treatment RDAI score was also statistically controlled. In order to investigate potential differences between treatment groups in the rate of change in the RDAI score, a repeated-measures analysis of variance was also conducted.	*controlling for sociodemograhic and baseline clinical predictors. Length of stay, mean (SD) days (calculated for the 145 admitted patients) NS group = 3.92 (5.24) HS group = 3.16 (2.11) This difference was not statistically significant (p=0.24) even after controlling for sociodemographic and baseline clinical variables. RDAI score, mean (SD) - NS group Pre-treat = 6.16 (2.91) Post-treat = 5.32 (3.14) - HS group Pre-treat = 5.96 (3.08) Post-treat = 4.88 (2.95) The difference between groups was not statistically significant (p=0.35). Supplemental therapies No significant differences were found in supplemental treatment use between groups.	use medical readiness for discharge as a standard criterion, therefore the length of stay outcome may not accurately reflect clinical status. Performance bias: - Admission and discharge were at discretion of the attending physician. Also, other care was provided per local clinical practise guidelines, but no significant differences were found between intervention and control group. Other limitations: - Failure to achieve planned sample size - Most of the participants were Hispanic (65.7% and 63.6% in NS and HS group, respectively), which limits the generalizability of the findings to other populations. - The study excluded patients with risk factors.

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	Patients were excluded if they had a prior illness with wheezing or bronchodilator use, if they were premature (gestational age <34 weeks), or if they had cyanotic congenital heart disease, chronic lung disease, or tracheostomy.			Among admitted patients, those in NS group received a mean of 27.3 hours of oxygen administration, compared to 28.6 hours in HS group. In the NS group 15 patients received supplemental albuterol and 8 received inhaled epinephrine; in the HS group, 15 received albuterol and 3 received epinephrine. Systemic corticosteroid use: 3 patients in the NS group and 7 in the HS group. Diuretics: 1 patient in NS group and no patients in HS group. No patients in either group received leukotriene receptor antagonists.	- Authors did not establish a minimum or maximum severity criterion for study entry (mean pre-treatment RDAI score = 6.01, which correlates to mild to moderate disease). Other information Other information Indirectness Does the study match the review protocol in terms of: Population: some (patients aged up to 24 months) Outcome: yes Intervention: yes Indirectness: some Setting Emergency department of 2 tertiary free-standing urban children's hospitals in California. Sample size calculation Authors reported that the study was originally designed to enrol 350 ED patients into each arm, giving 80% power to detect a 30%

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					change in admission rate. They also estimated that these numbers would yield 124 admitted patients in each arm, giving the study the possibility to detect a 0.5day difference in length of stay. Also, authors reported that, based on previous studies, only 5 patients in each arm would be needed to detect a difference in the RDAI score of 3 points or more between groups.
Full citation Florin,TA, Shaw,KN, Kittick,M, Yakscoe,S, Zorc,JJ, Nebulized hypertonic saline for bronchiolitis in the emergency department: a randomized clinical trial, JAMA Pediatrics, 168, 664-670, 2014 Ref Id 320194 Country/ies where the study was carried out United States Study type Double-blind randomized clinical trial.	Sample size 62 patients with bronchiolitis were randomized, enrolled and had RDAI score assessment conducted 1 hour after study treatment. 31 patients in each treatment group. Characteristics female sex = 52% HS, 58% NS age, mean (SD), mo = 7.2 (5.1) HS, 6.1 (3.60) NS	Interventions Intervention: 4 mL of 3% HS Control: 4 mL of NS Study medications administration occurred within 90 minutes after albuterol administration. Additional therapies were ordered at the discretion of the treating physician.	Details Enrolment Potential participants were identified and screened by trained research staff present in the ED from 7 am to 12 am daily. All patients received standard therapy for bronchiolitis per hour ED's bronchiolitis pathway, including nasal suctioning and a trial of a single dose of nebulized albuterol before enrolment, as follows:	Results Outcomes 1. Respiratory Assessment Change Score (RACS), which was measured 1 hour after the study intervention. RACS assessed the alteration in respiratory status using the change in the RDAI score and a standardized change in respiratory rate, with points being assigned by change increments of 10%. 2. Secondary outcomes: changes in	Limitations Based on Nice Manual Appendix C for randomised controlled trials selection bias: baseline characteristic "physician clinical impression" not completed for 1 infant in HS group. Low risk of bias. performance bias: additional therapies were requested at the discretion of the study physician, but not recorded or specified

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine whether nebulized 3% hypertonic saline (HS), compared with normal saline (NS), improves respiratory distress in infants presenting to the ED with acute bronchiolitis and persistent distress after a trial of nasal suctioning and nebulized albuterol sulfate. Study dates 2 consecutive bronchiolitis seasons, from November 1 to April 30 of 2010 and 2011. Source of funding This study was supported by a Young Investigator Award from the Academic Paediatric Association. Also, the study reported that participants received financial compensation (no additional info reported).	days of symptoms, mean (SD) = 3.4 (3.7) HS, 3.4 (2.4) NS RDAI score, mean (SD) = 7.8 (2.6) HS, 7.4 (2.5) NS RDAI score, median (IQR) = 7 (6-10) HS, 7 (5-9) NS Respiratory rate, mean (SD), breaths/min = 49.6 (12.4) HS, 52.4 (12.4) NS Heart rate, mean (SD), beats/min = 153.4 (18.4) HS, 159.3 (21.9) NS Oxygen saturation, mean (SD), No. (%) = 95.4 (3.8) HS, 96.3 (3.7) NS Inclusion criteria Children who presented to the ED with acute bronchiolitis, with respiratory distress persisting after a trial of nebulized albuterol and nasal suctioning were considered. Eligible patients included children aged 2 to less than 24 months presenting to		- 2.5 mg for children weighing <10kg - 3.75 mg for children weighing 10-20 kg - 5 mg for those weighing >20 kg All doses were diluted with 3 mL of NS. Within 90 minutes after albuterol treatment and suctioning, a paediatric emergency medicine physician trained in score determination assigned and RDAI score. No RDAI score was conducted before administration of albuterol. If the RDAI score was between 4 and 15, eligibility was confirmed and family was approached to obtain informed consent. Randomization Research pharmacists prepared study medications according to a randomization list generated by the investigational pharmacy using computer-generated random permuted block randomization. Study medications were stored	heart rate, changes in respiratory rate, changes in oxygen saturation, hospitalization, physician clinical impression, parental perception of improvement in breathing and feeding, and adverse events (like bronchospasm, excessive coughing, apnea, and cyanosis were recorded using a standardized medical record abstraction form). Results 3% HS: n = 31 NS: n = 31 RACS, mean 95%CI HS = -1.5 (-3.1 to 0.2) NS = -4 (-5.3 to -2.7) difference = 2.5 (0.5 to 4.6), p-value = 0.01 RACS, median (IQR) HS = -1 (-5 to 1) NS = -5 (-6 to -2) difference = 4, p-value = 0.01 RDAI score, mean 95% CI HS = 6.6 (5.5 to 7.6) NS = 5.1 (4.1 to 6.2) difference = 1.5 (-0.02 to 2.9), p-value = 0.05	in the study. Low risk of bias. attrition bias: low risk of bias. detection bias: unspecified if investigators were kept blind to other important confounding and prognostic factors. Low risk of bias. Other limitations: Researchers excluded patients with risk factors for severe bronchiolitis. Other information Indirectness Does the study match the review protocol in terms of Population: some (2-24 months) Intervention: yes Outcome: yes Indirectness: some Setting The study was conducted in a single urban, tertiary care ED within a freestanding children's hospital in Cincinnati.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ED with a first episode of bronchiolitis defined as their first episode of wheezing associated with signs and symptoms of respiratory distress and upper respiratory infection. Further inclusion criteria were a RDAI score of 4 to 15 (moderate to severe) obtained after albuterol treatment, and no intention for further respiratory therapy by the ED physician during the first hour after assessment. Exclusion criteria Children with a history of wheezing or asthma, bronchodilator therapy prior to the current illness, chronic lung or heart disease, critical illness, and inability to receive nebulized medications were excluded. Children with non-English speaking guardians were excluded because of the inability to provide fully informed consent		in sequentially numbered envelopes with blinded syringes labeled only with the study number to ensure allocation concealment. Blinding All investigators, ED and research staff, parents and guardians were unaware of group assignment. Both HS and NS are clear and odorless, and thus were indistinguishable in the syringe and nebulization chamber. Data collection Study clinicians performed the respiratory scoring at 1 and 2 hours after the study treatment. All patients received assessment at 1 hour after study treatment. All patients being discharged home were assessed at 2 hours after the study treatment to observe for adverse effects after the peak effect of HS. For hospitalized children, the 2-hour assessment was performed if the patient	RDAI score, median (IQR) HS = 6 (4 to 9) NS = 5 (3 to 8) difference = 1, p-value = 0.06 Respiratory rate change, mean (95% CI), breaths/min HS = -1.8 (-6.5 to 2.8) NS = -9.8 (-14.6 to -4.9) difference = 8 (1.4 to 14.5), p-value = 0.02 Heart rate change, (95% CI), beats/min HS = 3.4 (-5 to 11.8) NS = -2.6 (-11.2 to 6) difference = 6 (-5.7 to 17.8), p-value = 0.31 Oxygen saturation change, mean (95% CI), % HS = 1.1 (-0.4 to 2.6) NS = 0.1 (-1.6 to 1.8) difference = 1 (-1.2 to 3.2), p-value = 0.36 Physician clinical impression, No. (%) Mild HS = 15 (48) NS = 21 (68) difference = -6 (-20) Moderate HS = 16 (52) NS = 9 (29)	

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	within the study time costraints.		was still in the ED at that time. Disposition decisions were made by treating clinicians independent of study procedures. Research assistants performed brief parental surveys before physician assessment at 1 and 2 hours after the study treatment that asked about the patient's respiratory distress and ability to feed, and a standard medical history form was completed for all participants by treating clinicians. A research assistant performed a telephone interview with the parents or guardians approximately 7 days after the ED visit: the interview included questions about hospitalizations, return ED visits, and unscheduled visits to primary care physicians. Statistical analysis The study was designed to detect a clinically significant difference, defined as a mean change of 3, in the	difference = 7 (23) Severe HS = 0 NS = 1 (3) difference = -1 (3) overall p-value = 0.14 Hospitalization, No. (%) HS = 22 (71) NS = 20 (65) difference = 2 (6), p-value = 0.86 Parental perception of improvement, No. (%) Breathing HS = 15 (50) NS = 17 (55) difference = -2 (-5), p-value = 0.62 Feeding HS = 8 (27) NS = 6 (19) difference = 2 (8), p-value = 0.51	

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			RACS between the groups. The sample size required to detect this difference was estimated to be 30 children in each arm. Data for the primary outcome were analyzed using the intention-to-treat principle. Because prior literature reported that the RDAI score had not been normally distributed, the researchers decided to use nonparametric analyses. However, RDAI score was normally distributed in this study and therefore they've decided to conduct both parametric and nonparametric tests. The difference in mean RACS and RDAI values between the two groups was assessed using a 2-sample t test. Similarly, the difference in median RACS and RDAI values was examined using the Mann-Whitney test. Researchers also performed a subgroup analysis to assess the effect of severity using the median baseline		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			RDAI score to define severity groups.		
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mark L Everard DM[a], Daniel Hind PhD[b], Kelechi Ugonna MB ChB[c], Jennifer Freeman PhD[d], Mike Bradburn MSc[b], Cindy L Cooper PhD[b], Elizabeth Cross MA[b], Chin Maguire MPH[b], Hannah Cantrill BSc[b], John Alexander MB ChB[e], Paul S McNamara MB ChB[f], on behalf of The SABRE Study Team. SABRE: A multi-centre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. Thorax, 2014. Ref Id Country/ies where the study was carried out United Kingdom Study type Multicentre, parallel-group, open, randomised controlled trial. Aim of the study To determine whether hypertonic saline does	Sample size 142 + 149 infants with acute bronchiolitis. Characteristics Age (months), mean (SD) [redacted] Male gender, No. (%) [redacted] Birthweight (kg), median (range) [redacted] Smoker in household, No. (%) [redacted] Inclusion criteria Eligible participants were healthy infants under 1 year of age needing supplementary oxygen for SpO2 of less than	Interventions Intervention: Oxygen as required and fluid administration, plus 4 mls nebulised 3% hypertonic saline solution every 6 hours, administered by a nurse via the PARI Sprint nebuliser with appropriate face mask. The saline treatment was discontinued once the primary outcome had been achieved. Control: Standard supportive care involving oxygen as required, minimal handling and fluid administration as appropriate to the severity of the disease. All concomitant medications were recorded.	Details The time of admission was defined as when the paediatrician, or Advanced Paediatric Nursing Practitioner, made the decision to admit. Eligible participants required supplemental oxygen therapy on admission and were consented and randomised within 4 hours of admission. Randomisation and masking Infants were randomised using a centralised web-based randomisation system with a computer generated algorithm generated by Sheffield Clinical Trials Research Units. Randomisation was conducted in randomly ordered blocks of size two, four and six, stratified by hospital.	Outcomes Primary outcome: the time until the infant was assessed as being to “fit for discharge” which was defined as point at which the infant was feeding adequately (taking >755 of usual intake), and had been in air with a saturation of at least 92% for 6 hours. Secondary outcomes: actual time to discharge, readmission within 28 days from randomisation, adverse events, health care utilization and duration of respiratory symptoms post discharge. Results [redacted] Time to fit for discharge, h, mean (SD) [redacted]	Limitations Based on NICE appendix C checklist for RCTs Detection bias: - blinding was not possible for investigators Performance bias: - the study is not blinded Other information Indirectness Does the study match the review protocol in terms of: Population: Yes Intervention: Yes Comparator: Yes Outcome: Yes Indirectness: None Setting Participants were recruited from the assessment units and paediatric wards of ten participating centres in England and Wales.

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have beneficial effects in children with bronchiolitis. Study dates Between October 2011 and December 2013. Source of funding The study was funded by the National Institute for health Research Health Technology Assessment (HTA) Programme.	92% in air when admitted to hospital with a clinical diagnosis of acute bronchiolitis. The diagnosis was based on apparent viral respiratory tract infection associated with airways obstruction manifest by hyperinflation, tachypnoea and subcostal recession with widespread crepitations on auscultation. Exclusion criteria - a history of wheezy bronchitis or asthma - gastro-oesophageal reflux - previous lower respiratory tract infections - risk factors for severe disease - carers lacking fluent English in the absence of translational services - patients requiring admission to high dependency or intensive care units at presentation		This was an open study when blinding was not possible. Statistical Analysis The primary outcome was analysed by Cox proportional hazards regression model in which centre was fitted as a fixed effect. Researchers also assessed whether HS worked similarly in RSV+ and RSV- patients by including RSV status and its interaction with treatment group. The proportion of patients admitted to HDU/ICU and the proportion readmitted to hospital, were compare between the two groups by logistic regression. All analyses presented are by intention to treat unless otherwise stated. Analyses were conducted using SPSS v.20 or SAS v.9.3.	Time to discharge, h, mean (SD) [redacted] - Admitted to ICU/HDU, No. (%) [redacted]	Sample size The authors expected an average time to discharge of around 3 days with a standard deviation of 32 hours (based on data taken from UK hospital episode statistics). They also reported that, assuming a conservative SD of 46 hours, and taking a 25% reduction as the minimum clinically significant effect, the study needed 150 patients per group for a 90% power.

I.15 What is the efficacy of heliox?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cambonie,G., Milesi,C., Fournier-Favre,S., Counil,F., Jaber,S., Picaud,J.C., Matecki,S., Clinical effects of heliox administration for acute bronchiolitis in young infants, Chest, 129, 676-682, 2006 Ref Id 206476 Country/ies where the study was carried out France Study type Randomised, double-blinded, controlled Aim of the study To assess the effect of heliox on respiratory distress symptoms in infants <3 months old with RSV bronchiolitis, including ex-premature infants. Study dates November 1999 to March 2002	Sample size - 31 admitted to PICU with respiratory distress - 11 excluded for clinical scores <5 - 20 randomised - One infants excluded from the control group because oxygen saturation <90% that perisisted under the maximum 40% FI02 - 19 completed: 9 control group, 10 heliox group Characteristics Characteristic: heliox; control Mean±SD - Age, days: 29±5; 34±9 - Weight, kg: 3.5±0.46; 3.83±0.24 - Clinical score: 5.4±0.2; 5.6±0.2 - Respiratory rate, breaths/min: 59.4±6.4; 64.9±5.7 - Heart rate, beats/min: 152±14.9; 144±8.5 - Fraction of inspired oxygen (FI02), %: 31.4±4.0; 34.0±2.6	Interventions - Control group 21% oxygen/79% nitrogen - Heliox group 21% oxygen/79% helium - All treatment including bronchodilators, corticoids and kinesitherapy was stopped - After enrollment patients received gas mixtures through a hood, delievered by a double flowmeter system - Gas mixture flow maintained throughout the study at 7l/min, and the fractional inspired oxygen (FI02) under the hood was first adjusted to 0.40 - Delivery system consisted of two standard pressure-compensated flowmeters calibrated with air for gas A (control) and gas B (heliox)	Details Setting: PICU at University Hospital Arnaud de Villeneuve Randomisation and concealment: - During the study period none of the parents and only one investigator knew which group was receiving airox or heliox treatment - Blinding was accomplished by placing the two flowmeters in a box, each connected to one of the two gas tanks in such a way that the investigator had to select the output corresponding to group A (control) or B (heliox) and regulate the flow without knowing the nature of the gas - Randomisation not described, Cochrane contacted authors for details and reported computerised random listing and sealed envelopes	Results Protocol outcomes 1. Change in C02 Cochrane report change in pC02 in the first hour after starting treatment: Heliox group -2.2 SD 0.78 Control group -2.1 SD 0.93 (After calculated by NCC: heliox 54.3mm Hg, control 51.5mm Hg) 2. Need for high flow humidified oxygen, CPAP or mechanical ventilation One infant in each group required endotracheal intubation for respiratory failure, 10 hours following randomisation for the infant included in the control group for ARDS and 4 hours for the infant in the heliox group for recurring incidents of apnea	Limitations Based on NICE appendix C checklist: - Long study period (3 years) to recruit only 20 infants, small sample size - Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria - Results presented in figures, not all outcomes are reported separately - Randomisation not described, Cochrane contacted authors for details and reported computerised random listing and sealed envelopes - Oxygen saturation ≥90% for inclusion appears restrictive Other information - M-WACS described in table 1. Based on cyanosis, inspiratory breathing sounds, accessory muscle use, expiratory wheezing and cerebral function. 0 to 10

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Source of funding Air Liquide Santé provided the heliox and air tanks and set up the study equipment	- Partial pressure of oxygen (P02), mm Hg: 59.7±5.0; 64.3±8.1 - Partial pressure of carbon dioxide (Pac02), mm Hg: 56.5±4.9; 53.6±2.3 - pH: 7.30±0.02; 7.33±0.06 - Mean arterial BP (MABP), mm Hg: 61.4±5.7; 64.7±4.8 Inclusion criteria - <3 months old - Hospitalised in PICU for respiratory distress - RSV positive bronchiolitis - Pac02 >42mm Hg - Modified Wood clinical asthma score (M-WCAS) >5 - Signed authorisation from parents Exclusion criteria - Underlying cardiopulmonary disease - Pneumothorax on chest radiography - Corticosteriod or bronchodilator treatment	- Oxygen through another flowmeter was delivered through a 7l oxyhood in parallel with the gas mixture and was under the control of an oxygen analyser directly connected through an orifice on the top of the hood to monitor FI02 during the study period - After one hour gas delivery was stopped, 15 minutes later MWCAS determined and if ≤ value at 60 minutes weaning considered a success, if not gas delivery restarted and weaning was attempted 3 hours later in the same conditions	Outcome measures: - If oxygen saturation ≥90% monitored continuously - Respiratory rate, heart rate, MABP, oxygen saturation and M-WCAS recorded at 0, 30 and 60 minutes - To assess cyanosis with M-WCAS, FI02 was fixed at 0.21 (the cumulative time necessary for these FI02 changes was not >6 minutes and was not included in the study period) Statistical methods: - Independent sample t tests - Repeated measures analysis of variance to compare changes over one hour - Good agreement between two observers, kappa=0.8	3. Time to return to oral feeding Not reported 4. Length of hospital stay Cohrane report mean days: Heliox group 4.9 SD 0.9 Control group 5.1 SD 0.8 (hours calculated by NCC: heliox 117.6 SD 21.6, control 122.4 SD 19.2) 5. Change in disease severity score M-WCAS improved only in the heliox group, with a mean decrease between baseline and 60 minutes of 2.35 (SE 0.35), vs 0.05 (SE 0.01) in the control group, p<0.01 6. Change in O2 saturation Not reported 7. Adverse effects	scale. Also used by Hollman et al., 1998 and Martinon-Torres et al., 2002. Standardised scoring by assessing accessory muscle use and expiratory wheezing on a visual analogue scale. High score indicates increased severity. - The mean duration of gas administration was 3.6±1.8 hours in the control group and 13.0±3.8 hours in the heliox group, p<0.05 - Supplemental oxygen to maintain oxygen saturation >90% was necessary during a comparable period of 3.2±0.36 days in the control group, vs 3.5±0.07 days in the heliox group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	within 2 hours of study enrollment - If oxygen saturation <90%			None encountered	
Full citation Liet,J.M., Ducruet,T., Gupta,V., Cambonie,G., Heliox inhalation therapy for bronchiolitis in infants. [59 refs], Cochrane Database of Systematic Reviews, CD006915-, 2010 Ref Id 207443 Country/ies where the study was carried out UK Study type Systematic review Aim of the study To assess heliox in addition to standard medical care for acute bronchiolitis Study dates - Protocol first published: Issue 1, 2008 - Last assessed as up-to-date: 14 June 2009	Sample size - MEDLINE search retrieved 227 citations, CENTRAL 273 citations, EMBASE 209 and LILACS a total of 41 citations - Four trials met criteria for this review, 84 infants in total - Two parallel-group trials (Cambione 2006; Liet 2005), two cross-over designs (Hollmann 1998; Martinon-Torres 2008) Characteristics - All patients recruited in a PICU, admitted with RSV bronchiolitis and <2 years of age - No patients were intubated - Characteristics of included studies extracted in evidence tables Inclusion criteria Types of studies: RCTs and quasi-RCTs	Interventions Interventions of included studies extracted in evidence tables	Details Searches: - Searched the Cochrane Central Register of Controlled Trials (CENTRAL) which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1966 to June Week 3 2009), EMBASE (June 2009), LILACS (May 2009) and the NIH website (ClinicalTrials.gov) (May 2009) - Checked references of relevant systematic reviews and identified RCTs - Two review authors (VG, JML) contacted trial authors of all studies to locate other unpublished or in progress studies which met the inclusion criteria - There were no language or publication restrictions	Results Mortality One child died in the experimental group due to irreversible respiratory failure 34 days after stopping heliumtreatment (Liet 2005) Need for mechanical ventilation - Two trials (Cambione 2006; Liet 2005) failed to demonstrate a reduction in the need for mechanical ventilation with heliox - 58 participants - Total events: 5 (Heliox), 5 (Control) - RR 1.11, 95% CI 0.36 to 3.38, P = 0.86 Rate of intubation - Two trials (Cambione 2006; Liet 2005) failed to demonstrate a reduction in the rate of	Limitations Limitations of included studies extracted in evidence table Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
- Review first published: Issue 4, 2010 - Edited (no change to conclusions), published in Issue 10, 2013 Source of funding Jean-Michel Liet and Gilles Cambonie were investigators in two trials, both supported by Air Liquide Santé International. Air Liquide provided the heliox and air tanks, set up the study equipment and was involved in the study design. In both trials, Air Liquide Santé had no role in data management, data analysis or data interpretation, or writing of the report and decision to submit it for publication. The review authors have no financial relationship with Air Liquide Santé.	Types of participants: - Infants hospitalised with bronchiolitis - Bronchiolitis defined as: the presence of signs of respiratory distress secondary to respiratory syncytical virus (RSV) infection and/or those patients with respiratory distress and symptoms that occur within RSV epidemic periods and are not due to other medical conditions Types of interventions: Treatment with inhaled heliox versus a placebo (oxygen or air) Exclusion criteria Studies where heliox was used as a vector for nebulisation (to improve aerosol drug delivery), or studies where helium was used to assess lung volumes		- Two review authors (JML, GC) independently reviewed titles, abstracts and citations to assess potential relevance for full review - From the full text, both review authors independently assessed studies for inclusion based on the criteria for study design, population, intervention and outcomes Statistical analysis: - For endpoints with dichotomous measures, measured effect size using risk ratios (RR) - For endpoints with numerical outcomes, calculated mean difference (MD) - In case of missing values, contacted original trial authors to request missing data, otherwise data are assumed to be missing at random - Assessed heterogenity using I^2 - Fixed-effect model when studies were homogenous or a	intubation with heliox use - 58 participants - Total events: 5 (Heliox), 4 (Control) - RR 1.38, 95% CI 0.41 to 4.56, P = 0.60 Length of PICU stay - Two trials (Cambione 2006; Liet 2005) failed to demonstrate a reduction in the length of PICU stay with heliox use - 58 participants - MD -0.15 days, 95% CI -0.92 to 0.61, P = 0.69 Change in clinical respiratory scores within the first hour after starting heliox treatment - Three trials (Cambione 2006; Hollmann 1998; Martinon-Torres 2008) used the modified Wood clinical asthma score - 69 participants - Infants treated with heliox inhalation had a	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			random-effects model when studies were heterogeneous	statistically significant reduction in clinical respiratory scores - MD = -1.15, 95% CI -1.98 to -0.33, P = 0.006 - The addition of heliox therapy represents a 11.5% reduction in the clinical respiratory score Change in C02 within the first hour after starting treatment - Two studies (Cambione 2006; Martinon-Torres 2008) failed to demonstrate a reduction in change in CO2 - 43 participants - MD -2.09 mmHg, 95% CI -6.20 to 2.02, P = 0.32 Change in 02 within the first hour after starting treatment - One trial (Cambione 2006) failed to demonstrate a reduction in change in 02 - 19 participants	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- MD 2.06%, 95%CI -2.86 to 6.98, P = 0.41 Change in Sp02 within the first hour after starting treatment - One trial (Martinon-Torres 2008) failed todemonstrate a reduction in change in Sp02 - 24 participants - MD 1.10%, 95% CI -1.90 to 4.10, P= 0.47 Change in clinical score after 24 hours of heliox treatment - One trial (Liet 2005) failed to demonstrate a reduction in clinical score - 39 participants - MD -0.40, 95% CI -2.17 to 1.37, P = 0.66 Change in 02 needs after 24 hours of heliox treatment - One trial (Liet 2005) trial failed to demonstrate a reduction in O2 - 39 participants	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- MD -2%, 95% CI -13.40 to 9.40, P = 0.73 Change in C02 after 24 hours of heliox treatment - One trial (Liet 2005) failed to demonstrate a reduction in change in CO2 - 39 participants - MD 3 mmHg, 95% CI 0.17 to 5.83, P = 0.04 Adverse effects - No adverse effects reported related to heliox inhalation - One child included in the heliox group (Liet 2005) contracted both RSV and adenoviral respiratory tract infection, and died 38 days after the beginning of mechanical ventilation due to irreversible respiratory failure.	
Full citation Hollman,G., Shen,G., Zeng,L., Yngsdal-Krenz,R., Perloff,W.,	Sample size - 21 eligible infants admitted	Interventions - Use of bronchodilators was avoided if possible	Details Setting:	Results Protocol outcomes	Limitations Based on NICE appendix C checklist

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Zimmerman,J., Strauss,R., Helium-oxygen improves Clinical Asthma Scores in children with acute bronchiolitis, Critical Care Medicine, 26, 1731-1736, 1998 Ref Id 207111 Country/ies where the study was carried out USA Study type Randomised, double-blinded, controlled, crossover and Nonrandomised, prospective Aim of the study To determine the efficacy of a helium oxygen mixture in children admitted to the pediatric intensive care unit with acute respiratory syncytical virus (RSV) bronchiolitis Study dates Not reported	- 3 patients excluded: 1 for technical difficulties in setting up the gas delivery system and 2 for marked agitation - 18 studied - 13 randomised - 5 with severe bronchiolitis were intially given helium-oxygen Characteristics - Of the 13 randomised patients, 12 had clinical asthma scores <6 and one infant had a score of 7.5 but only mild signs of expiratory obstruction - To avert intubation five infants with severe bronchiolitis (clinical asthma score ≥6) were given helium-oxygen on admission at the discretion of the pediatric intensivist caring for the child (these infants were then scored at 20 minutes into helium-oxygen delivery) - 17 out of 18 infants had received bronchodilators before enrollment into the study - Only one infant with severe bronchiolitis	within 1 hour of beginning the study - After enrollment, patients received an air oxygen mixture delivered by non-rebreather reservoir mask to maintain oxygen saturation ≥93% - Placed on either a helium-oxygen mixture or an air-oxygen mixture for 20 minutes - 6 infants were randomised to receive helium-oxygen first - Nonrandomised infants received helium-oxygen as initial therapy as an attempt to avert intubation at discretion of pediatric intensivist, children in this subset with severe bronchiolitis were scored 20 minutes into heliox therapy - Gas delivery system consisted of three sources of gas flow: wall oxygen,	PICU at Univeristy of Wisconsin Children's Hospital Randomisation and concealment: - Random order determined by a coin toss - Study investigator measuring outcomes blinded to gas mixture - Blinding was maintained by covering the on-off valves to the air and helium sources using tape, such that the respiratory therapist was the only individual knowledgeable of its position - Study investigator was not present during gas changes Outcome measures: Modified Woods clinical asthmas score (M-WCAS), respiratory rate, heart rate and oxygen saturation recorded at the end of each 20 minute study period Statistical methods:	2. Need for high flow humidified oxygen, CPAP or mechanical ventilation - CPAP was administered to six children because of persistent severe respiratory distress - Only one infant required mechanical ventilation due to progressive respiratory insufficiency, this infant had coarctation of the aorta and was intubated for a total of 8 days, balloon angioplasty was performed on day 5 of intubation 5. Change in disease severity score (M-WACS) - Scores for the 13 randomised patients decreased an average of 0.46 during helium-oxygen administration p<0.05 (after calculated by NCC: 2.58) - Scores for the 18 patients overall decreased an average of 1.23 during	- Results presented in figures - Small sample size, not all randomised (18 enrolled, 13 randomised) - Three eligible patients were not enrolled in the study because of agitiation related to the face mask and technical difficulties - Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria - Air-oxygen and helium-oxygen mixtures not described (discussion sections refers to a 80% helium 20% oxygen mixture) - Nonrandomised severly ill infants treated with helium-oxygen at presentation at the dicretion of the pediatric intensivist to avoid intubation - 17 out of 18 enrolled infants received bronchodilators before admission to ICU and received nebulised albuterol as standard therapy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported by a grant from the University of Wisconsin General Clinical Research Centre	received a nebulised albuterol treatment within one hour of the study - Median age of the 18 infants was 2.5 months, range 3 weeks to 24 months - 11 infants had no underlying cardiac disease - 5 had underlying cardiac disease which consisted of coarctation of the aorta, aortic stenosis, cardiomyopathy, transposition of the great vessels after arterial switch procedure, and a surgically corrected complex congenital heart lesion - No infants had pulmonary artery hypertension - One infant had a history of laryngomalacia that had been surgically treated and had no signs of upper airway obstruction during the study - One infant had Treacher Collins syndrome but no history of upper airway problems - Mean M-WCAS for the 13 randomised infants was 3.04, range 1 to 7.5	wall air and 100% helium tank - Helium or air administration was accomplished by the respiratory therapist by adjusting a one-way valve located at the junction of the helium and air sources - An air-oxygen blender was adjusted to maintain a constant FI02 concentration - Gas flow rate was regulated through a standard pressure-compensated flow meter and delivered to the patient through a pediatric non-rebreather reservoir mask	- Paired data analysis using Wilcoxon signed rank test - Spearman's rank correlation coefficient used to assess change in clinical asthma score	helium-oxygen administration p<0.01 - Scores in patients placed on air-oxygen were virtually the same as the baseline scores - The order in which helium-oxygen was administered made no difference in responses - For infants with scores of <6 (n=12) a positive correlation (r=0.72) was observed between the score at baseline and the change in score during helium-oxygen administration p=0.009 - Helium-oxygen decreased scores to a greater extent in patients with moderate illness (scores 2.5 to 5) - Scores decreased by 2.67 in patients with severe bronchiolitis (n=6) during the helium-oxygen administration - Cochrane report:	- Wash-out period not described Other information - Clinical asthma score described in table 1. Based on cyanosis (oxygen saturation), inspiratory breath sounds, accessory muscles used, expiratory wheezing and cerebal funtion. Added mild categories for accessory mucles used and expiratory wheezing - One of the patients exlcuded because of agitation was intubated shortly after admission to ICU - All children were studied within 4 days of the start of respiratory symptoms. Except for one child who was hospitalised at the time of infection, all children were studied within 48 hours of admission to the hospital - 16 of the 18 infants required an FI02 of ≤0.35 during the study - FI02 concentrations of 0.40 to 0.45 were required

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Mean M-WCAS was 4.25 in the 18 patients overall, range 1 to 9 Inclusion criteria - Admitted to PICU with RSV bronchiolitis - RSV positive - Signs of lower respiraptory tract disease (tachypnea, wheezing, expiratory prolongation or rales) - Fraction of inspired oxygen (FI02) requirements <0.50 - Informed written parental consent Exclusion criteria - Intubated - Signs of upper respiratory airway obstruction			Heliox group (n=13) mean -0.46 SD 0.19 Control group (n=13) mean -0.04 SD 0.19 6. Change in O2 saturation - Oxygen saturation increased on average 1.5% (p<0.01) in randomised patients and 1.8% (p=0.02) in the patient population overall - No oxygen desaturations were encountered 7. Adverse effects None encountered Outcomes not reported: 1. Change in CO2 3. Time to return to oral feeding 4. Length of hospital stay	in two patients with severe disease - Standard therapy consisted of nebulised albuterol in all but one child, who had minimal signs of airway obstruction - Nine (50%) infants continued to receive helium-oxygen after the study period - The duration of administration ranged from 7 hours to 6 days
Full citation Kim,I.K., Phrampus,E., Sikes,K., Pendleton,J., Saville,A., Corcoran,T., Gracely,E., Venkataraman,S.,	Sample size - 2839 screened for enrollment - 2580 ineligible due to a WCAS <3	Interventions - Infants initially received nebulised albuterol treatment driven by 100% oxygen	Details Setting: Emergency department of a tertiary care hospital	Results Protocol outcomes 2. Need for high flow humidified oxygen,	Limitations Based on NICE appendix C checklist

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Helium-oxygen therapy for infants with bronchiolitis: a randomized controlled trial, Archives of Pediatrics and Adolescent Medicine, 165, 1115-1122, 2011 Ref Id 210353 Country/ies where the study was carried out USA Study type Randomised, single-blinded, controlled Aim of the study To compare nebulised racemic epinephrine delivered by 70% helium and 30% oxygen or 100% oxygen followed by helium-oxygen inhalation therapy via a high-flow nasal cannula vs oxygen inhalation via a high-flow nasal cannula in the treatment of bronchiolitis Study dates October 1, 2004 to May 31, 2008	- Eligibility criteria were met by 256 - 141 excluded for the following: Vapotherm issue (44), direct admission (41), corticosteriod use within 72 hours (28), declined to participate (15), chronic lung disease (13), the remaining 46 met other exclusion criteria - 72 randomised: 36 heliox group, 35 oxygen group - One heliox group infant opted out of the study and a second was intubated because of pneumonia - One oxygen group infant developed croup and was excluded - 69 completed: 34 heliox group, 35 oxygen group Characteristics Characteristic: heliox group; oxygen group n (%) - Mean age, months: 5.09; 6.11 - Median age, months: 3.78; 5.03 - Female: 11(32); 11(31) - Male: 23(68); 24(69)	- After randomisation received 11.25mg racemic epinephrine via a face mask - After nebulisation, humidified helium-oxygen or oxygen delivered by high-flow nasal cannula - Oxygen group started at a fraction of inspired oxygen of 100% and patients - Heliox group started at 70% helium and 30% oxygen - After 60 minutes of inhalation therapy, infants with an MWCAS ≥2 received a second delivery of nebulised racemix epinephrine followed by helium-oxygen or oxygen delivered by a high-flow nasal cannula - At 120 minutes randomised to gas via a high-flow nasal cannula 6l/min - At 240 minutes disposition (admit or discharge)	Randomisation and concealment: - Predetermined using a random number generator and occured in blocks of 10 - Assignments were kept in sealed opaque enevelopes and opened immediately after informed consent by the study investogator - The respiratory therapists were unmasked to the type of gas because they controlled and monitored the mixing of gases at the blender Outcomes measures: - Clinical assessments were perfomed at 0, 60, 120, 180 and 240 minutes - Clinical scores RDAI and M-WCAS - Wainwright readiness to discharge tool to determine length of stay: no supplemental oxygen for 10 hours, minimal or no chest retractions, and feeding adequately without the need for intravenous fluids	CPAP or mechanical ventilation Treatment failed in one patient in te heliox-group who required >50% oxygen, helium-oxygen and intubation, this patient was found to have a lobar pneumonia on chest radiography after enrollment 4. Length of hospital stay - Mean "readiness to discharge" for admitted patients: Heliox group 41.6 hours Oxygen group 43.0 hours p=0.87 - After discharge one infant in each group returned to the emergency department - (days calculated by NCC: heliox 1.73, control 1.79) 5. Change in disease severity score	- Results presented in figures, not all outcomes reported separately - Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria - Emergency department physicians were unmasked during the emergency department visit - Additional treatment: nebulised albuterol and racemic epinephrine - After 60 minutes if MWCAS≥2 infant received a second delivery of nebulised racemic epinephrine followed by helium-oxygen or oxygen by high-flow nasal cannula - Unclear if mean "readiness to discharge" for admitted patients only includes those admitted to the main hospital Other information - M-WCAS described in table 1, based on saturated oxygen, expiratory breathing,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Funded in part by an unrestricted research grant from Praxair Corporation	- RSV positive: 23(68); 17(49) - History of family asthma: 17(50); 17(49) - History of family atopy: 14(41); 9(26) - Parental smoking: 17(50); 16(46) - Albuterol use within 24 hours: 11(32); 14(40) - Duration of symptoms (mean/median), days: cough 1.59(1.50); 2.00(2.00) wheezing 1.03(1.00); 1.34(1.00) runny nose 1.50(1.50); 1.91(2.00) - At basline, the heliox group's mean MWCAS was higher by 0.17 than the oxygen group's mean MWCAS, 3.84 vs 3.67, p=0.16, analysis included this baseline difference Inclusion criteria - 2 to 12 months of age - Modified Woods clinical asthma score (M-WCAS) ≥3 - Bronchiolitis defined as: tachypnea, cough,	- Helium-oxygen or oxygen mixtures were administered from the nebuliser via a nonrebreathing face mask at 20ºC - Helium-oxygen concentrations of 70% helium and 30% oxygen were administered via a 280 regulator driven by a standardised pressure of 50 punds per square inch gauge - For nebulisation a small volume nebuliser with helium-oxygen flows of 16 l/min or oxygen flows of 10l/min was used - For inhalation via high-flow nasal cannula, all patients were started at 6l/min - Helium-oxygen flows were adjusted using a 1.6 correction factor because the flow meters were calibrated to oxygen	- Emergency department discharge was determined by an unmasked pediatric emergency medicine attending physician - Telephone follow-up at 24 hours and 7 days after hospital discharge, letters sent if no successful follow-up Statistical methods: - Categorical variables compared using chi squared or Fisher exact test - Mann-Whitney test to compare mean changes in MWCAS over time - Unpaired t tests - Two-way analysis of variance perfomed for both groups - Powered to detect a significant and clinically important difference in two clinical scores	- Mean change in MWCAS from baseline to 240 minutes or emergency department discharge was 1.84 for the heliox group compared with 0.31 for the oxygen group p<0.001 - (After calculated by NCC: heliox 2, oxygen 3.36) - Mean MWCAS was significantly improved for the heliox group compared with the oxygen group at 60 minutes (p=0.005), 120 minutes (p<0.001), 180 minutes (p<0.001) and 240 minutes (p<0.001) 7. Adverse effects: None encountered Outcomes not reported: 1. Change in CO2 3. Time to return to oral feeding 6. Change in O2 saturation	accessory muscles and cerebal function, score range 0 to 10, higher score implies increased severity - RDAI described in table 1, based on wheezing and retractions, used by Lowell et al., 1987 - 27 (79%) of infants in the heliox group and 24 (69%) of infants in the oxygen group were admitted to main hospital p=0.56 - Three infants in the heliox group and two infants in the oxygen group were admitted to a transitional intermediate intensive care unit - One infant in the oxygen group was admitted to PICU - No infants admitted to the intensive care unit in either group were intubated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	prolonged expiratory phase, wheezing, rales, chest retractions, and hyperinflation of lungs on chest radiography - Informed consent Exclusion criteria - Cyanotic heart disease - Lobar pneumonia on chest radiograophy - Croup - Foreign body aspiration - Preexisting chronic lung disease - Underlying chronic medical conditions - Supraventricular tachycardia secondary to albuterol or racemic epinephrine administration - Intolerance to the use of a nonrebreather face mask - Bronchodilator treatment within 2 hours of inititation of the study - Use of oral or parenteral corticosteriods within the preceeding 72 hours - History of persistent airway hyperactivity in the 3 months before the study	- Those patients who required >50% oxygen in the heliox group were designated as having received failed treatment, in these cases, administration of the helium-oxygen mixtures was stoppped and a rescue 100% oxygen therapy was started			
Full citation	Sample size	Interventions Additional treatment:	Details Setting:	Results Protocol outcomes	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Martinon-Torres,F., Rodriguez-Nunez,A., Martinon-Sanchez,J.M., Nasal continuous positive airway pressure with heliox versus air oxygen in infants with acute bronchiolitis: a crossover study, Pediatrics, 121, e1190-e1195, 2008 Ref Id 211702 Country/ies where the study was carried out Spain Study type Crossover Aim of the study To assess the effects on ventilation and clinical score of administering either heliox with nCPAP or air oxygen with nCPAP, as a rescue treatment in infants with refractory acute severe bronchiolitis Study dates February 2004 to February 2005	- 40 admitted to PICU with bronchiolitis - 12 enrolled Characteristics Characteristic: All infants (n=12) Mean±SD - 7 boys, 5 girls - Mean age, months: 4.7±2.5 - Median age 4 months, range 2 to 8 months - 2 infants had underlying heart disease - 2 infants had beeen preterm births without chronic lung disease - 1 infant had suffered from bronchiolitis in the preceding 2 months - M-WCAS: 7.7±1 - Transcutaneous C02 pressure (tcPCO2):61.6±10.5 mm Hg - Oxygen saturation: 88.6%±3.3% - nCPAP was set initally at 7.2cm H20 ± 1.2cm H20 to maintain oxygen saturation ≥94% with FI02 of 35%±6.2%	- All infants received one 3mg dose of nebulised l-epinephrine at the start of the study, it was then administered at 2 to 6 hour intervals at the discretion of one of three physicians - No patient received any nebulised medication other than epinephrine or systemic corticosteriod, either before enrollment or during the study - No patient required sedation to tolerate heliox and nCPAP - Nasal and pharyngeal secretions were deliberately removed before treatment in all of the patients Study treatment: - Heliox therapy included a mixture of 70% helium and 30% oxygen, warmed and humidified, administered at 10 to 15l/min through a	PICU Randomisation and concealment: - Predetermined balanced sequential allocation - Cochrane report coin tossing only for the first infant, then alternate inclusion in the treatment group or control group for the first cross-over study period - Patients were allocated sequentially to begin their treatment alternately with either heliox and nCPAP or air-oxygen and nCPAP - Not blinded Outcome measures: M-WCAS, tcPCO2, oxygen saturation and respiratory rate values were recorded after 30 minutes of treatment and afterward at hourly intervals for 6 and then at 8 hour intervals until the heliox-nCPAP was discontinued Statistical methods:	1. Change in CO2 - After treatment tcPCO2 levels were better with heliox-nCPAP than with air-oxygen-nCPAP: 51.9±8.7mm Hg vs 56.2±10.2mm Hg p<0.001 with falls from baseline 80% greater with heliox-nCPAP than with air-oxygen-nCPAP: 9.7±3.3mm Hg vs 5.4±1.6mm Hg Final tcPO2: - Air-oxygen, heliox second 52.3±11.2 - Heliox first, air-oxygen second 54.5±6.7 - p=0.694 Difference in tcPCO2: - Air-oxygen first, heliox second 11.3±3.7 - Heliox first, air-oxygen second 5.1±1.8 - p=0.008 Heliox group:	Based on NICE appendix C checklist - Not blinded - Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria - Inadequate randomisation, used a sequential allocation - Small sample sizes, only 12 out of 40 met inclusion criteria - Nebulised epinephrine at study entry, then at the discretion of physician - Wash-out period not described Other information - Total duration of heliox-nCPAP treatment was between 3 and 14 days, with a mean of 5.9 days SD 3.3 days - All patients recovered fully without sequelae continuing to develop normally over the follow-up period of 6 to 16 months - No patient required readmission to the PICU in the 3 months after discharge

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	Characteristic: air-oxygen group; heliox group; p value Mean±SD - Number: 6; 6 - Age, months: 5±2.9; 4.5±2.2; 0.749 - M-WCAS: 7.6±1.2; 7.7±1.0; 0.903 - Oxygen saturation: 87.8±3.7; 89.5±2.9; 0.409 - tcPCO2: 63.6±13.8; 59.6±6.4; 0.536 Inclusion criteria - Admitted to PICU for treatment of RSV severe acute bronchiolitis unresponsive to therapy - Diagnostic criteria of bronchiolitis included tachypnea, cough, prolonged expiratory time, wheezing, rales, chest retraction, and hyperinflation of the lungs on chest radiograph - 1 month to 2 years old - M-WCAS ≥5, oxygen saturation <92%, or transcutaneous C02 pressure (tcPCO2) >50mm Hg despite optimised supportive therapy	nonrebreathing reservoir face mask - A central wall supply of dry heliox with a fixed concentration was used - Infants received 30 minutes of treatment with each of heliox and air-oxygen via nCPAP - Inital optimal nCPAP was what could maintain oxygen saturation >94% using the lowest fraction of inspired oxygen (FI02), nCPAP ws increased at 1cm H20 increments to a maximum of 12cm H20 while the FI02 needed was above 0.4 by varying the flow of either air-oxygen or heliox - Minimum permitted levels were for nCPAP 5cm H20 and for FI02 0.3, after determining these values, the settings for nCPAP and FI02 were maintained	- Sample size of 12 patients using 95% CIs allowes >95% power in detecting a difference of ≥1 point on the M-WCAS scale and >70% power to detect a difference of ≥5mm Hg in tcPCO2 - Distribution of trial variables assessed using Shapiro-Wilk test - Differences between treatments analysed using paired t test - Data obtained after crossover phase analysed using Friedman test	- As first treatment 51.50±6.60 - As second treatment 52.30±11.20 - p=0.879 Air-oxygen group: - As first treatment 58.00±13.30 - As second treatment 54.50±6.70 - p=0.579 2. Need for high flow humidified oxygen, CPAP or mechanical ventilation No patients required endotracheal intubation or mechanical ventilation 5. Change in disease severity score (M-WCAS) - After treatment M-WCAS was better with heliox-nCPAP than air-oxygen-nCPAP: 5.58±0.9 vs 6.62±1.0 p<0.001 with falls from baseline almost double with heliox-nCPAP than with air-oxygen-nCPAP:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Nebulised epinephrine, and heliox therapy at 10 to 15l/min through a nonbreathing reservoir face mask for ≥1 hour - Written informed parental consent Exclusion criteria - Underlying chronic lung disease - During the crossover phase of the study, treatment with heliox-nCPAP or air-oxygen-nCPAP was considered to fail when oxygen saturation fell below 92% with nCPAP >10cm H20 and FI02 >0.6, tcPCO2 persistently >60mm Hg, if the infant could tolerate the procedure, or if the infant's clinical condition deteriorated acutely at any time during the study. In these circumstances, patients were to be returned to conventional therapy, reevaluated, and considered for endotracheal intubation and invasive mechanical ventilation	throughout the crossover phase of the study - After the experimental crossover study phase, infants either continued with or were started on heliox-nCPAP Human interface: Either nasal prongs or a nasal mask were selected for heliox and nCPAP delivery, determined by comfort, the size of the patient, and at the discretion of the physician		2.12±0.6 vs 1.08±0.4 Final score: - Air-oxygen first, heliox second 5.5±1 - Heliox first, air-oxygen second 6.5±0.8 - p=0.90 Difference in score: - Air-oxygen first, heliox second 2.1±0.6 - Heliox first, air-oxygen second 1.2±0.2 - p=0.12 Heliox group: - As first treatment 5.60±1.00 - As second treatment 5.50±1.00 - p=0.787 Air-oxygen group: - As first treatment 6.70±1.20 - As second treatment 6.50±0.80 - p=0.693 6. Change in O2 saturation - No statistically significant difference in oxygen saturation after	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				treatment between heliox-nCPAP and air-oxygen-nCPAP: 96.5±1.9% vs 95.5±1.7% p=0.170 Final oxygen saturation: - Air-oxygen first, heliox second 96.6±2.2 - Heliox first, air-oxygen second 96.1±2.1 - p=0.701 Difference in oxygen saturation: - Air-oxygen first, heliox second 8.8±5.1 - Heliox first, air-oxygen second 6.6±1.6 - p=0.361 Heliox group: - As first treatment 96.50±1.80 - As second treatment 96.60±2.25 - p=0.892 Air-oxygen group: - As first treatment 95.00±1.00 - As second treatment 96.10±2.10	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- p=0.271 7. Adverse effects None encountered Outcomes not reported: 3. Time to return to oral feeding 4. Length of hospital stay	
Full citation Liet,J.M., Millotte,B., Tucci,M., Laflammme,S., Hutchison,J., Creery,D., Ducruet,T., Lacroix,J., Canadian Critical Care Trials Group., Noninvasive therapy with helium-oxygen for severe bronchiolitis, Journal of Pediatrics, 147, 812-817, 2005 Ref Id 207442 Country/ies where the study was carried out Canada Study type Randomised, double-blinded, placebo-controlled, multicentre	Sample size - 157 screened for inclusion - Exluded because of intubation and institution of mechanical ventilation before PICU entry (n=83), age >9 months or weight >10kg (n=16), negative RSV (n=10), PICU stay >8 hours (8), uncorrected cyanotic heart disease or cardiac failure (8), unavaliable equipment (6), history of previous bronchiolitis episode (5), parents refused consent (4), bronchopulmonary dysplasia (4), pneumothorax (1) - 39 met eligibility criteria: 21 control group, 18 heliox group	Interventions - Plastic inflatable head hood used to administer gases - Heliox group: 78% helium, 22% oxygen - Control group: 78% nitrogen, 22% oxygen - The highest possible fraction of the study gas mixture was administered, and FI02 was reduced to the lowest level that allowed for adequate oxygenation (oxygen saturation ≥92%) - Other treatment was in accordance with a published	Details Setting: 4 PICUs Randomisation and concealment: - Patients, parents and all caregivers blinded, only respiratory therapists and data collectors not blinded - Randomisation schedule was prepared by the study statistician from a computeried random listing of the two treatment allocations stratified by centre - Allocation treatment was described in sealed opaque envelopes that were provided to each participating PICU and	Results Protocol outcomes Control group n=21 Helium group n=18 Mean±SEM 1. Change in CO2 Change in pC02 mm Hg: Control group -7±1 Heliox group -4±1 p=0.33 2. Need for high flow humidified oxygen, CPAP or mechanical ventilation Positive pressure ventilation*: Control group 4 (19%) Heliox group 4 (22%)	Limitations Based on NICE appendix C checklist - Inhaled bronchodilator therapy Other information - Mean FI02 was 62±5% during the first 24 hours after time zero - Inhaled corticosteriods were used once in the control group and never in the heliox group p=NS - Inhaled bronchodilator therapy was administered in 17 infants in the control group and 13 infants in the heliox group p=NS - Bacterial pneumonia occurred in 2 infants in the control group and in 3

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine whether noninvasive therapy using a helium-oxygen mixture reduced the use of positive-pressure ventilation in the treatment of respiratory failure caused by severe bronchiolitis Study dates October 2000 to May 2003 Source of funding Supported by Air Liquide Santé International, France	- 25 Sainte-Justine Hospital, 8 Centre Hospitalier Universitaire de Nates, 3 Centre Hospitalier Universitaire de Sherbrooke, 3 Children's Hospial of Eastern Ontario Characteristics Characteristic: control group; heliox group Mean±SEM or n(%) - Age, months: 1.0±0.2; 1.1±0.2 - Weight, kg: 4.2±0.3; 4.3±0.3 - Length of gestation, weeks: 38.8±0.6; 37.8±0.7 - Birth at <38 weeks gestation: 5(24); 6(37) - Female: 13(62); 7(44) - Congenital heart disease: 0(0); 1(6) - Other previous medical history: 3(14); 1(6) - History of asthma in parents: 9(43); 7(47) - History of smoking: 4(21); 8(53) - Duration of symptoms before PICU admission, days: 4.1±0.7; 3.5±0.4	practive guideline (Adcock et al., 1998) - The inflatable head hood and gas mixture studied were discontinued when oxygen requirements dropped to <25% (FI02≤25%) - Weaning should not begin until before 24 hours of therapy had elapsed - If the RDAI score points attributed to wheezing or retractions again increased to values >3 after initiation of weaning, then administration of the gas mixture selected at randomisation was resumed with the inflatable head hood - If FI02 requirements increased to the critical values cited earlier, then oxygen and air were administered using a hard plastic vent hood	given to a respiratory therapist who remained the only caregiver aware of the gas mixture administered to the patient - Respiratory therapists placed identical helium tanks at the bedside of all patients included in the study, and gas flow meters were covered with opaque bags to hide the dials Outcome measures: - Initiation of positive pressure ventilation, criteria included at least one of the following: clinical signs of extreme fatigue, severe hypoxemia (oxygen saturation <92% with FI02 ≥90%), severe respiratory acidosis (PCO2>70mm Hg with pH<7.25 that did not improve within a few hours) - Respiratory distress assessment instrument (RDAI) score 30 minutes after treatment and 2, 4, 8 and 24 hours and then twice daily whilst hospitalised in PICU	p=1 RR=1.17 95% CI 0.34 to 4.01 Endotracheal intubation: Control group 3 (14%) Heliox group 4 (22%) p=0.68 RR=1.56 95% CI 0.40 to 6.05 Noninvasive ventilation (mechanical ventilation through a nasopharyngeal tube) Control group 2 Heliox group 1 p=0.61 One infant in each group was mechanically ventilated using an endotracheal tube after noninvasive ventilation had failed * "This study did not detect any differences between the patients in the helium group and the control group with respect to the rate of positive-pressure ventilation (invasive or noninvasive)"	infants in the heliox group p=0.41 - Criteria for initiating ventilation were determined before the start of the trial and included at least one of the following: clinical signs of extreme fatigue, severe hypoxemia, and severe respiratory acidosis; ultimately the decision was left to the judgement of the physician - Time to intubation from study entry was 36±24 hours (range 2 to 108) in the heliox group and 26±15 hours (range 2 to 70) in the control group p=NS - For the 7 intubated infants the average FI02 requirement before intubation was 52±16% and the average RDAI score was 6±1 - Change in FI02 (%, mean±SEM): Control group 0±3 Heliox group -2±5 p=0.72

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Duration of hospital stay before PICU admission, days: 0.8±0.2; 1.4±0.3 - Duration of PICU stay before entry into study, hours: 2.1±0.1; 3.3±0.1 - Respiratory rate, per min: 53±1; 59±1 - Fraction of inspired oxygen (FI02), %: 40±1; 39±1 - Partial pressure of carbon dioxide (pC02) mm Hg: 65±1; 62±1 - pH: 7.28±0.01; 7.29±0.01 - RDAI: 8±0; 9±0 - Pediatric risk of mortality scores (PRISM): 8±1; 8±1 - Pediatric logistic organ dysfunction scores (PELOD): 1±1; 1±1 Inclusion criteria - <9 months old - Weight <10kg - Admitted to a PICU with a first episode of RSV bronchiolitis and signs of respiratory failure - Bronchiolitis defined as the presence of at least two fo the following: tachypnea, chest retractions, wheezing, and		- Oxygen saturation and FI02 noted on an houly basis - Changes in FI02, pC02 and RDAI are calculated as H0 value minus H24 value (or for children ventilated before H24, as H0 value minus the last value before mechanical ventilation) Statistical methods: - Expected the incidence rate of mechanical ventilation would decrease from 60% to 10% in the heliox group, sample size caluclated to be 18 in each group, type 1 error rate <5%(α=0.05) for a two sided test and a type 11 error <20%, power=80% - Fishers exact test n(%) or student t test mean±SEM	3. Time to return to oral feeding: Not reported 4. Length of hospital stay, days: Control group 3±1 Heliox group 6±3 p=0.27 5. Change in disease severity score, RDAI: Control group -2±0 Heliox group -2±0 p=0.76 6. Change in O2 saturation: Not reported 7. Adverse effects: - Six infants (2 control group, 4 heliox group) developed severe respiratory acidosis during the first 24 hours after randomisation. Among these six, 3 (1 control group and 2 heliox group) were never treated with mechanical ventilation	- Duration of study gas administration (hours, mean±SEM): Control group 31±10 Heliox group 30±5 p=0.90

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	hyperinflation on chest radiography - Respiratory failure defined by oxygen saturation <92% or Pa02 <40mm Hg Exclusion criteria - Pneumothorax or pneumomediastinum - Established diagnoses of cystic fibrosis, uncorrected cyanotic congential heart disease, cardiac failure, neuromuscular disease, or bronchopulmonary dysplasia - In PICU for >8 hours - Already received mechanical ventilation			- One infant in the heliox group contracted both RSV and adenoviral respiratory tract infection, died 38 days after the beginning of mechanical ventilation due to irreversible respiratory failure; helium therapy ws discontinued 4 days after randomisation	
Full citation Chowdhury,M.M., McKenzie,S.A., Pearson,C.C., Carr,S., Pao,C., Shah,A.R., Reus,E., Eliahoo,J., Gordon,F., Bland,H., Habibi,P., Heliox therapy in bronchiolitis: phase III multicenter double-blind randomized controlled trial, Pediatrics, 131, 661-669, 2013 Ref Id	Sample size - Assessed for eligibility 361 - Refused to participate 42 - Randomised 319 Heliox; control - Allocated to intervention: 160; 159 - Did not receive allocated treatment (withdrew consent or screening failure): 1; 2 - Protocol violation: 4; 4	Interventions - Gas A: Heliox 21% oxygen and 79% helium - Gas B: Airox (control): 21% oxygen and 79% nitrogen - Additional oxygen titrated via Y-connection tubing, resulting in 2 gas mixes: A or B with or	Details Setting Emergency department Randomisation and concealment - Patients allocated to Gas A or B by telephone using computer-stratified block-randomization - Parents/guardians and clinical/study personnel were blinded to randomization sequence	Results Protocol outcomes 2. Need for CPAP Heliox group: 24/140 (17%) Airox group: 27/141 (19%) Odds ratio (95% CI): 0.87 (0.47 to 1.60) P=0.78 4. Length of treatment	Limitations Based on NICE appendix C checklist - Inclusion criteria unclear - Unclear if all infants were tested for RSV - 35 infants did not complete treatment - Heliox group were younger at presentation - Time MWCAS was measured over not described

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
282261 Country/ies where the study was carried out United Kingdom and Australia Study type Multicenter, randomised, double-blind, controlled Aim of the study To compare efficacy of 2 treatment gases, Heliox and Airox (21% oxygen 1 79% helium or nitrogen, respectively), on length of hospital treatment for bronchiolitis Study dates Bronchiolitis seasons during 2005 to 2008 Source of funding Supported by a research grant from BOC Medical and equipment support from Fisher and Paykel Healthcare, EME (Electro-Medical Equipment) Carefusion, and Covidien Nellcor	- Withdrew consent: 2; 5 - Screening failure: 4; 7 - Clinician withdrawal: 1; 0 - Therapy pematurely disrupted: 8; 0 - Analysed: 140; 141 Characteristics Characteristic: heliox group (n=140); control group (n=141) Median (IQR) - Male:female ratio: 1:1.59; 1:1.52 - Gestation at birth, weeks: 39.0 (38.0to 40.0); 40.0 (38.0 to 40.0) - Age, weeks: 10.90 (5.85 to 25.50); 17.70 (6.80 to 29.40) - Weight, kg: 5.65 (4.34 to 7.70); 5.70 (4.40 to 7.70) - Temperature °C: 37.0 (37.0 to 38.0); 37.0 (37.0 to 38.0) - Heart rate beats per min: 152.0 (136.0 to 165.0); 148.5 (133.5 to 168.0) - Respiratory rate breaths per min: 56.0 (44.0 to 62.0); 53.0 (47.0 to 63.5) - Oxygen saturation: 92.0% (89.0 to 95.0); 91.0% (89.0 to 94.0)	without additional oxygen - Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask or a nasal cannula if the subject was FM intolerant - Gas A or B drove the CPAP device - Severe bronchiolitics received CPAP from the start - Intravenous fluids were preferred over nasogastric feeding in subjects with severe respiratory distress - Bronchodilator, epinephrine, or steroid use constituted trial protocol violations - Subjects had FM therapy for 30 minutes - If they were FM intolerant, the NC protocol was used - The optimum flow rate for trial gas was based on titration	and allocation, randomization codes remained secure until the end of the trial - Identical cylinders marked Gas A or B and identical equipment and connections were used Outcome measures Primary end point: total length of treatment (LoT) to alleviate hypoxia (SpO2 ≥93% in room air) and respiratory distress (minimal work of breathing). - LoT was calculated from the start to successful stop of the trial gas, as defined by clinical stability (minimal work of breathing and SpO2 $ 93%) for 1 hour breathing room air - Minimal work of breathing was qualified as having a normal respiratory rate, no cyanosis, no nasal flaring, no tracheal tug or grunting, no head bobbing, and no use of accessory muscles except for mild intercostal recessions	Mean LoT (95% CI), days; Median LoT (IQR), days All infants Heliox (n=140): 2.268 (1.993 to 2.544) 1.902 (1.083 to 3.173) Airox (n=141): 2.487 (2.180 to 2.794) 1.865 (1.114 to 3.344) P=0.41 NC (±CPAP) Heliox (n=40): 2.952 (2.335 to 3.569) 2.505 (1.210 to 4.315) Airox (n=47): 3.296 (2.643 to 3.948) 2.810 (1.450 to 4.780) P=0.53 FM (±CPAP) Heliox (n=44): 1.538 (1.234 to 1.841) 1.464 (0.852 to 1.947) Airox (n=40): 2.236 (1.744 to 2.728) 2.006 (0.928 to 2.859) P=0.03 5. Change in disease severity score	- Adverse effects not reported by treatment group - 87 infants received treatment via a nasal cannula and 84 infants received treatment via a facemask - Additional oxygen allowed if oxygen saturation <93% or worsening respiratory distress, unclear from the treatment protocol if this constituted CPAP Other information Treatment protocol - If subjects were hypoxic despite FM/NC, the CPAP protocol was started - FM tolerance was recorded at each assessment period, and FM tolerant was strictly defined as mask on all of the time except for or nasal suction and feeding - FM intolerance was defined as increasing agitation, distress, shaking head from side to side, and pulling the FM off the face for 30 minutes - NC was started in subjects who remained

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- MWCAS (maximum score): 11 3.0 (2.0 to 3.0); 3.0 (2.0 to 4.0) - NPA positive at presentation, n(%): 111 (79.3%); 116 (82.3%) Inclusion criteria - Pediatricians in the emergency departments or pediatric wards of participating hospitals, independent of the BREATHE study, assessed infants - Pediatricians clinically determined if the infants had a diagnosis of bronchiolitis (history of upper respiratory tract infection followed by wheezing, coughing, breathing difficulty, or chest crackles on auscultation) and if they needed hospitalization for respiratory distress or hypoxia (percutaneous oxygen saturation [SpO2] , 93% in room air) - Assessed premature infants at 12-months corrected age Exclusion criteria	against oxygen to achieve SpO2 ≥93% using the minimum flow of additional oxygen - For FM therapy, the maximum combined flow rate (gas A/B + oxygen) was 10 L/minute and for NC therapy it was 3 L/minute based on consensus of practice (see other information section for further treatment protocol information)	- Secondary end points: proportion of each treatment group needing CPAP and the change in respiratory distress over time measured by the Modified Wood's Clinical Asthma Score (MWCAS) Statistical methods - Analysis by intention to treat - Mann-Whitney test was used to compare LoT between treatment groups - Fisher's exact test was used to compare proportions progressing to CPAP in the two groups - Mixed Models methodology was used since it takes into account correlated measures - The square root transformation of MWCAS was used as the dependant variable for the modelling - Sample size: unpaired t test, power=80%, 2-sided α=5% to detect a 0.75 day LoT reduction, assumed a baseline	Results are Heliox effect relative to Airox over time Comparison Estimate of Fixed Effects (95% CI) All patients 20.1298 (20.202 to 20.057) P=0.01 FM relative to NC 0.093 (0.005 to 0.181) P=0.04 7. Adverse effects 6 infants required intubation: - CPAP equipment malfunction which precipitated emergency intubation (n=1) - Screening failure: suffered recurrent apnoea immediately following enrolment (n=2) - Intubated because of delay in high dependency bed availability (n=1) - Previously undetected patent	FM intolerant for 30 minutes - CPAP was started if subjects were hypoxic (SpO2 <93%) despite oxygen >4 L/minute via FM or >2 L/minute via NC - CPAP was discontinued once subjects were weaned to 1 to 2cmH2O pressure and were no longer hypoxic in fraction of inspired oxygen (FiO2) <0.4 for 1 hour - CPAP failure was defined as hypoxia (SpO2 <93%) despite 9cmH2O pressure and FiO2 0.6, whereupon subjects exited the trial. - Those subjects with severe bronchiolitis at presentation, who required immediate commencement of CPAP driven by gas A or B, followed the CPAP protocol Variations in treatment Received treatment via nasal cannula Heliox n=40 Airox n=47 Total n=87

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Imminent intubation - Oxygen saturation 93% despite 15 L/minute O2 via nonrebreathing facemask - Tracheostomy - Participation in another study in the previous 4 weeks - Salbutamol, epinephrine, or ipratropium therapy within 1 hour or systemic steroids within 4 hours of entry into the study - Bronchiolitis readmission within 24 hours of exit from BREATHE		mean LoT for bronchiolitis of 2.7 days (SD = 2.3 days), this required 298 subjects to be included	ductus arteriosus and referred to cardiologists (n=1) - One infant due to receive CPAP was intubated and transferred out because no high dependency bed available Outcomes not reported: 1. Change in CO2 3. Time to return to oral feeding 6. Change in O2 saturation	Received treatment via facemask Heliox n=44 Airox n=40 Total n=84

I.16 What is the efficacy of combined bronchodilator and corticosteroid therapy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Barlas,C., Kiper,N., Gocmen,A., Ozcelik,U., Dilber,E., Anadol,D., Ustacelebi,S., Haliloglu,M., Racemic adrenaline	Sample size Number randomised = 90 Number analysed= 90 Characteristics Age in months, mean (SD) 8.52 (0.59)	Interventions Group 1: Placebo - mist tent (nebulised) Dose - not reported Timing/duration - not reported Group 2: Albuterol (nebulised)	Details Consent Not reported in cochrane review from where the data for this study was extracted (see other information section) Setting	Results ALBUTEROL + PREDNISOLONE VERSUS PLACEBO 1. Hospital admission - day 1, n/N Albuterol + Prednisolone: 2/15	Limitations - Unclear method of randomisation and allocation concealment - No blinding - No missing outcome data reported Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and other treatment regimens in mild and moderate bronchiolitis: <ORIGINAL> HAFIF VE ORTA SIDDETTEKI BRONSIOLIT VAKALARINDA RASEMIK ADRENALIN VE DIGER TEDAVI YONTEMLERININ KARSILASTIRILMASI, Cocuk Sagligi Ve Hastaliklari Dergisi, 41, 155-165, 1998 Ref Id 240699 Country/ies where the study was carried out Turkey Study type Parallel design, multi-arm RCT (single-centre) Aim of the study Not reported in cochrane review from where the data for this study was extracted (see other information section)	Males, n (%) 50 (56) RSV +ve, n/N 19/57 Inclusion criteria - Age <24 months - 1st episode of wheezing - Clinical score between 4 to 10 Exclusion criteria - Patients with a history of premature heart disease, chronic heart and lung problems - Prior diagnosis of bronchial athma - Used bronchodilators and anti-inflammatory medications	Dose - 0.15mg/kg Timing/duration - every hour during the first 4 hours Group 3: Prednisolone (intravenous - systemic) Dose - 2mg/kg Timing/duration - single dose Group 4: Albuterol (nebulised) + Prednisolone (IV) Dose - 0.15mg/kg (albuterol) + 2mg/kg (prednisolone) Timing/duration: single dose for both interventions Group 5: racaemic adrenaline (nebulised) Dose - 0.1ml/kg Timing/duration: every 2 hours during the first 4 hours Group 6: budesonide (nebulised) Dose - 0.5mg Timing/duration: single dose Additional co-	Outpatients - emergency department/outpatient clinic Randomisation method Not reported in cochrane review from where the data for this study was extracted (see other information section) Concealment of allocation/blinding of treatment Not reported in cochrane review from where the data for this study was extracted (see other information section) Statistical methods Not reported in cochrane review from where the data for this study was extracted (see other information section)	Placebo: 3/15 Risk ratio (95% CI) : 0.67 (0.13 to 3.44) 2. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Clinical score - at 60 mins Albuterol + Prednisolone: 5.27 (2.28), n= 15 Placebo: 5.53 (1.96), n=15 Clinical score - at 120 mins Albuterol + Prednisolone: 4.40 (2.75), n= 15 Placebo: 4.80 (2.54), n=15 Clinical score - at 4 hours Albuterol + Prednisolone: 4.08 (3.25), n= 15 Placebo: 5.00 (2.31), n=15 3. Change in O2 saturation, mean (SD) Oxygen saturation - at 60 mins Albuterol +	- This study was published in Turkish and so the data has been extracted from the Cochrane review which included translated data - Fernandes 2013 - Data for other relevant comparisons in this study was not reported in the cochrane review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported in cochrane review from where the data for this study was extracted (see other information section) Source of funding Not reported		interventions for all groups - not reported		Prednisolone: 95.53 (2.00), n=15 Placebo: 95.33 (1.99), n=15 Oxygen saturation - at 120 mins Albuterol + Prednisolone: 95.47 (1.88), n=15 Placebo: 95.6 (1.95), n=15 Oxygen saturation - at 4 hours Albuterol + Prednisolone: 95.08 (1.75), n=15 Placebo: 95.62 (1.89), n=15 ALBUTEROL + PREDNISOLONE VERSUS ALBUTEROL 1. Hospital admission - day 1, n/N Albuterol + Prednisolone: 2/15 Albuterol: 2/15 2. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Clinical score - at 60 mins	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Albuterol + Prednisolone: 5.27 (2.28), n=15 Albuterol: 4.0 (1.73), n=15 Clinical score - at 120 mins Albuterol + Prednisolone: 4.40 (2.75), n=15 Albuterol: 2.85 (1.77), n=15 Clinical score - at 4 hours Albuterol + Prednisolone: 4.08 (3.25), n=15 Albuterol: 1.64 (1.75), n=15 3. Change in O2 saturation, mean (SD) Oxygen saturation - at 60 mins Albuterol + Prednisolone: 95.53 (2.00), n=15 Albuterol: 94.47 (2.92), n=15 Oxygen saturation - at 120 mins Albuterol + Prednisolone: 95.47 (1.88), n=15	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Albuterol: 95.31 (1.55), n=15 Oxygen saturation - at 4 hours Albuterol + Prednisolone: 95.08 (1.75), n=15 Albuterol: 95.36 (1.29), n=15 ALBUTEROL + PREDNISOLONE VERSUS PREDNISOLONE 1. Hospital admission - day 1, n/N Albuterol + Prednisolone: 2/15 Albuterol: 3/15 2. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Clinical score - at 60 mins Albuterol + Prednisolone: 5.27 (2.28), n=15 Prednisolone: 5.40 (1.92), n=15 Clinical score - at 120 mins Albuterol + Prednisolone: 4.40	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(2.75), n=15 Prednisolone: 4.27 (2.02), n=15 Clinical score - at 4 hours Albuterol + Prednisolone: 4.08 (3.25), n=15 Prednisolone: 3.57 (2.41), n=15 3. Change in O2 saturation, mean (SD) Oxygen saturation - at 60 mins Albuterol + Prednisolone: 95.53 (2.00), n=15 Prednisolone: 95.07 (1.62), n=15 Oxygen saturation - at 120 mins Albuterol + Prednisolone: 95.47 (1.88), n=15 Prednisolone: 95.07 (1.67), n=15 Oxygen saturation - at 4 hours Albuterol + Prednisolone: 95.08 (1.75), n=15 Prednisolone: 95.14 (1.56), n=15	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bentur,L., Shoseyov,D., Feigenbaum,D., Gorichovsky,Y., Bibi,H., Dexamethasone inhalations in RSV bronchiolitis: a double-blind, placebo-controlled study, Acta Paediatrica, 94, 866-871, 2005 Ref Id 210130 Country/ies where the study was carried out Israel Study type Randomised, double-blinded, placebo-controlled trial Aim of the study To evaluate the effect of inhaled dexamethasone on hospitalisation for RSV bronchiolitis Study dates	Sample size - 61 enrolled - Dexamethasone + epinephrine n= 29 - 0.9% saline + epinephrine: n=32 Characteristics Females/males, n Dexamethasone + epinephrine: 15/14 0.9% saline + epinephrine: 18/14 Age in months, mean (SEM) Dexamethasone + epinephrine: 3.3 (2.5) 0.9% saline + epinephrine: 3.8 (2) Prematurely born, n Dexamethasone + epinephrine: 7 0.9% saline + epinephrine: 6 02 saturation at admission %, mean (SEM) Premature infants - dexamethasone + epinephrine: 85.7 (25.2), 0.9% saline + epinephrine: 18.6 (84.6)	Interventions Dexamethasone + epinephrine*: 0.25mg inhaled dexamethasone and 1ml epinephrine 0.9% saline + epinephrine*: 0.5ml 0.9% saline and 1ml epinephrine (total volume 2ml completed with 0.9% saline) - Solutions given via a face mask, every 6 hours throughout the hospitalisation period - Nebulised solutions given with 100% oxygen at a flow of 5l/min - Nebulisation therapy continued until discharge** *Though the study arms have been referred to as the dexamethasone group and 0.9% saline group in the study itself, both groups received these treatments in combination with epinephrine and	Details Consent Informed consent obtained Setting Inpatient Randomisation method In blocks of 10 (five saline/five dexamethasone) Concealment of allocation/blinding of treatment The hospital pharmacist prepared the solutions, both in identical containers and indistinguishable to researchers, double-blind study Statistical methods - Sample size calculation: a sample size of 20 patients per group would be required to detect a clincal score change of SD 1, α=0.05, two-tailed test, power=80% - Intention to treat analysis: not reported - ANOVA measures and Spearman rank	Results 1. Hospital admission rate Subjects were inpatients so this outcome has been reported as patients with recurrent hospitalizations, n/N Dexamethasone + epinephrine: 12/29 0.9% saline + epinephrine: 14/32 p=NS 2. Length of hospital stay in days, (Mean±SEM) Prematurely born - dexamethasone + epinephrine: 6.5 (1.7) n=6, 0.9% saline + epinephrine: 9.1 (1.9) n=7, p=0.018 Full-term infants - dexamethasone + epinephrine: 5.2 (1.8) n=23, 0.9% saline + epinephrine: 5.5 (1.9) n=25, p=NS 3. Change in disease severity score at 1 to 7 days after starting treatment, mean	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - Number of patients presenting to hospital with bronchiolitis who did not meet inclusion criteria not reported - Some outcomes specified in methods not reported in results Other information - Scoring system based on clinical and oximetry results and assigned 0 to 2 points for each variable (maximum total of 10 points), with increasing severity receiving a higher score. Variables incoporated in this scoring system included respiratory rate, wheezing, retraction, general condition and oxygen saturation.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
September 2002 to March 2003 Source of funding The authors acknowledge the statistical contribution of Michael Huerta	Full-term infants - dexamethasone + epinephrine: 86 (18), 0.9% saline + epinephrine: 88 (15) Clincal score at admission, mean (SEM) Dexamethasone + epinephrine: 8.2 (1.1) n=29 0.9% saline + epinephrine: 8 (1.1) n=32 p= NS Inclusion criteria - Aged 3-12 months diagnosed with bronchiolitis* - First episode of wheezing and dyspnea - RSV antigen detected by ELISA - Parental signature of informed consent *Bronchiolitis not clearly defined Exclusion criteria - Previous treatment with systemic steroids - Administration of inhaled beta-2 agonists or inhaled steroids prior	therefore the arms have been treated as dexamethasone + epinephrine versus 0.9% saline + epinephrine for the purpose of this review Additional treatment - Supplemental oxygen was provided in the interval for any patient with an initial oxygen saturation ≤92% in room air as measured by pulse oximetry - If respiratory rate >60 breaths/min, oral feeding was stopped and intravenous fluids were started **Criteria for discharge - Evaluated by a senior physician who was part of the study - No dyspnea, at least 10 hours without the need for oxygen support and oral feeding without the need for IV fluids	correlation test for evaluating the effects. Differences between groups analysed using a proportionality test for chi-squared analysis of contingency tables for non-parametric variables and unparied t-test for parametric. For survival analysis, discharge rate expressed by the proportion of children in hospital was analysed using Kaplan-Meyer and log-rank test. Follow-up Outcomes and clinical status documented every 8 hours. Subjects re-evaluated by a pediatric pulmonologist at 1 week, 1 month and 3 months post-discharge.	(SEM) Clinical score at discharge - dexamethasone + epinephrine: 2.1 (0.5) n=29, 0.9% saline + epinephrine: 2.2 (0.4) n=32, p=NS 4. Change in O2 saturation No significant statistical differences between the groups was noted - data not presented in paper 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Adverse effects (including mortality) Not reported 8. Need for/use of feeding support (tube feeding, IV fluids) Reported as duration of IV fluids in hours, mean (SEM) Dexamethasone +	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	to admission - Other chronic diseases, e.g. bronchopulmonary dysplasia (BPD), cystic fibrosis (CF), and congenital heart disease			epinephrine: 78.6 (39.7), n=29 0.9% saline + epinephrine: 88.5 (35.6), n=32 p= NS	
Full citation Berger,I., Argaman,Z., Schwartz,S.B., Segal,E., Kiderman,A., Branski,D., Kerem,E., Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up, Pediatric Pulmonology, 26, 162-166, 1998 Ref Id 206370 Country/ies where the study was carried out Israel Study type Randomised, double-blinded, placebo-controlled study	Sample size - 42 enrolled, 38 completed the full 3 days of treatment - 20 prednisone + albuterol, 18 placebo + albuterol Characteristics Age in months, mean (SD) Prednisone + albuterol: 5.2 (0.7) Placebo + albuterol: 4.8 (0.9) Duration of illness in days, mean (SD) Prednisone + albuterol: 4.2 (0.4) Placebo + albuterol: 3.4 (0.4) History of apnea, n/N Prednisone + albuterol: 0/20 Placebo + albuterol: 2/18	Interventions - Patients recieved either oral prednisone + albuterol* (1mg/kg body weight per dose) or placebo + albuterol*, twice a day for 3 days - All patients received inhaled albuterol solution 0.03 ml/kg/dose (0.15mg/kg/dose) every 4-6 hours *Though the study arms have been referred to as the prednisone group and the placebo group in the study itself, both groups received these treatments in combination with inhaled albuterol and therefore the arms	Details Consent Written informed consent obtained from parents Setting Outpatients - pediatric emergency room Randomisation method Each patient was randomly assigned by a research pharmacist according to a standardised statistical method - details not reported Concealment of allocation/blinding of treatment - The solutions provided by the pharmacist appeared identical - Neither the investigators nor the families were aware of treatment assignments	Results 1. Hospital admission rate (day1), n/N (%) Prednisone + albuterol: 5/20 (25) Placebo + albuterol: 2/18 (11) 2. Length of hospital stay in days, mean (SD) Prednisone + albuterol: 5 (2.105**), n=5 Placebo + albuterol: 8* (2.828**), n=2 *Mean calculated by NCC-WCH technical team based on data reported in the article **SDs extracted from Cochrane review (Fernandes 2013) as not reported in the article itself	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - Method of randomisation not described - 28 (73.7%) of the 38 infants enrolled in the study were available for a telephone interview, 14 out of 20 for the prednisone + albuterol group and 14 out of 18 for the placebo + albuterol group - The parents recall 2 years after epidose of bronchiolitis may be inaccurate - 4 dropouts: unclear which arm they were assigned to Other information - Clinical scoring system based on respiratory rate, accessory

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the short-term and long-term effects of oral corticosteroids in infants suffering from mild to moderate bronchiolitis Study dates Winter months 1993-1994 Source of funding Not reported	Pretrial medications - albuterol, n/N Prednisone + albuterol: 7/20 Placebo + albuterol: 5/18 Pretrial medications - antibiotics, n/N Prednisone + albuterol: 4/20 Placebo + albuterol: 3/18 Inclusion criteria - Infants aged 1 to 18 months presenting with bronchiolitis* - All eligible infants were enrolled regardless of whether or not they required hospitalisation** * Bronchiolitis defined as the first episode of wheezing assoiated with low grade fever, rhinitis, tachypnea, and increased respiratory effort in a previously healthy infant during the winter months **The decision to hospitalize was usually	have been treated as prednisone + albuterol versus placebo + albuterol for the purpose of this review Additional treatments - Supportive treatment, such as oxygen supplementation and hydration, was given as necessary	- The examiner was blind to what treatment the patient had received Statistical methods - Sample size calculation: minimum of 15 patients in each group to detect a difference of 2 SD in the mean score between the groups at a significance level of <0.05, power =90% - Intention to treat analysis: not reported - t-test and Chi-square statistic were used to compare the parametric variables - Mann-Whitney U test with a z-statistic was used to analyse the nonparametric variables Follow-up - The same examiner evaluated all patients after 3 days of treatment - One week after the initiation of therapy, symptoms were reassessed either in person (for children still hospitalised) or by the telephone by the same investigating physician - Two years after the episode of bronchiolitis, a	3. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Reported as mean change in total score after 3 days of therapy Prednisone + albuterol: 2.45 (0.12), n=20 Placebo + albuterol: 2.45 (0.3), n=18 4. Change in O2 saturation, mean (SD) Reported as change after 3 days of therapy Prednisone + albuterol: 1 (0.5), n=20 Placebo + albuterol: 0.8 (0.3), n=18 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Reported as need for supplemental oxygen Prednisone + albuterol: 5/20 Placebo + albuterol:	muscle use and wheezing, scale 0 to 9 points

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	made within 4 hours after initiating therapy and was based solely on the infant's clinical condition. An attending physician in the emergency room who was not involved in the study made the decision. Exclusion criteria - Chronic cardiopulmonary disease, including asthma - Proven or suspected acute bacterial infection - Previous treatment with corticosteroids by any route - The presence of symptoms for more than 7 days - The presence of fever higher than 38.5°C - Severe bronchiolitis (respiratory distress, a total clinical score>7, or an infant requiring immediate medical care, including oxygen supplementation) - Children who vomited the syrup or did not		telephone interview was conducted by the same investigator	2/18 7. Adverse effects (including mortality) Not reported 8. Need for/use of feeding support (tube feeding, IV fluids) Not reported	

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	receive the nine doses of medication or did not use the inhalations according to the parent's report				
Full citation Goebel,J., Estrada,B., Quinonez,J., Nagji,N., Sanford,D., Boerth,R.C., Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis, Clinical Pediatrics, 39, 213-220, 2000 Ref Id 206952 Country/ies where the study was carried out USA Study type Double-blinded, randomised controlled trial Aim of the study To evaluate combination therapy of mild to	Sample size - 51 randomised, 3 excluded from analysis: medical noncompliance, initally unrecognised history of reactive airway disease or prematurity - 48 subjects: 24 prednisolone + albuterol, 24 placebo + albuterol - Complete follow-up: 17 prednisolone + albuterol, 15 placebo + albuterol Characteristics Age in months, median (range) Prednisolone + albuterol: 4.0 (0 to 13) Placebo + albuterol: 4.5 (0 to 16) Sex, female/male, n Prednisolone + albuterol: 6/18 Placebo + albuterol: 8/16	Interventions - All patients received albuterol therapy continued at 0.3mg/kg/day divided t.i.d by mouth or, when available, 0.15mg/kg/dose q.i.d by nebulizer, as was the case in the small number of hospitalized patients and in one outpatient who could use his sibling's nebulizer - Additionally, the patients were randomized to a 5 day oral course of either prednisolone* (2mg/kg/day divided by b.i.d.) or equal volumes per kg body weight of placebo* - Both treatments were formulated by the hospital pharmacist: 100ml each of water and	Details Consent Informed consent obtained Setting Outpatients: pediatric emergency department or children's clinic Randomisation method Computer generated randomisation Concealment of allocation/blinding of treatment Placebo was similar in appearance and taste, identical medication bottles numbered consecutively according to randomisation list. All study physicians, patients, and caregivers were blinded in regard to treatment. Statistical methods - Bronchiolitis scores on days 0, 2, 3 and 6 compared by one-way analysis of variance for repeated measures	Results 1. Hospital admission rate, n/N At enrollment Prednisolone + albuterol: 4/24 Placebo + albuterol: 2/24 [Four patients in the prednisolone group and two in the placebo group were hospitalised at enrollment for oxygen saturation in room air below 90% (three patients), young age with recent disease onset by history (two patients), and a history of possible apnea (one patient)]. 2. Length of hospital stay in days, mean (SD) Mean initial hospitalisation per patient (hospitalised at the time of	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - Nine patients in the placebo + albuterol group and seven in the prednisolone + albuterol group had incomplete follow-up: missing outcome data - Some patients were hospitalised later during the study - time point not reported - Number of physicians not reported Other information - Bronchiolitis score based on respiratory rate, flaring or retractions, oxygen saturation and wheezing - a maximum score of 12 - Though admission rates later during the study period reported, the time point is not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
moderate bronchiolitis with bronchiodilators and corticosteroids Study dates Not reported Source of funding Not reported	Nasopharyngeal wash positive for RSV, n/N Prednisolone + albuterol: 11/24 Placebo + albuterol: 15/24 Hospitalised at enrollment, n/N Prednisolone + albuterol: 4/24 Placebo + albuterol: 2/24 Initial bronchiolitis score, mean (SD) Prednisolone + albuterol: 4.5 (1.7) Placebo + albuterol: 4.9 (1.4) The above characteristics are for all 51 patients randomised Inclusion criteria - ≤ 23 months of age brought to the Pediatric Emergency Department or Children's Clinic of the University of South Alabama - Symptoms of viral repiratory tract infection (rhinorrhea, cough, or	glycerin with 5ml of cherry-flavoured Kool-Aid and 100mg of quinine *Although the study arms have been referred to as the prednisolone and placebo group in the study itself, both groups received these treatments in combination with albuterol therapy and therefore the arms have been treated as prednisolone + albuterol versus placebo + albuterol for the purpose of this review	(Student-New-man-Keuls method) - Scores on days 0 and 2 analysed by analysis of variance in a three-way factorial design with RSV-positive versus RSV-negative status and treatment with predinsolone versus placebo of the patients as the other factors Follow-up - Visits with a study physician on days 2 and 3 and after cessation of therapy on day 6 - Patients whose disease had not resolved by day 6 of the study were followed up until complete convalesence Setting: Infants managed predominantly as outpatients. Randomisation and concealment: - Computer generated.	enrollment)* Prednisolone + albuterol: 2.3 (1.7*), n=4 Placebo + albuterol: 2.5 (1.7*), n=2 *SDs extracted from Cochrane review (Fernandes 2013) as not reported in the study itself 3. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Reported as bronchiolitis score from 32 patients with complete follow-up Prednisolone + albuterol: day 0 - 4.7 (1.9), day 2 - 2.6 (1.5), n=17; p<0.05 Placebo + albuterol: day 0 - 4.9 (1.4), day 2 - 3.9 (1.5), n=15 ; p>0.05 4. Change in O2 saturation Not reported 5. Duration of cough Not reported 6. Need for CPAP	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	fever up to 38.5ºC rectally) - During the fall and winter of two consecutive years - First time wheezing that did not clear completely after one dose of nebulized albuterol (0.15mg/kg body weight) *Bronchiolitis definition unclear Exclusion criteria - History of immune defect, neurologic disease with possible aspiration, gastroesophageal reflux, congenital or acquired chronic heart or lung disease, mechanical ventilation, or birth before 36 weeks gestational age - Fever over 38.5°C rectally, antibiotic therapy within 1 week before enrollment or antipyretic therapy within 8 hours before enrollment - Evidence of concomitant bacterial infection on physical examination or any lab		- All study physicians, patients, and caregivers were blinded in regard to treatment. Outcome measure: - Clinical status, using a modification of the bronchiolitis scoring system published by Tal et al. (based on respiratory rate, retractions, oxygen saturation and wheezing). - Hospitlaisation. Statistical methods: - Bronchiolitis scores on days 0, 2, 3 and 6 compared by one-way analysis of variance for repeated measures (Student-New-man-Keuls method).	ventilation Not reported 7. Adverse effects (including mortality) One patient in the prednisolone + albuterol group appeared "jittery" by caretakers at times after enrollment, this resolved after a decrease in the albuterol dose	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	or radiographic studies (if obtained) - Emesis precluding the oral administration of medications - Inital bronchiolitis score less than 2 or greater than 9		- Scores on days 0 and 2 analysed by analysis of variance in a three-way factorial design with RSV-positive versus RSV-negative status and treatment with predinsolone versus placebo of the patients as the other factors. Follow-up: - Visits with a study physician on days 2, 3 and 6. - Patients whose disease had not resolved by day 6 of the study were followed up until complete convalesence.		
Full citation Klassen,T.P., Sutcliffe,T., Watters,L.K., Wells,G.A., Allen,U.D., Li,M.M., Dexamethasone in salbutamol-treated inpatients with	Sample size - 102 subjects approached - 30 subjects did not participate due to parental refusal to give consent, a communication barrier and an absent parent	Interventions Dexamethasone (oral) + salbutamol* - 0.5mg/kg as the first dose and 0.3mg/kg for the next 2 mornings, or until the patient was discharged from	Details Consent Informed written consent obtained Setting Inpatients - inpatient wards of a pediatric tertiary hospital	Results 1. Hospital admission rate*, n/N (%) The subjects of this study were already inpatients of a hospital and so this outcome is reported as readmission rate	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - Bronchiolitis not clearly defined - 5 postrandomisation exclusions

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
acute bronchiolitis: a randomized, controlled trial, Journal of Pediatrics, 130, 191-196, 1997 Ref Id 210267 Country/ies where the study was carried out Canada Study type Randomised, double-blind placebo controlled trial Aim of the study To determine the clinical benefit of oral dexamethasone in children admitted to the hospital with bronchiolitis treated with nebulized salbutamol Study dates February 1st 1993 to April 30th 1995; patients enrolled only from November 1 to April	or guardian - A further 5 subjects were excluded as they did not meet the eligibility criteria - Included in the analysis were 35 subjects in the dexamethasone + salbutamol group and 32 subjects in the placebo + salbutamol group Sample size at different time points in the study, n: - At baseline - dexamethasone + salbutamol: 35, placebo + salbutamol: 32 - At 12 hours - dexamethasone + salbutamol: 35, placebo + salbutamol: 31 - At 24 hours - dexamethasone + salbutamol: 33, placebo + salbutamol: 28 - At 36 hours - dexamethasone + salbutamol: 30, placebo + salbutamol: 25 - At 48 hours	hospital, whichever occurred first - Clear 70% sucrose solution and dexamethasone sodium phosphate intravenous solution Placebo + salbutamol* - Equal volume and appearance to dexamethasone - 70% sucrose solution *Although the study arms have been referred to as dexamethasone and placebo in the study itself, all patients received these treatments in combination with nebulized salbutamol at 0.15mg/kg every 4 hours for the first 24 hours and an oxygen concentration of 35% in a plastic tent. Therefore, the groups have been treated as dexamethasone + salbutamol versus placebo + salbutamol for the purpose of this review.	Randomisation method Computer generated random numbers, stratification by age (younger than 6 months or older than 6 months) Concealment of allocation/blinding of treatment All study medications were prepared and labelled with a study number. The randomisation list was concealed until the study was complete (details not reported), double blind study. Statistical methods - Sample size calculation: to detect a difference of 2 points in the RDAI score, the number required per group was 37 patients with a statistical power of 90%, α=0.05, two-sided test and standard deviation of 2.64. - Intention to treat analysis: not reported - Dichotomous events were analysed by using the chi-square test or the Fisher exact test as	to the hospital Dexamethasone + salbutamol: 4/35 (11) Placebo + salbutamol: 1/32 (3) p= 0.36 2. Length of hospital stay in hours, median (95% CI) Dexamethasone + salbutamol: 57 (38 to 76), n=35 Placebo + salbutamol: 48 (42 to 54), n=32 p= 0.19 3. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Reported as mean change in respiratory distress assessment index score (RDAI) from baseline to the following time points At 12 hours Dexamethasone + salbutamol: -1.3 (2.0), n= 35 Placebo + salbutamol: -1.0 (1.8), n=31 p=0.51 At 24 hours	and 1 child discharged with missing outcome data Other information - The RDAI is an ordinal scale from 0 to 17 that measures expiratory wheezing, inspiratory wheezing, location of wheeze and supraclavicular, intercostal, and subcostal indrawing - The standard study protocol included inhaled salbutamol every 4 hours for the first 24 hours. Thereafter, all treatment decisions were made by the treating physician. However, there were no significant differences between the groups with regard to the number of salbutamol inhalations after 24 hours of standard treatment. Additional treatment - 13 patients in the placebo + salbutamol group and 10 in dexamethasone + salbutamol group received antibiotics during their hospital say, p=0.30 - After the first 24 hours of standard treatment, there were no significant differences between the 2 groups with regard to the number of salbutamol inhalations - 5 patients in the placebo + salbutamol group and 3 in dexamethasone +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
30 during peak RSV season Source of funding Supported by a grant from Physicians Services	- dexamethasone + salbutamol: 23, placebo + salbutamol: 20 - At 60 hours - dexamethasone + salbutamol: 17, placebo + salbutamol: 11 Characteristics Age in years, mean (95% CI) Dexamethasone + salbutamol: 0.39 (0.30 to 0.48) Placebo + salbutamol: 0.39 (0.30 to 0.47) Male, n (%) Dexamethasone + salbutamol: 22 (63) Placebo + salbutamol: 15 (47) RSV infection, n (%) Dexamethasone + salbutamol: 30 (86) Placebo + salbutamol: 28 (88) Bronchodilator on admission to study, n (%) Dexamethasone + salbutamol: 9 (26) Placebo + salbutamol:	Additional treatment Antibiotics, intravenuous hydration, oxygen supplementation, hydrocortisone, prednisone - see other information section for number of subjects who received such medications. After the first 24 hours of standard treatment, all treatment decisions were made by the treating physician.	appropriate. A Kaplan-Meier survival analysis was applied to the length of hospital stay and significant differences were analysed by the log rank test. Follow-up All outcome measures were recorded twice daily for 4 days and then once daily until the child was discharged from hospital. Measurements were taken at least 1 hour after the last salbutamol dose and after the child had been taken out of the oxygen tent for 10 minutes. Patients contacted at 1 week after discharge from the hospital regarding subsequent visits to physician or hospitalisation.	Dexamethasone + salbutamol: -1.4 (2.0), n=33 Placebo + salbutamol: -1.6 (2.3), n=28 p=0.74 4. Change in O2 saturation Reported as mean change in oxygen saturation from baseline to the following time points, mean (SD) At 12 hours Dexamethasone + salbutamol: 0.7 (2.5), n=35 Placebo + salbutamol: 1.4 (2.8), n=31 p=0.29 At 24 hours Dexamethasone + salbutamol: 1.0 (3.6), n=33 Placebo + salbutamol: 1.9 (3.1), n=28 p= 0.28 5. Duration of cough Not reported 6. Need for high flow	salbutamol group received intravenous hydration during their hospitalisation, p=0.46. - One patient in the placebo + salbutamol group received intravenously administered hydrocortisone, and one patient in the dexamethasone + salbutamol group received orally administered prednisone after the three doses of dexamethasone

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	6 (19) Oxygen saturation with room air, mean (95%CI) Dexamethasone + salbutamol: 92.9 (92.0 to 93.9) Placebo + salbutamol: 93.0 (92.2 to 93.8) Respiratory distress assessment index (RDAI) score Dexamethasone + salbutamol: 6.6 (6.0 to 7.3) Placebo + salbutamol: 6.2 (5.6 to 6.7) Inclusion criteria - Patients who had, for the first time, a short-term (fewer than 7 days) episode of wheezing and had evidence of a viral infection (rhinorrhea or temperature >37.5 degrees) and who were admitted to inpatient wards meeting the above criteria - Children aged 6 weeks to 15 months - Oxygen saturation			humidified oxygen, CPAP or mechanical ventilation Not reported 7. Adverse effects (including mortality), n - Pneumonia developed in one subject from each group 8. Need for/use of feeding support (tube feeding, IV fluids) Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	less than 95% on admission to hospital - RDAI score greater than 6 Bronchiolitis definition unclear. Exclusion criteria - An underlying disease that might affect cardiopulmonary status (eg: cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, immunodeficiency) - Asthma that had been diagnosed by a physician - Wheezing or cough or both that had previously been treated with bronchodilators (not including the current acute episode) - Treatment with steroids within 2 weeks - History of adverse reactions to steroids				
Full citation Kuyucu,S., Unal,S., Kuyucu,N., Yilgor,E., Additive effects of	Sample size - 90 enrolled the study - 21 did not come to control visits on either the 24th hour, or fifth	Interventions 1. Epinephrine and dexamethasone 2. Salbutamol and	Details Consent Informed consent obtained	Results 1. Hospital admission rate None of the patients in any group required	Limitations Based on NICE guidelines manual 2012: Appendix C:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis, Pediatrics International, 46, 539-544, 2004 Ref Id 207374 Country/ies where the study was carried out Turkey Study type Randomised, placebo-controlled, prospective trial study Aim of the study To compare the early and late effects of nebulised L-epinephrine (EPI) and intramuscular dexamethasone (DEX) combination therapy with nebulised salbutamol (SAL) and dexamethasone combination and bronchodilators	day and were hence not included in analysis (reasons for dropout unknown) - 69 completed the study - Epinephrine and dexamethasone: n= 23 - Salbutamol and dexamethasone: n= 23 - Epinephrine and placebo: n= 11 - Salbutamol and placebo: n= 12 Characteristics Age in months, mean ± SEM Epinephrine and dexamethasone: 7.2±0.8 Salbutamol and dexamethasone: 7.9±1.0 Epinephrine and placebo: 9.6±1.3 Salbutamol and placebo: 9.9±1.7 Duration of illness in days, mean ± SEM Epinephrine and dexamethasone: 2.5±0.1 Salbutamol and dexamethasone: 3.5±0.3	dexamethasone 3. Epinephrine and placebo 4. Salbutamol and placebo Nebulised salbutamol (Ventolin®), 0.15mg/kg of a 1-mg/ml solution of salbutamol added to a 0.9% saline solution to make a total of 3ml Nebulised epinephrine 3ml (3mg) of 1:1000 L-epinephrine solution Both nebulised solutions were given through a compressed type nebuliser with continuous flow of oxygen 5-6l/min for 10 mins Fifteen minutes following the administration of both nebulised medications, dexamethasone	Setting Outpatients - paediatric outpatients clinic and the emergency department Randomisation method Not reported Concealment of allocation/blinding of treatment Allocation concealment not clearly described, 'parents and investigators remained blinded to administered medications throughout the study period' Statistical methods - Sample size calculation: not reported - Intention to treat analysis: not reported - Continuous variables: independent two-tailed t-test performed by using pooled or separate variance estimates - Dichotomous events: chi-squared test Follow-up Clinical assessment performed at 30, 60, 90 and 120 minutes after treatment. Patients were discharged and	hospitalization 2. Length of hospital stay None of the patients in any group required hospitalization 3. Change in disease severity score at 1 to 7 days after starting treatment Reported as respiratory distress assessment index score, mean (SE) At 120 mins 1. Epinephrine and dexamethasone: 3.8 (0.2), n=23 2. Salbutamol and dexamethasone: 4.0 (0.3), n=23 3. Epinephrine and placebo: 4.2 (0.3), n=11 4. Salbutamol and placebo: 4.4 (0.4), n=12 24th hour 1. Epinephrine and dexamethasone: 3.4 (0.2), n=23 2. Salbutamol and dexamethasone: 3.9 (0.3), n=23 3. Epinephrine and	Methodology checklist: randomised controlled trials - Randomisation method not described - Allocation concealment not clearly described - 21 lost to follow up - Small sample sizes Other information - The RDAI score was based on wheezing and retraction, a maximum score of 17 - A second dose of the same medication (epinephrine or salbutamol) was given to 5 (21.7%) patients from group 1, 8 (34.8%) patients from group 2, 5 (45.4%) patients from group 3 and 4 (33.3%) from group 4, since they did not show a substantial (≥ 4 points) improvement in RDAI score at 120 minutes. There were no significant differences between the retreatment rates of each group (p>0.05). All of these patients showed a decrease ≥ 4 points in their scores 60 minutes after the second dose of medication when compared to the score at baseline.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
alone in outpatients with acute bronchiolitis Study dates Winter months, dates not reported Source of funding Not reported	Epinephrine and placebo: 2.6±0.2 Salbutamol and placebo: 2.6±0.2 Passive smoking, n (%) Epinephrine and dexamethasone: 18 (78.2) Salbutamol and dexamethasone: 19 (82.6) Epinephrine and placebo: 8 (72.5) Salbutamol and placebo: 8 (66.7) Respiratory distress assessment index score (RDAI) at baseline, mean ± SE Epinephrine and dexamethasone: 7.3±0.2 Salbutamol and dexamethasone: 7.2±0.2 Epinephrine and placebo: 7.4±0.1 Salbutamol and placebo: 7.7±0.1 Inclusion criteria - Aged between 2 and 21 months - Admitted with first episode of wheezing	0.6mg/kg, or a placebo was given intramuscularly in a randomised fashion independent of the first randomisation Additional treatment If the patients had not experienced an improvement in RDAI of at least 4 points by 120 minutes, they were given the same medications (epinephrine or salbutamol) in the same doses again and reassessment was performed 30 and 60 minutes after the second dose	reassessed at 24 hours, and 5 days later.	placebo: 3.7 (0.3), n=11 4. Salbutamol and placebo: 3.8 (0.3), n=12 5th day 1. Epinephrine and dexamethasone: 2.3 (0.1)*, n=23 2. Salbutamol and dexamethasone: 2.5 (0.1)**, n=23 3. Epinephrine and placebo: 2.9 (0.2), n=11 4. Salbutamol and placebo: 3.4 (0.2), n=12 *significantly different from epi + pla group: p=0.02 and sal + pla: p=0.000 **significantly different from sal + pla group: p=0.01 4. Change in O2 saturation Not reported 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Clinical findings compatible with acute bronchiolitis* - Respiratory distress assessment index (RDAI) score ≥4 *Acute bronchiolitis defined as acute onset wheezing with or without cough, tachypnea, and increased respiratory effort, accompanied by clinical evidence of a viral illness such as coryza and fever Exclusion criteria - History of prior wheezing - Previous treatment with bronchiodilators - Previous diagnosis of asthma or allergic bronchitis by a physician - Personal history of atopic dermatitis or allergic rhinitis - Any chronic cardiac or pulmonary disease - Any steriod treatment within the previous 2 weeks - Signs of severe respiratory disease			ventilation Not reported 7. Adverse effects (including mortality), n (%) Respiratory complaints such as exercise-induced cough and mild wheezing Though this adverse event was reported, the data for the individual placebo groups has not been presented clearly and therefore not extracted for this review No side effects such as pallor, vomiting or tremor were encountered 8. Need for/use of feeding support (tube feeding, IV fluids) Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(pulse rate ≥200 beats/min, a respiratory of ≥100 breaths/min, RDAI score ≥15 or profound lethargy - Clinical and/or radiological evidence of a bacterial infection - Parental history of asthma or atopic disease				
Full citation Mesquita,M., Castro-Rodriguez,J.A., Heinichen,L., Farina,E., Iramain,R., Single oral dose of dexamethasone in outpatients with bronchiolitis: a placebo controlled trial, Allergologia et Immunopathologia, 37, 63-67, 2009 Ref Id 210066 Country/ies where the study was carried out Paraguay Study type Randomised double-blind	Sample size - 80 infants met the inclusion criteria and were enrolled - 15 excluded during the process: 5 had evidence of pneumonia, 2 children quit before the first hour of the protocol, 3 presented with vomiting within 20 mins after administration of the medication and parents of 5 children declined to participate - Of the 65 remaining infants, 33 were in the dexamethasone +adrenaline group and 32 in the placebo + adrenaline group Characteristics	Interventions Group 1 Single dose of oral dexamethasone 0.5mg/kg (1ml/kg) + adrenaline* Group 2 Single dose of oral placebo (1ml/kg) + adrenaline* *Immediately after the dexamethasone/placebo dose, children from both groups received two nebulisations with 4ml of physiological solution and 1ml of L-adrenaline solution (1:1000, 1ml=1mg) separated by 30 mins. Aerosol was generated by jet nebuliser powered by	Details Consent Written signed and fully informed consent obtained Setting Outpatients - emergency department Randomisation method Table of random numbers Concealment of allocation/blinding of treatment The active drug and placebo were prepared in identical sweet syrups and their bottles were labelled only with the randomised numbers. Double blind study, in the whole period of the trial,	Results 1. Hospital admission rate, n/N (%) At 4th hour (end of study) Dexamethasone + adrenaline: 8/33* (24) Placebo + adrenaline: 7/32* (22) p=0.82, OR (95%CI): 1.14 (0.36 to 3.63) *n calculated by NCC-WCH technical team 2. Length of hospital stay Not reported 3. Change in disease severity score at 1 to 7 days after starting treatment Reported as respiratory distress	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - No serious limitations: adequate randomisation and allocation concealment, adeqaute blinding - 15/80 children were excluded post-enrolment: reasons adequately described - Infants from the dexamethasone + adrenaline group had a signficantly higher weight than the placebo + adrenaline group Other information - The RDAI is a scale of 0 to 17 with higher scores indicating more severe disease

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
placebo controlled trial Aim of the study To compare the efficacy of a single dose of oral dexamethasone in infants with moderate to severe bronchiolitis presenting to an emergency department Study dates During 5 months, dates not reported Source of funding Not reported	Age in months, mean (SD) Dexamethasone + adrenaline: 7.3 (4) Placebo + adrenaline: 5.9 (3) p= 0.1 Male, n (%) Dexamethasone + adrenaline: 19* (58) Placebo + adrenaline: 15* (47) p= 0.4 * n calculated by NCC-WCH technical team Weight in kg, mean (SD) Dexamethasone + adrenaline: 8.098±2.530 Placebo + adrenaline: 6.543±1.670 p=0.005 RDAI score at baseline, mean (SD) Dexamethasone + adrenaline: 10 (2) Placebo + adrenaline: 10 (2) p= 1.0 Oxygen saturation (%) at baseline, mean (SD) Dexamethasone + adrenaline: 92 (1.5)	continuous flow of oxygen (6l) for 7 mins and delivered via a tight fitting face mask. Although the study arms have been referred to as the dexamethasone and placebo groups in the study itself, as both groups received these treatments in combination with adrenaline, the groups have therefore been treated as dexamethasone + adrenaline versus placebo + adrenaline for the purpose of this review. Additional treatment - Any episode of vomitting within 20 min after administration of the oral study medication was recorded, but the dose was not repeated - Child admitted to hospital if Sp02 ≤ 90% and/or respiratory rate above normal values for age - Additional oxygen	the investigators were blinded of the treatment administered. Statistical methods - Sample size calculation: Chnages in the RDAI score of 2 points were reported to clearly differentiate patients who required admission; to detect a RDAI 2 score change the number required per group was 27, with a statistical power of 80% (β=0.20), α=0.05, two-sided test, SD 2.6 - Intention to treat analysis: not reported - To evaluate differences between groups, the chi-square was used for categorical and the t-test for continuous variables Follow-up After 1 and 4 hours of the study medication administration, the patients were re-evaluated by 2 study clinicians and outcomes measured. No systematic follow-up after the 4th hour was done.	assessment index (RDAI) score, mean (SD) At 1st hour Dexamethasone + adrenaline: 8 (2), n=33 Placebo + adrenaline: 8 (2), n=32 p= 1.0 At 4th hour Dexamethasone + adrenaline: 7 (3), n=33 Placebo + adrenaline: 7 (2), n=32 p= 1.0 4. Change in O2 saturation Reported as oxgen saturation (%) at the following time points, mean (SD) At 1st hour Dexamethasone + adrenaline: 94 (1), n=33 Placebo + adrenaline: 94 (2), n=32 p= 1.0 At 4th hour Dexamethasone + adrenaline: 94 (3), n=33	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Placebo + adrenaline: 92 (2) p= 1.0 RSV+, n (%) Dexamethasone + adrenaline: 17/29* (59) Placebo + adrenaline: 19/23** (83) * RSV sampling was done in only 29/33 infants in the dexamethasone + adrenaline group ** RSV sampling was done in only 23/32 infants in the placebo + adrenaline group Inclusion criteria - Children 2-24 months of age who came to the emergency department with their first episode of bronchiolitis* *Bronchiolitis defined as respiratory distress with respiratory rate between 40-80/min and wheezing; and within 7 days after onset of a cold Exclusion criteria - Clinical or radiological pneumonia	was administered to the patient if Sp02 <90% - Aspiration for cleaning the nose was carried out - Antipyretic medication was provided when necessary		Placebo + adrenaline: 94 (3), n=32 p= 1.0 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Adverse effects (including mortality) Not reported 8. Need for/use of feeding support (tube feeding, IV fluids) Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Cardiopulmonary congenital malformations - Bronchopulmonary dysplasia - Cystic fibrosis - Foreign body aspiration - Neuological alteration - Previous wheezing/asthma episode - Inhaled or systemic corticosteroids used in the previous 15 days - Beta-2 agonists used within the previous 4 hours - Antecedents of atopy (dermatitis or allergic rhinitis) in the child or parental asthma - Severe wheezing attack (respiratory rate ≥100/min and/or heart rate ≥200/min and/or shock or lethargy)				
Full citation Plint,A.C., Johnson,D.W., Patel,H., Wiebe,N., Correll,R., Brant,R., Mitton,C., Gouin,S., Bhatt,M., Joubert,G., Black,K.J.,	Sample size - 3556 assessed for eligibility - 800 enrolled - 3 lost to follow-up - Included in analysis: 199 epinephrine-dexamethasone, 198 epinephrine + placebo,	Interventions 1. Epinephrine-dexamethasone Two treatments of nebulised epinephrine and six oral doses of dexamethasone	Details Consent Written informed consent obtained from parents/guardians Setting Outpatients - eight pediatric emergency	Results 1. Hospital admission rate, n/N (%) At enrollment Epinephrine-Dexamethasone: 23/200 (11.5), relative risk (95% CI): 0.65 (0.41 to 1.04)	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - Adequate randomisation, allocation concealment and blinding

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Turner,T., Whitehouse,S., Klassen,T.P., Pediatric Emergency Research Canada (PERC), Epinephrine and dexamethasone in children with bronchiolitis, New England Journal of Medicine, 360, 2079-2089, 2009 Ref Id 207913 Country/ies where the study was carried out Canada Study type Multicenter, randomised, double-blind, placebo-controlled trial (with a factorial design at multiple sites) Aim of the study To determine whether treatment with nebulised epinephrine, a short course of oral dexamethasone, or	199 dexamethasone + placebo and 201 placebo Characteristics Age in months, median (interquartile range) Epinephrine-Dexamethasone: 5 (3-7) Epinephrine: 5 (3-7) Dexamethasone: 5 (3-7) Placebo: 5 (3-7) Male sex, n (%) Epinephrine-Dexamethasone: 124 (62.0) Epinephrine: 122 (61.3) Dexamethasone: 127 (63.5) Placebo: 120 (59.7) RDAI score, median (interquartile range) Epinephrine-Dexamethasone: 8 (6-10) Epinephrine: 8 (6-10) Dexamethasone: 8 (6-10) Placebo: 8 (6-10) Oxygen saturation %,	2. Epinephrine + placebo Nebulised epinephrine and oral placebo 3. Dexamethasone + placebo Nebulised placebo and oral dexamethasone 4. Placebo Nebulised placebo and oral placebo Nebulised treatments Administered 30 minutes apart, oxygen flow rate of 8l per minute, consisted of 3ml of generic epinephrine in a 1:1000 solution or an equivalent volume of saline Oral treatments Consisted of 1.0mg dexamethasone per kg of body weight (maximum dose 10mg) or placebo given after the first nebulised treatment in the emergency department, followed by five once-daily	departments Randomisation method Computer generated randomisation sequence stratified by centre, used randomized permuted blocks of 8 and 12 Concealment of allocation/blinding of treatment Study drugs prepared in sequentially numbered, visually identical packets - drugs (and placebo) identical in appearance, volume, weight, odor and taste. Double-blind study. Statistical methods - Sample size calculation: a sample size of 800 infants was chosen to provide 80% power (with a 5% type I error state) to detect an absolute difference of 10 percentage points in admission rates resulting from administration of each drug and assumed no interaction between epinephrine and dexamethasone - Intention to treat analysis	Epinephrine + placebo: 29/199 (14.6), relative risk (95% CI): 0.79 (0.51 to 1.23) Dexamethasone + placebo: 31/200 (15.5), relative risk (95% CI): 0.85 (0.56 to 1.31) Placebo: 36/201 (17.9), relative risk (95% CI): 1.00 - reference group By day 7 Epinephrine-Dexamethasone: 34/200 (17.1), relative risk (95% CI): 0.65 (0.45 to 0.95) Epinephrine + placebo: 47/199 (23.7), relative risk (95% CI): 0.88 (0.63 to 1.23) Dexamethasone + placebo: 51/200 (25.6), relative risk (95% CI): 0.96 (0.69 to 1.33) Placebo: 53/201 (26.4), relative risk (95% CI): 1.00 - reference group By day 22	- 3/800 subjects with missing outcome data - At follow-up parents reported that they stopped administering the study syrup so that a physician could prescribe oral corticosteriods: 19 in epinephrine-dexamethasone group, 13 in epinephrine+ placebo group, 20 in dexamethasone + placebo group and 12 in placebo group Other information - Drugs were administered by the research nurse in the emergency department and parents were taught how to administer the oral drug at home - The RDAI rates wheezing and respiratory distress on a scale from 0 to 17 with higher scores indicatiing more severe illness; a score below 4 indicates very mild illness and a score above 15 very severe illness - The additional use of bronchodilators 90 minutes after enrollment were similar across groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
both resulted in a clinically important decrease in hospital admissions among infants with bronchiolitis who were seen in the emergency department Study dates Bronchiolitis season (December through April) from 2004 to 2007 Source of funding - Supported by grants from the Canadian Institutes of Health Research and Alberta Children's Hospital Foundation - One of the authors was supported in part by a salary award from the Canadian Institutes of Health Research - One other author reports receiving grant support from Cumberland Pharmaceuticals	median (interquartile range) Epinephrine-Dexamethasone: 97 (95-98) Epinephrine: 97 (95-98) Dexamethasone: 97 (95-98) Placebo: 97 (95-98) Duration of symptoms before enrollment days, median (interquartile range) Epinephrine-Dexamethasone: 3 (2-5) Epinephrine: 4 (3-6) Dexamethasone: 3 (2-5) Placebo: 4 (2-6) RSV positive, n (%) Epinephrine-Dexamethasone: 128 (64.0) Epinephrine: 129 (64.8) Dexamethasone: 127 (63.5) Placebo: 136 (67.7) Previous treatment, n (%) Epinephrine-Dexamethasone: bronchodilators 27 (13.5), antibiotics 24	doses of dexamethasone (0.6mg per kg; maximum daily dose, 10mg) or placebo. Additional treatment Any child with oxygen saturation <92% while breathing ambient air received supplemental oxygen and any child with fever (rectal temperature >38ºC) received acteminophen (15mg per kg body weight). The treating physician in the emergency department was allowed to provide cointerventions after 90 minutes and independently determined whether to admit or discharge the infant.	- Admission visits analysed with the use of relative-risk regression for binary outcomes - Time to discharge analysed using a Cox proportional-hazards model - Time to symptom relief analysed using parametric survival models with Weibull distributions - Clinical characteristics analysed using linear mixed-effects regression Follow-up RDAI score and oxygen saturation assessed at 60, 90, 120, 180 and 240 minutes. Telephone follow-up performed daily until day 7, then every 2 days until day 14, and then every 3 days until day 22.	Epinephrine-Dexamethasone: 37/200 (18.5), relative risk (95% CI): 0.69 (0.48 to 0.99) Epinephrine + placebo: 50/199 (25.1), relative risk (95% CI): 0.92 (0.66 to 1.27) Dexamethasone + placebo: 53/200 (26.5), relative risk (95% CI): 0.98 (0.71 to 1.35) Placebo: 54/201 (26.9), 1.00 - reference group 2. Length of hospital stay Reported as time to discharge* in hours, median (interquartile range) *Time to discharge was defined as the time between the triage time at the enrollment visit and the time of discharge from the last emergency department visit or the last hospitalisation for each patient within the next 7 days	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(12.0) Epinephrine: bronchodilators 21 (10.6), antibiotics 20 (10.1) Dexamethasone: bronchodilators 20 (10.0), antibiotics 21 (10.5) Placebo: bronchodilators 24 (11.9), antibiotics 17 (8.5) Inclusion criteria - Infants aged 6 weeks to 12 months with bronchiolitis* - A respiratory distress assessment index (RDAI) score of 4 to 15 *Bronchiolitis definined as the first episode of wheezing associated with signs of an upper respiratory tract infection during the peak RSV season Exclusion criteria - Infants who received bronchodilator treatment in the emergency department before being assessed by a research nurse			Epinephrine-Dexamethasone: 4.6 (3.5 to 7.0), n=199, p value (unadjusted): 0.02, p value (adjusted**): 0.94 Epinephrine + placebo: 4.9 (3.7 to 9.6), n=198, p value (unadjusted): 0.78, p value (adjusted**): 0.94 Dexamethasone + placebo: 5.1 (3.6 to 17.0), n=199, p value (unadjusted): 0.99, p value (adjusted**): 1.00 Placebo: 5.3 (3.8 to 21), n=200, p value - reference group **adjusted for multiple comparisons 3. Change in disease severity score at 1 to 7 days after starting treatment Reported as change in respiratory distress assessment index score, mean ± SD At 30 mins Epinephrine-Dexamethasone: -	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Infants who received oral or inhaled corticosteriods during the preceding 2 weeks - Infants with a previous episode of wheezing or diagnosis of asthma - Previous bronchodilator use - Any chronic cardiopulmonary disease or immunodeficiency - Infants in severe distress (pulse rate >200 beats per min, respiratory rate >80 breaths per min or an RDAI score >15) or with profound lethargy - Infants exposed to varicella within the preceding 3 weeks - Infants born <37 weeks of gestation who had a corrected age of less than 6 weeks at presentation - Insurmountable barriers to communication with the family			1.62 ± 2.23, n=199 Epinephrine + placebo: -1.44 ± 1.94, n=198 Dexamethasone + placebo: -0.98 ± 2.07, n=199 Placebo: -1.06 ± 2.16, n=200 At 60 mins Epinephrine-Dexamethasone: -2.50 ± 2.58, n=199 Epinephrine + placebo: -2.45 ± 2.32, n=198 Dexamethasone + placebo: -1.75 ± 2.40, n=199 Placebo: -1.65 ± 2.42, n=200 4. Change in O2 saturation, % At 30 mins Epinephrine-Dexamethasone: -0.35 ± 2.61, n=199 Epinephrine + placebo: 0.17 ± 2.09, n=198 Dexamethasone + placebo: -0.52 ± 2.45, n=199 Placebo: -0.24	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				± 2.77, n=200 At 60 mins Epinephrine-Dexamethasone: -0.73 ± 2.56, n=199 Epinephrine + placebo: 0.07 ± 2.70, n=198 Dexamethasone + placebo: -1.02 ± 2.57, n=199 Placebo: -0.77 ± 3.23, n=200 5. Duration of cough Reported as number of days with no coughing, median (interquartile range) Epinephrine-Dexamethasone: 12.6 (7.8 to 18.5), mean ratio (95%CI): 0.94 (0.84 to 1.07) Epinephrine + placebo: 13.2 (8.1 to 19.3), mean ratio (95%CI): 0.99 (0.88 to 1.12) Dexamethasone + placebo: 13.8 (8.5 to 20.2), mean ratio (95%CI): 1.04 (0.92 to 1.18) Placebo: 13.3 (8.2 to 19.5), mean ratio	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(95%CI): 1.00 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Adverse effects, n (%) Observed in the emergency department by research nurse Tremor Epinephrine-Dexamethasone: 4 (2.0) Epinephrine + placebo: 4 (2.0) Dexamethasone + placebo: 5 (2.5) Placebo: 2 (1.0) Pallor Epinephrine-Dexamethasone: 23 (11.5) Epinephrine + placebo: 22 (11.1) Dexamethasone + placebo: 15 (7.5) Placebo: 16 (8.0) Vomiting Epinephrine-Dexamethasone: 2 (1.0)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Epinephrine + placebo: 4 (2.0) Dexamethasone + placebo: 5 (2.5) Placebo: 3 (1.5) Reported by families during the 22 day telephone follow-up Varicella Epinephrine-Dexamethasone: 0 (0) Epinephrine + placebo: 0 (0) Dexamethasone + placebo: 0 (0) Placebo: 0 (0) Dark stools Epinephrine-Dexamethasone: 17.5 (8.5) Epinephrine + placebo: 14 (7.0) Dexamethasone + placebo: 12 (6.0) Placebo: 16 (8.0) Observed in infants admitted to hospital Hypertension Epinephrine-Dexamethasone: 0 (0) Epinephrine + placebo: 1 (0.5) Dexamethasone +	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				placebo: 1 (0.5) Placebo: 0 (0) Hyperkalemia Epinephrine-Dexamethasone: 0 (0) Epinephrine + placebo: 0 (0) Dexamethasone + placebo: 1 (0.5) Placebo: 0 (0) 8. Need for/use of feeding support (tube feeding, IV fluids) Reported as number of days with normal feeding, median (interquartile range) Epinephrine-Dexamethasone: 0.6 (0.2 to 1.3), mean ratio (95%CI): 0.63 (0.50 to 0.80) Epinephrine + placebo: 0.5 (0.2 to 1.2), mean ratio (95%CI): 0.60 (0.47 to 0.76) Dexamethasone + placebo: 0.8 (0.3 to 1.9), mean ratio (95%CI): 0.89 (0.70 to 1.31) Placebo: 0.9 (0.3 to 2.1), mean ratio (95%CI): 1.00	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Schuh,S., Coates,A.L., Binnie,R., Allin,T., Goia,C., Corey,M., Dick,P.T., Efficacy of oral dexamethasone in outpatients with acute bronchiolitis, Journal of Pediatrics, 140, 27-32, 2002 Ref Id 210201 Country/ies where the study was carried out Canada Study type Randomised, double-blinded, placebo-controlled trial Aim of the study To investigate in outpatients younger than 2 years with acute bronchiolitis the clinical benefits of oral dexamethasone within 4 hours of administration in the	Sample size - 1464 presented at emergency department with first time episode of wheezing that was diagnosed as bronchiolitis - 920 not approached as research nurse was not present - 427 excluded for various reasons - 47 declined to participate - 70 participated: 36 dexamethasone + albuterol, 34 placebo + albuterol - Of the 70 participating infants, 48 were discharged home from the emergency department, of those 26 in dexamethasone + albuterol group and 13 in the placebo + albuterol group agreed to continue the experimental therapy at home Characteristics Sex (male/female), n Dexamethasone + albuterol: 20/16 Placebo + albuterol:	Interventions Children were randomised to one of two groups that both received the same dosage (1mg/kg) 1) Dexamethasone + albuterol*: a single dose of oral dexamethasone syrup 2) Placebo + albuterol*: a single dose of oral placebo syrup *Subjects also received nebulized albuterol (Ventolin 5% solution) via a vented Pari LC STAR nebuliser 2.5mg per dose (0.5ml) in 3ml of normal saline solution with oxygen flow of 6 to 7 l/min with tight fitting face mask at times 0, 30, 60 and 120 minutes. Although the study arms have been referred to as the dexamethasone and placebo group in the study itself, both groups received	Details Consent Written consent obtained from parents Setting Outpatients - emergency department Randomisation method Blocked randomisation code prepared by pharmacy from a computer generated list of random numbers Concealment of allocation/blinding of treatment Both treatments of identical colour, texture, taste and smell. Identity of the treatment assignment was completely masked to patients, family, clinicians, and research personnel with the exception of the research pharmacists. Randomisation code revealed only after all patients had completed the study. Statistical methods - Sample size calculation: the study	Results 1. Hospital admission rate, n/N (%) Dexamethasone + albuterol: 7/36 (19) Placebo + albuterol: 15/34 (44%) p=0.039 (Of the 22 hospitalised children, 21 were admitted after the 240 minutes of the initial treatment and outcome assessment and one required hospitalisation shortly after the initial discharge) No child was hospitalised between day 7 and 28 2. Length of hospital stay Not reported 3. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) Reported as respiratory disease assessment instrument score	Limitations - 9 patients dropped out once discharged - 920 of 1464 children at the emergency department were not approached because the research nurse was not present Other information - The RACS score assesses changes in the retractions and wheezing as measured by changes in RDAI and change in respiratory rate. The RDAI assigns a maximum of 8 points for wheezing and 9 points for retraction, depending on the location and severity of these 2 signs. The overall RACS was calculated as the arithmetic sum of the RDAI change and of the standardized respiratory rate change.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
emergency department and after 5 days of continued therapy and discharge Study dates 6 month winter periods between November 1997 to April 2000 Source of funding - Supported by grants from the Medical Research Council of Canada and Merck Foseet, Canada - The Paediatric Outcomes Research Team is supported by The Hospital for Sick Children Foundation - One of the authors receives financial support from the Onatario Ministry of Health and Long-Term Care through a Career Scientist Award	23/11 Age in months, mean (SD) Dexamethasone + albuterol: 6.1 (3.5) Placebo + albuterol: 6.9 (3.9) Medications before arrival, n/N Inhaled albuterol: dexamethasone + albuterol - 8/36, placebo + albuterol - 4/34 Oral albuterol: dexamethasone + albuterol - 1/36, placebo + albuterol - 3/34 Orciprenaline: dexamethasone + albuterol - 2/36, placebo + albuterol - 3/34 Oxygen saturation %, mean (SD) Dexamethasone + albuterol: 96.8 (2.3) Placebo + albuterol: 96.0 (2.5) RSV positive, n/N Dexamethasone + albuterol: 15/28	these treatments in combination with albuterol and therefore the arms have been treated as dexamethasone + albuterol versus placebo + albuterol for the purpose of this review. Additional treatment - The dose was repeated once in cases of vomitting within 20 minutes of administration, and further vomitting necessitated withdrawal from the study - All decisions regarding the need for further hospitalisation were made by the attending physicians not involved in the study who were unaware of the research nurse's scoring as well as the patients' treatment assignment and requested not to administer addtional therapy (other than	was designed to detect a mean change in respiratory assessment change score (RACS) score between the groups of 2. With an α of 0.05 and β of 0.20, the sample size required to detect this difference was estimated to be 71 children. - Intention to treat analysis - Differences in mean values between the dexamethasone and placebo groups were tested with a t-test - Proportions were compared with a Fisher exact test - The change in clinical scores over 4 hours evaluated by repeated measures regression analysis - Logistic regression analysis used to assess the effects of covariates on risk of hospitalisatio Follow-up Clinical outcomes assessed hourly between baseline and 240 minutes in the emergency department and at the patient's home on day 7. Parents of all	(RDAI) at 4 hours Dexamethasone + albuterol: 5.4 (2.1), n=36 Placebo + albuterol: 7.2 (2.8), n=34 p= 0.064 Reported as respiratory disease assessment instrument score (RDAI) at 7 days Dexamethasone + albuterol: 2.4 (3.1), n=35 Placebo + albuterol: 2.6 (3.0), n=32 p= 0.754 4. Change in O2 saturation %, mean (SD) At 4 hours Dexamethasone + albuterol: 96.4 (2.8), n=36 Placebo + albuterol: 95.7 (3.0), n=34 p=0.944 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Placebo + albuterol: 15/30 Inclusion criteria - Between 8 weeks and 23 months of age with acute bronchiolitis* - Seen between 8AM and 9PM in the emergency department - First wheezing episode associated with respiratory distress and an upper respiratory tract infection - RDAI rating of ≥6 at baseline *Acute bronchiolitis definition unclear Exclusion criteria - Children with history of wheezing or bronchodilator therapy - Prematurity - Neonatal ventilation - Chronic lung/cardiac disease - Aspiration - Neurologic/neuromuscular problems - Immunodeficiency - Critically ill infants	acetominophen for fever). Children with persistent signs of respiratory distress 240 minutes after experimental therapy were admitted to the hospital. - Children discharged home after the 4 hour observation period continued to recieve either daily oral dexamethasone (0.6/mg/kg/dose) or placebo for 5 days, and albuterol (1.5/mg [0.3ml]) 4 times daily with the same nebuliser - Five children received racemic epinephrine during the study because of persistent respiratory distress, one in the dexamethasone group and four in the placebo group - 7 out of 32 infants in the placebo group received cointervention with corticosteriods from their primary care provider after	patients telephoned on day 28.	Not reported 7. Adverse effects Not reported 8. Need for/use of feeding support (tube feeding, IV fluids) Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	who required immediate airway stabalisation - Infants previously given oral or inhaled corticosteriods - Infants exposed to varicella within 21 days before arrival	discharge because of persistent symptoms, none in the dexamethasone group received additional corticosteriods p=0.004			
Full citation Alansari,K., Sakran,M., Davidson,B.L., Ibrahim,K., Alrefai,M., Zakaria,I., Oral dexamethasone for bronchiolitis: a randomized trial, Pediatrics, 132, e810-e816, 2013 Ref Id 299640 Country/ies where the study was carried out Qatar Study type RCT Aim of the study Determine whether dexamethasone treatment added to	Sample size - 200 randomised: Dexamethasone + salbutamol - 102; Placebo + salbutamol - 98 - Analysed: Dexamethasone + salbutamol - 100; Placebo + salbutamol - 90 Characteristics Age in months, mean (SD) Dexamethasone + salbutamol: 3.4 (2.2) Placebo + salbutamol: 3.9 (2.0) p=0.8 Male/female, n Dexamethasone + salbutamol: 70/32 Placebo + salbutamol: 57/41	Interventions Dexamthasone*: 1mg/kg for the first day then 0.6mg/kg for 4 more days (orally) Placebo*: not defined *Though the study arms have been referred to as the dexamethasone and placebo group in the study itself, both groups received these treatments in combination with 2.5mg salbutamol (nebulised) mixed with 2ml normal saline at 0, 30, 60 and 120 min and then every 2 hours until ready for discharge. Additional treatment Supplementary	Details Consent Informed consent obtained Setting Short stay unit of pediatric emergency centre Randomisation method Randomisation list containing generated random numbers with 1 or 2 codes identifying sterilely prepared dexamethasone or placebo Concealment of allocation/blinding of treatment Same colour, smell and taste, sealed envelopes Statistical methods - Sample size	Results 1. Hospital admission rate Reported as hospital admission in the week after discharge Dexamethasone + epinephrine: 0 Placebo + epinephrine: 0 2. Length of hospital stay in hours Reported as geometric mean time (95%CI) to readiness for discharge in hours Dexamethasone + epinephrine: 18.6 (14.9 to 23.1) Placebo + epinephrine: 27.1 (21.8 to 33.8) Ratio of geometric means (95%CI): 0.69 (0.51 to 0.93), p=0.015	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials - Indirect population: patients with asthma risk, as determined by eczema or a family history of asthma in a first degree relative Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
salbutamol reduces time to readiness for discharge in patients with bronchiolitis and possible asthma Study dates February 2010 to March 2012 Source of funding Hospital sponsored by Hamad Medical Corporation	RSV positivity, n (%) Dexamethasone + salbutamol: 39 (38) Placebo + salbutamol: 38 (39) p=0.9 Baseline Wang severity score, mean (SD) Dexamethasone + salbutamol: 6.45 (3.34) Placebo + salbutamol: 6.84 (1.62) p=0.09 Inclusion criteria - Infants aged ≤18 months presenting to the unit for treatment of moderate to severe viral bronchiolitis* who has a positive history for eczema** or were known to have a parent or a full sibling with a prior physician diagnosis of asthma *Moderate to severe bronchiolitis was defined as a prodromal history consistent with viral upper respiratory tract infection followed by wheezing or crackles on auscultation and a	oxygen, hydration were given at the discretion of the treating physician	calculation: with a sample size of 93 patients per group, there would be 80% power to find a significant difference. To compensate for dropouts, the aim was to recruit 200 patients altogether. - Intention to treat analysis: not reported - Time for readiness for discharge was plotted by univariate Kaplan-Meier survival analysis. Follow-up Daily follow-up by study nurse by telephone was mandatory for 1 week after discharge. The patient could return to the emergency centre earlier if needed.	3. Change in disease severity score at 1 to 7 days after starting treatment Not reported 4. Change in O2 saturation Not reported 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Adverse effects (including mortality) Not reported 8. Need for/use of feeding support (tube feeding, IV fluids) Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Wang bronchiolitis severity score of ≥4 on presentation **Eczema was considered present if there was a prior physician diagnosis or the patient had rash consistent with eczema on presentation Exclusion criteria - Preterm birth ≤34 weeks gestation - Previous history of wheezing - Steroid use within 48 hours of presentation - Obtundation and progressive respiratory failure necessitating ICU admission - History of apnea within 24 hours before presentation - Oxygen saturation ≤85% on room air at the time of recruitment - History of a diagnosis of chronic lung disease, congenital heart disease and immunodeficiency or exposure to varicella within 21 days before enrollment				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bawazeer,M., Aljeraisy,M., Albanyan,E., Abdullah,A., Al,Thaqa W., Alenazi,J., Al,Otaibi Z., Al,Ghaihab M., Effect of combined dexamethasone therapy with nebulized r-epinephrine or salbutamol in infants with bronchiolitis: A randomized, double-blind, controlled trial, Avicenna Journal of Medicine, 4, 58-65, 2014 Ref Id 321418 Country/ies where the study was carried out Saudi Arabia Study type Randomised, double-blind controlled clinical trial Aim of the study	Sample size - 604 screened for eligibility - 162 randomised - Dexamethasone + epinephrine: 45, Dexamethasone + salbutamol: 40, Placebo + epinephrine: 39, Placebo + salbutamol: 38 Characteristics Age in months, mean (SD) Dexamethasone + epinephrine: 4.74 (2.84) Dexamethasone + salbutamol: 4.55 (2.21) Placebo + epinephrine: 4.23 (2.46) Placebo + salbutamol: 4.85 (2.35) p=0.5839 Gender, n (%) Dexamethasone + epinephrine: male - 28 (62.22), female - 17 (37.78) Dexamethasone + salbutamol: male - 21 (52.50), female - 19 (47.50) Placebo + epinephrine:	Interventions 1. Oral* Dexamethasone + Nebulised** Epinephrine group 2. Oral* Dexmathasone + Nebulised** Salbutamol group 3. Oral* Placebo + Nebulised** Epinephrine group 4. Oral* Placebo + Nebulised** Salbutamol group *Oral treatments consisted of 1.0mg of dexamethasone per kilogram of body weight (maximum dose, 12mg) or placebo fiven after the first nebulised treatment in the ED and were subsequently followed by two once-daily doses of dexamethasone (0.6mg per kg; maximum daily dose 12mg) or placebo to be taken at home. **The 3 doses of nebulised treatments	Details Consent Consent obtained Setting Emergency department Randomisation method Computer-generated random sequences Concealment of allocation/blinding of treatment Sequentially numbered visually identical envelopes, active drugs and placebos identical in appearance, volume, weight, odor and taste Statistical methods - Sample size calculation: to attain 80% power with a 5% type I error rate, the required sample size was 600 infants: 300 infants in the dexamethasone groups, including nebulized epinephrine plus oral dexamethasone (group A) and nebulised salbutamol plus oral dexamethasone (group c) and 300 infants in the	Results 1. Hospital admission rate, n (%) - day 7 a) Oral Dexamethasone + Nebulised Epinephrine group - 14/45 (31.1%) b) Oral Dexmathasone + Nebulised Salbutamol group - 10/40 (25%) c) Oral Placebo + Nebulised Epinephrine group - 12/39 (30.7%) d) Oral Placebo + Nebulised Salbutamol group - 11/38 (28.9%) a) + b) pooled data - 24/85* c) + d) pooled data - 23/77* 2. Length of hospital stay Not reported 3. Change in disease severity score at 1 to 7 days after starting treatment, mean (SD) a) Oral Dexamethasone + Nebulised	Limitations Only limitations that arise in the study are reported - Bronchiolitis not defined Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To examine the clinical benefit of combining dexamethasone with either nebulized epinephrine or slabutamol compared to bronchodilators alone, in children younger than 12 months admitted to the emergency department with acute bronchiolitis Study dates Patients recruited during bronchiolitis season between November 2010 and March 2011 Source of funding Supported by a grant from King Abdulla International Medical Research Center	male - 20 (51.28), female - 19 (48.72) Placebo + salbutamol: male - 17 (45.95), female - 20 (54.05) p=0.5093 Smoker at home, n (%) Dexamethasone + epinephrine: yes - 15 (33.33), no - 30 (66.67) Dexamethasone + salbutamol: 12 (30.00), no - 28 (70.00) Placebo + epinephrine: yes - 15 (38.46), no - 24 (61.54) Placebo + salbutamol: yes - 15 (40.54), no - 22 (59.46) p=0.7575 Nasopharyngeal aspiration Not taken, n (%) Dexamethasone + epinephrine: 35 (77.78) Dexamethasone + salbutamol: 32 (80.00) Placebo + epinephrine: 28 (71.79) Placebo + salbutamol: 29 (76.32) Negative Dexamethasone + epinephrine: 7 (15.56) Dexamethasone +	were administered at 0, 30 and 90 minutes apart by means of a Salter Labs nebulizer with an oxygen flow rate of 8 litres per minute and 0.25ml racemic epinephrine at 2.25% concentration or an equivalent volume of saline Additional treatment The treating physician in the emergency department was allowed to provide co-interventions only after 90 minutes and independently determined whether to admit or discharge the infant	placebo groups, included nebulised epinpehrine plus oral placebo (group B) and nebulised salbutamol plus oral placebo (group D). This allowed the detection of a 9-10% absolute reduction in admission rates, equating to approximately 33% relative reduction in admission rate. - Intention to treat: not reported Follow-up Follow-up telephone calls and chart reviews were performed at day 3 and day 7 following enrollment	Epinephrine group - 0 mins: 7.69 (1.36), 240 mins: 4.41 (1.73) b) Oral Dexmathasone + Nebulised Salbutamol group - 0 mins: 8.6 (1.66), 240 mins: 5.14 (2.03) c) Oral Placebo + Nebulised Epinephrine group - 0 mins: 8.18 (2.05), 240 mins: 4.79 (1.65) d) Oral Placebo + Nebulised Salbutamol group - 0 mins: 8 (1.58), 240 mins: 5.03 (2.26) p=0.8312 a) + b) pooled mean (SD) -240 mins - 4.75 (1.90)* c) + d) pooled mean (SD) -240 mins - 4.90 (1.97)* 4. Change in oxygen saturation a) Oral Dexamethasone + Nebulised Epinephrine group - 0 mins: 96.64 (2.64), 240 mins: 96.83 (2.46) b) Oral	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	salbutamol: 5 (12.50) Placebo + epinephrine: 9 (23.08) Placebo + salbutamol: 6 (15.79) RSV Dexamethasone + epinephrine: 3 (6.67) Dexamethasone + salbutamol: 3 (7.50) Placebo + epinephrine: 2 (5.13) Placebo + salbutamol: 3 (7.89) p=0.9310 Inclusion criteria - Infants with mild to moderate bronchiolitis presenting to ED within 7 days of the onset of symptoms - RDAI score between 5 and 15 Exclusion criteria - Infants who received a bronchodilator or steroids prior to admission to the ED - Infants who had a prior wheeze or asthma or known chronic cardiopulmonary disease, neurological disease or			Dexmathasone + Nebulised Salbutamol group - 0 mins: 96.18 (2.84), 240 mins: 97.06 (2.39) c) Oral Placebo + Nebulised Epinephrine group - 0 mins: 96.36 (2.99), 240 mins: 96.88 (2.6) d) Oral Placebo + Nebulised Salbutamol group - 0 mins: 96.66 (2.72), 240 mins: 96.77 (2.82) p=0.8312 a) + b) pooled mean (SD) - 240 mins: 96.94 (2.42)* c) + d) pooled mean (SD) - 240 mins: 96.83 (2.69)* 5. Duration of cough Not reported 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation Not reported 7. Adverse effects (including mortality) Not reported 8. Need for/use of	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	immunodeficiency - Infants who experienced severe respiratory distress - Infants who had an history of Varicella infection - If the infant exhibited clinical or radiological evidence of bacterial pneumonia and require pediatric intensive care unit admission or intubation or had been previously intubated			feeding support (tube feeding, IV fluids) Not reported *Calculated by NCC-WCH technical team based on data reported in the article	

I.17 What is the efficacy of montelukast?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Amirav,I., Luder,A.S., Kruger,N., Borovitch,Y., Babai,I., Miron,D., Zuker,M., Tal,G., Mandelberg,A., A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis, Pediatrics, 122, e1249-e1255, 2008 Ref Id 206274	Sample size 131 admitted with bronchiolitis 94 offered participation (met entry criteria) 55 randomly assigned 24 to montelukast; 31 to placebo 23 completed montelukast; 30 completed placebo Characteristics	Interventions Montelukast (in sodium salt form) 4 mg, daily until discharge from unit. The excipients were mannitol, hydroxypropyl cellulose and magnesium stearate Matching placebo daily until discharge from unit. The excipients were mannitol,	Details Ethics National ethics approval Informed consent from parents Setting Two Medical center. Randomisation	Results Change in O2 saturation Not reported Duration of cough Not reported Length of hospital stay Montelukast group = 4.65 +/- 1.97 days	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials High proportion of parents refused to join study, and no assessment of if

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Israel Study type RCT Aim of the study Evaluate the effect of montelukast on clinical progress and on cytokine profiles in infants hospitalized with acute bronchiolitis Study dates Not stated Source of funding Not stated	Characteistic: Montelukast (n = 23); Placebo (n = 30) Age, months: 3.2 +/- 2.8; 4.5 +/- 4.2 Male/Female: 15:8, 14:16 Illness days before admission: 2.9, 3.9 Positive RSV test: 74%; 80% Inclusion criteria Hospitalised Aged > 4 weeks and <2 years Respiratory symptoms for < 4 days Symptoms of bronchiolitis include: prodromal rhinorrhoea and cough, followed by at elast 2 of the following signs: chest retractionsm tachypnoea, wheezing, or rales. First episode of wheezing or shortness of breath Randomisation within 12 hours of admission Informed consent Exclusion criteria Not stated	hydroxypropyl cellulose and magnesium stearate. Decision to discharge based on clinical assessment by physician.	Block randomisation, patients stratified by age <3> months. Randomisation by third party. Concealment Sealed envelopes. All parent, staff and investigators blinded to allocation. Statistical methods Data tested for normal distribution T-test for continuous variables Mann-Whitney U test for dichotomous variables Sample size calulcation Decrease Length of Stay by 30% at 80% power and alpha 0.05	Placebo group = 4.63 +/- 1.88 days Time to medical fit for discharge Montelukast group = 3.42+/- 1.22 days Placebo group = 3.52 +/- 1.77 days Change in Respiratory rate Not reported Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation Not reported Hospital admission rate Inpatient study Adverse effects (including mortality) No described by group Clinical score (not selected by GDG)	these differed from those randomised. Other sources of bias Children up to the age of 24 months included in study Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Montelukast group = 6.1 +/- 2.4 days Placebo group = 4.8 +/- 2.2 days	
Full citation Zedan,M., Gamil,N., El-Assmy,M., Fayez,E., Nasef,N., Fouda,A., Settin,A., Montelukast as an episodic modifier for acute viral bronchiolitis: a randomized trial, Allergy and Asthma Proceedings, 31, 147-153, 2010 Ref Id 208554 Country/ies where the study was carried out Egypt Study type RCT with additional observational control group Aim of the study Evaluate the use of montelukast as a line of therapy in acute phase of clinically diagnosed bronchiolitis Study dates Not stated	Sample size 105 admitted 85 offered participation 85 randomly assigned Montelukast = 47; placebo = 38 Completed = 46; = 37 Characteristics Characteristic: Montelukast, Placebo Age (months): 3.5 +/- 2.37, 3.3 +/- 2.36 Male/Female ratio: 30/16, 22/15 Inclusion criteria Aged 1 to 24 months Clinically diagnosed bronchiolitis - repiriatory distress preceded by flu-like symptoms resulting into a sort of obstrcutive emphysema with wheezes and inconstant rales Exclusion criteria	Interventions Montelukast (in sodium salt form) 4 mg, daily until discharge from unit. The excipients were mannitol, hydroxypropyl cellulose and magnesium stearate Matching placebo daily until discharge from unit. The excipients were mannitol, hydroxypropyl cellulose and magnesium stearate.	Details Ethics University ethics approval Informed consent from parents Setting University hospital Randomisation Randomisation by computer via third-party. Concealment Sealed envelopes. All parent, staff and investigators blinded to allocation. Statistical methods Data tested for normal distribution T-test for continuous variables	Results Change in O2 saturation Not reported Duration of cough Not reported Length of hospital stay Montelukast group: 3.34 (SD 1.38) Placebo group: 5.42 (SD 3.47) Change in Respiratory rate Not reported Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation Not reported	Limitations Based on NICE guidelines manual 2012: Appendix C: Methodology checklist: randomised controlled trials High proportion of parents refused to join study, and no assessment of if these differed from those randomised. Other sources of bias Children up to the age of 24 months included in study Other information Study appears to have copied methods of Amirav 2008 study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not stated	History of prematurity, previous hospitalisation due to respiratory condition, previous use of bronchodilators or corticosteroids. Immunodeficiency or underlying cardiopulmonary disease		Mann-Whitney U test for dichotomous variables Sample size calulcation Decrease Length of Stay by 30% at 80% power and alpha 0.05	Hospital admission rate Inpatient study Adverse effects (including mortality) Not reported Clinical score at discharge (not selected by GDG based on clinical score by Wang et al, 1992) Montelukast group = 2.12 +/- 0.66 Placebo group = 2.42 +/- 0.9	

I.18 What is the efficacy of oxygen supplementation (non-humidified, humidified and high-flow) and of CPAP?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Milesi,C., Matecki,S., Jaber,S., Mura,T., Jacquot,A., Pidoux,O., Chautemps,N., Novais,A.R., Combes,C., Picaud,J.C.,	Sample size - 58 infants admitted to PICU with RSV bronchioitis - 37 not eligible: 25 infants presented with M-WCAS <4, 6 infants >6 months old, 6	Interventions Initial management: - Aspiration of secretions, if necessary, and delivery of a humidified air/oxygen blender from a heating	Details Setting: PICU of a University Hospital Randomisation and concealment:	Results Protocol outcomes nCPAP group n=10; control group n=9 Mean (SEM)	Limitations Based on NICE appendix C checklist - Not blinded - Some infants received β-adrenergic agent and/or

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cambonie,G., 6 cmH2O continuous positive airway pressure versus conventional oxygen therapy in severe viral bronchiolitis: a randomized trial, Pediatric Pulmonology, 48, 45-51, 2013 Ref Id 282188 Country/ies where the study was carried out France Study type Randomised, controlled Aim of the study To compare the effects of nasal continuous positive airway pressure (nCPAP) and conventional oxygen therapy on the clinical signs of respiratory distress and the respiratory muscle workload in acute viral bronchiolitis Study dates Three consecutive RSV epidemic periods from November 2006 to March 2009	intubated by ambulance crew before admission, 3 already treated by nCPAP - 21 eligible - 2 refused consent - 19 randomised: 10 nCPAP group, 9 control group Characteristics Characteristic: nCPAP group; control group; p value Mean (SEM) - Age, weeks: 6.8(0.9); 8.2(1.7); 0.47 - Weight, kg: 4.5(0.5); 4.1(0.2); 0.4 - M-WCAS: 5(0.2); 4.7(0.2); 0.24 - Respiratory rate (breaths/min): 51(4.5); 49(3.5); 0.94 - Oxygen saturation: 97(1); 95(1.6); 0.42 - Fraction of inspired oxygen (Fi02): 33(2); 32(1.6); 0.59 - Heart rate (beats/min): 165(3); 162(4); 0.56 - Mean arterial blood pressure (MAP, mmHg): 66(6); 68(8); 0.83	base in order to reach an oxygen saturation of 94-98% - 120ml/kg venous perfusion with a binary parental nutrition preparation was started - Corticosteriod and bronchodilator administration were stopped on admission, and no enteral nutrition was given during the protocol Study treatment: - nCPAP was generated with the Infant Flow Ventilator, the flow was adjusted to deliver a positive continuous pressure of 6cmH20 via a mask connected to a twin injector nozzle fixed to the patient by a specifically designed bonnet - Infants in the control group continued to receive a heated and humidified air/oxygen mixture delivered through a nasal cannula, which	Randomised using sequentially numbered, opaque sealed envelopes from the Department of Medical Information of the institution Outcome measures: - Single observer who was not involved in patient care or pressure recordings, quantified the respiratory distress using M-WCAS, with the help of a visual analogue scale to standardise the scoring of accessory muscle use and wheezing - An investigator who was unaware of the M-WCAS was designated to measure esophageal pressure using an esophageal balloon catheter connected to a differential pressure transducer system - M-WCAS was assessed hourly and esophageal pressure was measured 1 and 6 hours after the start of the procedure Statistical methods: - 15 patients needed to demonstrate a twofold	1. Change in O2 saturation (%): 0.7(1); 2.4(3) 2. Change in arterial or capillary carbon dioxide levels: - Change in PC02: 6(2); 4(4) - PC02 decreased in the nCPAP group from 55torr to 49torr at H6 p=0.047. Not reported for control group. 3. Change in disease severity score: - Change in M-WCAS: 2.4(0.4); 0.5(0.4) - The linear model confirmed the variation in M-WCAS between h0 and H6 only in the nCPAP group -2.4(1.05) vs -0.5(1.3) p=0.03 - The decline in M-WCAS between H0 and H6 in the nCPAP group was correlated with the M-WCAS value at H0, with a Spearman correlation coefficient of 0.64 p=0.04	corticosteriods before study treatment - Small sample size - Only 8 out of 10 nCPAP group patients and 7 out of 9 control group patients completed esophageal pressure measurements - 4 patients switched from the nCPAP group to the control group because of worsening condition (ITT used LOCF) Other information Switching patients from one group to the other: - At any moment during this study, an increase of more than 30% in M-WCAS justified a switch to the other treatment group - Switching only occured in the control group: 4/9 vs 0/10 p=0.032 - The change in group of the 4 patients occured 1, 3, 4 and 5 hours after the protocol had begun

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Clinical Research Department of Montpellier Univeristy Hospital Centre	- Partial pressure of C02 (PC02, torr): 55(2); 57(4); 0.58 - PTPesinp/breath (cmH20/s): 14.6(0.9); 14.6(1); 0.99 - PTPesinsp/min (cmH20/s/min): 975(169); 918(172); 0.81 - Four infants in each group had received a nebulised β-adrenergic agent 4-6 hours before study enrollment - Corticosteriod treatment had been administered to three infants of the nCPAP group and two infants of the control group Inclusion criteria - <6 months old - Admitted to PICU with severe respiratory syncytical virus bronchiolitis - RSV bronchiolitis confirmed by nasopharyngeal enzyme immunoassay - Severe respiratory distress defined by a modified Wood's clinical	allowed a maximum gas flow of 2.5l/min - In both groups air/oxygen blend was adjusted in order to reach an oxygen saturation of 94-98% - Protocol last 6 hours after the allocated treatment was begun nCPAP group - 6cmH20 pressure support delivered by a jet flow generator Control group - air/oxygen mixture from a heated humidifier	greater decrease in M-WCAS in the nCPAP with an alpha risk of 5% and a power of 80% - Intention-to-treat analysis used last-observation-carried-forward - Variations in outcomes between 0 and 6 hours for each group and between groups assessed using student t-test or Kruskal-Wallis - Changes between groups used a linear mixed model for longitudinal data with intercept and random slope effects - Qualitative variables compared with chi-squared or Fischer's exact test - Spearman correlation coefficient for continuous variables	- In the control group observed an inverse correlation between the M-WCAS at H0 and the difference between M-WCAS at H0 and H6, with a Spearman correlation coefficient of -0.76 p=0.02 4. Length of hospital stay: - nCPAP group: nCPAP lasted 72(11) hours and hospital stay was 5(0.5) days - In the control group nCPAP lasted 112(12) hours for the four patients that changed groups during the study - The hospital stay for the control group was 5(0.5) days 5. Change in respiratory rate (breaths/min): 7(4); 1.3(4) 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation:	- After nCPAP was started in these infants, M-WCAS improved from 5.8(1) to 2.5(1.5) p=0.039 Change in respiratory distress - nCPAP group; control group: Mean (SEM) - Fi02: 7(3); -5(5) - MAP: -4(6); -4(5) - PTPesinsp/breath (cmH20/s): [n=8] 10(2); [n=7] 1.4(3) - PTPesinsp/min (cmH20/s/min): [n=8] 666(134); [n=7] 116(117)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	asthma score (M-WCAS) >4 - No invasive or noninvasive ventilation, including nCPAP, prior to PICU admission - No underlying cardiopulmonary or neuromuscular disease and no pneumothorax on chest radiograph - Signed authorisation by the parents Exclusion criteria Not described			No patients had to be intubated and none presented pneumothorax 8. Adverse effects Need to switch treatment groups because of a >30% worsening of clinical score: 4 control and 0 nCPAP Not reported: 7. Need for/Use of feeding support	
Full citation Hilliard,T.N., Archer,N., Laura,H., Heraghty,J., Cottis,H., Mills,K., Ball,S., Davis,P., Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis, Archives of Disease in Childhood, 97, 182-183, 2012 Ref Id 211690 Country/ies where the study was carried out United Kingdom Study type	Sample size 19 infants randomized to intervention or control group. Characteristics Median age = 3.0 months, range 0.3 to 11.3 months. Inclusion criteria Infants aged less than 12 months admistted to a general paediatric ward with a clinical diagnosis of bronchiolitis (cough, tachypnoea, chest retractions, and crackles on	Interventions High flow nasal cannula therapy via Vapoterm 2000i device, started at flow of 4 L/min with 100% oxygen, and flow rate increased by 0.5 L every 5 minutes up to 8 L/min if tolerated to achieve target SpO2 for 24 hours. If clinically stable, FiO2 decreased in steps of 10% at 4-hourly intervals, with same target SpO2. Control	Details Following parental inormed consent, infants were randomised as follows: - 11 to HHHFNC group - 8 to HBO group Statistical analysis Treatment effects in this study were analysed by using Mann-Whitney tests to compare results between groups.	Results Outcomes Primary: SpO2 at 8 hours post-randomisation Secondary: HR, RR, blood pressure, FiP2, combined bronchiolitis severity score Outcomes were recorded at 4, 8, 12, 24, 36, 48 hours. Additional outcomes recorded: the time to switch to dry nasal cannula oxygen, the total time in oxygen, time to feed, time to	Limitations Based on NICE appendix C checklist The study used a randomised design but the risk of bias was unclear as the method to generate the sequence was not reported. The trial was not blind. One participant was changed from the control to intervention group due to "clinical reasons", but no details were provided. Weaning protocols have been reported to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Prospective, randomised, open pilot study. Aim of the study To assess safety and feasibility of using heated humidified high flow nasal cannula (HHHFNC) therapy in children with bronchiolitis. Study dates Not reported. Source of funding Two vapoterm devices were provided free of charge by the distributing company. There was no other funding reported for this study.	auscultation); moderately severe disease defined as a head-box oxygen requirement of at least 35%, moderate to severe tachypnoea, increased effort of breathing and in whom feeding had been discontinued. Exclusion criteria Congenital cyanotic heart disease, repeated severe apnoeas, or severe hypercapnia with acidosis on blood gas analysis of pH < 7.2.	Conventional therapy head-box oxygen (HBO).		discharge and total lenght of stay. Results SpO2% at 8h, median (range) and p-value - HHHFNC = 100% (94-100) - HBO = 96% (93-100) p-value = 0.04 SpO2% at 12h, median and p-value - HHHFNC = 99% (96-100) - HBO = 96% (93-99) p-value = 0.04 SpO2% at 24h, median and p-value HHHFNC and HBO groups reported to be not significantly different. Severity score Clinical outcomes were reported as not being significantly different. However, severity scores were not available. Lenght of hospital stay in hours, median (range) and p-value	be different, and these differences could have biased outcomes like length of stay and time to discharge. Small trial, authors reported that to show even a large reduction in the need for further respiratory support would need a study with over 100 patients in each arm. Other information Indirectness does the study macth the review protocol in terms of population: yes intervention: yes outcome: yes indirectness: none Setting Bristol Children's Hospital, Department of Paediatric Respiratory Medicine.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- HHHFNC = 162 (96-300) - HBO = 164 (84-233) p-value = 0.7 Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation no infant required additional respiratory support FiO2 at 8, 12, and 24h reported to be significantly higher in HHHFNC group. Adverse events All participants in the intervention group tolerated the treatment well.	
Full citation Thia,L.P., McKenzie,S.A., Blyth,T.P., Minasian,C.C., Kozlowska,W.J.,	Sample size - 53 eligible - 11 families not approached for consent	Interventions Setting: Peditric HDU at royal London Hospital	Details - Study lasted 24 hours - Randomised to receive either standard treatment plus nasal CPAP for 12 hours followed by standard	Results Protocol outcomes	Limitations Based on NICE appendix C checklist

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Carr,S.B., Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis, Archives of Disease in Childhood, 93, 45-47, 2008 Ref Id 208307 Country/ies where the study was carried out UK Study type Randomised, crossover, controlled Aim of the study To compare continuous positive aiways pressure (CPAP) with standard treatment in the management of bronchiolitis Study dates Over three winters from October 2002 to March 2005 Source of funding None declared	(language barrier or study team not avaliable) - 11 families refused consent - 31 randomised: 16 CPAP first, 15 standard care first - 2 infants from standard care withdrawn: 1 ventilated, 1 transferred to CPAP - 29 completed: 19 CPAP first, 13 standard care first Characteristics Characteristic: CPAP first; standard treatment first Mean(SD), median(IQR) or n - Number: 16; 15 - Premature (<37/40): 3; 2 - Age, months: 2.6 (1.5 to 4.9); 2.5 (1.2 to 5.4) - Days from onset of illness: 3.5(1.5); 3.2(0.9) - HR: 151(21); 150(17) - RR: 53(10); 56(19) - pH: 7.33(0.04); 7.30(0.05) - PC02 (kPa): 7.38(1.0); 7.51(1.2) - RSV positive: 10; 10	Randomisation and concealment: Randomised into blocks of four, blind to those who recruited for subjects Outcomes measures: PR, RR, capillary PC02 and capillary pH were recorded at 6 hour intervals (before treatment or change in treatment and midway through the 12 hours) Statistical methods: - 28 patients to show a difference of a fall of 1kPa in PC02 with 80% power at 0.05 significance at 12 hours - Paired t tests for continuous variables and Mann-Whitney for other - Analysis of variance to compare dempgraphic and presenting PC02	treatment alone for the next 12 hours OR standard treatment alone for 12 hours followed by standard treatment plus nasal CPAP for the next 12 hours - Standard treatment was defined as: minimal handling, intravenous fluids and oxygen by nasal prongs or face mask - Nasal CPAP was applied using the Infant Flow System with pressures of 5-6cm H20 - Both groups had supplemental oxygen to achieve oxygen saturation >92% - Corticosteriods, bronchodilators or adrenaline were not used - Withdrawn from study if: recurrent apnoeas, worsening hypercapnia and profound hypoxia despite maximal oxygenation	2. Change in arterial or capillary carbon dioxide levels (kPa) Change in PC02: standard treatment first; CPAP first - 0 to 12 hours: -0.53 (SD 1.25, SE 0.29); -1.35 (SD 1.37, SE 0.34) - 12 to 24 hours: -0.41 (SD 0.87, SE 0.24); 0.5 (SD 0.90, SE 0.22) - Change after CPAP - Change after standard care: 0.12 (SE 0.46); -1.85 (SE 0.47) - Overall change: +0.04, -0.92 (p < 0.015) 4. Length of hospital stay, mean days Based on combined treatment periods. CPAP first: 6.3 (SD 2.3) Standard treatment first: 5.6 (SD 1.5) p=0.16	- 11 eligible patients not approached for consent - 9 patients received triclofos as sedation to tolerate CPAP - Randomisation unclear - Blinding unclear - Bronchiolitis not defined Other information - Three infants who received CPAP first and six infants who received standard treatment first required one dose of triclofos as sedation to tolerate CPAP - No significant difference in PC02 in the infants who had triclofos and those who did not at the end of the treatment periods

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Number ventilated: 0; 2 Inclusion criteria - <1 year of age - Clinical diagnosis of bronchiolitis - Capillary partial pressure of C02 measurements >6kPa - Written informed consent from parents Exclusion criteria - Infants with congenital heart disease, neuromuscular disease, and mid-face dysmorphism prohbiting use of nasal prongs - Requiring immediate invasive ventilation due to recurrent apnoeas, profound hypoxia, collapse or PC02 >12 kPa - Chronic lung disease - Premature			7. Need for/Use of feeding support: All children received intravenous fluids 6. Need for high flow humidified oxygen, CPAP or mechanical ventilation 1 in standard care group; 0 in CPAP group 8. Adverse effects Two infants receiving standard treatment first were withdrawn: - The first infant was withdrawn at 10 minutes because of profound hypoxia, the infant was electively treated with CPAP and improved - The second infant was withdrawn with a PC02 >12kPa at 9 hours for invasive ventilation - 9 of 29 infants required one dose of triclofos to tolerate CPAP. Not reported:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1. Change in O2 saturation 3. Change in disease severity score 5. Change in respiratory rate	

I.19 What is the efficacy of suction to remove secretions from the upper respiratory tract?

No studies meeting the specified inclusion criteria were identified

Appendix J: GRADE tables

The GRADE tables are in a separate appendix document.

Appendix K: Forest plots

K.1 Hospital admission rate

Figure 4: 1ALL STUDIES – Very Low

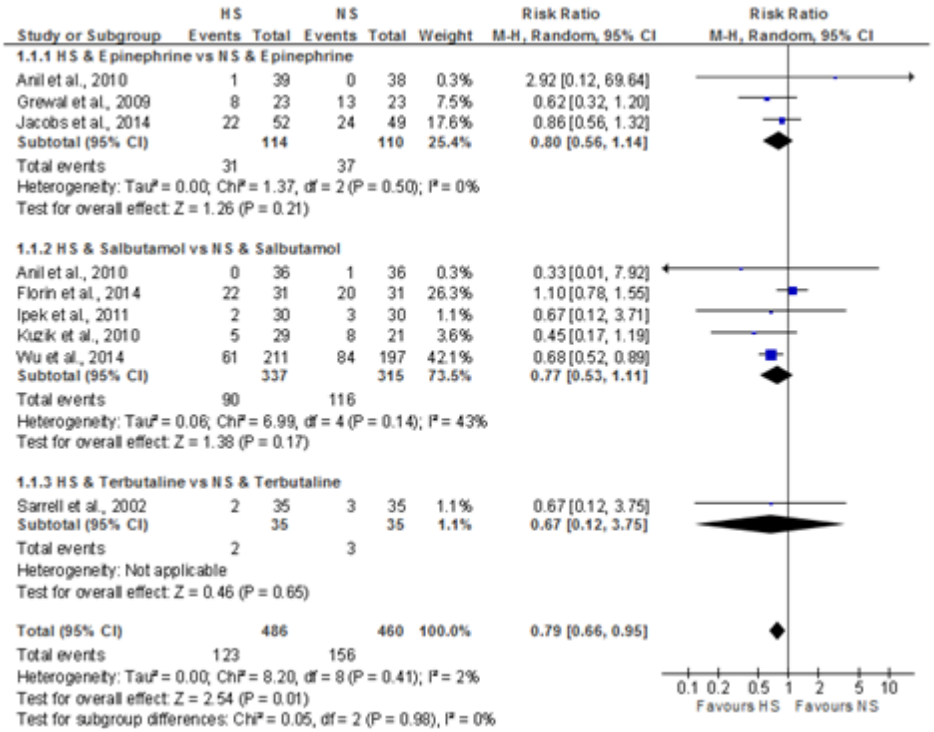


Figure 5: OLD STUDIES – Very Low

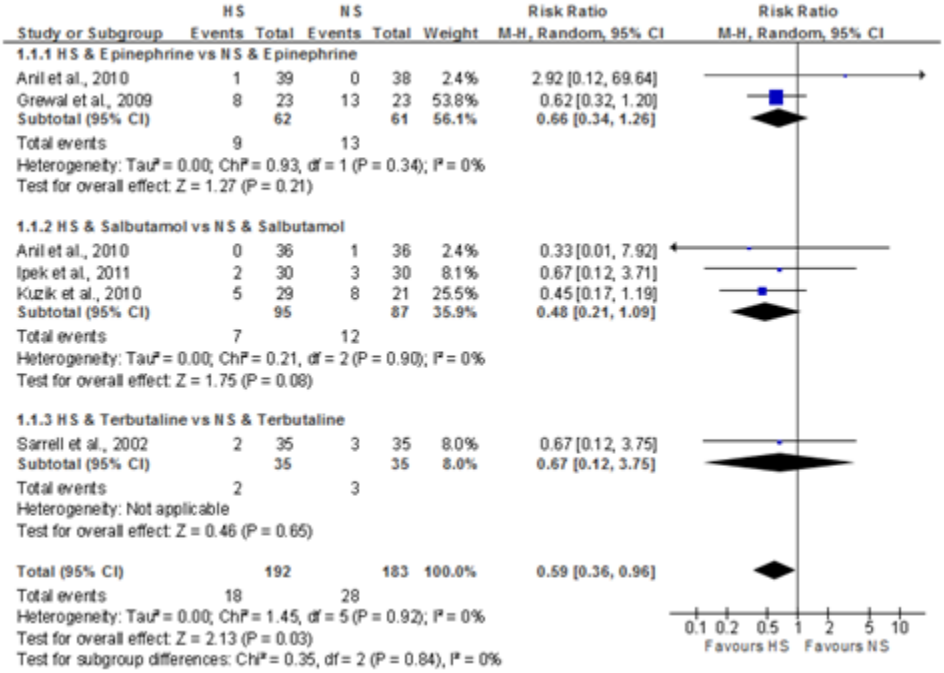
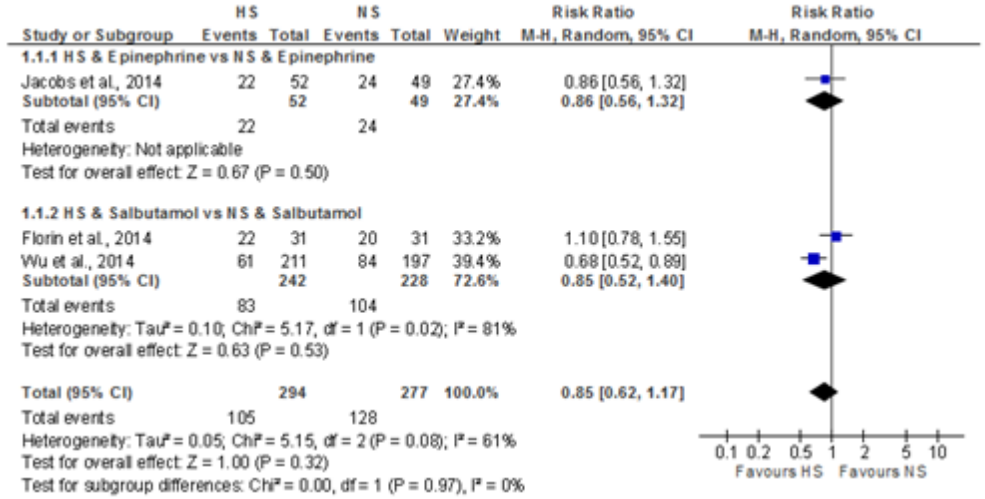
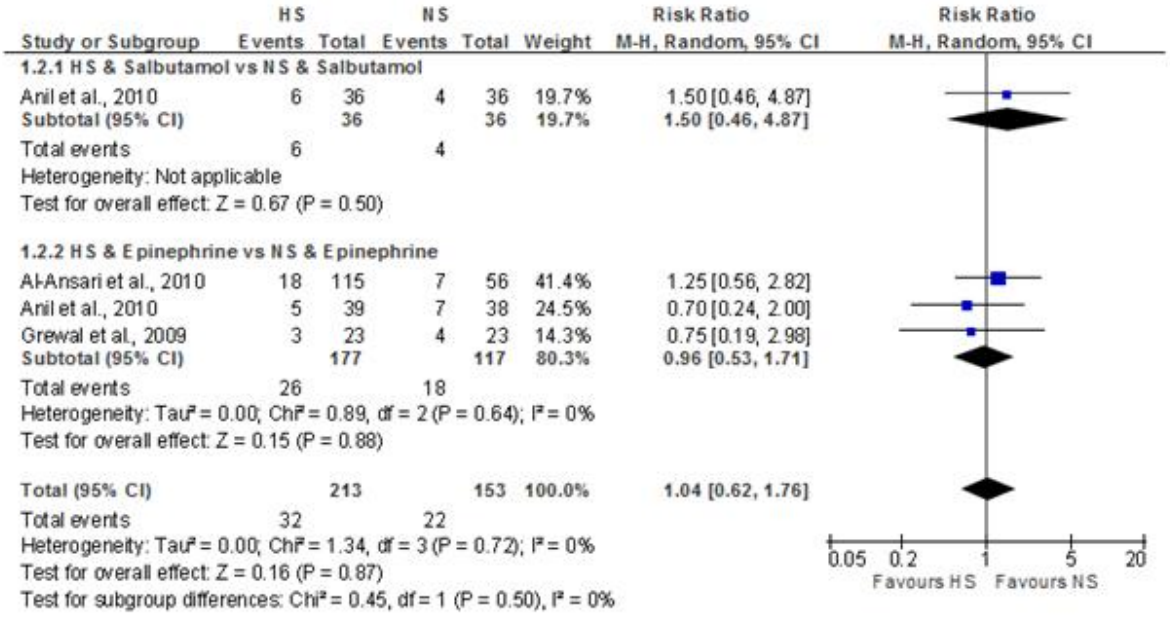


Figure 6: NEW STUDIES – Very Low



K.2 Hospital re-admission rate

Figure 7: OLD STUDIES – Very Low



K.3 Length of stay I

Figure 8: ALL STUDIES – Very Low

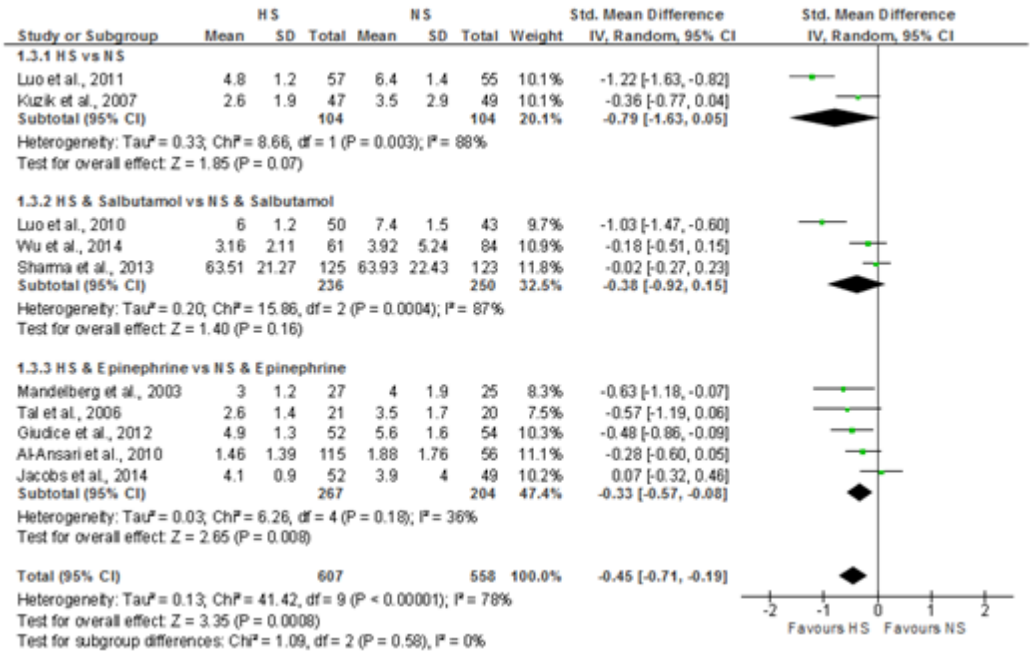


Figure 9: OLD STUDIES – Very Low

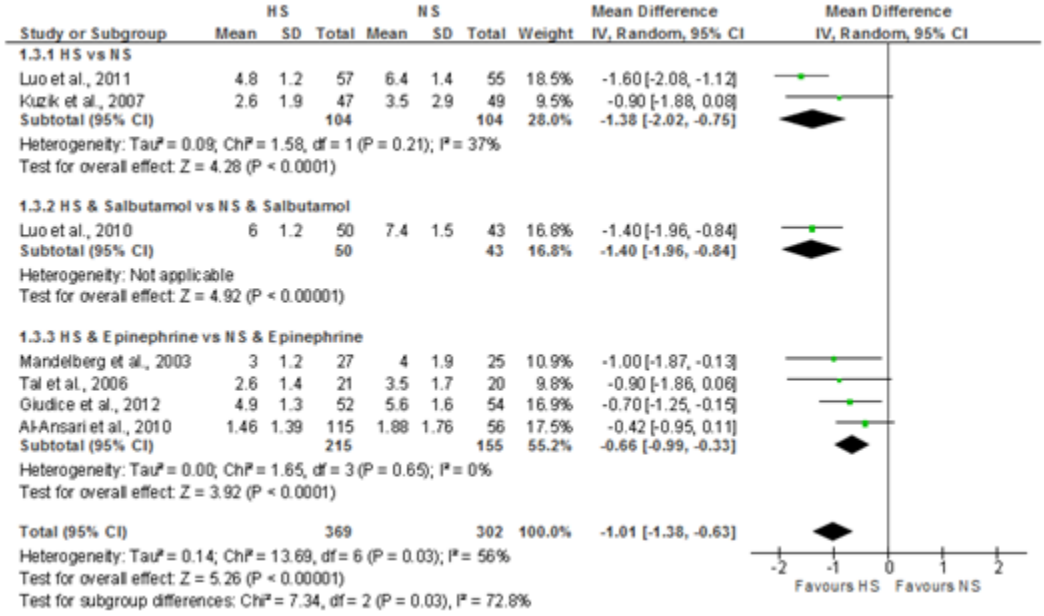
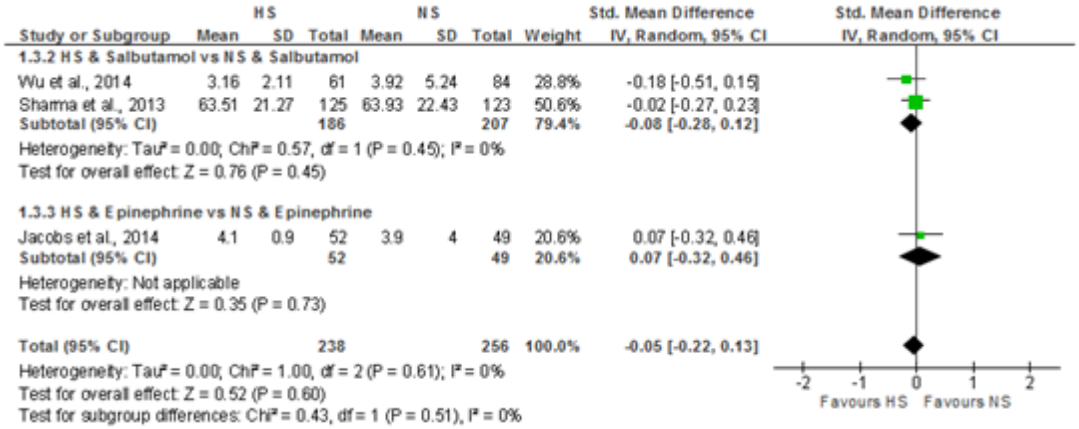


Figure 10: NEW STUDIES – Low



K.4 Length of stay II

Figure 11: SABRE TRIAL comparing HS with usual care: moderate quality

K.5 Disease severity score at 60 minutes

Figure 12: ALL STUDIES – Very Low

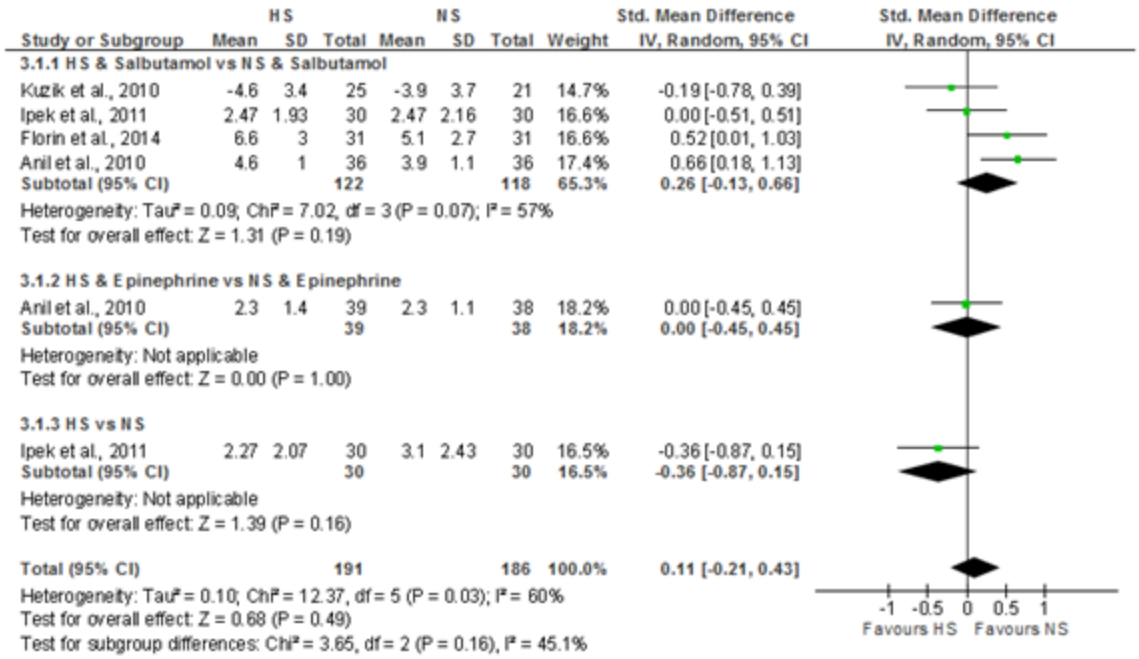


Figure 13: OLD STUDIES - Very Low

1) OLD STUDIES – Very Low

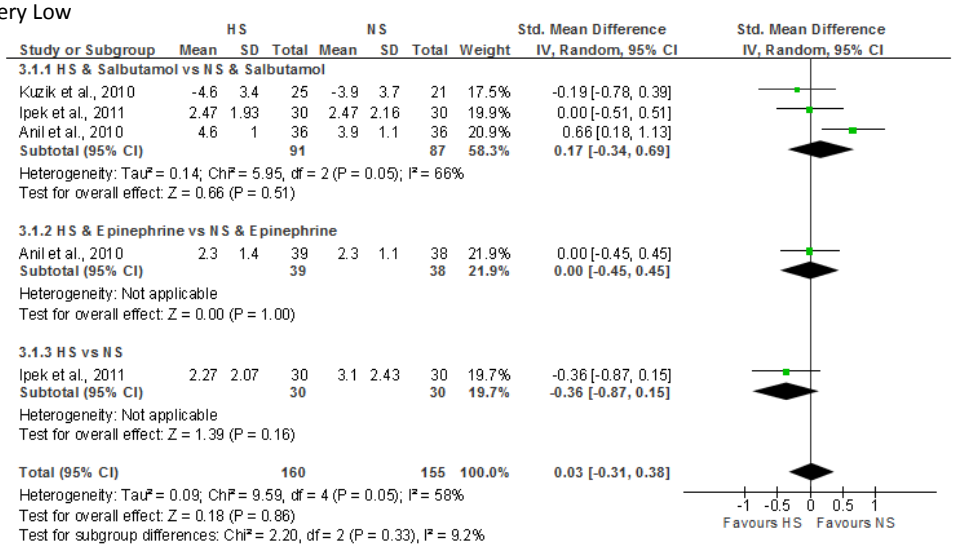
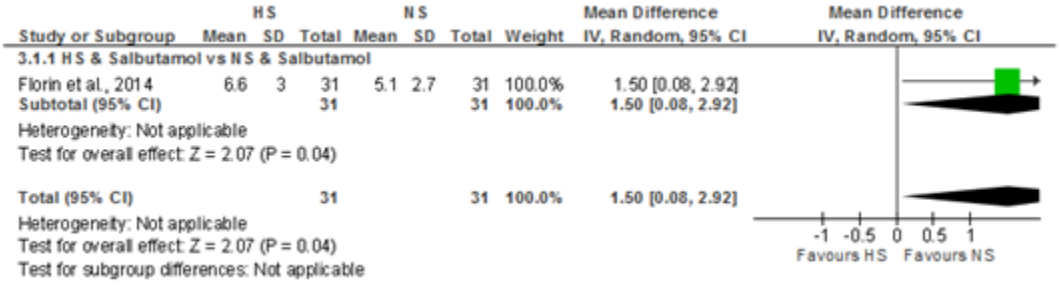


Figure 14: NEW STUDIES – Low



K.6 Disease severity score at 24 hours / 1 day

Figure 15: ALL STUDIES – Very Low

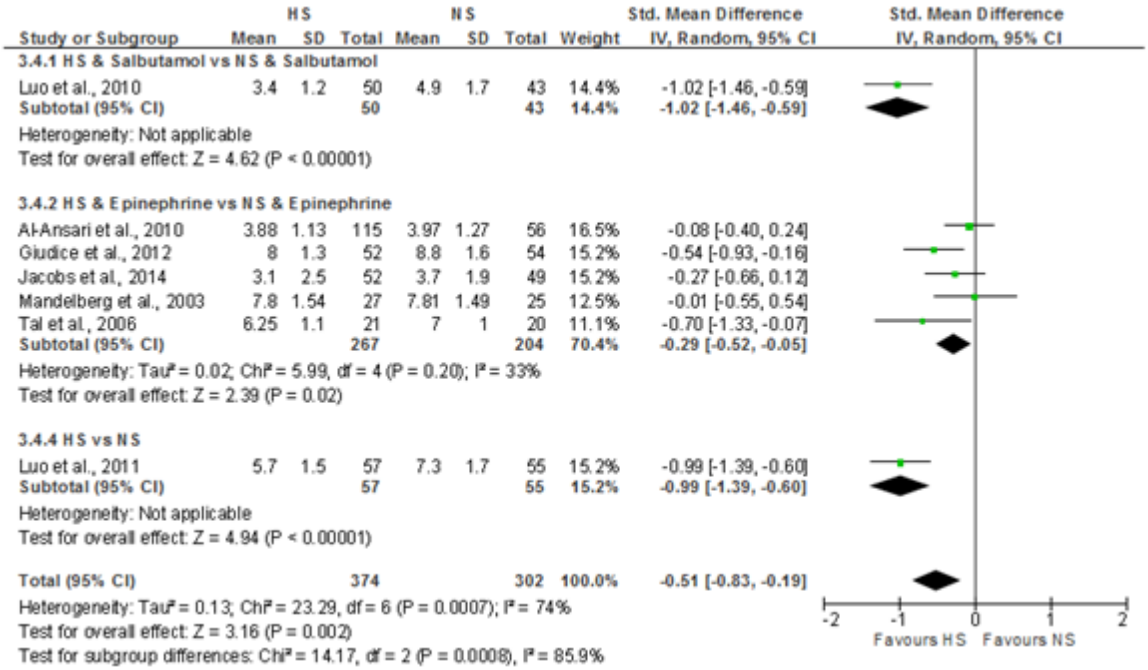


Figure 16: OLD STUDIES – Very Low

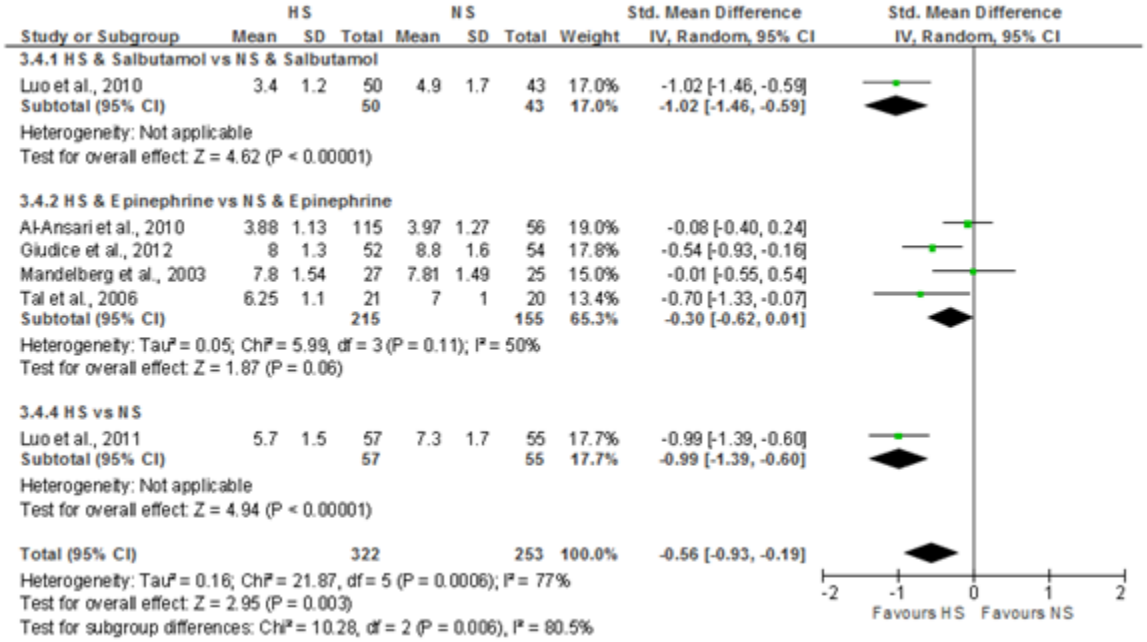
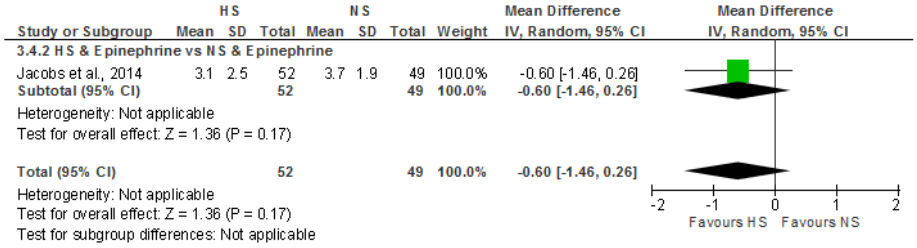


Figure 17: NEW STUDIES – Low

1) NEW STUDIES – Low



K.7 Respiratory rate (change)

Figure 18: ALL STUDIES – Very Low

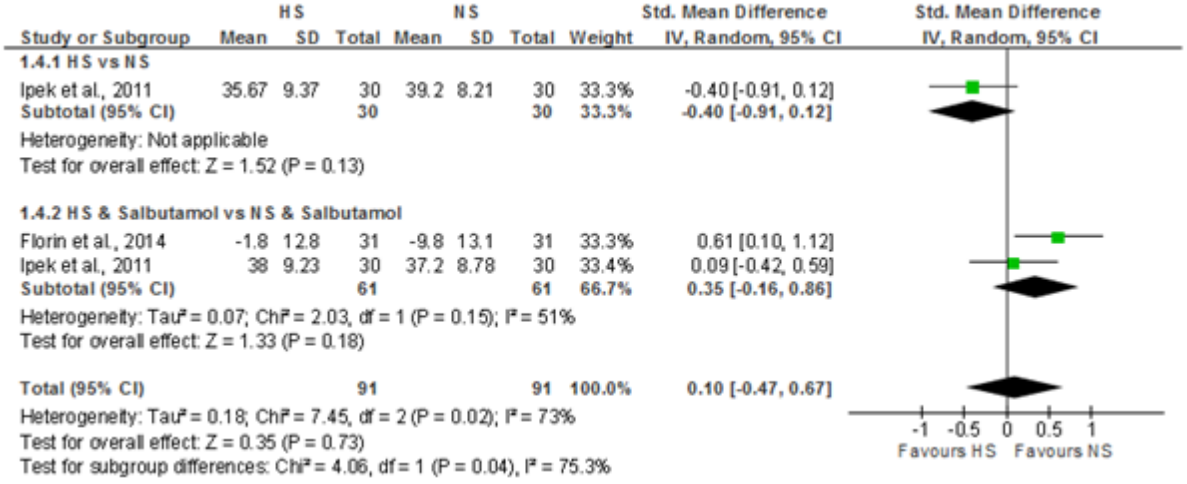


Figure 19:OLD STUDIES – Very Low

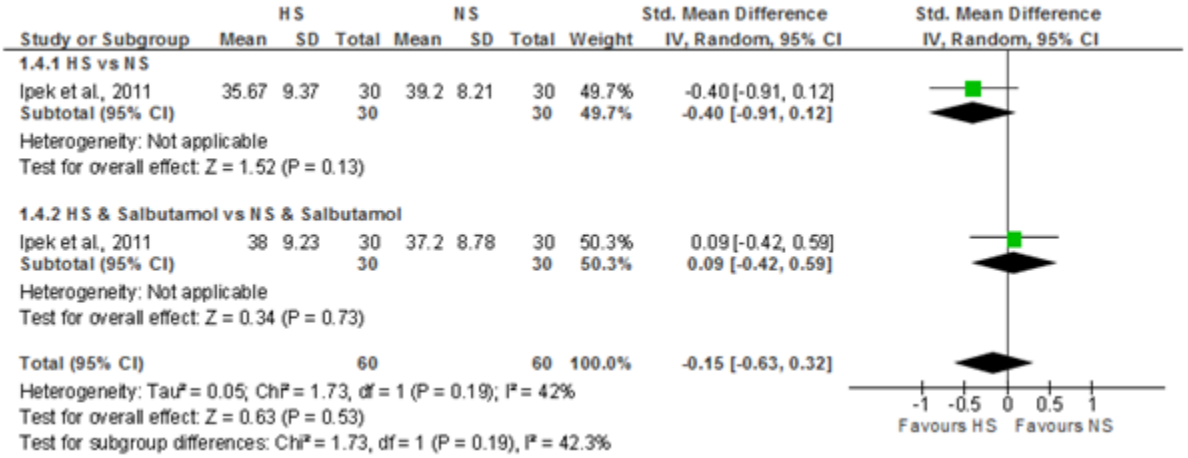


Figure 20: NEW STUDIES – Low