National Institute for Health and Care Excellence

Final

Bronchiolitis in children: diagnosis and management

[A] Evidence reviews for criteria for referral, admission, oxygen supplementation, and discharge

NICE guideline NG9

Evidence reviews underpinning recommendations 1.2.1, 1.2.2, 1.3.2, 1.4.4 and 1.5.1

August 2021

Final

These evidence reviews were developed by the Guideline Updates Team

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Contents

1 Criteria for referral, admission, oxygen supplementation, and discharge

1.1 Review question

What thresholds of oxygen saturation should indicate that a baby or child with suspected or confirmed bronchiolitis should be immediately referred to hospital, admitted to hospital, given supplementary oxygen, and can be safely discharged?

1.1.1 Introduction

Bronchiolitis is a lower respiratory tract infection most reported in babies under the age of one. Symptoms are similar to those of the common cold but can be associated with serious outcomes. Therefore, identifying babies and children who are experiencing, or are likely to experience, more severe disease is important for choosing appropriate care. Current NICE guidance recommends that oxygen saturation below 92% should be considered alongside other criteria when deciding if babies and children with suspected bronchiolitis should be referred to hospital, admitted, given supplementary oxygen, or discharged.

A Health Technology Assessment concluded that a lower oxygen saturation threshold could be no less safe than the current threshold of 92%. A review of this evidence is timely, as the incidence of new cases of bronchiolitis may not follow typical seasonal trends during the SARS-COV-2 pandemic (diagnosis of COVID in babies and children presenting with suspected bronchiolitis is outside of the scope of this update, but guidance on this has been produced by the Royal College of Paediatrics and Child Health). It is important to avoid unnecessary admissions and excessive length of stay in hospital as these may not be of benefit to some babies and children with bronchiolitis and may also have wider impacts on provision of care. This review will assess if an oxygen saturation threshold lower than the current recommendation of 92% is safe with respect to referral to hospital, admission to hospital, indicating oxygen supplementation, and discharge.

1.1.2 Summary of the protocol

Field	Content
Population	Inclusion: babies and children with suspected or confirmed bronchiolitis, including subgroups particularly at risk from severe disease for example: babies and children born prematurely and babies and children with: • congenital heart disease • cystic fibrosis • immunodeficiency • chronic lung disease. Exclusions: • Adults • Babies and children on invasive ventilation

Intervention	Target oxygen saturation in air at a range of thresholds.
Comparator	Target oxygen saturation in air greater than or equal to 92%.
Outcomes	Related to admission or discharge • change in respiratory rate • change in oxygen saturation • reported feeding difficulty • readmission rate Related to management: • length of stay • need for high flow humidified oxygen, Continuous positive airway pressure (CPAP) or mechanical ventilation

1.1.3 Methods and process

Risk of bias was assessed in randomised controlled trials (RCTs) with the Cochrane risk of bias tool (2.0), and in observational studies with the ROBINS-I tool. Results of the risk of bias assessments can be found alongside the evidence table for each study (Appendices D.1 and D.2). Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to present results and to evaluate the quality of evidence by outcomes (see Appendix E). GRADE assessment domains include risk of bias, inconsistency, indirectness, and imprecision. Outcomes start at High, for example, for a randomised controlled trial, and can be marked down 1 or 2 levels for each domain through to Moderate, Low and Very Low evidence. Observational studies start at Low. Each of the evidence quality ratings are explained below:

High – Further research is very unlikely to change our confidence in the estimate of effect.

Moderate – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low – Any estimate of effect is very uncertain.

No evidence pooling was done for this review, therefore the evidence for each outcome in GRADE is provided by 1 study only.

There were no published minimally important differences (MIDs) available, so imprecision was graded based on default thresholds of 0.7 and 1.25 for risk ratios and hazard ratios. If either confidence interval crosses a threshold, the evidence is downgraded by 1 level. If both thresholds are crossed, the evidence is downgraded 2 levels.

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual using Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Evidence from the 2015 review

The studies included in the review conducted for the 2015 version of this guideline did not meet the inclusion criteria set out in the protocol for the 2021 review. This is because the studies did not compare 2 or more pre-specified oxygen saturation thresholds at which babies and children should be referred, admitted, given supplemental oxygen, and discharged from hospital, as specified by the current review protocol.

1.1.4.2 Included studies from the 2021 review

528 studies were identified by the search, 481 were excluded based on a title and abstract sift, and 47 were included for full text review. 2 studies were included: 1 randomised controlled trial reported in 2 publications, and 1 prospective observational study.

1.1.4.3 Excluded studies from the 2021 review

44 studies were excluded after full text review (Appendix I).

1.1.5 Summary of studies included in the effectiveness evidence review

Study	Population	Intervention	Outcomes
Cunningham 2015 RCT UK	Babies ≥6 weeks and ≤12 months of age admitted to hospital with bronchiolitis. n=307 in the 90% SpO_2 threshold group. n=308 in the 94% SpO_2 threshold group.	Babies' oxygen saturation was monitored with modified oximeters. Oxygen saturation of 90% was displayed as 94%. Healthcare professionals would stop supplemental oxygen at a displayed 94% when actual saturation was at 90%.	Time to actual discharge. Use of nasogastric tube feeding. Use of intravenous fluids. Need for supplemental oxygen. Time to readmission. Readmission to hospital within 7 & 28 days. High-dependency care. Respiratory rate at discharge. Mortality. Time to cough resolution. *
van Hasselt 2020 Prospective observational UK	Babies ≥6 weeks and ≤12 months of age admitted to hospital with bronchiolitis. n=162 in the 90% SpO_2 threshold group. n=158 in the 92% SpO_2 threshold group.	12 centres were included in the analysis. 6 centres had protocols that specified 90% SpO_2 as a threshold, and 6 that had protocols that specified 92% SpO_2 as a threshold.	Length of stay.
RCT – randomised controlled trial; SpO_2 – oxygen saturation.			
* Included even though not a protocol-specified outcome because it was the study's primary outcome.			

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

There were 2 studies relevant to the review protocol: a Health Technology Assessment (HTA) randomised controlled trial that compared management to a target of 90% oxygen saturation to the level of 94% oxygen saturation recommended at the time by the Scottish Intercollegiate Guidelines Network (SIGN 91, 2006); and a prospective observational study that compared 90% to 92% oxygen saturation as a threshold for admission.

The HTA reported 10 outcomes relevant to the review protocol.

The primary outcome of the HTA (time to cough resolution) was not included in the review protocol. However the HTA was an equivalence trial designed around cough resolution, therefore in a deviation from the protocol, evidence on cough was included in the current review and presented to the committee to allow them to decide on its relevance to the discussion around changes to oxygen saturation thresholds.

In GRADE, evidence quality ranged from high to low quality across the outcomes. The only domain where outcomes were marked down was imprecision, since the outcomes were considered to have a low risk of bias as the study is directly applicable to the review question, and could not be downgraded for inconsistency because it was not included in a meta-analysis. The committee believed that although the HTA used a comparator saturation threshold of 94% (rather than 92% which was the threshold recommended in the 2015 version of the guideline), it should not be marked down for indirectness.

For the results below, lower values indicate a better outcome for the 90% intervention arm unless otherwise stated.

Outcome	No. of participants	Effect estimate (95% CI)	Quality
Time to actual discharge (hours)	90% arm: 276 94% arm: 283	HR 1.46 (1.23 to 1.73) Higher values indicate quicker discharge for 90% arm	Medium
Use of nasogastric tube feeding (no. of events)	90% arm: 303 94% arm: 305	RR 0.9 (0.7 to 1.1)	Medium
Use of intravenous fluids (no. of events)	90% arm: 304 94% arm: 305	RR 1.0 (0.6 to 1.6)	Low
Need for supplemental oxygen (no. of events)	90% arm: 304 94% arm: 305	RR 0.8 (0.7 to 0.9)	High
Time to readmission (days)	90% arm: 307 94% arm: 308	HR 0.93 (0.43 to 1.98)	Low
Readmission to hospital within 7 days (no. of babies)	90% arm: 307 94% arm: 308	RR 0.6 (0.2 to 1.8)	Low
Readmission to hospital within 28 days (no. of babies)	90% arm: 307 94% arm: 308	RR 0.4 (0.2 to 0.7)	High
High-dependency care (no. of events)	90% arm: 307 94% arm: 308	RR 1.1 (0.5 to 2.6)	Low
Respiratory rate at discharge (breaths per minute)	90% arm: 307 94% arm: 308	MD 0 (-0.58 to 0.58)	High

Mortality (no. of events)	90% arm: 307 94% arm: 308	RR 0.2 (0.0 to 3.7)	Low
Time to cough resolution (days)	90% arm: 307 94% arm: 308	Median difference 1 (-1 to 2)	Low

The prospective observational study reported 1 outcome relevant to the protocol – length of stay. The study was rated as having a serious risk of bias, which translates as a very serious risk of bias in GRADE. As observational data starts in GRADE as "Low", the outcome was rated as Very Low quality.

Outcome	No. of participants	Effect estimate (95% CI)	Quality
Length of stay (hours)	90% arm: 181 94% arm: 139	MD -16 (8.47 to -23.53) Lower values indicate better outcome for intervention arm.	Very Low

See appendix E for full GRADE tables.

1.1.7 Economic evidence

A full literature search for economic studies was not conducted. However, a search was conducted to look for economic evaluations linked to any of the studies included in the clinical evidence review.

1.1.7.1 Included studies

One relevant study was identified for this review question, the Cunningham 2015 HTA report, which included an economic evaluation. A summary of the results is given below, with the full details reported in Appendix F.

1.1.7.2 Excluded studies

No studies which were identified as potentially relevant to this evidence review were excluded.

1.1.7.3 Summary of included economic evidence

One directly applicable trial-based economic evaluation with minor limitations conducted in the UK found that an oxygen saturation target of ≥90% dominated (was both more effective and less expensive) an oxygen saturation target of ≥94% in babies between 6 weeks and 12 months with a clinical diagnosis of bronchiolitis who were admitted to hospital.

Cunningham 2015			
Population & interventions	**Costs**	**Outcomes**	**Cost effectiveness**

Population: Babies between 6 weeks and 12 months with a clinical diagnosis of bronchiolitis who were admitted to hospital. **Interventions** Oxygen saturation target of ≥90% versus an oxygen saturation target of ≥94%.	**Cost differences:** Total NHS costs (£) **90% target:** 1612.30 **94% target:** 1901.83 **Difference:** -289.53 (95% CI -657, 78)	**Outcome differences:** Time to cough resolution (days – complete cases) **90% target:** 22.35 **94% target:** 23.13 **Difference:** -0.78 (95% CI -5.25, 3.69)	**Base-case analysis:** Probability 90% target cost-effective at different willingness-to-pay thresholds for a reduced day to cough resolution: **£0 – 91.5%** **£25 – 90.3%** **£50 – 86.5%**

1.1.7.4 Economic model

No economic modelling was undertaken for this review question, as it was decided the published economic evidence was sufficient for decision making.

1.1.8 The committee's discussion and interpretation of the evidence

1.1.8.1. The outcomes that matter most

The committee noted that once bronchiolitis is resolved there are usually no long-term consequences, and the key objective in bronchiolitis management is to ensure that babies and children have full resolution without complications.

The critical outcomes are change in respiratory rate, change in oxygen saturation, reported feeding difficulty, readmission rate, length of stay, and the need for high flow humidified oxygen, CPAP or mechanical ventilation. Length of stay and readmission rate were noted as contributing to improved flow of patients through the system.

The committee noted that the significantly reduced number of readmissions to hospital within 28 days in the 90% saturation threshold arm of the HTA appeared to be clinically implausible. The study investigators suggested that this may be linked to a shorter hospital stay and consequently a lower risk of oxygen toxicity (though the committee felt this was unlikely to be an issue in readmissions up to 28 days) or less exposure to nosocomial infections.

The HTA reported an outcome of return to feeding at 75% of normal. However, data for this outcome were not included in the guideline update because the definition of this outcome was not well reported, and hence its relevance to the 'reported feeding difficulty' outcome of the review protocol was uncertain.

Important outcomes are dehydration, work of breathing, adverse events (including mortality), change in oxygen saturation, change in arterial or capillary blood carbon dioxide levels, change in disease severity score, change in respiratory rate, and need for feeding support (either tube feeding or intravenous fluids). Mortality was considered an important rather than a critical outcome because bronchiolitis has a relatively low mortality rate. However, the committee noted that the 2 deaths reported in the HTA were events that they did not expect to have occurred in a low-risk population (i.e. babies and children aged 6 weeks to 1 year without certain comorbidities) and that ordinarily no baby or child should die from this condition.

Although the primary outcome of the HTA was cough resolution, the committee stated that this was an unusual choice and was not a key clinical concern, therefore cough resolution was not considered a critical or important outcome. However, they acknowledged that cough resolution was an important factor for parents and carers, which could trigger reattendance if it is causing concern, and lay members recalled from experience that cough can linger for

several weeks and prevent babies from sleeping. Lay members noted that overall, cough was not the key concern for them, and breathing difficulties were the more worrying issue.

The committee also noted that some babies in hospital improve on very little oxygen to reach the target saturation threshold, but when asleep saturation can suddenly dip which may cause a delay to discharge in a baby or child who is otherwise recovering.

1.1.8.2 The quality of the evidence

Two studies were included in the update.

A Health Technology Assessment (HTA) study involving an RCT was assessed as low risk of bias. Overall, the RCT was well conducted and reported, with minor issues relating to the reporting of the definition of cough resolution and return to normal feeding. The overall outcome quality in the HTA ranged from high to low. The only domain in which outcomes were marked down was imprecision, since the outcomes were considered to have a low risk of bias as the study is directly applicable to the review question, and could not be downgraded for inconsistency because it was not included in a meta-analysis.

A prospective observational study was assessed as serious risk of bias. A key issue was that it compared 2 different groups of centres and baseline characteristics were not reported or adjusted for, therefore population and use of co-interventions were unlikely to be balanced across the 2 groups. It reported only 1 outcome relevant to the protocol which was rated as very low quality due to serious risk of bias of the study.

The committee felt the population of the HTA (babies aged 6 weeks to 12 months with bronchiolitis, newly admitted to hospital in the UK) was directly applicable to the review question, and that an upper age limit of 12 months was appropriate to exclude other wheezing phenotypes more common in older babies which could complicate the evidence. The committee did however note that that the study excluded babies with certain comorbidities that made them a higher risk for a more serious case of bronchiolitis and so the included population was at lower risk than is typically seen in hospital.

The intervention of the HTA did not align exactly with the existing NICE recommendation on oxygen saturation thresholds of 92%, instead comparing 90% with 94% saturation thresholds. The committee agreed that this was still of relevance to the review question, but noted that if a threshold of 92% had been used in the HTA then differences between the intervention arms may have been slightly attenuated.

The committee discussed in detail the relevance of the HTA to the 4 distinct domains of the review question: referral, admission, management and discharge. They agreed that the HTA was directly relevant to management and discharge, of some relevance to admission (because the babies in the study were being assessed in an emergency department and therefore undergoing a period of observation), but of no relevance to referral. The committee were therefore able to transpose the findings of the HTA directly to recommendations on management and discharge, and cautiously to recommendations on admission. The HTA was not considered in the committee's discussion of recommendations on referral.

The committee judged the observational study to be of very low quality because of its observational study design and very serious risk of bias for evaluating an intervention. Although it was of relevance to the admission domain of the review question, the committee did not consider it during their discussion of recommendations on admission.

1.1.8.3 Benefits and harms

Referral

The committee noted that there was no evidence identified by the review that covered referral. However, as the committee had agreed based on the evidence to amend the recommendations for oxygen saturation for admission, management and discharge to a 90% threshold, some babies and children could theoretically get stuck within the care pathway. A scenario could arise where a child discharged with an oxygen saturation of 91% was re-referred immediately back to hospital if the discharge threshold were lowered to 90% oxygen saturation, while the referral threshold remained at 92%. To overcome this, they decided to move the oxygen saturation referral criterion so that it no could no longer trigger an immediate referral to emergency care in the absence of other indications, but would instead be a criterion which healthcare professionals could use to consider a non-immediate referral.

The committee considered whether the change in other recommendations would mean babies and children would be re-referred immediately after being discharged. They considered whether this was a possibility in clinical practice, rather than only a problem with pathway logic. The committee noted that it was unlikely for a child to be brought back to primary care by parents unless they also had other symptoms. By the time children are discharged from hospital, the child's status is improving, and their oxygen saturation is unlikely to decrease. When a child needs referring based on other symptoms, oxygen saturation is made redundant by the other presenting symptoms. However, the committee brought up that some children are visited by community nurses who do take oxygen saturation measurements. By leaving the recommendation as immediate referral based on 92% oxygen saturation, this could mean the child is unnecessarily re-referred by healthcare professionals following the guidance.

To stop this loop, the committee assessed how oxygen saturation should be used in decision making. They indicated that the current recommendation places too much emphasis on the importance of oxygen saturation. Therefore, the committee decided to remove the oxygen saturation criterion from the immediate referral recommendation and place it with the criteria that healthcare professionals should use to consider non-immediate referral to hospital. This will allow healthcare professionals to exercise more clinical judgement for individual cases concerning oxygen saturation. The committee agreed that the other criteria for immediate referral were more serious and did require an immediate referral into hospital. They did not think that an oxygen saturation of below 92% alone was sufficient for immediate referral.

In addition, the committee noted that, in some cases, children may not be referred to hospital when they are displaying other symptoms listed needing immediate referral because their oxygen saturation is above the threshold for immediate referral, even if other referral criteria are present. Moving the oxygen saturation threshold to the list of criteria where a hospital referral can be considered puts less emphasis on oxygen saturation alone as the reason for referral. The committee also wanted the guideline to demonstrate that other criteria are more clinically useful than oxygen saturation.

The committee did not want to remove the oxygen saturation criterion completely or to change the oxygen saturation threshold. They said that oxygen saturation for young children might sometimes be less reliably measured in primary care, particularly if centres do not have the correct probes for children and babies. This could mean people are given a false sense of security if a reading is above the threshold for referral. The committee agreed that healthcare professionals in primary care were not able to make assessments on bronchiolitis based on oxygen saturation alone. They said that at this stage it is better to be cautious and allow specialists to make judgements since low oxygen saturation can also indicate other conditions. They also stated that oxygen saturations below 92% are likely to co-present with other symptoms.

Admission

The committee considered both studies in the review for this recommendation. Even though the prospective observational study was directly applicable to admission, the committee did not feel that the evidence was of a sufficiently high quality to influence their decision making. They considered that the RCT evidence, which assessed discharge criteria, could be applied to this part of the pathway because children are assessed in the same departments as they were treated in in the trial. Therefore, their considerations come from the RCT evidence, their own experiences, with an additional motivation to ensure a logical and consistent approach with the recommendations for management and discharge.

The committee agreed that the oxygen saturation threshold for admission could be lowered to 90% for children who were not otherwise considered to be at high risk of a serious case of bronchiolitis due to their age or any co-existing health conditions. The recommendations currently advise that a 'persistent' oxygen saturation of concern indicates admission. From their experience, when children are assessed they can remain in units for a few hours before an admission decision is made. Within this time oxygen saturation can be monitored persistently, but other symptoms would also be observed. If the child does not present any other symptoms listed in recommendation 1.3.2 during assessment, the committee were satisfied that a child with oxygen saturations over 90% could safely not be admitted. However, the committee agreed it would be safer to retain the threshold of 92% for children at higher risk (i.e. babies under 6 weeks or babies and children of any age with underlying health conditions), as these were not represented in the evidence discussed.

The committee noted that the stage at which the child is in the disease course will affect how healthcare professionals should interpret oxygen saturation. The condition of a child at day 1 or 2 with lower oxygen saturation should be treated with more caution than a child with the same oxygen saturation threshold at day 4 or 5. The committee noted the importance of identifying whether the child is in the worsening stage or the improving stage of the illness. This should influence how the healthcare professionals interpret oxygen saturation and other symptoms.

The committee were satisfied that recommendation 1.6.1 provided enough information to support parents and carers when children were not admitted. This was another safety measure that was seen as necessary as parents and carers are often moved between GP surgeries, walk-in centres and A&E. As recommendation 1.6.1 provides additional information that healthcare professionals should provide to parents and carers (recognising red flag symptoms; that people should not smoke in the child's home because it increases the risk of more severe symptoms in bronchiolitis; how to get immediate help from an appropriate professional if any red flag symptoms develop; arrangements for follow-up if necessary) the committee said children who do not meet the admission criteria can be more safely released home.

On balance, the committee were assured that the oxygen saturation threshold could be safely lowered in the recommendations for admission. The committee stressed the importance of taking other symptoms into account and not using oxygen saturation in isolation to make decisions.

Management

The committee considered the RCT evidence to be directly applicable to this recommendation. They also took into account the resource burden of delivering oxygen supplementation and whether the child is in a worsening or improving phase of illness.

The evidence from the RCT showed that the need for supplemental oxygen at a threshold of 90% was significantly lower than with a 94% threshold. The previous committee made a recommendation for 92% based on consensus. As there is now RCT evidence that demonstrates a lower need for supplemental oxygen at lower thresholds the committee

agreed to adjust the threshold in line with the evidence. In addition, this may give healthcare professionals flexibility to manage resources during periods of high demand such as localised outbreaks of respiratory conditions.

They were also reassured by knowing that oxygen is not considered alone during decision making. Assessments on heart function, feeding, and percussion, for example, are used alongside oxygen saturation to provide a fuller picture of the child's status. Additionally, oxygen supplementation is not the only treatment for low oxygen saturation and these treatments may be indicated by other symptoms. As changing oxygen saturation affects only one part of the whole picture, the committee were satisfied that it was a safe decision.

The committee were concerned that the trial had excluded high-risk children (i.e. babies under 6 weeks or with underlying health conditions) and therefore retained the previous threshold of 92% oxygen saturation for children in this group. There are also other recommendations in the Management of bronchiolitis section of the guideline provide advice for managing children in this group.

Discharge

The committee considered the RCT in this review to be directly applicable to discharge. The outcomes were either equivalent across the two groups or indicated a benefit of a lower oxygen saturation discharge threshold. As the previously recommended 92% was based on committee consensus, the committee decided that the evidence presented for a threshold of 90% superseded committee consensus in children who were not considered to be at high risk based on age or co-existing conditions. For these children, the previous threshold of 92% was retained.

The RCT was an equivalence trial, designed to demonstrate that there should be no difference in outcomes between treatment arms. However, there were 2 outcomes relating to discharge where the lower oxygen threshold of 90% was statistically associated with a more favourable result. The first was time to actual discharge in hours, which was reduced for the modified oximeter group, and which the committee said was reflective of clinical practice. This is because children who had higher oxygen saturation levels than the oximeter was showing would have fewer symptoms than children whose oxygen saturations were lower. This was reassuring for the committee as it showed a benefit for reducing the threshold by improving patient flow and allowing children to go home earlier if they are well enough. Additionally, the observational study was aligned with the findings of the RCT in that length of stay was significantly lower with a 90% versus a 92% saturation threshold for admission.

The committee felt this demonstrates that other factors are taken into account when healthcare professionals are decision making. They were confident that the other criteria in the discharge recommendation (clinical stability and adequate intake of oral fluids), would be a good barrier to prevent unwell children from being discharged. In addition, the committee noted that this may allow children who are well or consistently improving, but only have a slightly lower oxygen saturation measure than the current threshold to return home and avoid an unnecessarily prolonged stay. The committee noted that there remained a need to make healthcare professionals aware of factors that may mean discharge is not suitable (for example, social circumstances, the skill and confidence of the parent or carer in looking after a child with bronchiolitis at home, confidence in the parent or carer being able to spot red flag symptoms, distance to healthcare in case of deterioration) and that this awareness would provide a safety net.

The second outcome relevant to discharge that was significantly different between the trial arms was readmission to hospital within 28 days, with fewer readmissions in the 90% versus the 94% saturation threshold group. However, the trial authors explained this unexpected result by children not picking up infections by being in the hospital for a shorter duration, and also considered the potential role of oxygen toxicity caused by treatment during the initial

admission, which may lead to readmission at a later date. The committee commented on this finding by saying it was biologically implausible and therefore potentially a chance finding.

1.1.8.4 Cost effectiveness and resource use

The economic analysis conducted alongside the Cunningham HTA report found a reduction in both within-hospital and follow-up costs with a 90% oxygen saturation target compared to a 94% target. The committee were not convinced by the finding around follow-up costs as they were not clear of the mechanism by which the use of a lower saturation target would result in lower follow-up costs but did agree the reductions in within hospital costs matched their expectations, due to both reduced oxygen therapy and reduced length of stay with a lower target. The committee agreed the study showed the lower target was highly likely to be both cost-saving and cost-effective. The committee noted this study was directly applicable to the recommendations on management and discharge, and therefore reductions in costs would be expected from the implementation of those recommendations.

The economic analysis in the HTA was less directly applicable to the recommendations around referral and admission. The committee were unsure how many fewer people would be admitted based on a lowering of the oxygen saturation threshold for admission, as some people not meeting the lower target would still be admitted for other reasons (for example, based on their symptoms). However, they agreed this recommendation could not increase costs, as it would lead to either very similar or a reduced number of people being admitted but could not lead to an increase.

1.1.8.5 Other factors the committee took into account

In consideration of issues identified in the equality impact assessment, the committee acknowledged emerging reports in other areas of clinical care that there may be variation in the accuracy of pulse oximetry for some patients due to variations in skin tone. The committee stated that they were not presented with any evidence during this update which could lead to a specific recommendation on this topic. They agreed that this issue sits outside the scope of this update and is not unique to the diagnosis and management of bronchiolitis, and therefore no research recommendation was made. The NHS Race and Health Observatory published a rapid review of the evidence in this area in March 2021. NICE will monitor for formal guidance from NHS England and NHS Improvement in this area, and update this guideline further as needed.

The committee noted that socioeconomic status and geographical factors may influence the ability of people to travel to hospital by private transport. They said that getting to hospital urgently if a child's health is deteriorating is an important factor to consider when discharging children. They were reassured that recommendation 1.6.1 covered this adequately by noting 'distance to healthcare in case of deterioration' is a factor to take into account when discharging.

The committee noted from their experience some issues with implementation of existing recommendations. Some children may not be referred to hospital when they present with symptoms that are recommended for immediate referral because their oxygen saturations are above 92%. The committee hoped that the changes to recommendations for admission, which reduce the importance of oxygen saturation, will improve care in this area.

The committee noted that there was no direct evidence to guide referral to hospital based on oxygen saturation thresholds. The need for a research recommendation in this area was discussed, but it was felt that there could be ethical concerns with denying children referral to hospital on the basis of an oxygen saturation reading.

1.1.9 References – included studies

1.1.9.1 Effectiveness

Cunningham, Steve, Rodriguez, Aryelly, Adams, Tim et al. (2015) Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. Lancet (London, England) 386(9998): 1041-8

Cunningham, Steve, Rodriguez, Aryelly, Boyd, Kathleen A et al. (2015) Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. Health technology assessment (Winchester, England) 19(71): i-172

van Hasselt, Tim J, Singham, Bhavna, Bassett, Eve et al. (2020) Oxygen saturation thresholds in bronchiolitis: examining admissions. Archives of disease in childhood 105(12): 1197-1199

1.1.9.2 Economic

Cunningham, Steve, Rodriguez, Aryelly, Boyd, Kathleen A et al. (2015) Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. Health technology assessment (Winchester, England) 19(71): i-172

1.1.9.3 Other

None

Appendices

Appendix A – Review protocols

Review protocol for criteria for referral, admission, oxygen supplementation, and discharge

ID	Field	Content
0.	PROSPERO registration number	NA
1.	Review title	A systematic review of oxygen saturation thresholds in children with bronchiolitis in relation to referral, admission, management and discharge in a secondary care setting.
2.	Review question	What thresholds of oxygen saturation should indicate that a baby or child with suspected or confirmed bronchiolitis should be immediately referred to hospital, admitted to hospital, given supplementary oxygen, and can be safely discharged?
3.	Objective	The aim of this review is to establish if it is safe to refer, admit, give oxygen supplementation to, and discharge a baby or child with bronchiolitis using a threshold of oxygen saturation when breathing air that is different to the threshold of 92% currently recommended by NICE.
4.	Searches	Targeted searches of the following databases will be carried out: MEDLINE, Embase, CENTRAL, Cochrane Database of Systematic Reviews, Trials registries (for example, ClinicalTrials.gov)

		Searches will be restricted by: • 1 August 2014 to current • English language • Human studies • Publication type: RCTs and systematic reviews of RCTs comparing discharge from secondary care/no discharge from secondary care Other searches: Targeted searches of related guidance from professional bodies and Royal Colleges. Guidance will be prioritised from UK organisations followed by guidance from organisations based in other countries. A systematic review of published guidelines (Kirolos 2019) was identified, so this search will only include March 2017 onwards as the review covered the period up until then. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Bronchiolitis
6.	Population	Inclusion: babies and children with suspected or confirmed bronchiolitis, including subgroups particularly at risk from severe disease for example: babies and children born prematurely and babies and children with: • congenital heart disease • cystic fibrosis • immunodeficiency

		• chronic lung disease. Exclusion: Adults.
7.	Intervention/Exposure/Test	Target oxygen saturation in air at a range of thresholds
8.	Comparator/Reference standard/Confounding factors	Target oxygen saturation in air greater than or equal to 92%.
9.	Types of study to be included	• RCTs • Systematic reviews of RCTs • Observational evidence will be considered if RCT evidence is not available for each part of the patient pathway (referral, admission, management and discharge).
10.	Other exclusion criteria	• Babies and children on invasive ventilation • Studies of pan bronchiolitis and bronchiolitis obliterans
11.	Context	Current NICE guidance recommends that oxygen saturation below 92% should be considered alongside other criteria when deciding if babies and children with suspected bronchiolitis should be referred to hospital, admitted, given supplementary oxygen, or discharged. A Health Technology Assessment concluded that a lower oxygen saturation threshold could be no less safe as the current threshold of 92%. A review of this evidence is timely, as the incidence of new cases of bronchiolitis may not follow typical seasonal trends during the SARS-COV-2 pandemic. It is important to avoid unnecessary admissions and excessive length of stay in hospital as these may not be of benefit to some babies and children with bronchiolitis and may also have wider impacts on provision of care.

		Currently bronchiolitis (NICE guideline NG9) recommendations 1.2.1, 1.3.2, 1.4.4 and 1.5.1 use oxygen saturation when breathing air of 92% as criteria for referral, admission, giving oxygen supplementation, and discharge. This review will assess if an oxygen saturation threshold lower than the current recommendation of 92% is safe with respect to referral to hospital, admission to hospital, indicating oxygen supplementation, and discharge.
12.	Primary outcomes (critical outcomes)	**Related to admission or discharge:** • change in respiratory rate • change in oxygen saturation • reported feeding difficulty • readmission rate **Related to management:** • length of stay • need for high flow humidified oxygen, CPAP or mechanical ventilation
13.	Secondary outcomes (important outcomes)	**Related to admission or discharge:** • dehydration • work of breathing • adverse events (including mortality) **Related to management:** • change in O_2 saturation • change in arterial or capillary blood carbon dioxide levels • change in disease severity score • change in respiratory rate • need for feeding support (either tube feeding or intravenous fluids)

		• adverse effects (including mortality)
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.

		Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. Network meta-analysis is not planned for this review.
17.	Analysis of sub-groups	Babies and children with suspected or confirmed co-infection with SARS-COV-2
18.	Type of Review	Intervention
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	1 June 2021
22.	Anticipated completion date	August 2021
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest.

		Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an Independent Expert Advisory Panel who will use the review to inform the development of evidence-based recommendations in line with Developing NICE guidelines: the manual (Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies, section 4). Members of the guideline committee are available on the NICE website.
29.	Other registration details	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Bronchiolitis; oxygen saturation; admission; referral; oxygen supplementation; discharge
33.	Details of existing review of same topic by same authors	NA

35.	Additional information	NA
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

What thresholds of oxygen saturation should indicate that a child with suspected or confirmed bronchiolitis should be immediately referred to hospital, admitted to hospital, given supplementary oxygen, and can be safely discharged?

Medline: Systematic Reviews and RCTs

1st August 2014 to 28th May 2021

1 exp Child/ (1970664)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab. (2025559)
3 exp Infant/ (1169550)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab. (833856)
5 exp Pediatrics/ (60084)
6 p?ediatric*.ti,ab. (320152)
7 or/1-6 (3755371)
8 exp Bronchiolitis/ (8876)
9 Bronchioles/ (527)
10 bronchiol*.ti,ab. (17838)
11 or/8-10 (20277)
12 exp Oximetry/ (15651)
13 Oxygen/ (167905)
14 (oximet* or S?O2 or O?SAT?).ti,ab. (32480)
15 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab. (31383)
16 or/12-15 (211277)
17 exp Oxygen Inhalation Therapy/ (26841)
18 exp Positive-Pressure Respiration/ (26887)
19 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab. (21073)
20 high flow nasal cannul*.ti,ab. (932)
21 (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. (29427)
22 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab. (17600)
23 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab. (236)
24 positive end expiratory pressur*.ti,ab. (5538)
25 continuous distend* pressur*.ti,ab. (66)
26 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab. (3195)
27 or/17-26 (88099)
28 16 or 27 (283399)
29 7 and 11 and 28 (975)
30 limit 29 to ed=20140801-20210531 (375)
31 limit 30 to (english language and yr="2014 -Current") (340)
32 Animals/ not humans/ (4800821)
33 31 not 32 (334)
34 (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or historical article or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or portraits or video-audio media or webcasts).pt. (4259504)
35 (case report* or case series).ti. (227187)
36 34 or 35 (4287041)
37 33 not 36 (280)
38 (MEDLINE or pubmed).tw. (187488)

39 systematic review.tw. (143079)
40 systematic review.pt. (152897)
41 meta-analysis.pt. (132958)
42 intervention$.ti. (134949)
43 or/38-42 (425632)
44 37 and 43 (36)
45 randomized controlled trial.pt. (531705)
46 randomi?ed.mp. (843480)
47 placebo.mp. (203157)
48 or/45-47 (896593)
49 37 and 48 (88)
50 44 or 49 (97)

Medline: Observational studies

1st August 2014 to 9th June 2021

1 exp Child/ (1973913)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab. (2029768)
3 exp Infant/ (1171150)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab. (835436)
5 exp Pediatrics/ (60164)
6 p?ediatric*.ti,ab. (321093)
7 or/1-6 (3761758)
8 exp Bronchiolitis/ (8891)
9 Bronchioles/ (528)
10 bronchiol*.ti,ab. (17863)
11 or/8-10 (20305)
12 exp Oximetry/ (15662)
13 Oxygen/ (168043)
14 (oximet* or S?O2 or O?SAT?).ti,ab. (32601)
15 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab. (31450)
16 or/12-15 (211560)
17 exp Oxygen Inhalation Therapy/ (26887)
18 exp Positive-Pressure Respiration/ (26916)
19 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab. (21143)
20 high flow nasal cannul*.ti,ab. (944)
21 (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. (29544)
22 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab. (17634)
23 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab. (238)
24 positive end expiratory pressur*.ti,ab. (5549)
25 continuous distend* pressur*.ti,ab. (66)
26 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab. (3196)
27 or/17-26 (88316)
28 16 or 27 (283879)
29 7 and 11 and 28 (976)
30 limit 29 to ed=20140801-20210630 (376)
31 limit 30 to (english language and yr="2014 -Current") (341)
32 Animals/ not humans/ (4806148)
33 31 not 32 (335)
34 (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or historical article or in

vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or portraits or video-audio media or webcasts).pt. (4265333)
35 33 not 34 (281)
36 Observational Studies as Topic/ (6396)
37 Observational Study/ (100472)
38 Epidemiologic Studies/ (8691)
39 exp Case-Control Studies/ (1181454)
40 exp Cohort Studies/ (2148266)
41 Cross-Sectional Studies/ (369939)
42 Controlled Before-After Studies/ (618)
43 Historically Controlled Study/ (204)
44 Interrupted Time Series Analysis/ (1252)
45 Comparative Study.pt. (1891461)
46 case control$.tw. (119257)
47 case series.tw. (65288)
48 (cohort adj (study or studies)).tw. (195295)
49 cohort analy$.tw. (7601)
50 (follow up adj (study or studies)).tw. (46837)
51 (observational adj (study or studies)).tw. (97897)
52 longitudinal.tw. (221973)
53 prospective.tw. (529706)
54 retrospective.tw. (488624)
55 cross sectional.tw. (318421)
56 or/36-55 (4589118)
57 35 and 56 (166)

Medline in-Process: Systematic Reviews and RCTs

1st August 2014 to 28th May 2021

1 exp Child/ (0)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab,kw. (50824)
3 exp Infant/ (0)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab,kw. (19453)
5 exp Pediatrics/ (0)
6 p?ediatric*.ti,ab,kw. (14069)
7 or/1-6 (68911)
8 exp Bronchiolitis/ (0)
9 Bronchioles/ (0)
10 bronchiol*.ti,ab,kw. (330)
11 or/8-10 (330)
12 exp Oximetry/ (0)
13 Oxygen/ (0)
14 (oximet* or S?O2 or O?SAT?).ti,ab,kw. (1006)
15 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab,kw. (859)
16 or/12-15 (1553)
17 exp Oxygen Inhalation Therapy/ (0)
18 exp Positive-Pressure Respiration/ (0)
19 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab,kw. (599)
20 high flow nasal cannul*.ti,ab,kw. (104)
21 (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,kw. (1307)
22 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab,kw. (491)
23 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (3)
24 positive end expiratory pressur*.ti,ab,kw. (108)

25 continuous distend* pressur*.ti,ab,kw. (1)
26 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (28)
27 or/17-26 (2138)
28 16 or 27 (3537)
29 7 and 11 and 28 (37)
30 limit 29 to dt=20140801-20210531 (37)
31 limit 30 to yr=2014-current (37)
32 Meta-Analysis.pt. (61)
33 Review.pt. (40441)
34 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (11265)
35 (review$ or overview$).ti. (22781)
36 (systematic$ adj4 (review$ or overview$)).tw. (14201)
37 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (603)
38 ((studies or trial$) adj1 (review$ or overview$)).tw. (670)
39 (integrat$ adj2 (research or review$ or literature)).tw. (672)
40 (pool$ adj1 (analy$ or data)).tw. (1089)
41 (handsearch$ or (hand adj2 search$)).tw. (237)
42 (manual$ adj2 search$).tw. (187)
43 or/32-42 (60280)
44 31 and 43 (2)
45 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (36904)
46 (random$ adj2 allocat$).tw. (990)
47 placebo$.tw. (4790)
48 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (3607)
49 (crossover$ or (cross adj over$)).tw. (1976)
50 or/45-49 (40053)
51 31 and 50 (5)
52 44 or 51 (5)

Medline in-Process: Observational studies

1st August 2014 to 9th June 2021

1 exp Child/ (0)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab,kw. (50322)
3 exp Infant/ (0)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab,kw. (19195)
5 exp Pediatrics/ (0)
6 p?ediatric*.ti,ab,kw. (13985)
7 or/1-6 (68182)
8 exp Bronchiolitis/ (0)
9 Bronchioles/ (0)
10 bronchiol*.ti,ab,kw. (338)
11 or/8-10 (338)
12 exp Oximetry/ (0)
13 Oxygen/ (0)
14 (oximet* or S?O2 or O?SAT?).ti,ab,kw. (939)
15 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab,kw. (855)
16 or/12-15 (1483)
17 exp Oxygen Inhalation Therapy/ (0)
18 exp Positive-Pressure Respiration/ (0)
19 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab,kw. (595)
20 high flow nasal cannul*.ti,ab,kw. (104)
21 (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,kw. (1288)

22 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab,kw. (494)
23 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (1)
24 positive end expiratory pressur*.ti,ab,kw. (108)
25 continuous distend* pressur*.ti,ab,kw. (1)
26 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (30)
27 or/17-26 (2121)
28 16 or 27 (3443)
29 7 and 11 and 28 (40)
30 limit 29 to dt=20140801-20210630 (40)
31 limit 30 to yr=2014-current (40)

Medline epub: Systematic Reviews and RCTs

1st August 2014 to 28th May 2021

1 exp Child/ (0)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab,kw. (36895)
3 exp Infant/ (0)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab,kw. (14463)
5 exp Pediatrics/ (0)
6 p?ediatric*.ti,ab,kw. (9994)
7 or/1-6 (50198)
8 exp Bronchiolitis/ (0)
9 Bronchioles/ (0)
10 bronchiol*.ti,ab,kw. (297)
11 or/8-10 (297)
12 exp Oximetry/ (0)
13 Oxygen/ (0)
14 (oximet* or S?O2 or O?SAT?).ti,ab,kw. (933)
15 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab,kw. (615)
16 or/12-15 (1345)
17 exp Oxygen Inhalation Therapy/ (0)
18 exp Positive-Pressure Respiration/ (0)
19 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab,kw. (548)
20 high flow nasal cannul*.ti,ab,kw. (93)
21 (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,kw. (993)
22 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab,kw. (421)
23 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (7)
24 positive end expiratory pressur*.ti,ab,kw. (77)
25 continuous distend* pressur*.ti,ab,kw. (0)
26 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (39)
27 or/17-26 (1748)
28 16 or 27 (2955)
29 7 and 11 and 28 (27)
30 limit 29 to dt=20140801-20210531 (26)
31 limit 30 to yr=2014-current (26)
32 Meta-Analysis.pt. (92)
33 Review.pt. (45355)
34 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (8005)
35 (review$ or overview$).ti. (16703)
36 (systematic$ adj4 (review$ or overview$)).tw. (11174)
37 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (510)
38 ((studies or trial$) adj1 (review$ or overview$)).tw. (497)
39 (integrat$ adj2 (research or review$ or literature)).tw. (396)
40 (pool$ adj1 (analy$ or data)).tw. (709)

41 (handsearch$ or (hand adj2 search$)).tw. (221)
42 (manual$ adj2 search$).tw. (156)
43 or/32-42 (60177)
44 31 and 43 (4)
45 ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw. (24585)
46 (random$ adj2 allocat$).tw. (653)
47 placebo$.tw. (3195)
48 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (2333)
49 (crossover$ or (cross adj over$)).tw. (1379)
50 or/45-49 (26981)
51 31 and 50 (4)
52 44 or 51 (7)

Medline epub: Observational Studies

1st August 2014 to 9th June 2021

1 exp Child/ (0)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab,kw. (36977)
3 exp Infant/ (0)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab,kw. (14449)
5 exp Pediatrics/ (0)
6 p?ediatric*.ti,ab,kw. (10050)
7 or/1-6 (50287)
8 exp Bronchiolitis/ (0)
9 Bronchioles/ (0)
10 bronchiol*.ti,ab,kw. (281)
11 or/8-10 (281)
12 exp Oximetry/ (0)
13 Oxygen/ (0)
14 (oximet* or S?O2 or O?SAT?).ti,ab,kw. (879)
15 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab,kw. (614)
16 or/12-15 (1296)
17 exp Oxygen Inhalation Therapy/ (0)
18 exp Positive-Pressure Respiration/ (0)
19 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab,kw. (541)
20 high flow nasal cannul*.ti,ab,kw. (101)
21 (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,kw. (1010)
22 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab,kw. (408)
23 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (7)
24 positive end expiratory pressur*.ti,ab,kw. (79)
25 continuous distend* pressur*.ti,ab,kw. (0)
26 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab,kw. (38)
27 or/17-26 (1740)
28 16 or 27 (2901)
29 7 and 11 and 28 (25)
30 limit 29 to dt=20140801-20210630 (24)
31 limit 30 to yr=2014-current (24)

Embase: Systematic Reviews and RCTs

1st August 2014 to 28th May 2021

1 exp child/ (2737778)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab. (2917885)
3 exp infant/ (1023254)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab. (1125735)
5 exp pediatrics/ (112406)
6 p?ediatric*.ti,ab. (587666)
7 or/1-6 (4696109)
8 exp bronchiolitis/ (23130)
9 exp bronchiole/ (3635)
10 bronchiol*.ti,ab. (27588)
11 or/8-10 (36536)
12 exp oximetry/ (28902)
13 oxygen saturation/ (57220)
14 oxygen/ (209416)
15 (oximet* or S?O2 or O?SAT?).ti,ab. (70699)
16 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab. (54359)
17 or/12-16 (333855)
18 exp oxygen therapy/ (66597)
19 oxygen breathing/ (3368)
20 exp intermittent mandatory ventilation/ (1411)
21 exp intermittent positive pressure ventilation/ (3408)
22 exp positive pressure ventilation/ (8347)
23 pressure support ventilation/ (1736)
24 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab. (34953)
25 high flow nasal cannul*.ti,ab. (2384)
26 (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. (65977)
27 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab. (28862)
28 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab. (498)
29 positive end expiratory pressur*.ti,ab. (7865)
30 continuous distend* pressur*.ti,ab. (86)
31 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab. (4089)
32 or/18-31 (174309)
33 17 or 32 (473034)
34 7 and 11 and 33 (2538)
35 (201408* or 201409* or 20141* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).dc. (11680750)
36 34 and 35 (1437)
37 limit 36 to (english language and yr="2014 -Current") (1348)
38 nonhuman/ not human/ (4805559)
39 37 not 38 (1333)
40 conference.pt. (4869711)
41 book.pt. (1105)
42 book series.pt. (0)
43 editorial.pt. (692027)
44 letter.pt. (1174850)
45 note.pt. (851054)
46 short survey.pt. (360319)
47 case report/ (2615970)
48 (case report* or case series).ti. (370023)
49 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (10038790)
50 39 not 49 (607)
51 (MEDLINE or pubmed).tw. (299537)
52 exp systematic review/ or systematic review.tw. (356045)
53 meta-analysis/ (216221)
54 intervention$.ti. (218201)

55 or/51-54 (741085)
56 50 and 55 (52)
57 random:.tw. (1667264)
58 placebo:.mp. (474734)
59 double-blind:.tw. (220184)
60 or/57-59 (1928376)
61 50 and 60 (148)
62 56 or 61 (167)

Embase: Observational Studies

1st August 2014 to 9th June 2021

1 exp child/ (2742167)
2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*).ti,ab. (2922515)
3 exp infant/ (1024769)
4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies).ti,ab. (1127147)
5 exp pediatrics/ (112525)
6 p?ediatric*.ti,ab. (589451)
7 or/1-6 (4702810)
8 exp bronchiolitis/ (23159)
9 exp bronchiole/ (3631)
10 bronchiol*.ti,ab. (27602)
11 or/8-10 (36562)
12 exp oximetry/ (28977)
13 oxygen saturation/ (57536)
14 oxygen/ (209617)
15 (oximet* or S?O2 or O?SAT?).ti,ab. (70925)
16 ((oxygen* or O2) adj3 (saturat* or monitor*)).ti,ab. (54469)
17 or/12-16 (334623)
18 exp oxygen therapy/ (66988)
19 oxygen breathing/ (3375)
20 exp intermittent mandatory ventilation/ (1412)
21 exp intermittent positive pressure ventilation/ (3409)
22 exp positive pressure ventilation/ (8516)
23 pressure support ventilation/ (1739)
24 ((oxygen* or O2) adj3 (therap* or supplement* or humidif* or unhumidif* or high flow or insufflat* or inhal*)).ti,ab. (35038)
25 high flow nasal cannul*.ti,ab. (2395)
26 (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. (66120)
27 (positive adj3 pressure adj3 (ventilat* or respirat* or breath* or airway*)).ti,ab. (28898)
28 (airway pressure release adj3 (ventilat* or respirat* or breath*)).ti,ab. (498)
29 positive end expiratory pressur*.ti,ab. (7866)
30 continuous distend* pressur*.ti,ab. (86)
31 (intermittent adj3 (ventilat* or respirat* or breath*)).ti,ab. (4082)
32 or/18-31 (174942)
33 17 or 32 (474308)
34 7 and 11 and 33 (2549)
35 (201408* or 201409* or 20141* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021*).dc. (11731207)

36 34 and 35 (1449)
37 limit 36 to (english language and yr="2014 -Current") (1360)
38 nonhuman/ not human/ (4808195)
39 37 not 38 (1345)
40 conference.pt. (4875254)
41 book.pt. (1105)
42 book series.pt. (0)
43 editorial.pt. (692952)
44 letter.pt. (1176240)
45 note.pt. (852364)
46 short survey.pt. (360300)
47 40 or 41 or 42 or 43 or 44 or 45 or 46 (7958215)
48 39 not 47 (731)
49 Clinical study/ (155557)
50 Case control study/ (173129)
51 Family study/ (25308)
52 Longitudinal study/ (156349)
53 Retrospective study/ (1084669)
54 comparative study/ (902010)
55 Prospective study/ (688970)
56 Randomized controlled trials/ (204458)
57 55 not 56 (681182)
58 Cohort analysis/ (713997)
59 cohort analy$.tw. (14665)
60 (Cohort adj (study or studies)).tw. (345010)
61 (Case control$ adj (study or studies)).tw. (147393)
62 (follow up adj (study or studies)).tw. (66211)
63 (observational adj (study or studies)).tw. (191672)
64 (epidemiologic$ adj (study or studies)).tw. (111282)
65 (cross sectional adj (study or studies)).tw. (252954)
66 case series.tw. (116607)
67 prospective.tw. (928059)
68 retrospective.tw. (986746)
69 or/49-54,57-68 (4421208)
70 48 and 69 (342)

Cochrane Database of Systematic Reviews (CDSR) & CENTRAL

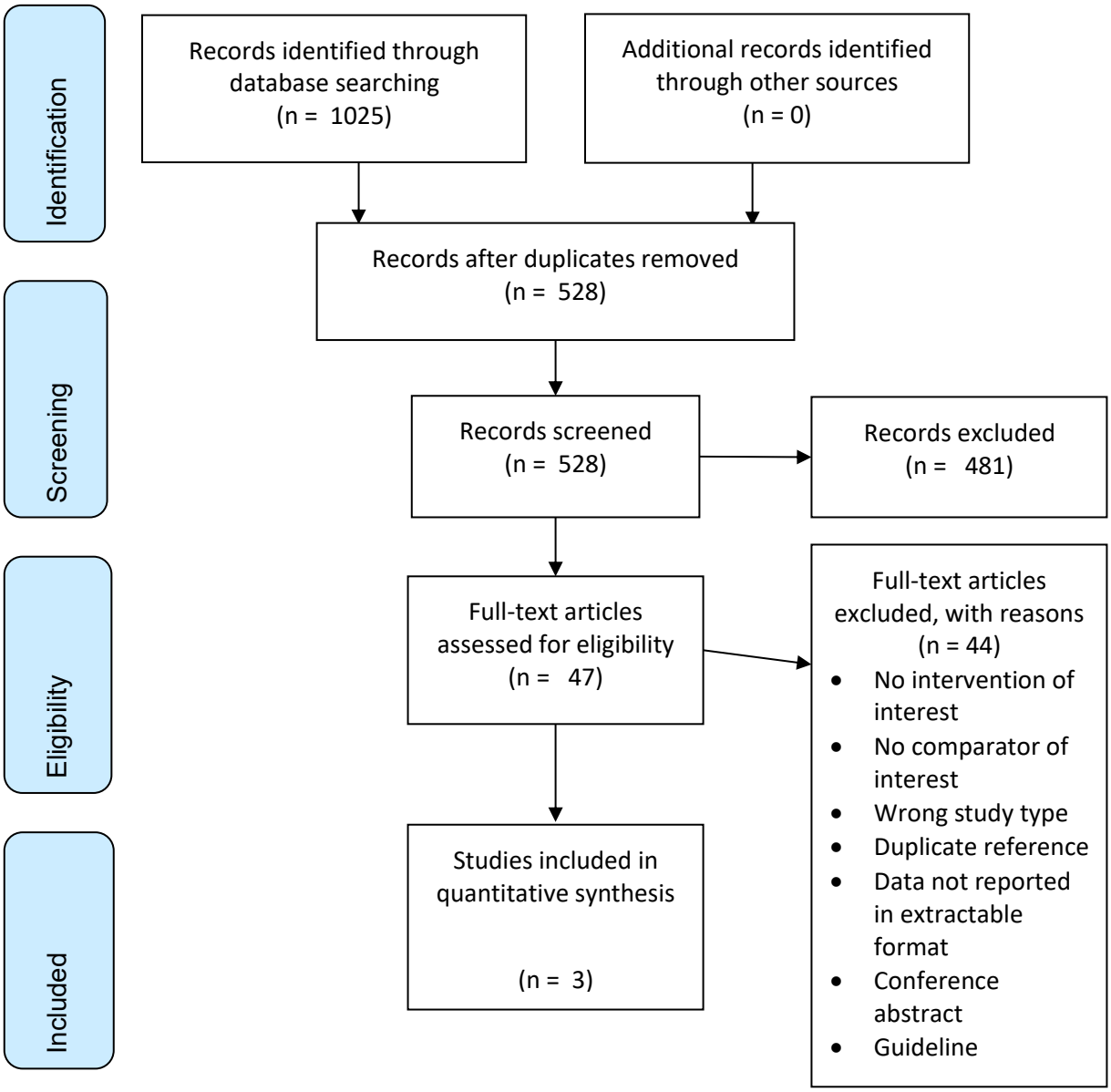
Issue 5 of 12, May 2021

#1 MeSH descriptor: [Child] explode all trees 57029
#2 (child* or preschool* or pre-school* or toddler* or kid* or kindergar* or minor or minors or boy* or girl* or daycare or day-care or nurser*):ti,ab 182632
#3 MeSH descriptor: [Infant] explode all trees 32600
#4 (infan* or prematur* or pre-matur* or preterm* or pre-term* or neonat* or neo-nat* or perinat* or peri-nat* or newborn* or baby or babies):ti,ab 73136
#5 MeSH descriptor: [Pediatrics] explode all trees 692
#6 p?ediatric*:ti,ab 33148
#7 {OR #1-#6} 260152
#8 MeSH descriptor: [Bronchiolitis] explode all trees 545

#9 MeSH descriptor: [Bronchioles] this term only 2
#10 bronchiol*:ti,ab 1446
#11 {OR #8-#10} 1499
#12 MeSH descriptor: [Oximetry] explode all trees 1036
#13 MeSH descriptor: [Oxygen] explode all trees 5523
#14 (oximet* or S?O2 or O?SAT?):ti,ab 9129
#15 ((oxygen* or O2) NEAR/3 (saturat* or monitor*)):ti,ab 11314
#16 {OR #12-#15} 20394
#17 MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees 1595
#18 MeSH descriptor: [Positive-Pressure Respiration] explode all trees 2795
#19 ((oxygen* or O2) NEAR/3 (therap* or supplement* or humidif* or unhumidif* or "high flow" or insufflat* or inhal*)):ti,ab 6511
#20 (high NEXT flow NEXT nasal NEXT cannul*):ti,ab 784
#21 (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 8643
#22 (positive NEAR/3 pressure NEAR/3 (ventilat* or respirat* or breath* or airway*)):ti,ab 6176
#23 (airway NEXT pressure NEXT release NEAR/3 (ventilat* or respirat* or breath*)):ti,ab 79
#24 (positive NEXT end NEXT expiratory NEXT pressur*):ti,ab 1384
#25 (continuous NEXT distend* NEXT pressur*):ti,ab 22
#26 (intermittent NEAR/3 (ventilat* or respirat* or breath*)):ti,ab 860
#27 {OR #17-#26} 18155
#28 #16 or #27 34442
#29 #7 and #11 and #28 437
#30 #29 with Cochrane Library publication date Between Aug 2014 and May 2021, in Cochrane Reviews, Cochrane Protocols 7 (CDSR)
#31 #29 with Publication Year from 2014 to 2021, in Trials 231
#32 "conference":pt or (clinicaltrials or trialsearch):so 543843
#33 #31 not #32 97 (CENTRAL)

Appendix C – Effectiveness evidence study selection

C.1 PRISMA flow diagram of study selection



Appendix D – Effectiveness and observational evidence

D.1 Effectiveness evidence

Cunningham, 2015

Bibliographic Reference	Cunningham, Steve; Rodriguez, Aryelly; Boyd, Kathleen A; McIntosh, Emma; Lewis, Steff C; BIDS Collaborators, Group; Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation.; Health technology assessment (Winchester, England); 2015; vol. 19 (no. 71); i-172

Study details

Trial registration number and/or trial name	ISRCTN28405428 Bronchiolitis of Infancy Discharge Study
Study location	UK
Study setting	Eight paediatric hospitals (Aberdeen, Bristol, Dundee, Edinburgh, Exeter, Glasgow, Kilmarnock and Truro) - emergency department (ED) or acute assessment area (AAA)
Study dates	In season 1, randomisation was open from 3 October 2011 to 30 March 2012 in the 5 Scottish sites only. In season 2, randomisation was open from 1 October 2012 to 29 March 2013 in all 8 sites. The addition of 3 sites in south-west England was in response to a quieter respiratory syncytial virus (RSV) season than expected in season 1.
Duration of follow-up	6 months
Sources of funding	UK National Institute for Health Research (NIHR) HTA programme

Inclusion criteria	Infants with a corrected age of ≥ 6 weeks and ≤ 12 months of age Infants under 6 weeks of age were excluded for 2 reasons. First, a recruitment feasibility assessment before the study found that parents of children in this age group would decline consent to the study because of concerns about the age of their child and their first acute illness. Second, infants in this age group frequently present with apnoea, which was accommodated within the protocol, but clinical and parental anxiety associated with infant apnoea may have skewed towards greater length of stay in this age range. The investigators also felt that infants under 6 weeks of age require greater personalisation of oxygen saturation targets depending on their disease course (some may be stable and can be managed at an oxygen saturation target of ≥90%, but others will require a higher target for management and discharge, particularly those with apnoea, as clinically appropriate). Admitted to hospital with a clinical diagnosis of bronchiolitis made by a medically qualified practitioner in ED/AAA Clinical diagnosis of bronchiolitis consistent with SIGN guideline 91
Exclusion criteria	Preterm infant (< 37 weeks' gestation) who received oxygen therapy in the previous 4 weeks< Cyanosis/haemodynamically significant heart disease Documented immune function defect Direct admission to high-dependency unit (HDU)/paediatric intensive care unit (PICU) from ED/AAA Previously recruited to Bronchiolitis of Infancy Discharge Study (BIDS)
Sample size	n=615 The sample size was determined for the primary outcome of time to resolution of cough following randomisation. An estimate of 544 participants was made by assuming that there would be no difference between the treatment groups, with a common standard deviation of 8.3 days. The standard deviation of 8.3 days was calculated by dividing the interquartile range by 1.35. This used a two-sided test (overall alpha 0.05), with power of 80% and limits of equivalence of 2 days (i.e. the difference between the two arms could be up to 2 days in either direction). To allow for skewness in the outcome measure, as well as any dropouts and non-compliance, the recruitment target was 600 infants.

	Although the number of infants admitted to these hospitals during the study would be more than 600, the sample size estimate included an allowance for infants with exclusion criteria, infants admitted on more than one occasion and parents who did not wish to participate (all exclusions estimated at 25%).
Intervention	Supplemental oxygen to maintain an apparent oxygen saturation of ≥94% as measured by a modified pulse oximeter (Rad-8 with LNC 10 patient cable; Masimo Corporation Limited, CA, USA). Oxygen saturation monitors are ubiquitous in the care of infants admitted to hospital with acute bronchiolitis and guide supplementation of oxygen and decision-making for discharge. It was expected that infants on modified oximeters might go home sooner. The modified oximeters measured arterial oxygen saturation as per standard oximeters but manufacturer-altered internal algorithms provided a non-standard display: in the oxygen saturation measured range of 85–90%, the display was within the range of oxygen saturation of 85–94%. In this way infants with modified oximeters would appear to have a more rapid improvement with regard to oxygen requirement and, consequently, could stop supplemental oxygen at a displayed 94% oxygen saturation level when the actual oxygen saturation level was 90%. Study pulse oximeters were of identical appearance and function, identified only by a study number. Infants remained on their study oximeter for the duration of their admission. Infants who suffered post-randomisation deterioration and required admission to a HDU/PICU were transferred to a standard non-study pulse oximeter during the HDU/PICU stay and recommenced on the same blinded study oximeter on transfer back to the ward for the remainder of their stay until discharge. Infants could be eligible for discharge once oral feeding was re-established and continuously monitored oxygen saturation was displayed as ≥94% in room air for a minimum of 4 hours including a period of sleep.
Comparator	Supplemental oxygen to maintain oxygen saturation of ≥94% as measured by a standard oximeter (Rad-8 with LNC 10 patient cable; Masimo Corporation Limited, CA, USA). Standard oximeters displayed true oxygen saturation values therefore oxygen given at a displayed value of <94% reflected the actual saturation measurement of the infant. Infants remained on their study oximeter for the duration of their admission. Infants who suffered post-randomisation deterioration and required admission to a HDU/PICU were transferred to a standard non-study pulse oximeter during the

	HDU/PICU stay and recommenced on the same blinded study oximeter on transfer back to the ward for the remainder of their stay until discharge. Infants could be eligible for discharge once oral feeding was re-established and continuously monitored oxygen saturation was displayed as ≥94% in room air for a minimum of 4 hours including a period of sleep.
Methods of analysis	**Outcome selection** The study investigators assessed time to resolution of cough as the primary outcome, which they noted is associated with airway inflammation and might be influenced by hypoxia. They stated cough is a ubiquitous symptom in bronchiolitis consistently identified by parents and has a duration well documented in many trials. The study investigators stated they did not use a bronchiolitis clinical score for 3 reasons. First, bronchiolitis scores are not used clinically in the majority of UK hospitals, in particular in sites participating in this study, as they have not been demonstrated to be of greater value than routine clinical decision-making. Second, there is no agreed best clinical score. Third, agreement between observers tends to be poor unless the number of trained observers is limited. To have study staff available 24 hours per day for scoring would have been expensive for measurement of a single outcome. The alternative approach of training clinical staff across all sites to clinical score accurately and precisely for bronchiolitis may have changed behaviour with regard to routine care (which the investigators wished to observe) and still have been associated with unacceptable variance in scoring with corresponding concerns for data surety. **Data collection** Demographic information was collected by research nurses within 24 hours of admission. Data related to the hospital stay were collected progressively during the period of hospitalisation and at discharge. Parents were contacted by the study team on four occasions, at 7, 14 and 28 days and at 6 months following randomisation. Standardised interview questions were asked to obtain study-related data. In season 1, infants and parents were met in person at 28 days for measurement of oxygen saturation and parents were asked day-28 information at this visit. In season 2, the same information was obtained by telephone call. **Data analysis**

All analyses were by intention to treat (ITT) unless otherwise specified. All applicable statistical tests were two-sided using a 5% significance level. Ninety-five per cent (two-sided) confidence intervals (CIs) were presented. The primary analysis was an unadjusted analysis. Where there were missing data for an outcome variable, in the first instance, those records were removed from any formal statistical analysis, unless otherwise specified.

Primary outcome

There is no published evidence to support the limit of equivalence for cough resolution. The investigators sampled the expert opinion of consultant paediatricians who contribute to the general paediatric service at the Royal Hospital for Sick Children, Edinburgh (and who provide clinical management of infants with bronchiolitis), and identified a variance of 2 days as being clinically meaningful with adequate safety.

For resolution of cough, the treatment arms were considered equivalent if the 95% CI lay entirely within the equivalence limits of ± 2 days. If the precise date of cough resolution was unknown, a random value was chosen between the date that the cough was last known to be present and the date of the follow-up when it was found that the cough had stopped. The random value was chosen from infants in the same treatment group whose cough stopped in a similar time frame. If it was known that the cough had not resolved by 6 months, the date of cough was predicted by taking a random value from a uniform distribution capped from 180 days to 200 days. If it was known that the cough had not stopped by the last follow-up but the infant was not followed to 6 months, then a random value was chosen from a uniform distribution with the lower cap pegged to the last known follow-up time (i.e. 7, 14 or 28 days) instead of 180 days. This process was repeated 100 times, and the analysis done on each data set. The mean values for the estimate of the median and the estimates of the CI limits were used. If 100 repetitions did not produce a stable estimate, then this number was to be increased, but this was not necessary. As a sensitivity analysis, a complete-case analysis was also done.

Secondary outcomes: testing for differences

For the outcome measures, the times, split by treatment group, were presented using a Kaplan–Meier plot. Cox proportional hazards regression was used to estimate the treatment effect: time from randomisation to (1) fit for discharge and (2) actual discharge for all infants admitted with acute viral bronchiolitis; (3) time to no supplemental oxygen; (4) time to readmission to hospital. It was considered whether or not the season-1 data for Glasgow should be removed from the analysis of time to fit for discharge, as this variable was not recorded consistently at this centre in season 1. However, this made no difference to the results so these data were left in. The results are presented at multiple time points, and due allowance would be made for this if any of them proved to be statistically significant. The effect of the intervention was estimated using binary logistic regression and reported as an adjusted odds ratio and 95% CI for the proportion of infants

	with at least one health-care reattendance (primary care, ED, hospital readmission) at days 7, 14 and 28 and at 6 months. The effect of the intervention was estimated using Poisson regression for the number of health-care reattendances (primary care, ED, hospital readmission) at days 7, 14 and 28 and at 6 months. For the outcome measures, the mean difference in times between the two trial arms was estimated from a normal linear model, and presented with a 95% CI: respiratory rate at discharge. Secondary outcomes: testing for equivalence For time to return to satisfactory feeding, a typical infant feed interval of 4 hours was used as equivalence. The same method as the primary outcome was used for time in hours from randomisation to re-established feeding (equivalence limits of ± 4 hours). For time to re-establish adequate feeding, no imputations for missing data were performed, as the data were recorded only at the end of discharge and they were almost complete. The difference in mean oxygen saturation measurements between the 2 trial arms was estimated with its corresponding 95% CI for awake oxygen saturation at 28 days after randomisation (equivalence limits of ± 1.0% oxygen saturation – season-1 data collection only).
Loss to follow-up	Number of infants who reached the end of the study with >90% of data: n=584 (95%). Thirty-one infants did not reach 6-month follow-up (15 standard care, 16 modified care): there were 2 deaths (both in standard care), 1 infant was withdrawn by the clinician, 21 infants were lost to follow-up and the parents declined further contact in another 7 cases. Protocol deviations occurred in 34 infants with standard care, and 42 with modified care. Categories of deviation were: attached to the monitor late, removed early, never attached, discharge criteria not met, other. It will be reported if the outcome data relate to a number infants that is fewer than the total number randomised (n=615).
% Female	All: 263/615 (42.8%)
Mean age (SD)	**Median age (IQR), weeks** All: 21.3 (11.7–31.6)

Study arms

- Standard care (N = 308)

Supplemental oxygen at <94% oxygen saturation as measured by a standard oximeter (displayed true values; therefore oxygen given at SpO_2 <94%)

- Modified care (N = 307)

Supplemental oxygen at <94% oxygen saturation as measured by a modified oximeter (displayed a measured value of 90% as 94%; therefore oxygen not actually given until SpO_2 <90%)

Characteristics

- Arm-level characteristics

Characteristic	Standard care (N = 308)	Modified care (N = 307)
Age (Weeks) Median (IQR)	21.3 (12.6 to 31.1)	21.1 (11.1 to 32)
% Female Sample size	n = 122 ; % = 39.6	n = 141 ; % = 45.9
Preterm (<37 weeks) Standard care n=278, modified care n=279 Sample size	n = 28 ; % = 10.1	n = 45 ; % = 16.1

Characteristic	Standard care (N = 308)	Modified care (N = 307)
Household smoking Standard care n=303, modified care n=304 Sample size	n = 133 ; % = 43.9	n = 130 ; % = 42.8
Number of primary care attendances in previous 4 weeks Standard care n=301, modified care n=303 Median (IQR)	1 (1 to 2)	1 (0 to 2)
Heart rate on arrival at ED (BPM) Standard care n=305, modified care n=303 Median (IQR)	159 (146 to 173)	158 (148 to 172)
Respiratory rate on arrival at ED (Breaths per minute) Standard care n=299, modified care n=302 Median (IQR)	50 (44 to 58)	49 (42 to 58)
Antibiotics on arrival at ED Standard care n=305, modified care n=304 Sample size	n = 24 ; % = 7.9	n = 23 ; % = 7.6
Bronchodilator on arrival at ED Standard care n=305, modified care n=304 Sample size	n = 17 ; % = 5.6	n = 16 ; % = 5.3
Length of illness on arrival at ED, (days) Standard care n=305, modified care n=302 Median (IQR)	4 (3 to 5)	4 (3 to 5)

Characteristic	Standard care (N = 308)	Modified care (N = 307)
Apnoea on arrival at ED Standard care n=303, modified care n=304 Sample size	n = 3 ; % = 1	n = 3 ; % = 1
SpO_2 on arrival at ED Standard care n=304, modified care n=303 Median (IQR)	95 (93 to 97)	95 (93 to 97)
SpO_2 on arrival at ED ≤94% Standard care n=304, modified care n=303 Sample size	n = 121 ; % = 39.8	n = 119 ; % = 39.3

Outcomes

Outcome	Standard care, , N = 308	Modified care, , N = 307
Time to cough resolution (days) Primary outcome (standard care n=296, modified care n=293) Median (IQR)	15 (10 to 42.5)	15 (10 to 41)
Time feeding returned to ≥75% normal (hours) Standard care n=304, modified care n=296 Median (IQR)	24.1 (6.5 to 62.1)	19.5 (6.3 to 47.2)

Outcome	Standard care, , N = 308	Modified care, , N = 307
Time to fit for discharge (hours) Standard care n=283, modified care n=276 Median (IQR)	44.2 (18.6 to 87.5)	30.2 (15.6 to 59.7)
Time to actual discharge (hours) Standard care n=303, modified care n=301 Median (IQR)	50.9 (23.1 to 93.4)	40.9 (21.8 to 67.3)
Time to no further supplemental oxygen (hours) Standard care n=305, modified care n=304 Median (IQR)	27.63 (0 to 68)	5.65 (0 to 32.4)
Time to readmission to hospital (days) Standard care n=23, modified care n=12 Median (IQR)	17 (7 to 22)	11 (2 to 21)
High-dependency care (Episodes) No of events	n = 8 ; % = 3	n = 13 ; % = 4
Respiratory rate at discharge (Breaths per minute) Median (IQR)	38 (34 to 41)	38 (34 to 42)
Respiratory rate at discharge (Breaths per minute) Mean (SD)	38 (7.9)	38 (6.4)
Readmission to hospital within 7 days (Episodes) No of events	n = 8	n = 5

Outcome	Standard care, , N = 308	Modified care, , N = 307
Readmission to hospital within 7 days (Infants) Sample size	n = 6 ; % = 1.9	n = 5 ; % = 1.6
Readmission to hospital within 28 days (Episodes) No of events	n = 26	n = 12
Readmission to hospital within 28 days (Infants) Sample size	n = 23 ; % = 7.5	n = 12 ; % = 3.9
Reattendance at health care within 7 days (Episodes) No of events	n = 41	n = 43
Reattendance at health care within 7 days (Infants) Standard care n=270, modified care n=267 Sample size	n = 39 ; % = 14.4	n = 34 ; % = 12.7
Reattendance at health care within 14 days (Episodes) Standard care n=270, modified care n=267 No of events	n = 92	n = 88
Reattendance at health care within 14 days (Infants) Standard care n=267, modified care n=258 Sample size	n = 76 ; % = 28.5	n = 70 ; % = 27.1
Deaths Sample size	n = 2 ; % = 0.6	n = 0 ; % = 0

Outcome	Standard care, , N = 308	Modified care, , N = 307
Reattendance at health care within 28 days (Episodes) Standard care n=290, modified care n=288 No of events	n = 199	n = 188
Reattendance at health care within 28 days (Infants) Standard care n=274, modified care n=262 Sample size	n = 127 ; % = 46.4	n = 128 ; % = 48.9
Reattendance at health care within 6 months (Episodes) Standard care n=295, modified care n=293 No of events	n = 802	n = 774
Reattendance at health care within 6 months (Infants) Standard care n=253, modified care n=261 Sample size	n = 214 ; % = 84.6	n = 209 ; % = 80.1
SpO_2 measured at 28 days Season 1 only (Standard care n=94, modified care n=101) Median (IQR)	99 (97 to 100)	99 (97 to 100)
Need for supplemental oxygen Standard care n=305, modified care n=304 Sample size	n = 223 ; % = 73.1	n = 169 ; % = 55.6
Use of nasogastric tube feeding Standard care n=305, modified care n=303 Sample size	n = 141 ; % = 46.2	n = 125 ; % = 41.3

Outcome	Standard care, , N = 308	Modified care, , N = 307
Use of intravenous fluids Standard care n=305, modified care n=304 Sample size	n = 29 ; % = 9.5	n = 28 ; % = 9.2

Time to cough resolution - Polarity - Lower values are better
Time feeding returned to ≥75% normal - Polarity - Lower values are better
Time to fit for discharge - Polarity - Lower values are better
Time to actual discharge - Polarity - Lower values are better
High-dependency care - Polarity - Lower values are better
Respiratory rate at discharge - Polarity – N/A
Readmission to hospital within 7 days - Polarity - Lower values are better
Readmission to hospital within 7 days - Polarity - Lower values are better
Readmission to hospital within 28 days - Polarity - Lower values are better
Readmission to hospital within 28 days - Polarity - Lower values are better
Reattendance at health care within 7 days - Polarity - Lower values are better
Reattendance at health care within 7 days - Polarity - Lower values are better
Reattendance at health care within 14 days - Polarity - Lower values are better
Reattendance at health care within 14 days - Polarity - Lower values are better
Deaths - Polarity - Lower values are better
Reattendance at health care within 28 days - Polarity - Lower values are better
Reattendance at health care within 28 days - Polarity - Lower values are better
Reattendance at health care within 6 months - Polarity - Lower values are better
Reattendance at health care within 6 months - Polarity - Lower values are better
SpO_2 measured at 28 days - Polarity - Higher values are better
Need for supplemental oxygen - Polarity - Lower values are better
Use of nasogastric tube feeding - Polarity - Lower values are better
Use of intravenous fluids - Polarity - Lower values are better

Relative outcomes

Outcome	Modified care vs Standard care, N1 = 308, N2 = 307
Time feeding returned to ≥75% normal Upper and lower CIs fall outside the prespecified equivalence limits of –4 to 4 hours, and confidence interval crosses 0, so equivalence cannot be inferred. (Standard care n=304, modified care n=296) Median (IQR)	2.7 (-0.3 to 7)
Time feeding returned to ≥75% normal (Standard care n=304, modified care n=296) Hazard ratio/95% CI	1.22 (1.04 to 1.44) (p = 0.015)
Time to cough resolution (days) Primary outcome. Intention to treat analysis (shows equivalence as upper and lower CIs fall within the prespecified equivalence limits of –2 to 2 days) (standard care n=296, modified care n=293) Median (95% CI)	1 (-1 to 2)
Time to fit for discharge (hours) Standard care n=283, modified care n=276 Hazard ratio/95% CI	1.46 (1.23 to 1.73) (p<0.0001)
Time to actual discharge (hours) Standard care n=303, modified care n=301 Hazard ratio/95% CI	1.28 (1.09 to 1.5) (p = 0.003)
Time to no further supplemental oxygen (hours) Standard care n=305, modified care n=304 Hazard ratio/95% CI	1.37 (1.12 to 1.68) (p = 0.002)

Outcome	Modified care vs Standard care, N1 = 308, N2 = 307
Time to readmission to hospital (days) Standard care n=23, modified care n=12 Hazard ratio/95% CI	0.93 (0.43 to 1.98) (p = 0.84)
Time to cough resolution (days) [Change IQR to 95% CI] Per-protocol analysis (shows equivalence as upper and lower CIs fall within the prespecified equivalence limits of –2 to 2 days) (n values not specified for the PP analysis) Median (IQR)	0 (-1 to 2)
Respiratory rate at discharge (Breaths per minute) Mean (95% CI)	0.09 (-1.05 to 1.23) (p = 0.88)
Reattendance at health care within 7 days (Infants) Standard care n=270, modified care n=267 Odds ratio/95% CI	0.98 (0.65 to 1.49) (p = 0.94)
Reattendance at health care within 14 days (Infants) Standard care n=267, modified care n=258 Odds ratio/95% CI	1.07 (0.73 to 1.57) (p = 0.73)
Reattendance at health care within 28 days (Infants) Standard care n=274, modified care n=262 Odds ratio/95% CI	0.9 (0.64 to 1.27) (p = 0.56)
Reattendance at health care within 6 months (Infants) Standard care n=253, modified care n=261 Odds ratio/95% CI	1.37 (0.87 to 2.16) (p = 0.18)

Outcome	Modified care vs Standard care, N1 = 308, N2 = 307
SpO_2 measured at 28 days Season 1 only (Standard care n=94, modified care n=101) Mean (95% CI)	0.11 (-0.35 to 0.57) (p= 0.64)

Time feeding returned to ≥75% normal - Polarity - Lower values are better
Time to cough resolution - Polarity - Lower values are better
Time to fit for discharge - Polarity - Lower values are better
Time to actual discharge - Polarity - Lower values are better
Time to no further supplemental oxygen - Polarity - Lower values are better
Time to readmission to hospital - Polarity - Higher values are better
Time to cough resolution - Polarity - Lower values are better
Respiratory rate at discharge - Polarity – N/A
Reattendance at health care within 7 days - Polarity - Lower values are better
Reattendance at health care within 14 days - Polarity - Lower values are better
Reattendance at health care within 28 days - Polarity - Lower values are better
Reattendance at health care within 6 months - Polarity - Lower values are better
SpO_2 measured at 28 days - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Parallel RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes *(Sequence generation Randomisation was by central internet-based secure password-protected randomisation database. Patient identifiers and some clinical details were entered to confirm eligibility (inclusion and exclusion criteria) and to prevent re-recruitment. The random allocation sequence was generated by the programmers at the Edinburgh Clinical Trials Unit (ECTU). Type of*

Section	Question	Answer
		randomisation Randomisation was by blocks of varying length (four and six) without stratification.)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes *(The person randomising the infant did not know the allocation until the infant was definitely enrolled into the study via the system.)*
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No *(No chi squared test for baseline differences, but no cause for concern between study arms)*
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No *(The monitors were identical in appearance and general function, with the exception of the study number. All study staff involved in day-to-day running of the trial, hospital staff and parents were blind to study intervention and could not tell what the randomised group was from the study numbers on the machines. To further reduce the opportunity for accidental unblinding, study numbers on oximeters were changed in the period between season 1 and season 2. Those assessing outcomes were blind to the assigned intervention. The blind was not broken for any infant during the study.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No *(As above)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes *(All analyses were by intention to treat (ITT) unless otherwise specified. The ITT population included all infants randomised into the BIDS study. Infants were analysed in the group to which they were randomised, regardless of treatment received.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No *(The monitors were identical in appearance and general function, with the exception of the study number. All study staff involved in day-to-day running of the trial, hospital staff and parents were blind to study intervention and could not tell what the randomised group was from the study numbers on the machines. To further reduce the opportunity for accidental unblinding, study numbers on oximeters were changed in the period between season 1 and season 2. Those*

Section	Question	Answer
		assessing outcomes were blind to the assigned intervention. The blind was not broken for any infant during the study.)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No *(As above)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Probably no *(In eight instances the incorrect treatment was allocated (by staff attaching the wrong oximeter): in seven instances a modified oximeter was provided to an infant randomised to standard care and in one instance a standard oximeter was attached to an infant randomised to modified care. These infants are included in the group to which they were allocated as per ITT. In 44 instances (22 in each arm) treatment was interrupted, the majority per protocol during an admission to the HDU, with treatment restarted on discharge from the HDU. Seventy-six participants had a protocol deviation, 34 (11.0%) in the standard care group and 42 (13.7%) in the modified care group. The deviation categories (oximeter was attached late, removed early, never attached, discharge criteria not met, other) are similar between groups.)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes *(As above)*
Domain 2b: Risk of bias due to deviations from the intended	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis	Not applicable

Section	Question	Answer
interventions (effect of adhering to intervention)	used to estimate the effect of adhering to the intervention?	
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes *(584/615 infants reached last available time point (6 months) with >90% of data available, which were split evenly among the study arms.)*
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably no *(Two of the main outcomes (resolution of cough, and time to return to feeding at 75% or more of normal) could have some subjectivity. No clear definition of cough resolution was reported, nor for return feeding (the Lancet article notes the discharge criteria included 'feeding orally at 75% or more of their expected intake of milk daily'*

Section	Question	Answer
		but there is no mention of milk anywhere else in the reports, and at the upper end of the age inclusion criteria of 12 months most children are mainly on solid food). 'Fit for discharge' also included the feeding criteria, so also could have some subjectivity. All other outcomes were objective measurements).
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No *(Measurement of outcomes was the same in each arm and unlikely to have led to differences between arms.)*
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No *(The monitors were identical in appearance and general function, with the exception of the study number. All study staff involved in day-to-day running of the trial, hospital staff and parents were blind to study intervention and could not tell what the randomised group was from the study numbers on the machines. To further reduce the opportunity for accidental unblinding, study numbers on oximeters were changed in the period between season 1 and season 2. Those assessing outcomes were blind to the assigned intervention. The blind was not broken for any infant during the study.)*
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded	Yes *(Population and outcomes pre-specified in the ISRCTN protocol match those in the study report.)*

Section	Question	Answer
	outcome data were available for analysis ?	
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no *(Results reported for all outcomes and timepoints mentioned in the methods.)*
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no *(Reported results correspond to all intended analyses. All analyses were by intention to treat (ITT) unless otherwise specified. A pre-planned per-protocol analysis was done for the primary outcome which had to match the ITT outcome for equivalence to be claimed.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(Oxygen supplementation given, and discharge, based on different thresholds of O_2 saturation, for infants aged 6 weeks to 12 months with bronchiolitis newly admitted into eight paediatric hospital units in the UK. Directly relevant to the review question and NG9 guideline scope.)*

D.2 Observational evidence

van Hasselt, 2020

Bibliographic Reference	van Hasselt, Tim J; Singham, Bhavna; Bassett, Eve; Wacogne, Ian D; Paediatric Research Across the Midlands (PRAM), Network; Oxygen saturation thresholds in bronchiolitis: examining admissions.; Archives of disease in childhood; 2020; vol. 105 (no. 12); 1197-1199

Study details

Trial registration number and/or trial name	NA
Study type	Prospective cohort study
Study location	West Midlands, UK.
Study setting	Paediatric departments across 12 hospitals. 11 secondary care and 1 tertiary children's hospital.
Study dates	November 2018.
Duration of follow-up	As long as duration of stay in hospital, typically less than a week.
Sources of funding	The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.
Inclusion criteria	Infants with a corrected age of ≥ 6 weeks and ≤ 12 months of age Admitted to hospital with a clinical diagnosis of bronchiolitis made by a medically qualified practitioner in ED/AAA
Exclusion criteria	• Preterm infant (<37 weeks' gestation) who received oxygen therapy in the previous 4 weeks • Cyanosis/haemodynamically significant heart disease • Documented immune function defect • Direct admission to high-dependency unit (HDU)/paediatric intensive care unit (PICU) from ED/AAA

	• Cystic fibrosis • Interstitial lung disease
Sample size	N=320 n=162 at centres with a 90% threshold. n=158 at centres with a 92% threshold.
Intervention	6 centres admitted patients at 90% oxygen saturation. Outcomes for these patients were compared to patients at centres with other oxygen saturation thresholds. Routinely collected data were used, ethical approval was not required for this service evaluation. The project was registered with each centre's audit and clinical governance department.
Comparator	6 centres admitted patients at 92% oxygen saturation.
Methods of analysis	Analysis was performed using Excel (Microsoft, USA) and Graphpad Quickcalcs (GraphPad Software, USA). $\chi 2$ was used for categorical data, Mann-Whitney U test for non-parametric data.
Loss to follow-up	None reported. Study procedures unlikely to allow loss to follow-up.
% Female	Not reported.
Mean age (SD)	Not reported.

Study arms

- 90% oxygen saturation (N = 162)

Patients admitted to hospital with oxygen saturation of 90%.

- 92% oxygen saturation (N = 158)

Patients admitted to hospital with oxygen saturation of 92%.

Characteristics

Arm-level characteristics

Characteristic	90% oxygen saturation (N = 162)	92% oxygen saturation (N = 158)
Low SpO_2 Sample size	n = 43 ; % = 27	n = 58 ; % = 37
Inadequate feeding Sample size	n = 129 ; % = 80	n = 126 ; % = 80
Social concerns/anxiety Sample size	n = 15 ; % = 9	n = 17 ; % = 11
Repeat attendance Sample size	n = 30 ; % = 19	n = 21 ; % = 13
Tachycardia Sample size	n = 32 ; % = 20	n = 21 ; % = 13
Tachypnoea Sample size	n = 47 ; % = 29	n = 48 ; % = 30
Unwell/deteriorating Sample size	n = 17 ; % = 10	n = 18 ; % = 11
Apnoea Sample size	n = 1 ; % = 1	n = 4 ; % = 3

Critical appraisal - GUT ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes *(The two thresholds are used in different centres. The centres' choice of threshold could mean a difference in care between the centres. Centres may have different populations, affecting outcome. This could mean there are confounding factors.)*
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No *(No adjustments for difference in population or care were conducted.)*

Section	Question	Answer
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Confounding not accounted for; centres may have different populations.)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No *(Centres used specific oxygen saturation thresholds and did not decide intervention status.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No *(Centres had specific oxygen saturation thresholds)*
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	Probably no *(Different centres are likely to have different treatment regimens.)*
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Yes
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Serious *(Important co-interventions are unlikely to be balanced across the 2 groups. No analysis conducted to estimate the effect of starting and adhering to intervention.)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low *(No missing outcome data.)*
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no *(Not explicitly stated, but healthcare staff treating patients were likely not aware they were creating data for a study. The data was collected from standard data collection spreadsheets and proformas. The study only mentions the audit and clinical governance staff in who was made aware of the study.)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably yes *(Even if healthcare staff were not aware that they were in a study, having a specific threshold may cause them to act differently than if they were working with a another threshold.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Possible link between knowledge of the threshold and decision-making.)*
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(Serious risk of bias judgement for deviations from intended interventions and confounding.)*

Section	Question	Answer
Overall bias	Directness	Directly applicable

Appendix E – GRADE tables

E.1 GRADE profiles from randomised controlled trial evidence

Quality assessment							No of patients		Effect		Quality
Study	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	No intervention control	Absolute	Relative	
Time to actual discharge (hours; higher values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Serious[1]	None	276	283	-	HR 1.46 (1.23 to 1.73)	MEDIUM
Use of nasogastric tube feeding (no. of events; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Serious[1]	None	303	305	-	RR 0.9 (0.7 to 1.1)	MEDIUM
Use of intravenous fluids (no. of events; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Very serious[2]	None	304	305	-	RR 1.0 (0.6 to 1.6)	LOW
Need for supplemental oxygen (no. of events; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	No serious	None	304	305	-	RR 0.8 (0.7 to 0.9)	HIGH
Time to readmission (days; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Very serious[2]	None	307	308	-	HR 0.93 (0.43 to 1.98)	LOW
Readmission to hospital within 7 days (no. of infants; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Very serious[2]	None	307	308	-	RR 0.6 (0.2 to 1.8)	LOW
Readmission to hospital within 28 days (no. of infants; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	No serious	None	307	308	-	RR 0.4 (0.2 to 0.7)	HIGH

High-dependency care (no. of events; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Very serious[2]	None	307	308	-	RR 1.1 (0.5 to 2.6)	LOW
Respiratory rate at discharge (breaths per minute)											
Cunningham	RCT	No serious	NA	No serious	No serious	None	307	308	MD 0 (-0.58 to 0.58)	-	HIGH
Mortality (no. of events; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	No serious	Very serious[2]	None	307	308	-	RR 0.2 (0.0 to 3.7)	LOW
Time to cough resolution (days; lower values indicate better outcome for intervention arm)											
Cunningham	RCT	No serious	NA	Very serious[3]	No serious	None	307	308	Median difference 1 (-1 to 2)	-	LOW

Acronyms: 95%CI – 95% confidence interval; RCT – randomised controlled trial; HR – hazard ratio; RR – risk ratio; MD – mean difference; MID – minimal important difference.

[1] Downgraded 1 level for imprecision because the 95%CI crossed 1 MID boundary.

[2] Downgraded 2 levels for imprecision because the 95%CI crossed 2 MID boundaries.

[3] Downgraded 2 level as outcome is not relevant to the review protocol.

All RRs and MDs were calculated by the reviewer.

E.2 GRADE profiles from observational evidence

Quality assessment							No of patients		Effect		Quality
Study	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	No intervention control	Absolute	Relative	
Length of stay (hours; lower values indicate better outcome for intervention arm)											

van Hasselt	Prospective	Very serious[1]	NA	No serious	No serious	Observational data[2]	181	139	MD -16 (8.47 to -23.53)	-	VERY LOW

[1] Marked down 2 quality levels due to serious risk of bias as measured by ROBINS-I tool.
[2] The highest quality observational data can achieve in GRADE is “low”.

Appendix F – Economic evidence tables

Study	Cunningham, Steve, Rodriguez, Aryelly, Boyd, Kathleen A et al. (2015) Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. Health technology assessment (Winchester, England) 19(71): i-172			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost effectiveness analysis **Study design:** Within-trial economic evaluation **Approach to analysis:** Clinical outcomes and resource use data were collected directly within the RCT, and costs were then attached to the resource use data. **Perspective:** NHS perspective **Time horizon:** 6 months (trial duration) **Intervention effect duration:** 6 months (trial duration) **Discounting:** N/A due to 6-month time horizon.	**Population:** Infants between 6 weeks and 12 months with a clinical diagnosis of bronchiolitis who were admitted to hospital. **Interventions** Oxygen saturation target of ≥90% versus an oxygen saturation target of ≥94%.	**Cost differences:** Before admission costs (£) **90% target:** 195.10 **94% target:** 199.09 **Difference:** -3.99 (95% CI -56.83, 48.84) Hospital costs (£) **90% target:** 1159.64 **94% target:** 1298.16 **Difference:** -138.53 (95% CI -363, 86) Follow-up costs (£) **90% target:** 452.66 **94% target:** 603.67 **Difference:** -151.01 (95% CI -400, 99) Total NHS costs (£) **90% target:** 1612.30 **94% target:** 1901.83 **Difference:** -289.53 (95% CI -657, 78) **Currency & cost year:** Sterling 2013	**Outcome differences:** Time to cough resolution (days – complete cases) **90% target:** 22.35 **94% target:** 23.13 **Difference:** -0.78 (95% CI -5.25, 3.69) Time to cough resolution (days – imputed data) **90% target:** 36.48 **94% target:** 39.65 **Difference:** -3.17 (95% CI -11.18, 4.84)	**Base-case analysis:** Probability 90% target cost-effective at different willingness-to-pay thresholds for a reduced day to cough resolution: **£0 – 91.5%** **£25 – 90.3%** **£50 – 86.5%** The results from probabilistically bootstrapping the trial data were not meaningfully different from the deterministic results. **Sensitivity analyses:** Broadening to a societal perspective by including parental costs did not qualitatively change the conclusions of the analysis.

Data sources
Outcomes: Time to cough resolution in days was directly measured within the RCT (with multiple imputation done for missing values), with anxiety also included as a secondary outcome. **Quality of life weights:** N/A – study conducted a cost-effectiveness rather than cost-utility analysis. **Costs:** Resource use data from the BIDS trial were analysed using a GLM regression model, adjusting for participants baseline characteristics, and then standard reference costs or data from trial authors were used to attached costs to this resource use.
Comments
Source of funding: National Institute for Health Research Health Technology Assessment programme
Overall applicability: Directly applicable
The study design does not directly match the review question, but the differences were felt to be unlikely to undermine the conclusions of the study for its primary purpose.
Overall quality: Minor limitations
No significant limitations identified

Quality assessment checklist

Cunningham, Steve, Rodriguez, Aryelly, Boyd, Kathleen A et al. (2015) Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. Health technology assessment (Winchester, England) 19(71): i-172

Category	Rating	Comments
Applicability		
1.1 Is the study population appropriate for the review question?	Partly	Exclusion of infants under 6 weeks of age, exclusion of emergency departments and primary care. These limitations were not considered to undermine the conclusions of the study for its primary purpose.
1.2 Are the interventions appropriate for the review question?	Partly	The study compared an oxygen saturation target of 94% with one of 90%, whilst current NICE guidance is a target of 92%
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	

1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	No	Quality of life was not measured in the study, but because the modified intervention was dominant this was not considered a significant limitation.
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix G – Health economic model

No economic modelling was undertaken for this review question, as it was decided the published economic evidence was sufficient for decision making.

Appendix H – Excluded studies

Study	Code [Reason]
American Association for Respiratory Care (2021) AARC Clinical Practice Guideline Management of Pediatric Patients with Oxygen in the Acute Care Setting.	- Duplicate reference
Angurana, Suresh K.; Takia, Lalit; Williams, Vijai (2020) Acute Viral Bronchiolitis: A Narrative Review. Journal of Pediatric Intensive Care	- Data not reported in an extractable format
Anonymous. (2017) Erratum: Infants with artificially elevated pulse oximetry levels less likely to be hospitalised during an episode of mild to moderate bronchiolitis (Arch Dis Child Ed Pract (2016) 101 (162-3) DOI: 10.1136/archdischild-2016-310570). Archives of Disease in Childhood: Education and Practice Edition 102(1): 54	- Secondary publication of an included study that does not provide any additional relevant information
BMJ Best Practice (2020) Bronchiolitis.	- Guidelines
Boyd, K, McIntosh, E, Lewis, S et al. (2015) Cost-effective management of bronchiolitis in infants: 90% versus 94% oxygen saturation. European respiratory journal 46(suppl59): oa1988	- Conference abstract
Canadian Paediatric Society (2018) Use of high-flow nasal cannula oxygen therapy in infants and children.	- Study does not contain a relevant intervention
Canadian Paediatric Society (2014) Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age Updated 2018.	- Guidelines
Clinical Knowledge Summaries (2021) Cough - acute with chest signs in children: bronchiolitis.	- Not a relevant study design
Colombo, Jacopo, Gattoni, Chiara, Nacoti, Mirco et al. (2020) Risk factors for intubation in severe bronchiolitis: a useful tool to decide on an early intensive respiratory support. Minerva pediatrica	- Study does not contain a relevant intervention Oxygen saturation measured as a dichotomous variable, above and below 75%. - Not a relevant study design Preprint
Coskun, Yesim, Saglam, Filiz, Mamal-Torun, Muzeyyen et al. (2017) Risk factors for intensive care need in children with bronchiolitis: A case-control study. The Turkish journal of pediatrics 59(5): 520-523	- Not a relevant study design Case-control study with cross-sectional data.
Cunningham, Steve (2018) Respiratory Support in Bronchiolitis: Trial Evidence. American journal of perinatology 35(6): 553-556	- Not a relevant study design

Cunningham, Steve (2020) Critical Care Thresholds in Children with Bronchiolitis. American journal of perinatology 37(s02): 42-s45	- Not a relevant study design Literature review not a study.
Department for Health and Wellbeing GOSA (2018) Bronchiolitis in Children.	- Guidelines
Fernandes, Ricardo M; Plint, Amy C; Terwee, Caroline B; Sampaio, Cristina; Klassen, Terry P; Offringa, Martin; van der Lee, Johanna H (2015) Validity of bronchiolitis outcome measures. Paediatrics 135:6 e1399-408	- Study does not contain a relevant intervention Does not assess oxygen saturation or compare two different oxygen saturation levels.
Franklin, Donna, Hasan, Nadia, Kapoor, Vishal et al. (2019) Nasal High Flow in Room Air for Hypoxemic Bronchiolitis Infants. Frontiers in Pediatrics 7: 426	- Study does not contain a relevant intervention
Freire, Gabrielle, Kuppermann, Nathan, Zemek, Roger et al. (2018) Predicting Escalated Care in Infants With Bronchiolitis. Pediatrics 142(3)	- Comparator in study does not match that specified in protocol No comparison with 92% oxygen saturation.
Hendaus, Mohamed A.; Alhammadi, Ahmed H.; Jomha, Fatima A. (2015) Pulse oximetry in bronchiolitis: Is it needed?. Therapeutics and Clinical Risk Management 11: 1573-1578	- Data not reported in an extractable format
Kaditis, Athanasios G, Katsouli, Georgia, Malakasioti, Georgia et al. (2015) Infants with viral bronchiolitis demonstrate two distinct patterns of nocturnal oxyhaemoglobin desaturation. Acta paediatrica (Oslo, Norway : 1992) 104(3): e106-11	- Study does not contain a relevant intervention Compares oxygen saturation in children with bronchiolitis, partial upper airway obstruction, and controls
King, David; Dicks, Rebecca Amy; Wacogne, Ian D (2016) Infants with artificially elevated pulse oximetry levels less likely to be hospitalised during an episode of mild to moderate bronchiolitis. Archives of disease in childhood. Education and practice edition 101(3): 162-3	- Not a relevant study design
Kirolos, Amir, Manti, Sara, Blacow, Rachel et al. (2020) A Systematic Review of Clinical Practice Guidelines for the Diagnosis and Management of Bronchiolitis. The Journal of infectious diseases 222(suppl7): 672-s679	- Guidelines
Luarte-Martinez, Soledad; Rodriguez-Nunez, Ivan; Astudillo, Paula (2019) Validity and reliability of the modified Tal score in Chilean children. A multicenter study. Archivos argentinos de pediatria 117(4): e340-e346	- Comparator in study does not match that specified in protocol Study uses oxygen saturation as a reference standard. There was no comparison between different saturation levels.

Mansbach, Jonathan M, Clark, Sunday, Piedra, Pedro A et al. (2015) Hospital course and discharge criteria for children hospitalized with bronchiolitis. Journal of hospital medicine 10(4): 205-11	- Comparator in study does not match that specified in protocol Does not compare oxygen saturation levels. Description of outcomes after new discharge criteria were used.
Martin, Shirley; Martin, Jennifer; Seigler, Theresa (2015) Evidence-Based Protocols to Guide Pulse Oximetry and Oxygen Weaning in Inpatient Children with Asthma and Bronchiolitis: A Pilot Project. Journal of pediatric nursing 30(6): 888-95	- Comparator in study does not match that specified in protocol Follows the development of local guidelines for weaning children from oxygen and at which oxygen saturations this is safe to do. Comparison between before and after guidelines were used but unknown what the oxygen saturation threshold was before guideline implementation.
Masarweh, Kamal, Gur, Michal, Leiba, Ronit et al. (2020) Factors predicting length of stay in bronchiolitis. Respiratory medicine 161: 105824	- Study does not contain a relevant intervention Did not assess oxygen saturation.
Mayor, Susan (2016) Reduced oxygen saturation is not linked to repeat hospital visits in infant bronchiolitis. BMJ (Clinical research ed.) 352	- Not a relevant study design Commentary on the area and not a study.
Meenaghan, S; Breatnach, C; Smith, H (2020) Risk Factors for Respiratory Syncytial Virus Bronchiolitis Admissions. Irish medical journal 113(1): 9	- Study does not contain a relevant intervention Does not assess oxygen saturation levels.
Mendlowitz, Andrew B, Widjaja, Elysa, Phan, Cathy et al. (2018) A Cost Analysis of Pulse Oximetry as a Determinant in the Decision to Admit Infants With Mild to Moderate Bronchiolitis. Pediatric emergency care	- Health economics
Napolitano, Natalie, Berlinski, Ariel, Walsh, Brian K. et al. (2021) AARC Clinical Practice Guideline Management of Pediatric Patients with Oxygen in the Acute Care Setting. Respiratory care	- Guidelines
NHS Children's Acute Transport Service (2020) Clinical Guidelines - Bronchiolitis.	- Not a relevant study design
NSW Government (2018) Infants and Children - Acute Management of Bronchiolitis.	- Guidelines
Ohlsen, Timothy J D, Knudson, Alexander M, Korgenski, E Kent et al. (2021) Nine Seasons of a Bronchiolitis Observation Unit and Home Oxygen Therapy Protocol. Journal of hospital medicine 16(5): 261-266	- Study does not contain a relevant intervention The OU-HOT intervention is an at home oxygen delivery system. The study did not compare outcomes based on oxygen saturation levels.

Praznik, Ajda, Vinsek, Neza, Prodan, Ana et al. (2018) Risk factors for bronchiolitis severity: A retrospective review of patients admitted to the university hospital from central region of Slovenia. Influenza and other Respiratory Viruses 12(6): 765-771	- Study does not contain a relevant intervention Did not report oxygen saturation.
Principi, Tania, Coates, Allan L, Parkin, Patricia C et al. (2016) Effect of Oxygen Desaturations on Subsequent Medical Visits in Infants Discharged From the Emergency Department With Bronchiolitis. JAMA pediatrics 170(6): 602-8	- Comparator in study does not match that specified in protocol Only compares infants with desaturations <90% to infants with no desaturations below that point.
Ralston, Shawn L., Lieberthal, Allan S., Meissner, H. Cody et al. (2014) Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. Pediatrics 134(5): e1474-e1502	- Guidelines
Rebnord, Ingrid Keilegavlen, Sandvik, Hogne, Hunskaar, Steinar et al. (2017) Factors predicting antibiotic prescription and referral to hospital for children with respiratory symptoms: Secondary analysis of a randomised controlled study at out-of-hours services in primary care. BMJ Open 7(1): e012992	- Study does not contain a relevant intervention
Rojas-Reyes, Maria Ximena; Granados Rugeles, Claudia; Charry-Anzola, Laura Patricia (2014) Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age. The Cochrane database of systematic reviews: cd005975	- Study does not contain a relevant intervention
Royal Children's Hospital Melbourne (2020) Clinical Practice Guidelines - Bronchiolitis.	- Guidelines
Royal College of Paediatrics and Child Health (2020) National guidance for the management of children with bronchiolitis and lower respiratory tract infections during COVID-19 Last modified 24 May 2021.	- Guidelines
Schuh, Suzanne, Freedman, Stephen, Coates, Allan et al. (2014) Effect of oximetry on hospitalization in bronchiolitis: a randomized clinical trial. JAMA 312(7): 712-8	- Already looked at by NG9 guideline
Slain, Katherine N, Rotta, Alexandre T, Martinez-Schlurmann, Natalia et al. (2019) Outcomes of Children With Critical Bronchiolitis Meeting at Risk for Pediatric Acute Respiratory Distress Syndrome Criteria. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 20(2): e70-e76	- Study does not contain a relevant intervention Compares children with severe disease to children with mild disease.

Stollar, Fabiola, Glangetas, Alban, Luterbacher, Fanny et al. (2020) Frequency, Timing, Risk Factors, and Outcomes of Desaturation in Infants With Acute Bronchiolitis and Initially Normal Oxygen Saturation. JAMA network open 3(12): e2030905	- Study does not contain a relevant intervention
Suessman, Anna, Gray, Lauren L, Cavenaugh, Sarah et al. (2020) Clinical factors associated with intubation in the high flow nasal cannula era. The American journal of emergency medicine 38(12): 2500-2505	- Study does not contain a relevant intervention Oxygen saturation not reported. - Not a relevant study design Cross-sectional study.
Vincent, Jennifer Orr; Lo, Huay-Ying; Wu, Susan (2017) Bronchiolitis Care in the Hospital. Reviews on recent clinical trials 12(4): 246-252	- Data not reported in an extractable format
Zorc, Joseph J. (2015) Randomised controlled trial: Pulse oximetry may lead to unnecessary hospital admissions for infants with bronchiolitis and mild hypoxaemia. Evidence-Based Medicine 20(1): 19	- Not a relevant study design

Appendix I – Research recommendations

The committee did not opt to make any research recommendations related to this evidence review.