National Institute for Health and Care Excellence

Final

Neonatal infection: antibiotics for prevention and treatment

[E] Evidence reviews for maternal and neonatal risk factors for late-onset neonatal infection

NICE guideline NG195

Evidence reviews underpinning recommendations 1.4.1-1.4.2 and research recommendations in the NICE guideline

April 2021

Final

These evidence reviews were developed by NICE Guideline Updates Team

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1.1 Review question

What is the accuracy of clinical prediction models for late-onset neonatal infection and what is their effectiveness in guiding management in the baby?

1.1.1 Introduction

Neonatal infection is a significant cause of mortality and morbidity in newborn babies. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. For the purpose of this guideline, late-onset neonatal infection is defined as infection which occurs between 72 hours of birth and 28 days of age (corrected for gestational age).

Predicting which babies are most at risk of late-onset neonatal infection is important to help determine who should receive antibiotic treatment. A culture taken from blood or cerebrospinal fluid which tests positive for the organisms associated with infection is the gold-standard for identifying which babies should receive treatment. However, waiting for the results of these tests may delay treatment. A tool which can predict which babies are most at risk of late-onset neonatal infection is therefore important to help identify those who will benefit from early treatment, whilst reducing the number of babies who receive unnecessary treatment. This will also reduce other associated risks such as antimicrobial resistance. The aim of this review is therefore to evaluate existing clinical prediction models for late-onset neonatal infection and determine their effectiveness in guiding management of the baby.

1.1.2 Summary of the protocol

The review was divided into 2 parts. Part A aimed to identify studies assessing the accuracy of clinical prediction models in identifying babies with late onset infection. Part B aimed to identify 'test and treat' randomised controlled trials that assessed the effectiveness of clinical prediction models in guiding management.

Part A

Population	• Term babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age • Pregnant women
Interventions	Any validated risk tool using multiple predictors to predict the risk of development or the presence of late-onset neonatal infection
Reference standard	• culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate)
Outcomes	For each outcome, accuracy measures will be reported where available, for example: • Odds ratios/hazard ratios

	• Model fit, including discrimination (C statistic, area under ROC curve) and calibration (r squared) • Sensitivity, specificity, positive and negative likelihood ratios

Part B

Population	• Term babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age • Pregnant women
Interventions	• Any risk tool for late-onset neonatal development identified in Part A of the protocol (any validated risk tool using multiple predictors to predict the risk of development or the presence of late-onset neonatal infection)) followed by treatment (for example provision of antibiotics or further testing) according to risk stratification by the tool results.
Comparator	• Standard care: treatment according to risk stratification based on clinician experience or existing clinical protocols (for example, existing NICE guidance) • Comparisons between risk tools followed by treatment according to risk stratification by tool results will also be included.
Outcomes	Neonatal outcomes: • culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • suspected bloodstream infection based on clinical symptoms • mortality from 72 hours of birth onwards (at different time points – peri-natal mortality (within 7 days from birth) or greater than 7 days from birth) • health-related quality of life, measured using a validated tool (during the neonatal period and at the latest timepoint reported in study) • hospital length of stay • number prescribed antibiotic treatment Family outcomes: • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the neonatal period and at the latest timepoint reported in study)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A. For full details of the methods used see the methods document.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Prospective and retrospective observational cohort or cross-sectional studies (part A) and test and treat randomised controlled trials (part B) were considered in addition to systematic reviews. The review protocol specified that, where possible, subgroup analyses would be conducted for gestational age of the baby (preterm vs term) and for babies who had been admitted to the hospital from home. However, this was not possible as most studies included both preterm and term babies, and the results were not separated by gestational age. Studies did not state the admission route of the babies. No studies matched the protocol for Part B of the review (RCTs for different risk predictor tools).

1.1.4 Prognostic evidence

1.1.4.1 Included studies

A joint search was carried out to identify studies specified for this evidence review, and a similar evidence review for studies assessing clinical prediction models for early-onset infection (for details, see evidence review D - risk factors for early onset). This returned a total of 1,252 results, of which 68 were identified as potential included studies. Full text articles were ordered and reviewed against the inclusion criteria, of which 8 met the inclusion criteria for the review. Three studies investigated the use of the RALIS model, 2 assessed the NOSEP model and 3 looked at other, unnamed, models which used a combination of demographic and clinical factors to predict whether a baby is at risk of late-onset neonatal infection.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This combined search for early- and late-onset prediction models returned a total of 244 results of which 14 were identified as possible included studies. After full text review, all were excluded. In total there were therefore 9 studies which met the inclusion criteria for this review (5 prospective cohort studies, 4 retrospective cohort studies).

1.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the prognostic evidence

Table 2 Summary of included clinical studies

Study	Study type and follow-up time	Population	Prediction model
Celik 2013 (n=304)	• Retrospective cohort • Follow-up time not reported	• Not reported *Possibly all babies in neonatal intensive care unit*	• Celik model 1, 2 and 3
Griffin 2003 (n=633)	• Prospective cohort • Follow-up time not reported	• All infants admitted to NICUs • *at University of Virginia (UVA) and Wake Forest University (WFU)*	• Demographics and heart rate monitoring model (2 models)
Gur 2014 (n=46)	• Retrospective cohort	• Preterm infants *<33 weeks gestation*	• RALIS model

Study	Study type and follow-up time	Population	Prediction model
	• 10 day follow-up	• Birth weight <1500 g	
Gur 2015 (n=118)	• Prospective cohort • 21 day follow-up	• Preterm infants *<33 weeks gestation* • Birth weight <1500 g	• RALIS model
Mithal 2016 (n=73)	• Retrospective cohort • Follow-up time not reported	• Preterm infants *<28 weeks gestation* • Complete vital signs data from birth to 28 days of life	• RALIS model
Mahieu 2000 (n=80)	• Prospective cohort • Follow-up time not reported	• Infants admitted to the NICU *University Hospital of Antwerp*	• NOSEP-1 score
Mahieu 2002 (n=93)	• Prospective cohort • Follow-up time not reported	• Infants admitted to the NICU *University Hospital of Antwerp*	• NOSEP-1 score • NOSEP-New-1 score • NOSEP-New-2 score
Mani 2014 (n=299)	• Retrospective cohort • 60 hour follow-up (finishing 12 hours after first blood culture)	• Infants evaluated for late-onset sepsis *defined as neonatal sepsis occurring over 72 h after birth*	• Machine learning models (8 models)
Xiao 2010 (n=676)	• Prospective cohort • Follow-up time not reported	• Infants admitted to the NICU *University of Virginia NICU* • Age >7 days	• Nearest neighbour model *Using physiological and demographic monitoring*

See appendix D for full evidence tables.

1.1.6 Model summaries

RALIS model

The RALIS model was developed in Israel and is designed to predict the risk of late-onset neonatal infection for preterm babies with a birthweight less than 1500 g. This is a computerised algorithm including heart rate, respiratory rate, core body temperature, body

weight, desaturations and bradycardias. The model is designed to produce an alarm to indicate that a baby is at risk of late-onset neonatal infection.

NOSEP model

The NOSEP models (NOSEP, NOSEP-New-I, NOSEP-New-II) were developed in Belgium and are designed to predict a baby's risk of developing nosocomial sepsis. The models include information on C-reactive protein (CRP) levels, thrombocytopenia, neutrophil fraction, fever and duration of total parenteral nutrition. There is no evidence of a web-based tool or software that can be used directly by a clinician.

Celik models

Three models developed by Celik 2013 in Turkey, based on a combination of parameters obtained from a blood sample, and used to predict the risk of a baby developing neonatal sepsis. There is no evidence of a web-based tool or software that can be used directly by a clinician.

Machine learning models

The models reported by Mani 2014 were developed in the USA, based on machine learning from medical data and data from electronic medical records and used to predict the risk of a baby developing late-onset sepsis. Either sensitivity or specificity was fixed in each of the models to match the predictive ability of a clinician. There is no evidence of a web-based tool or software that can be used directly by a clinician.

Demographics and heart rate models

The models reported by Griffin 2003 were developed in the USA, based on demographic information and heart rate data and used to predict the risk of a baby developing neonatal sepsis or sepsis-like illness. There is no evidence of a web-based tool or software that can be used directly by a clinician.

Nearest neighbour model

The nearest neighbour model was developed in the USA and used information from heart rate data and laboratory tests to match babies with similar symptoms or test results and provide an indication of their diagnoses and outcomes. The most successful model included the heart rate characteristics index, white blood cell count, I/T (immature/total) ratio and HCO_3. There is no evidence of a web-based tool or software that can be used directly by a clinician.

1.1.7 Summary of the prognostic evidence

Sensitivity and specificity

Comparison	No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
RALIS model	3	2279	0.81 (0.67, 0.90)	0.70 (0.44, 0.87)	LR+ 2.82 (1.38, 5.78)	Very low
					LR- 0.29 (0.16, 0.52)	Low
NOSEP model	2	173	0.87 (0.47, 0.98)	0.50 (0.37, 0.64)	LR+ 1.68 (1.34, 2.12)	Moderate
					LR- 0.26	Very low

Comparison	No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
					(0.06, 1.11)	
NOSEP New-I model	1	93	0.84 (0.72, 0.92)	0.43 (0.29, 0.58)	LR+ 1.48 (1.11, 1.97)	High
					LR- 0.37 (0.18, 0.76)	Moderate
NOSEP New-II model	1	93	0.82 (0.69, 0.91)	0.67 (0.51, 0.79)	LR+ 2.47 (1.58, 3.86)	Moderate
					LR- 0.26 (0.14, 0.50)	Moderate
Model 1 (Celik 2013)	1	304	0.88 (0.79, 0.94)	0.92 (0.88, 0.95)	LR+ 11.82 (7.43, 18.82)	Moderate
					LR- 0.13 (0.07, 0.24)	Moderate
Model 2 (Celik 2013)	1	304	0.88 (0.79, 0.94)	0.92 (0.88, 0.95)	LR+ 11.82 (7.43, 18.82)	Moderate
					LR- 0.13 (0.07, 0.24)	Moderate
Model 3 (Celik 2013)	1	304	0.96 (0.89, 0.99)	0.91 (0.87, 0.94)	LR+ 10.95 (7.19, 16.68)	Moderate
					LR- 0.04 (0.01, 0.13)	Moderate
NB model (Mani 2014)	1	299	0.83 (0.74, 0.89)	0.18 (0.13, 0.24)	LR+ 1.02 (0.91, 1.14)	Low
					LR- 0.93 (0.55, 1.58)	Low
RF model (Mani 2014)	1	299	0.83 (0.74, 0.89)	0.18 (0.13, 0.24)	LR+ 1.00 (0.90, 1.12)	Low
					LR- 0.99 (0.59, 1.66)	Low
CART model (Mani 2014)	1	299	0.75 (0.65, 0.82)	0.18 (0.13, 0.24)	LR+ 0.91 (0.80, 1.04)	Low
					LR- 1.39 (0.89, 2.19)	Very low
AODE model (Mani 2014)	1	299	0.88 (0.80, 0.94)	0.18 (0.13, 0.24)	LR+ 1.08 (0.98, 1.19)	Low
					LR- 0.64 (0.34, 1.20)	Low
NB model 2 (Mani 2014)	1	299	0.75 (0.65, 0.82)	0.32 (0.26, 0.38)	LR+ 1.10 (0.94, 1.27)	Low
					LR- 0.79 (0.53, 1.18)	Low

Comparison	No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
RF model 2 (Mani 2014)	1	299	0.75 (0.65, 0.82)	0.23 (0.18, 0.29)	LR+ 0.97 (0.84, 1.12)	Low
					LR- 1.10 (0.72, 1.68)	Low
CART model 2 (Mani 2014)	1	299	0.75 (0.65, 0.82)	0.18 (0.13, 0.24)	LR+ 0.91 (0.80, 1.04)	Low
					LR- 1.39 (0.89, 2.19)	Very low
AODE model 2 (Mani 2014)	1	299	0.75 (0.65, 0.82)	0.36 (0.30, 0.43)	LR+ 1.16 (1.00, 1.36)	Low
					LR- 0.71 (0.48, 1.04)	Very low

c-statistics (Higher values reflect better classification accuracy. C-statistics from 0.7 – 1.0 reflect good to outstanding accuracy for predicting neonatal infection)

No. studies	Sample size	c-statistic (95% CI) (or SD if stated)	Quality
NOSEP model			
1 (Mahieu 2002)	80	0.82 (SD ±0.04)	Low
1 (Mahieu 2002)	93	0.66 (SD ±0.06)	Low
NOSEP-New-I model			
1 (Mahieu 2002)	93	0.71 (SD ±0.05)	Low
NOSEP-New-II model			
1 (Mahieu 2002)	93	0.82 (SD ±0.04)	Low
Celik 2013 (Model 1)			
1 (Celik 2013)	304	0.95 (0.92, 0.98)	Moderate
Celik 2013 (Model 2)			
1 (Celik 2013)	304	0.95 (0.91, 0.97)	Moderate
Celik 2013 (Model 3)			
1 (Celik 2013)	304	0.98 (0.95, 0.99)	Moderate
Mani 2014 (NB model – specificity fixed at 0.18)			
1 (Mani 2014)	299	0.64 (0.51, 0.79)	Low
Mani 2014 (RF model – specificity fixed at 0.18)			

No. studies	Sample size	c-statistic (95% CI) (or SD if stated)	Quality
1 (Mani 2014)	299	0.57 (0.50, 0.73)	Very low
Mani 2014 (CART model – specificity fixed at 0.18)			
1 (Mani 2014)	299	0.65 (0.53, 0.77)	Very low
Mani 2014 (AODE model – specificity fixed at 0.18)			
1 (Mani 2014)	299	0.61 (0.51, 0.75)	Very low
Mani 2014 (NB model 2 – sensitivity fixed at 0.75)			
1 (Mani 2014)	299	0.64 (0.51, 0.79)	Very low
Mani 2014 (RF model 2 – specificity fixed at 0.18)			
1 (Mani 2014)	299	0.57 (0.50,0.73)	Very low
Mani 2014 (CART model 2 – specificity fixed at 0.18)			
1 (Mani 2014)	299	0.65 (0.53, 0.77)	Very low
Mani 2014 (AODE model 2 – specificity fixed at 0.18)			
1 (Mani 2014)	299	0.61 (0.51, 0.75)	Very low
Demographics and heart rate monitoring models: demographics and HR characteristics			
1 (Griffin 2003)	633	0.72 CI not reported	Moderate
Demographics and heart rate monitoring models: demographics and HR characteristics index			
1 (Griffin 2003)	633	0.77 CI not reported	Moderate
Nearest neighbour model (optimal model: HRC index, WBC, I:T ratio, HCO3)			
1 (Xiao 2010)	676	0.86 CI not reported	Moderate

See appendix F for full GRADE tables.

1.1.8 Economic evidence

1.1.8.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see appendix B). This search retrieved 4,398 studies. Based on title and abstract screening, all of the studies could confidently be excluded for this question.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 577 results. Based on title and abstract screening, all the studies could confidently be excluded for this question. Thus, the review for this question does not include any study from the existing literature.

1.1.9 Economic model

This question was not prioritised for original economic analysis.

2.1 Review question

Which maternal risk factors for late-onset neonatal infection should be used to guide management in the baby?

2.1.1 Introduction

Neonatal infection is a significant cause of mortality and morbidity. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. For the purpose of this guideline, late-onset neonatal infection is defined as infection which occurs between 72 hours of birth and 28 days of age (corrected for gestational age).

Predicting which babies are most at risk of late-onset neonatal infection is important to help determine who should receive antibiotic treatment. A culture taken from blood or cerebrospinal fluid which tests positive for the organisms associated with infection is the gold-standard for identifying which babies should receive treatment. However, waiting for the results of these tests may delay treatment. Identifying the factors which can put a baby at high risk of neonatal infection is therefore important to help determine whether a baby should be given antibiotics while waiting for the results of a blood culture to confirm infection. The aim of this review is therefore to evaluate potential risk factors in the mother and determine how well they can guide management of the baby.

2.1.2 Summary of the protocol

Population	• Term babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age • Pregnant women
Risk factors	• Invasive group B streptococcal (GBS) infection in a previous baby • Maternal GBS colonisation, bacteriuria, detection (including vaginal or rectal swab) or infection in the current pregnancy • Suspected or confirmed infection in another baby in the case of a multiple pregnancy • Maternal wound infections (including perineal infections) • Maternal suspected bacterial infection in the puerperium • Maternal obesity • Behavioural and hygienic factors (for example adherence to infection control measures by medical professionals and parents/carers) • Maternal carriage of Methicillin-resistant Staphylococcus aureus (MRSA)
Reference standard	• culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given between 72 hours (where available) and 28 days of age (term babies) or 28 days CGA (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection

Outcomes	Outcomes for predictive accuracy studies: • Sensitivity • Specificity • Positive and negative likelihood ratios If association studies are included due to a lack of predictive accuracy data: • Adjusted Risk ratios, Odds ratios, hazard ratios

2.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A. For full details of the methods used see the methods document.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Predictive accuracy studies were considered in addition to systematic reviews. For outcomes where no predictive accuracy studies were available, multivariate cohort studies that reported adjusted measures of association were included. The review protocol specified that, where possible, subgroup analyses would be conducted for gestational age of the baby (preterm vs term), multiple births, age of the baby (72 hours to 6 days vs 7+ days) and for babies who had been admitted to the hospital from home. However, no evidence was available for any of the specified subgroup analyses.

Some studies reported outcomes that matched the protocol but were only reported as part of univariate analysis. These outcomes were not included in the analysis as they did not meet the inclusion criteria for multivariate analyses methods.

Protocol deviation

The review protocol specified the risk factors that would be included *a priori* based on the knowledge and experience of the committee. However, on presentation of the evidence, the committee identified further risk factors that were important that were missing from the evidence review. The protocol was subsequently expanded to include all risk factors and clinical indicators on which evidence was available, not just the factors pre-specified in the review protocol.

2.1.4 Prognostic evidence

2.1.4.1 Included studies

A joint search was carried out to identify studies specified for this review question, and a similar review question for studies assessing risk factors and signs and symptoms in the baby for late-onset infection (for details, see section 3.1 on neonatal factors). This returned a total of 7,146 results, of which 134 were identified as potential included studies for either of the reviews. Full text articles were ordered and reviewed against the inclusion criteria, of which 3 met the inclusion criteria for this review. All 3 studies reported predictive accuracy data (2 retrospective cohort studies and 1 prospective cohort study).

The joint search was re-run in July 2020 to identify any studies that had been published since the date of the original search. This returned a total of 670 results of which 14 were identified as possible included studies for either of the reviews. After full text review, 3 retrospective cohort studies met the inclusion criteria for this review and reported adjusted measures of association. In total there were therefore 6 studies which met the inclusion criteria for this review. This included 3 predictive accuracy studies and 3 association studies.

One multivariate cohort study (Rastogi 2015) reported on the association between maternal obesity and late-onset neonatal infection. The reference standard for this study was neonatal sepsis, based on an ICD-9 code of 771.81. This study was presented to the committee, but the committee expressed concerns about the diagnosis, suggesting that many babies categorised using the ICD-9 code may not have had a diagnosis confirmed by blood culture. There was also no information about whether babies had early- or late-onset infection. This study was therefore excluded from the review because it did not use the reference standard specified in the review protocol, leaving 5 applicable studies for this review question.

2.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

2.1.5 Summary of studies included in the prognostic evidence

Table 3 Summary of included clinical studies

Study	Study type and follow-up time	Population	Predictive factors
Garcia-Munoz Rodrigo 2014 (n=8330)	• Retrospective cohort • Duration of follow-up not reported	• Birthweight <1500g • Gestational age <32 weeks • Admitted to a neonatal unit	• Maternal chorioamnionitis
Lee 2019 (n=2900)	• Retrospective cohort • Duration of follow-up not reported	• Very low birthweight *<1500 g* • <34 weeks' gestational age	• Antenatal steroids *(receipt of at least one dose of any corticosteroid during pregnancy)*
Njagu 2020	• Retrospective cohort • Duration of follow-up not reported	• Women with class III obesity Body mass index >40 kg/m2. • Women delivered at term *>37 weeks*	• Gestational weight gain *(women who gained <20 lbs vs women who gained >20 lbs)*
Olivier 2016 (n=20,038)	• Retrospective cohort • Duration of follow-up not reported	• Admitted to a neonatal unit • Gestational age 22 - 32 weeks	• Mode of delivery (vaginal or caesarean section)
Ward 2020 (n=34,371)	• Retrospective cohort • Duration of follow-up not reported	• All women with preterm and term singleton pregnancies	• Women given an epidural

See appendix D for full evidence tables.

2.1.6 Summary of the prognostic evidence

Sensitivity and specificity – predictive accuracy studies

No. of studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Quality
Maternal chorioamnionitis					
	8330	0.196	0.83	LR+ 1.16 (1.06, 1.28)	Moderate

No. of studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Quality
1 (Garcia-Munoz 2014)		(0.18, 0.21)	(0.82, 0.84)	LR- 0.96 (0.95, 0.99)	Moderate
Intra-amniotic infection					
1 (Nayeri 2018)	378	0.50 (0.23, 0.78)	0.53 (0.47, 0.59)	LR+ 1.07 (0.57, 2.0)	Very low
				LR- 0.94 (0.5, 1.77)	Very low
Vaginal mode of delivery (vs caesarean)					
1 (Olivier 2016)	20038	0.5 (0.32, 0.68)	0.59 (0.57, 0.63)	LR+ 1.23 (0.83, 1.8)	Low
				LR- 0.84 (0.57, 1.45)	Low

Adjusted ORs – association studies

No. of studies	Sample size	Effect size (95%CI)	Quality
Antenatal steroids (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Lee 2019)	2900	Adjusted OR 1.13 (0.87, 1.47)	Moderate
Gestational weight gain for women with BMI ≥40 mg/kg^2 (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Njagu 2020)	374	Adjusted OR 2.85 (1.06, 7.67)	Low
Epidural (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Ward 2020)	34,371	Adjusted OR 0.53 (0.29, 0.98)	Low

See appendix F for full GRADE tables.

2.1.7 Economic evidence

2.1.7.1 Included studies

A systematic review of the economic literature was conducted. 4,398 studies were retrieved by the search. No economic studies were identified which were applicable to this review question and no full-text copies of articles were requested.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 577 results. Based on title and abstract screening, all the studies could confidently be excluded for this question. Thus, the review for this question does not include any study from the existing literature.

2.1.8 Economic model

No economic modelling was undertaken for this review because of a lack of economic evidence and because the committee agreed that other topics were higher priorities for economic evaluation.

3.1 Review question

Which risk factors in the baby (including symptoms and signs) should raise suspicion of late-onset neonatal infection?

3.1.1 Introduction

Neonatal infection is a significant cause of mortality and morbidity in newborn babies. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. For the purpose of this guideline, late-onset neonatal infection is defined as infection which occurs between 72 hours of birth and 28 days of age (corrected for gestational age).

Predicting which babies are most at risk of late-onset neonatal infection is important to help determine who should receive antibiotic treatment. A culture taken from blood or cerebrospinal fluid which tests positive for the organisms associated with infection is the gold-standard for identifying which babies should receive treatment. However, waiting for the results of these tests may delay treatment. Identifying the factors which can put a baby at high risk of neonatal infection is therefore important to help determine whether a baby should be given antibiotics while waiting for the results of a blood culture to confirm infection. The aim of this review is therefore to evaluate potential risk factors as well as signs and symptoms in the baby to determine how they can guide management of the baby.

3.1.2 Summary of the protocol

Population	• Babies from 72 hours up to 28 days of age (term babies) and up to 28 days corrected gestational age (preterm babies)
Risk factors	**Signs and symptoms (diagnostic)** • Altered behaviour or responsiveness • Altered muscle tone (for example, floppiness) • Feeding difficulties (for example, feed refusal) • Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension • Abnormal heart rate (bradycardia or tachycardia) • Signs of respiratory distress • Hypoxia (for example, central cyanosis or reduced oxygen saturation level) • Jaundice • Apnoea • Seizures • Need for cardio-pulmonary resuscitation • Need for mechanical ventilation • Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors • Signs of shock • Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulopathy (International Normalised Ratio greater than 2.0) • Oliguria • Altered glucose homeostasis (hypoglycaemia or hyperglycaemia) • Metabolic acidosis (base deficit of 10 mmol/litre or greater) • Local signs of infection (for example, affecting the skin or eye)

	Risk factors (prognostic) • History of surgery (excluding surgical site infections) • Presence of a catheter (intravascular or urinary) or other indwelling device • Prematurity • Admission to neonatal unit • Prior Group B streptococcus (GBS) infection in the neonate • Colonisation with GBS or Methicillin-resistant Staphylococcus aureus (MRSA)
Reference standard	• Culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • Antibiotics for suspected bloodstream infection (in neonate) given between 72 hours (where available) and 28 days of age (term babies) or 28 days CGA (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study
Outcomes	Outcomes for predictive accuracy studies: • Sensitivity • Specificity • Positive and negative likelihood ratios If association studies are included due to a lack of predictive accuracy data: • Adjusted Risk ratios, Odds ratios, hazard ratios

3.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol **Error! Reference source not found.**. For full details of the m ethods used see the methods document.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Predictive accuracy studies were considered in addition to systematic reviews. For outcomes where no predictive accuracy studies were available, multivariate cohort studies that reported adjusted measures of association were included. The review protocol specified that, where possible, subgroup analyses would be conducted for gestational age of the baby (preterm vs term), multiple births, age of the baby (72 hours to 6 days vs 7+ days) and for babies who had been admitted to the hospital from home. Data was available for gestational age and, in some cases, multiple births, but no data was reported for the other subgroups.

Protocol deviation

The review protocol specified the risk factors that would be included *a priori* based on the knowledge and experience of the committee. However, on presentation of the evidence, the committee identified further risk factors that were important that were missing from the evidence review. The protocol was subsequently expanded to include all risk factors and clinical indicators on which evidence was available, not just the factors pre-specified in the review protocol.

3.1.4 Prognostic and diagnostic evidence

3.1.4.1 Included studies

A joint search was carried out to identify studies specified for this review question, and a similar review question for studies assessing maternal risk factors for late-onset neonatal infection (for details, see section 2.1 on maternal risk factors). This returned a total of 7,146 results, of which 134 were identified as potential included studies for either of the reviews. Full text articles were ordered and reviewed against the inclusion criteria, of which 11 met the inclusion criteria for this review. No studies reported predictive accuracy data. Sixteen multivariate cohort studies were identified (6 prospective and 10 retrospective studies), with most studies reporting on the association between late-onset neonatal infection and gestational age (5 studies), the presence of catheters (5 studies) or the use of ventilation (3 studies). The association of other factors with late-onset neonatal infection included history of surgery (2 studies) and altered behaviour (1 study). Results of the review were separated into prognostic (risk factors) and diagnostic (signs and symptoms) outcomes.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 670 results of which 14 were identified as possible included studies for either of the reviews. After full text review, no additional studies met the inclusion criteria.

3.1.4.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

3.1.5 Summary of studies included in the prognostic evidence

Table 3 Summary of included clinical studies

Study	Study type and follow-up time	Population	Predictive factors
Auriti 2003 (n=280)	• Retrospective cohort • Duration of follow-up not reported	• All consecutive infants admitted to the NICU during one year and discharged after a hospital stay of at least 48 h	• Gestational age • Presence of a central venous catheter
Babazono 2008 (n=871)	• Retrospective cohort • Duration of follow-up not reported	• Participation in the Japanese nosocomial infection surveillance (JANIS)	• Presence of a central venous catheter • Gender • Birth weight • Artificial ventilation • Presence of an umbilical cord catheter • Presence of a catheter in the bladder • Umbilical artery catheterisation • Umbilical venous catheterisation
Bekhof 2013 (n=142)	• Prospective cohort	• Gestational age <34 weeks • More than 72 hours of age	• Increased respiratory support • Lethargy

Study	Study type and follow-up time	Population	Predictive factors
	• Follow-up until 35 weeks' duration or discharge to another hospital	• Not on antibiotic therapy for the previous 24 hours	• Capillary refill >2s • Weight at episode <1200g
Boghossian 2013 (n=20,472)	• Retrospective cohort • Duration of follow-up not reported	• Birth weight 401-1500 g Gestational age 22-28+6 weeks *Inclusion criteria changed to include gestational age in January 2008 (final year of study)*	• Gestational age • Gender • Duration of mechanical ventilation • History of surgery • Length of stay • Age when full feeds achieved • Small for gestational age • Parenteral nutrition
Garland 2017 (n=2913)	• Retrospective cohort • Duration of follow-up not reported	• PICC in place for >72 hours	• Gestational age • Patent ductus arteriosus • Catheter related infection during initial catheterisation
Hylander 1998 (n=212)	• Retrospective cohort • Follow up until hospital discharge	• All preterm infants weighing up to 1500 g at birth and hospitalized in the NICU	• Type of feeding (human milk vs formula)
Kim 2018 (n=364)	• Retrospective cohort • Duration of follow-up not reported	• Admitted to a neonatal unit • Gestational age 22 - 32 weeks	• Intubation duration • Necrotising enterocolitis >= stage 2b
Leal 2012 (n=11,790)	• Retrospective cohort • Mean duration of follow up 4.2 (±14.6 days)	• Newborns	• Gestational age • Birth weight • Artificial ventilation • Apgar score <5 • Perinatal asphyxia • Surgical procedure required • Invasive medical procedure required
Makhoul 2006 (n=111)	• Prospective cohort • Duration of follow-up not reported	• Neonates who developed clinically suspected late-onset sepsis beyond 3 d of age	• Artificial ventilation
Nayeri 2018 (n=378)	• Prospective cohort	• Consecutive preterm singleton newborns born to mothers who delivered	• Gestational age • Intrauterine infection

Study	Study type and follow-up time	Population	Predictive factors
	• Follow-up util death or discharge	preterm between 23–34 weeks of gestation	
Padula 2014 (n=409)	• Prospective cohort • Duration of follow-up not reported	• Presence of a central venous catheter • Apnea • Hypotension • Enteral contrast within 48 hours	• Presence of a central venous catheter • Apnea • Hypotension • Enteral contrast within 48 hours
Sanderson 2017 (n=3,985)	• Retrospective cohort • Duration of follow-up not reported	• Babies who had an umbilical venous catheter or central venous catheter inserted	• Gestational age • History of surgery • Presence of a catheter • UVC vs PICC • Congenital abnormality • Age of catheter insertion
Smith 2008 (n=882)	• Retrospective cohort • Duration of follow-up not reported	• Babies who had a PICC inserted	• Presence of a central venous catheter compared with peripheral cannula • Age of catheter insertion • Duration of catheter insertion
Stoll 1996 (n=6911)	• Retrospective cohort • Duration of follow-up not reported	• Birth weight 401-1500 g • Admitted to neonatal unit	• Respiratory distress syndrome • Duration of mechanical ventilation • Intubation • Bronchopulmonary dysplasia • Steroids for brochopulmonary dysplasia • Patent ductus arteriosus • Intraventricular haemorrhage (grade 3-4) • Proven Necrotising enterocolitis • Bell stage HA or greater
Troger 2014 (n=5,886)	• Prospective cohort • Duration of follow-up not reported	• Birth weight <1500 g • Gestational age ≤36+6 weeks	• Gestational age • Duration of total parental nutrition

Study	Study type and follow-up time	Population	Predictive factors
			• Small for gestational age • Treatment with antenatal steroids • German descendance
Yapicioglu 2011 (n=413)	• Prospective cohort • Duration of follow-up not reported	• All babies admitted to the NICU	• Duration of mechanical ventilation • Hood oxygen use • Total parenteral nutrition

See appendix D for full evidence tables.

3.1.6 Summary of the prognostic and diagnostic evidence

3.1.6.1 Risk factors (prognostic outcomes)

Gestational age

No. of studies	Sample size	Effect size (95%CI)	Quality
Extremely pre-term babies (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017) *22-25 weeks vs 26-27 weeks*	3985	Adjusted HR 1.58 (1.23, 2.04)	Low
Extremely pre-term vs pre-term (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Garland 2017) *<25 weeks vs >32 weeks*	2913	Adjusted OR 4.40 (2.50, 7.80)	Moderate
1 (Garland 2017) *25-28 weeks vs >32 weeks*	2913	Adjusted OR 2.20 (1.30, 3.70)	Moderate
Extremely pre-term vs pre-term (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017) *22-25 weeks vs 28-31 weeks*	3985	Adjusted HR 3.57 (2.70, 4.76)	Moderate
1 (Sanderson 2017) *22-25 weeks vs 32-36 weeks*	3985	Adjusted HR 6.67 (4.34, 10.0)	Moderate
Very pre-term vs term (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Garland 2017) *29-32 weeks vs >32 weeks*	2913	Adjusted OR 2.04 (1.11, 3.70)	Moderate
Very pre-term vs term (RR >1 indicates risk factor of late-onset neonatal infection)			
1 (Auriti 2003) *<32 weeks vs >32 weeks*	280	Adjusted RR 3.58 (No CI provided)	Very low
Pre-term vs term (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Leal 2012) *<37 weeks vs >37 weeks*	11,790	Adjusted HR 1.08 (1.03, 1.14)	Moderate

No. of studies	Sample size	Effect size (95%CI)	Quality
Gestational age (no specific age comparisons provided) (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Nayeri 2018)	378	Adjusted OR 1.42 (1.25, 1.66)	Moderate
1 (Smith 2008)	882	Adjusted OR 1.25 (1.32, 1.19)	Low
1 (Troger 2014)	5886	Adjusted OR 1.33 (1.28, 1.39)	Moderate
Singleton birth subgroup (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013) *Weeks (from <25 to >32)*	15,178	Adjusted OR 1.23 (1.20, 1.27)	Moderate
Multiple births subgroup (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013) *Weeks (from <25 to >32)*	5294	Adjusted OR 1.20 (1.15, 1.27)	Moderate

History of surgery

No. of studies	Sample size	Effect size (95%CI)	Quality
Single births only (OR/HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013)	20,472	Adjusted OR 1.43 (1.26, 1.61)	Moderate
1 (Sanderson 2017)	3985	Adjusted HR 1.00 (0.77, 1.29)	Very low

Presence of a catheter

No. of studies	Sample size	Effect size (95%CI)	Quality
Central venous catheter (RR/OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Auriti 2003)	280	Adjusted RR 3.61 (No CI reported)	Very low
1 (Babazono 2008)	871	Adjusted OR 2.27 (1.28, 4.02)	Moderate
1 (Bekhof 2013)	142	Adjusted OR 7.13 (3.15, 16.16)	Moderate
1 (Padula 2014)	409	OR 2.52 (1.44, 4.38)	Moderate
Umbilical catheter (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Babazono 2008)	871	Adjusted OR 0.87 (0.34, 2.56)	Low
1 (Babazono 2008)	871	Adjusted OR 1.46 (0.60, 3.54)	Low
Urinary catheter (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Babazono 2008)	871	Adjusted OR 1.34 (0.69, 2.60)	Low
PICC vs UVC (HR >1 indicates risk factor of late-onset neonatal infection)			

No. of studies	Sample size	Effect size (95%CI)	Quality
1 (Sanderson 2017)	3985	Adjusted HR 0.51 (0.40, 0.66)	Low
Peripheral cannula vs central PICC (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Smith 2008)	882	Adjusted OR 0.50 (0.26, 0.96)	Low

Other catheter related factors

No. of studies	Sample size	Effect size (95%CI)	Quality
Catheter related infection during initial catheterisation – refers to infections after catheter removal (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Garland 2017)	2913	Adjusted OR 2.0 (1.06, 3.79)	Moderate
Catheter dwell time (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Smith 2008)	882	Adjusted OR 0.98 (0.96, 0.995)	Low
Age at central venous catheter insertion 7-13 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017)	3985	Adjusted HR 0.8 (0.56, 1.15)	Very low
Age at central venous catheter insertion 14-20 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017)	3985	Adjusted HR 0.92 (0.57, 1.5)	Very low
Age at central venous catheter insertion 21-27 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017)	3985	Adjusted HR 0.28 (0.1, 0.75)	Low
Age at central venous catheter insertion >=28 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017)	3985	Adjusted HR 0.53 (0.33, 0.85)	Low

Weight

No. of studies	Sample size	Effect size (95%CI)	Quality
Birthweight <1000g vs =>1500g (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Babazono 2008)	871	Adjusted OR 8.82 (4.8, 16.21)	Moderate
Birthweight 1000g-1499g vs =>1500g (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Babazono 2008)	871	Adjusted OR 2.35 (1.02, 5.38)	Moderate
Birthweight =< 2500g (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Leal 2012)	11790	HR 1.04 (1.01, 1.08)	Moderate
Small for gestational age – singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			

No. of studies	Sample size	Effect size (95%CI)	Quality
1 (Boghossian 2013)	20038	Adjusted OR 1.22 (1.06, 1.43)	Moderate
Small for gestational age (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Troger 2016)	5886	Adjusted OR 1.31 (1.02, 1.68)	Low
Weight at episode <1200g (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Bekhof 2013)	142	Adjusted OR 1.72 (0.87, 3.4)	Low

Parenteral nutrition

No. of studies	Sample size	Effect size (95%CI)	Quality
Parenteral nutrition – singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013)	20038	Adjusted OR 7.66 (3.1, 19.1)	Moderate
Duration of parenteral nutrition (per day)			
1 (Troger 2016)	5886	Adjusted OR 1.016 (1.011, 1.021)	Low
Duration of total parenteral nutrition (per day)			
1 (Yapicioglu 2011)	378	OR 1.09 (1.06, 1.14)	Moderate

Human milk

No. of studies	Sample size	Effect size (95%CI)	Quality
Human milk vs formula (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Hylander 1998)	212	Adjusted OR 0.50 (0.25, 1.02)	Low

Gender

No. of studies	Sample size	Effect size (95%CI)	Quality
Female gender- singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013)	20038	Adjusted OR 0.89 (0.81, 0.98)	Moderate
Male gender (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Babazono 2008)	871	Adjusted OR 1.86 (1.04, 3.35)	Moderate

Length of hospital stay

No. of studies	Sample size	Effect size (95%CI)	Quality
Length of hospital stay, per day – singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			

No. of studies	Sample size	Effect size (95%CI)	Quality
1 (Boghossian 2013)	20038	Adjusted OR 1.003 (1.002, 1.004)	Moderate
Length of hospital stay, per day – multiple pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013)	20038	Adjusted OR 1.005 (1.002, 1.009)	Moderate

Age when full feeds achieved

No. of studies	Sample size	Effect size (95%CI)	Quality
Age when full feeds achieved (per day)- singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013)	20038	Adjusted OR 1.041 (1.037, 1.045)	Moderate
Age when full feeds achieved (per days) - multiple pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Boghossian 2013)	20038	Adjusted OR 0.827 (0.789, 0.867)	Moderate

Patent ductus arteriosus

No. of studies	Sample size	Effect size (95%CI)	Quality
Patent ductus arteriosus – relates specifically to infections following catheter removal (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Garland 2017)	2913	Adjusted OR 0.49 (0.27, 0.9)	Moderate
1 (Stoll 1996)	6911	OR 2.03 (1.33, 2.3)	Moderate

Surgical procedure required

No. of studies	Sample size	Effect size (95%CI)	Quality
Surgical procedure required (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Leal 2012)	11790	HR 2.85 (1.49, 5.46)	Moderate

Invasive medical procedure required

No. of studies	Sample size	Effect size (95%CI)	Quality
Invasive medical procedure required (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Leal 2012)	11790	HR 2.07 (1.63, 2.62)	Moderate

Enteral contrast in previous 48hrs

No. of studies	Sample size	Effect size (95%CI)	Quality
Enteral contrast in previous 48hrs (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Padula 2014)	409	OR 9.58 (2.03, 45.2)	Moderate

Congenital abnormality

No. of studies	Sample size	Effect size (95%CI)	Quality
Congenital abnormality (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Sanderson 2017)	3985	Adjusted HR 1.45 (1.11, 1.89)	Low

Treatment with antenatal steroids

No. of studies	Sample size	Effect size (95%CI)	Quality
Treatment with anti-natal steroids (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Troger 2016)	5886	Adjusted OR 0.7 (0.53, 0.92)	Low

German descendance

No. of studies	Sample size	Effect size (95%CI)	Quality
German descendance (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Troger 2016)	5886	Adjusted OR 0.76 (0.63, 0.91)	Low

3.1.6.2 Signs and symptoms (diagnostic outcomes)

Assisted ventilation

No. of studies	Sample size	Effect size (95%CI)	Quality
Need for mechanical ventilation (OR/HR/RR >1 indicates risk factor of late-onset neonatal infection)			
1 (Babanoza 2008)	871	Adjusted OR 1.49 (0.82, 2.72)	Low
1 (Leal 2012)	11,790	Adjusted HR 1.60 (1.19, 2.40)	Moderate
1 (Makhoul 2006)	111	Adjusted RR 2.37 (1.36, 4.15)	Very low
Intubation (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Stoll 1996)	6911	OR 1.52 (1.31, 1.78)	Moderate
Duration of ventilation (per day) (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Yapicioglu 2011)	378	OR 0.96 (0.94, 0.99)	Moderate
Duration of intubation (per week) (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Kim 2018)	364	OR 1.12 (1.05, 1.18)	Low
Hood O2 Use (per day) OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Yapicioglu 2011)	378	OR 1.13 (1.06, 1.2)	Moderate

Altered behaviour or responsiveness

No. of studies	Sample size	Effect size (95%CI)	Quality
Lethargy (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Bekhof 2013)	142	Adjusted OR 2.61 (1.14, 6.01)	Moderate

Capillary refill >2s

No. of studies	Sample size	Effect size (95%CI)	Quality
Capillary refill >2 s (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Bekhof 2013)	142	Adjusted OR 2.32 (1, 5.37)	Low

Pallor/grey skin

No. of studies	Sample size	Effect size (95%CI)	Quality
Pallor/grey skin (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Bekhof 2013)	142	Adjusted OR 1.25 (0.52, 2.97)	Low

Apgar score=<5

No. of studies	Sample size	Effect size (95%CI)	Quality
Apgar score=<5 (HR >1 indicates risk factor of late-onset neonatal infection)			
1 (Leal 2012)	11790	HR 1.4 (1.19, 1.76)	Moderate

Respiratory difficulties

No. of studies	Sample size	Effect size (95%CI)	Quality
Apnoea (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Padula 2014)	409	OR 2.86 (1.43, 5.73)	Moderate
Respiratory distress syndrome (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Stoll 1996)	6911	OR 1.52 (1.31, 1.78)	Moderate
Bronchopulmonary dysplasia (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Stoll 1996)	6911	OR 2.2 (1.91, 2.55)	Moderate
Steroids for bronchopulmonary dysplasia (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Stoll 1996)	6911	OR 1.59 (1.81, 2.48)	Moderate

Necrotising enterocolitis

No. of studies	Sample size	Effect size (95%CI)	Quality
NEC stage 2A or greater (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Stoll 1996)	6911	OR 4.58 (3.63, 5.66)	Moderate

No. of studies	Sample size	Effect size (95%CI)	Quality
NEC stage 2B or greater at 23-26 weeks' gestational age (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Kim 2018)	364	OR 3.38 (1.51, 7.55)	Low

Hypotension

No. of studies	Sample size	Effect size (95%CI)	Quality
Hypotension (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Padula 2014)	409	OR 2.64 (1.26, 5.5)	Moderate

Intraventricular haemorrhage

No. of studies	Sample size	Effect size (95%CI)	Quality
IVH grade 3/4 (OR >1 indicates risk factor of late-onset neonatal infection)			
1 (Stoll 1996)	6911	OR 1.27 (1.08, 1.52)	Moderate

See appendix F for full GRADE tables.

3.1.7 Economic evidence

3.1.7.1 Included studies

A systematic review of the economic literature was conducted. 4,398 studies were retrieved by the search. No economic studies were identified which were applicable to this review question and no full-text copies of articles were requested.

3.1.8 Economic model

No economic modelling was undertaken for this review because of a lack of economic evidence and because the committee agreed that other topics were higher priorities for economic evaluation.

4.1 The committee's discussion and interpretation of the evidence

4.1.1. The outcomes that matter most

The committee discussed the potential effects of true positive, true negative, false positive and false negative outcomes from tools designed to predict risk of late-onset neonatal infection. A model that correctly identifies all those with infection (true positives) would result in antibiotics being prescribed to all those who need treatment, reducing the serious harms associated with neonatal infection. If a model correctly identifies all those without infection (true negatives) then it will avoid over-prescribing of antibiotics. This is a particular concern when evaluating neonatal infection as it is difficult to diagnose and can therefore result in all, or most, babies being prescribed antibiotics to avoid any infections being missed and being left untreated.

If a model does not accurately predict true positives and true negatives, then there are a number of potential harms. False positive results will result in babies being given antibiotics unnecessarily, and admission to hospital will lead to separation of the mother and baby, potentially causing anxiety and distress to the family. False positive results will also incur the costs associated with a hospital stay and can contribute to the development of antibiotic resistance. However, a false negative result is the biggest concern for parents and clinicians as there can be serious consequences if neonatal infection is left untreated. The most serious consequence is death of the baby, but delayed treatment can also have long-term health consequences, such as neuro-disability, which can have both emotional and financial impacts on the family as well as downstream treatment costs for the healthcare system. Consequently, the committee prioritised negative likelihood ratios over positive likelihood ratios – the committee believed that it was important that negative test results were accurate, and that neonatal infection was not incorrectly ruled out.

Some studies only reported c-statistics and did not include data which allowed sensitivity, specificity or likelihood ratios to be calculated. The committee agreed that this outcome was less useful as it weighs false negatives and false positives as equally important, which the committee agreed was not appropriate.

No evidence was available on the sensitivity, specificity and likelihood ratios for risk factors and signs of infection. Instead, the committee decided that information about the associations between potential risk factors and infection was useful, provided it were from multivariate analyses that adjusted for potential confounding variables. Adjusted risk ratios, odds ratios and hazard ratios were therefore considered important.

4.1.2 The quality of the evidence

Eight studies investigated the use of clinical prediction models for late-onset neonatal infection, with quality the of the outcome measures ranging from high to very low quality. Most of the evidence was moderate or low quality, with outcomes most commonly downgraded for imprecision and for studies being at moderate risk of bias. Some of the results for the models had wide confidence intervals, raising questions over the imprecision of the results. Others, such as the demographics and heart rate model and the nearest neighbour model, reported very limited information on the statistical outcomes. These studies only reported c-statistics with no confidence intervals, and there was insufficient information to allow for the calculation of sensitivity or specificity. The models developed by Mani 2014

had low specificity, and had negative likelihood ratios that crossed 1, suggesting that a negative test outcome could indicate both a decrease and an increase in the probability of a baby having an infection. None of the studies were based in the UK and all but two of the models had only been evaluated by one study with no evidence of external validation. The committee still considered these relevant to the review and they were not downgraded for indirectness.

Two models (RALIS and NOSEP) did include evidence of external validation. However, the studies which investigated the use of the NOSEP model were published in 2000 and 2002, with no further evidence available since that time. Three studies published between 2014 and 2016 assessed the use of the RALIS model. However, the model does not appear to be available as a tool outside of the hospitals where it was evaluated. Given the age and location of some of the studies the committee agreed that any tool would need to be re-evaluated to reflect changes in clinical practice, and the differences in practice between the UK and the countries in which the research took place. The quality of outcomes from these studies were not downgraded, as they met the inclusion criteria for the protocol, but the committee decided that the issues with location and age of the research meant that the evidence was not sufficient for these models to be recommended. Instead it supported the need for a research recommendation to validate new or existing prognostic models for late-onset infection (Appendix K).

The majority of the evidence for the risk factors and signs of infection was of moderate or low quality. Evidence was sparse, with no information about some well-known clinical signs and symptoms of sepsis, such as abnormal heart rate, temperature abnormalities, and altered muscle tone. In addition, many of the studies only reported results when there was a significant association between sepsis and a risk factor or symptom of infection. The evidence base is therefore likely to be biased as evidence reporting no significant association between risk factors or symptoms and neonatal infection is likely to have been under-reported. Where studies reported limited information about the analysis methods, or did not report non-significant associations, their outcomes were downgraded for risk of bias. There was very limited evidence for maternal risk factors for late-onset infection, and although some of the studies reported diagnostic accuracy measures, such as sensitivity and specificity, much of this was low quality. The committee therefore focused on the risk factors and signs and symptoms in the baby when developing the recommendations.

The committee discussed the methodological limitations of the studies, as most reported limited or no information on the multivariate analysis, particularly which variables were adjusted for in the model. Most studies were therefore downgraded for risk of bias. Some studies did not report whether blood cultures were taken before or after babies were given antibiotics, and so these were also downgraded for risk of bias. The applicability of the studies was also discussed as many stated that they were investigating sepsis, late-onset infection or nosocomial infection but did not state a maximum age at which their definition of infection ended. It was therefore unclear whether the studies matched the definition in the protocol of infection up to 28 days of age. However, as the studies were based in neonatal units the committee decided that they were likely to be applicable to the research question. Studies were therefore not downgraded for indirectness.

Some of the studies had limited information about the risk factors that were investigated. This was a particular issue for the 3 studies that compared babies with a central venous catheter (CVC) to babies who were not given a catheter. Some of the studies did not specify whether the catheters inserted were umbilical arterial, umbilical venous or peripherally inserted central catheters (PICCs). The committee thought that this information was important as each type of catheter has a different use, is inserted at a different time, and can remain in

place for different lengths of time. However, it decided that the evidence was sufficient to support current clinical consensus that the insertion of a central catheter can increase a baby's risk of developing late-onset neonatal infection.

All of the evidence was based in neonatal units, meaning that it reflected some of the risk factors faced by babies who are being cared for in hospital. However, the committee highlighted that babies who are admitted to hospital from home are usually admitted to a paediatric, rather than neonatal ward. Consequently, there was no evidence available for the risk factors for a baby who is being cared for at home. The committee agreed that there is a big difference between an infection which occurs in hospital and infection in the community. Although some of the findings, such as those related to gestational age, could be applied to these group of babies, many were not relevant, supporting the need for a research recommendation (Appendix K).

4.1.3 Benefits and harms

A tool that can accurately predict whether a baby is at high or low risk of late-onset neonatal infection would help to ensure that only babies who were likely to develop an infection would be given antibiotics. This would also reduce the adverse effects associated with unnecessary treatment for both the baby and the baby's family as well as reducing the costs associated with treatment. A model based on clinical signs and symptoms would help to make this decision more quickly than current practice whereby babies are screened for infection and treated with antibiotics until culture results are available. However, although some of the models that have been investigated, such as the Celik models, showed high sensitivity and specificity and likelihood ratios that were beyond the clinical decision threshold, they also included factors that would require substantial changes to clinical practice, such as the need to run tests that are not currently part of routine practice. Using these models would therefore involve resource implications such as training for clinicians prior to their implementation. The committee also had concerns over the age of some of the studies and the reasons why some of the models, despite showing good sensitivity and specificity, had not been investigated in more recent studies. The risk factors for late-onset neonatal infection may have changed in the last 10 years, and so more recent studies are needed to ensure the safety of these models and allow a particular clinical prediction model to be recommended.

Given the limited evidence for prognostic models for late-onset infection, the committee decided that recommendations should be based on the risk factors and signs and symptoms of late-onset neonatal infection. Evidence was found on a small subset of the risk factors and signs and symptoms specified in the review protocol, and was limited to association studies, rather than studies reporting predictive accuracy. Consequently, the committee were unable to make specific recommendations about when late-onset infection should be suspected and investigated further. However, the committee agreed that it was important that clinicians were aware of the risk factors for infection. The signs identified in the clinical indicators table were thought to be useful for clinicians in both a specialist and non-specialist setting. Some were more relevant to babies being treated in a hospital, and these were stated as risk factors in a separate recommendation. Given the potentially serious consequences of late-onset neonatal infection, the committee agreed that it was important that more research into the factors associated with late-onset infection should take place. However, it decided that this should be in relation to prognostic models for late-onset neonatal infection as these consider a range of potential risk factors and use them to predict a baby's risk of infection. This was considered more useful in clinical practice than a list of individual risk factors, and so a research recommendation was made in relation to the development and validation of prognostic models (Appendix K).

The evidence showed that late-onset infection was associated with lower gestational age. When comparing the results for gestational age, the committee noted that there was a variety of comparisons. Some of these were preterm compared to term babies, as stated in the protocol, but many comparisons were based on the number of weeks' gestation (such as extremely preterm compared to very preterm babies). With this lack of consistency in comparisons, and the low or moderate quality of many of the outcomes, the committee could not be specific about which babies were most at risk of infection based on gestational age. However, it agreed that the results indicated that the more pre-term a baby is, the greater their risk of developing infection. This was therefore included as one of the additional risk factors in the recommendations.

There was some conflict in the results for the use of catheters. When results were reported for central venous catheters, with no specific type of catheter stated, they indicated that the presence of a catheter may increase the risk of infection. In contrast, results for umbilical catheters suggested there was no clear difference in the risk of infection compared to when a baby does not have a catheter. However, with no other evidence on specific types of central catheters, the committee decided that it should report central catheters as a risk factor without specifying which type is most associated with infection.

There were also conflicting results for the association between history of surgery and late-onset infection. While one study indicated that a history of surgery could increase a baby's chance of infection the other suggested that surgery did not alter the risk of infection. The study which suggested history was a risk factory had a much larger sample size than the study which reported no clear effect on infection rates. This, in addition to the clinical experience of the committee, led them to include history of surgery as a potential risk factor for late-onset infection.

The evidence available on the signs and symptoms of late-onset infection was limited and likely to be biased, due to the limited reporting of non-significant outcomes in many of the studies. The amount of evidence available for many of the risk factors and signs and symptoms was also very limited. Many of the outcomes (such as lethargy, capillary refill time, Apgar scores, hypotension, intraventricular haemorrhage and various outcomes for respiratory difficulties) had only one study to evaluate whether they are a risk factor or sign of infection, and so the committee did not think this was sufficient to justify including them in the recommendations. The committee therefore did not use the evidence directly to formulate a list of clinical indicators of late-onset infection. However, the high-risk criteria listed in the NICE sepsis guideline (NG51 - Section 1.4, Table 3) matched those that the committee considered important based on clinical experience. All of the risk factors included in the high-risk criteria from the sepsis guideline were therefore used as the important indicators of infection, with the exception of 'no response to social cues'. The sepsis guidelines are based on all children under 5 and the committee did not think that this factor was applicable to a neonate population. Instead, they replaced 'no response to social cues' with 'parental or carer concern over changes in behaviour'. Concern over changes in behaviour was highlighted as an important indicator of infection for newborn babies in the community. This was consistent with the knowledge and experience of the committee, who agreed that late-onset infection should be considered whenever a baby (under 28 days, corrected age) presented with altered behaviour that was causing concern, particularly in a non-specialist setting where a baby would not already be undergoing monitoring. Four other factors were also added to the clinical indicators (alterations in feeding pattern, abdominal distension, seizures and bulging fontanelle). These factors are specific to neonates and so are not part of the sepsis guidelines for children under 5 years. However, the committee decided that these were important factors that need to be considered when deciding on whether a baby is at risk of late-onset infection. The committee noted that babies with late-onset infection often

deteriorate quickly, so it is important for non-specialist clinicians to have a low threshold for suspecting late-onset infection, and to seek specialist advice quickly.

Given the limited evidence on the signs and symptoms of late-onset infection, the committee discussed a number of other potential clinical indicators that were not included in the recommendations. However, the committee were concerned about the risk of over-treatment if too many clinical indicators were listed in the recommendations, especially if some of those indicators could have causes other than neonatal infection. The committee decided that the signs included in the recommendation were those that were most likely to indicate infection and therefore the most important to consider when assessing whether a baby may need treatment.

A benefit of increasing awareness of the risk factors for late-onset neonatal infection in non-specialist settings is that babies at risk of infection may be identified sooner and receive early treatment to avoid the negative effects of infection. Increasing the number of babies receiving treatment could potentially increase the development of antibiotic resistance. However, the recommendations are not expected to cause a major change in practice and so this was not seen as a major concern.

4.1.4 Cost effectiveness and resource use

For risk factors and signs of infection, the committee agreed that, while there are good reasons to be judicious about prescribing antibiotics, the costs of the medicines themselves are negligible. In contrast, the costs and consequences associated with infection, including but not limited to death and lifelong morbidity, are potentially very high. The committee agreed that increasing awareness of the risk factors for late-onset neonatal infection may result in cases of late-onset neonatal infection being identified sooner and receiving treatment earlier. This could be important in decreasing hospital stays and is bound to be cost-saving at the population level.

4.1.5 Other factors the committee took into account

A key issue when discussing the prognostic models was the lack of general availability of the models. The committee agreed that it could not recommend a model that was based purely on statistical modelling and did not have a user-friendly design, such as a web-based tool, that could be easily used by clinicians in a neonatal unit.

When considering risk factors, the committee discussed the differences in knowledge between clinicians working in specialist (for example neonatal and paediatric units) and non-specialist (for example community settings and A&E) settings. For instance, while factors such as gestational age are commonly considered risk factors by people working in neonatal units, a baby who is born at a low gestational age would not necessarily be flagged as being at greater risk of infection to community workers, such as GPs. This supported the committee's decision to include prematurity as a risk factor alongside other issues, such as mechanical ventilation and presence of a catheter, both of which were identified as risk factors from the evidence, that are primarily risk factors for babies who are already in hospital. The committee also decided to highlight that suspected or confirmed infection in another baby in the case of a multiple birth should be a reason to consider the possibility of infection in siblings. Although this is a rare event, the committee decided that it was important to include this in the recommendations as it is something that would not necessarily be considered when evaluating a baby for risk of infection.

The committee discussed whether there should be a recommendation to begin antibiotic treatment based on the presence of a particular number of risk factors and clinical indicators.

However, because of the low quality of evidence identified for this question and the lack of an appropriate prediction model, the committee agreed that a prescriptive recommendation for antibiotic treatment was not appropriate. Instead the committee specified risk factors and clinical indicators that clinicians should be aware of when considering late-onset neonatal infection. As there are high risks associated with delayed treatment of neonatal infection, the committee decided that clinicians should begin treatment if late-onset neonatal infection is suspected, based on clinical judgement. This is in line with current practice, where a baby will be given antibiotics until blood culture results are available, and so it was agreed that an additional recommendation for this was not required.

The committee considered also equality issues. It noted that the risk of having a premature baby was higher in some ethnic groups, such as people of Black African family origin (Puthussery et al. 2019). It also noted that the likelihood of having a baby who is preterm also increased with maternal age (Fuchs et al 2018. Prematurity is noted as a factor in table 1 that can increase the risk of neonatal infection that clinicians should be particularly aware of.

4.1.6 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1-1.4.2 and the research recommendation on clinical prediction models for late-onset infection.

4.1.7 References – included studies

4.1.7.1 Clinical prediction models

Celik, I H, Demirel, G, Sukhachev, D et al. (2013) Neutrophil volume, conductivity and scatter parameters with effective modeling of molecular activity statistical program gives better results in neonatal sepsis.. International journal of laboratory hematology 35(1): 82-7

Griffin, M Pamela, O'Shea, T Michael, Bissonette, Eric A et al. (2003) Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness.. Pediatric research 53(6): 920-6

Gur, Ilan, Markel, Gal, Nave, Yaron et al. (2014) A mathematical algorithm for detection of late-onset sepsis in very-low birth weight infants: a preliminary diagnostic test evaluation.. Indian pediatrics 51(8): 647-50

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Mahieu LM, De Dooy JJ, Cossey VR et al. (2002) Internal and external validation of the NOSEP prediction score for nosocomial sepsis in neonates.. Critical care medicine 30(7): 1459-1466

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Mani, Subramani, Ozdas, Asli, Aliferis, Constantin et al. (2014) Medical decision support using machine learning for early detection of late-onset neonatal sepsis.. Journal of the American Medical Informatics Association : JAMIA 21(2): 326-36

Mithal, Leena Bhattacharya, Yogev, Ram, Palac, Hannah et al. (2016) Computerized vital signs analysis and late onset infections in extremely low gestational age infants.. Journal of perinatal medicine 44(5): 491-7

Xiao, Yuping, Griffin, M Pamela, Lake, Douglas E et al. (2010) Nearest-neighbor and logistic regression analyses of clinical and heart rate characteristics in the early diagnosis of neonatal sepsis.. Medical decision making : an international journal of the Society for Medical Decision Making 30(2): 258-66

4.1.7.2 Maternal risk factors

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Lee, H.-S. and Kim, S.Y. (2019) Histological chorioamnionitis, antenatal steroids, and neonatal outcomes in very low birth weight infants: A nationwide study. PLoS ONE 14(10): e0224450

Njagu, R., Adkins, L., Tucker, A. et al. (2020) Maternal weight gain and neonatal outcomes in women with class III obesity. Journal of Maternal-Fetal and Neonatal Medicine

Olivier, F, Bertelle, V, Shah, P S et al. (2016) Association between birth route and late-onset sepsis in very preterm neonates. Journal of perinatology : official journal of the California Perinatal Association 36(12): 1083-1087

Ward, C. and Caughey, A.B. (2020) Does the presence of epidural analgesia reduce the risk of neonatal sepsis in the setting of an intrapartum fever?. Journal of Maternal-Fetal and Neonatal Medicine

4.1.7.3 Neonatal risk factors

Auriti, C, Maccallini, A, Di Liso, G et al. (2003) Risk factors for nosocomial infections in a neonatal intensive-care unit. The Journal of hospital infection 53(1): 25-30

Babazono, Akira, Kitajima, Hiroyuki, Nishimaki, Shigeru et al. (2008) Risk factors for nosocomial infection in the neonatal intensive care unit by the Japanese Nosocomial Infection Surveillance (JANIS). Acta medica Okayama 62(4): 261-8

Bekhof, Jolita, Reitsma, Johannes B, Kok, Joke H et al. (2013) Clinical signs to identify late-onset sepsis in preterm infants. European journal of pediatrics 172(4): 501-8

Boghossian, Nansi S, Page, Grier P, Bell, Edward F et al. (2013) Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. The Journal of pediatrics 162(6): 1120-1124e1

Garland, J S, Kanneberg, S, Mayr, K A et al. (2017) Risk of morbidity following catheter removal among neonates with catheter associated bloodstream infection. Journal of neonatal-perinatal medicine 10(3): 291-299Kim, J.K., Chang, Y.S., Sung, S. et al. (2018) Trends in the incidence and associated factors of late-onset sepsis associated with improved survival in extremely preterm infants born at 23-26 weeks' gestation: A retrospective study. BMC Pediatrics 18(1): 172

Hylander, M A; Strobino, D M; Dhanireddy, R (1998) Human milk feedings and infection among very low birth weight infants. Pediatrics 102(3): e38

Leal, Yelda A, Alvarez-Nemegyei, Jose, Velazquez, Juan R et al. (2012) Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up. BMC pregnancy and childbirth 12: 48

Makhoul, Imad R, Yacoub, Afeefi, Smolkin, Tatiana et al. (2006) Values of C-reactive protein, procalcitonin, and Staphylococcus-specific PCR in neonatal late-onset sepsis. Acta paediatrica (Oslo, Norway : 1992) 95(10): 1218-23

Nayeri, Unzila Ali, Buhimschi, Catalin S, Zhao, Guomao et al. (2018) Components of the antepartum, intrapartum, and postpartum exposome impact on distinct short-term adverse neonatal outcomes of premature infants: A prospective cohort study. PloS one 13(12): e0207298

Padula, Michael A, Dewan, Maya L, Shah, Samir S et al. (2014) Risk factors associated with laboratory-confirmed bloodstream infections in a tertiary neonatal intensive care unit. The Pediatric infectious disease journal 33(10): 1027-32

Sanderson, E, Yeo, K T, Wang, A Y et al. (2017) Dwell time and risk of central-line-associated bloodstream infection in neonates. The Journal of hospital infection 97(3): 267-274

Smith, P Brian, Benjamin, Daniel K Jr, Cotten, C Michael et al. (2008) Is an increased dwell time of a peripherally inserted catheter associated with an increased risk of bloodstream infection in infants?. Infection control and hospital epidemiology 29(8): 749-53

Stoll, B J, Gordon, T, Korones, S B et al. (1996) Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. The Journal of pediatrics 129(1): 63-71

Troger, Birte, Gopel, Wolfgang, Faust, Kirstin et al. (2014) Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network. The Pediatric infectious disease journal 33(3): 238-43

Yapicioglu, H., Ozcan, K., Sertdemir, Y. et al. (2011) Healthcare-associated infections in a Neonatal Intensive Care Unit in Turkey in 2008: Incidence and risk factors, a prospective study. Journal of Tropical Pediatrics 57(3): 157-16

4.3.2 Other citations

Fuchs, F., Monet, B., Ducruet, T., Chaillet, N. and Audibert, F., 2018. Effect of maternal age on the risk of preterm birth: A large cohort study. *PloS one*, *13*(1), p.e0191002.

Puthussery, S., Li, L., Tseng, P.C., Kilby, L., Kapadia, J., Puthusserry, T. and Thind, A., 2019. Ethnic variations in risk of preterm birth in an ethnically dense socially disadvantaged area in the UK: a retrospective cross-sectional study. BMJ open, 9(3), p.e023570.

Appendices

Appendix A – Review protocols

A.1 Clinical prediction models – part A (prognostic accuracy studies)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Risk factors for late-onset infection and clinical indicators of possible infection
2.	Review question	What is the accuracy of clinical prediction models for late-onset neonatal infection and what is their effectiveness in guiding management in the baby?
3.	Objective	To identify risk factors for late-onset neonatal infection/sepsis that should be used to guide management in the UK • includes risk factors (including previous pregnancy history), symptoms and signs in the mother (including factors such as GBS carriage when known (GBS screening is not currently recommended by the UK national screening committee)) and gestational age • covers events relating to the baby after birth (postnatal events) and signs of sibling infection up to 28 days after birth

		• This review has been divided into 2 parts. Part A (outlined in this review protocol) will assess the predictive accuracy of risk prediction tools. Part B (outlined in a separate protocol) will assess the effectiveness of these tools in guiding management. Risk tools may take information about both risk factors and clinical signs and so effectively use what could be classed as strictly prognostic and diagnostic information.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language

		• Human studies Conference abstractsOther searches: NoneThe searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.The full search strategies for MEDLINE database will be published in the final review. No date restrictions have been applied for this question.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. It may late-onset (more than 72 hours after birth) and can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Term babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age • Pregnant women Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections.

		• Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a history of surgery which was not the cause of the infection will not be excluded. • Babies with suspected or confirmed meningitis who are not receiving care in neonatal units (covered by the NICE guideline on bacterial meningitis and meningococcal septicaemia) • Women with pre-labour rupture of membranes at term (covered in the NICE intrapartum care guideline)
7.	Intervention/Exposure/Test	Any validated risk tool using multiple predictors to predict the risk of development or the presence of late-onset neonatal infection. If sufficient evidence is not found on risk prediction tools for late-onset neonatal infection, a review of individual factors in the mother and the baby will be carried out.
8.	Comparator/Reference standard/Confounding factors	Reference standard (predictive models): • culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate)

9.	Types of study to be included	Prospective or retrospective observational cohorts or cross-sectional studies which evaluate risk prediction tools. Studies will only be included if they include data on model validation (internal or external validation) Systematic reviews of the above study types
10.	Other exclusion criteria	Studies that do not report results specifically for late-onset neonatal infection (onset of infection between 72 hours and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies) Non-Organisation for Economic Cooperation and Development (OECD) countries Non-English language studies
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question.
12.	Primary outcomes (critical outcomes)	For each outcome, accuracy measures will be reported where available, for example: • Odds ratios/hazard ratios • Model fit including discrimination (C statistic, area under ROC curve) and calibration (r squared)

		• Sensitivity, specificity, positive and negative predictive values
13.	Secondary outcomes (important outcomes)	Not applicable. The committee did not wish to distinguish between critical and important outcomes as they considered all of the specified outcomes important for decision making.
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 6.4). Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the PROBAST checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual

17.	Analysis of sub-groups	Results will be stratified according to whether the population included term or preterm neonates and according to whether babies have been admitted to hospital from home (where data allows).
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	02/09/2019
22.	Anticipated completion date	12/08/2020

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐ ☐ ☐	☐ ☐ ☐
		Piloting of the study selection process	☐ ☐ ☐	☐ ☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐ ☐	☐ ☐ ☐
		Data extraction	☐ ☐ ☐	☐ ☐ ☐
		Risk of bias (quality) assessment	☐ ☐ ☐	☐ ☐ ☐
		Data analysis	☐ ☐ ☐	☐ ☐ ☐
24.	Named contact	**5a. Named contact** Guideline Updates Team		

		5b Named contact e-mail NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Wesley Hubbard
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from 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 advisory committee who will use the review to inform the development of evidence-

		based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10111
29.	Other registration details	None
30.	Reference/URL for published protocol	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	Late onset neonatal infection, risk factors
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.2 Clinical prediction models – part B (Test and treat RCTs)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Risk factors for late-onset infection and clinical indicators of possible infection
2.	Review question	What is the accuracy of clinical prediction models for late-onset neonatal infection and what is their effectiveness in guiding management in the baby?
3.	Objective	To identify risk factors for late-onset neonatal infection/sepsis that should be used to guide management in the UK

		• includes risk factors (including previous pregnancy history), symptoms and signs in the mother (including factors such as GBS carriage when known (GBS screening is not currently recommended by the UK national screening committee)) and gestational age • covers events relating to the baby after birth (postnatal events) and signs of sibling infection up to 28 days after birth • includes which risk factors, symptoms and signs (individual or in combination) should lead to antibiotic treatment This review has been divided into 2 parts. Part A (outlined in a separate review protocol) will assess the predictive accuracy of risk prediction tools. Part B (outlined in this protocol) will assess the effectiveness of these tools in guiding management.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by:

		• English language • Human studies • Conference abstracts Other searches: None The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. No date restrictions have been applied for this question.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. It may late-onset (more than 72 hours after birth) and can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Term babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age

		• Pregnant women Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections. • Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a history of surgery which was not the cause of the infection will not be excluded. • Babies with suspected or confirmed meningitis who are not receiving care in neonatal units (covered by the NICE guideline on bacterial meningitis and meningococcal septicaemia) • Women with pre-labour rupture of membranes at term (covered in the NICE intrapartum care guideline)
7.	Intervention/Exposure/Test	Any risk tool* for late-onset neonatal development identified in Part A of the protocol (any validated risk tool using multiple predictors to predict the risk of development or the presence of late-onset neonatal infection)) followed by treatment (for example provision of antibiotics or further testing) according to risk stratification by the tool results.

		If sufficient evidence is not found on risk prediction tools for late-onset neonatal infection (parts A and B, of which this protocol is part B), a review of individual factors in the mother and the baby will be carried out.
8.	Comparator	• standard care: treatment according to risk stratification based on clinician experience or existing clinical protocols (for example, existing NICE guidance) • Comparisons between risk tools followed by treatment according to risk stratification by tool results will also be included.
9.	Types of study to be included	'Test and treat' randomised controlled trials which assess the effectiveness of treatment based on the results of risk prediction tools Systematic reviews of test and treat RCTs
10.	Other exclusion criteria	Studies that do not report results specifically for late-onset neonatal infection (onset of infection between 72 hours and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies) Non-Organisation for Economic Cooperation and Development (OECD) countries Non-English language studies
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question.

12.	Primary outcomes (critical outcomes)	Neonatal outcomes: • culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • suspected bloodstream infection based on clinical symptoms • mortality from 72 hours of birth onwards (at different time points – peri-natal mortality (within 7 days from birth) or greater than 7 days from birth) • health-related quality of life, measured using a validated tool (during the neonatal period and at the latest timepoint reported in study) • hospital length of stay • number prescribed antibiotic treatment Family outcomes: • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the neonatal period and at the latest timepoint reported in study)

13.	Secondary outcomes (important outcomes)	Not applicable. The committee did not wish to distinguish between critical and important outcomes as they considered all of the specified outcomes important for decision making.
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 6.4). Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane risk of bias 2.0 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual
17.	Analysis of sub-groups	If heterogeneity is found between the different categories for term and preterm neonates or for babies who have/have not been admitted from home

		(subgroup differences p<0.05) then results will be stratified by corrected age where possible		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	02/09/2019		
22.	Anticipated completion date	12/08/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**

		Preliminary searches	☐ ☐ ☐	☐ ☐ ☐
		Piloting of the study selection process	☐ ☐ ☐	☐ ☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐ ☐	☐ ☐ ☐
		Data extraction	☐ ☐ ☐	☐ ☐ ☐
		Risk of bias (quality) assessment	☐ ☐ ☐	☐ ☐ ☐
		Data analysis	☐ ☐ ☐	☐ ☐ ☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail**		

		NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Wesley Hubbard
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from 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 advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines:

		the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10111
29.	Other registration details	None
30.	Reference/URL for published protocol	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	Late onset neonatal infection, risk factors
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.3 Maternal risk factors

ID	Field	Content
0.	PROSPERO registration number	CRD42019158429
1.	Review title	Maternal risk factors for late-onset infection
2.	Review question	Which maternal risk factors for late-onset neonatal infection should be used to guide management?
3.	Objective	To identify risk factors for late-onset neonatal infection/sepsis that should be used to guide management in the UK • includes symptoms and signs in the mother (including previous pregnancy history)

		• This review follows on from a review of clinical prediction models for late-onset neonatal infection. Evidence from this review did not support a positive recommendation for any risk prediction model, therefore a review of individual risk factors is required. • This is a prognostic review because it investigates maternal risk factors that are predictive of future infection in the neonate that should guide management.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language • Human studies • Conference abstracts Other searches: None

		The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. No date restrictions have been applied for this question.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in newborn babies. Late-onset neonatal infection occurs more than 72 hours after birth and can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Babies from 72 hours up to 28 days of age (term babies) and up to 28 days corrected gestational age [CGA] (preterm babies) • Pregnant women Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections.

		• Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a history of surgery which was not the cause of the infection will not be excluded. • Babies with suspected or confirmed meningitis who are not receiving care in neonatal units (covered by the NICE guideline on bacterial meningitis and meningococcal septicaemia) • Women with pre-labour rupture of membranes at term (covered in the NICE intrapartum care guideline)
7.	Risk factors	• Invasive group B streptococcal (GBS) infection in a previous baby • Maternal GBS colonisation, bacteriuria, detection (including vaginal or rectal swab) or infection in the current pregnancy • Suspected or confirmed infection in another baby in the case of a multiple pregnancy • Maternal wound infections (including perineal infections) • Maternal suspected bacterial infection in the puerperium • Maternal obesity • Behavioural and hygienic factors (for example adherence to infection control measures by medical professionals and parents/carers) • Maternal carriage of Methicillin-resistant Staphylococcus aureus (MRSA)

8.	Reference standard	• culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days CGA (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given between 72 hours (where available) and 28 days of age (term babies) or 28 days CGA (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection
9.	Types of study to be included	Predictive accuracy studies (cohort) reporting data from which a 2*2 contingency table can be calculated (True positives, false negatives, true negatives, false positives). Multivariate cohort studies that report adjusted measures of association (adjusted risk ratios, odds ratios or hazard ratios) will be included only for risk factors where no predictive accuracy data is available. Predictive accuracy studies were prioritised over multivariate cohort studies (association studies) as they provide data that is more directly relatable to outcomes that are important to patients and their families. This approach is also consistent with the approach taken for a similar question on early onset infection in the 2012 version of the NICE guideline on Neonatal infection. Systematic reviews of included studies types.

10.	Other exclusion criteria	• Non-English language studies • Non-Organisation for Economic Cooperation and Development (OECD) countries • Conference abstracts, theses, dissertations • Case-control studies will be excluded
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question. Care is usually provided in hospitals with facilities to care for mothers and neonates. The question will also cover neonates admitted to hospital from home, and so will be include risk factors identified in the community.
12.	Primary outcomes (critical outcomes)	Outcomes for predictive accuracy studies: • Sensitivity • Specificity • Positive and negative likelihood ratios If association studies are included due to a lack of predictive accuracy data (see section 9 for details): • Adjusted Risk ratios, Odds ratios, hazard ratios
13.	Secondary outcomes (important outcomes)	Not applicable
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. Data will be extracted from the included studies into a standardised form for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the QUIPS checklist as described in Developing NICE guidelines: the manual. The ROBIS checklist will be used to assess systematic reviews.
16.	Strategy for data synthesis	Meta-analyses of predictive test accuracy data will be conducted for all factors that are reported by more than one study, with reference to the Cochrane Handbook for systematic reviews on diagnostic test accuracy (the same principles for meta-analysis will be followed as for diagnostic test accuracy studies).

		Random-effects models will be fitted for all analyses. A bivariate model will be fitted when 5 or more studies are available to be meta-analysed. A univariate model will be fitted when there are fewer than 5 studies available. • Bivariate meta-analyses will be performed in R using the 'mada' package • Univariate meta-analysis will be performed in excel. Modified GRADE will be used to assess certainty in the evidence base. Heterogeneity will be assessed by considering whether studies are sufficiently similar in their populations, reference standards and adjustment for confounding factors to allow meaningful pooling of data to take place. If meta-analysis is conducted, I^2 will be used as a statistical measure of heterogeneity. In cases where heterogeneity make meta-analysis inappropriate, data for each study will be presented as separate lines in the GRADE profile. Meta-analysis will not be carried out for data from multivariate association studies as it is very unlikely that data from different studies will have adjusted for identical confounding factors as well as being heterogenous in terms of their population,
17.	Analysis of sub-groups	**Stratifications** • term vs preterm babies

		• multiple births • age of the baby (72 hours - 6 days; 7+ days) • babies who have been admitted to hospital from home
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	01/11/2019
22.	Anticipated completion date	12/08/2020

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** Guideline Updates Team		

		5b Named contact e-mail NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Gabriel Rogers • Mr Wesley Hubbard
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which is part of 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 advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10111
29.	Other registration details	None
30.	Reference/URL for published protocol	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	Late onset neonatal infection, maternal risk factors
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.4 Neonatal risk factors

ID	Field	Content
0.	PROSPERO registration number	CRD42019158414
1.	Review title	Neonatal risk factors and clinical indicators of late-onset neonatal infection
2.	Review question	Which risk factors in the baby (including symptoms and signs) should raise suspicion of late-onset infection?
3.	Objective	To identify risk factors for late-onset neonatal infection that should be used to guide management in the UK covers events relating to the baby after birth (postnatal events)

		includes consideration of how soon after birth symptoms, signs or other indicators should raise suspicion of late-onset neonatal infection includes which symptoms and signs (individually or in combination) should lead to antibiotic treatment The review is partly prognostic and partly diagnostic because it covers factors that affect a baby's risk of future infection as well as signs and symptoms of current infection. Both prognostic and diagnostic factors guide management decisions in practice – a baby could be treated for infection on the basis of risk factors alone if the risk of developing infection is very high, or because of a suspected infection based on signs and symptoms.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language • Human studies • Conference abstracts Other searches: None

		The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. No date restrictions have been applied for this question.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in newborn babies. Late-onset neonatal infection occurs more than 72 hours after birth and can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Babies from 72 hours up to 28 days of age (term babies) and up to 28 days corrected gestational age (CGA) (preterm babies) Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections only. • Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a history of surgery which was not the cause of the infection will not be excluded. • Babies with suspected or confirmed meningitis who are not receiving care in neonatal units (covered by the NICE guideline on bacterial meningitis and meningococcal septicaemia) • Women with pre-labour rupture of membranes at term (covered in the NICE intrapartum care guideline)
7.	Risk factors	**Signs and symptoms (diagnostic)**

		• Altered behaviour or responsiveness • Altered muscle tone (for example, floppiness) • Feeding difficulties (for example, feed refusal) • Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension • Abnormal heart rate (bradycardia or tachycardia) • Signs of respiratory distress • Hypoxia (for example, central cyanosis or reduced oxygen saturation level) • Jaundice • Apnoea • Seizures • Need for cardio-pulmonary resuscitation • Need for mechanical ventilation • Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors • Signs of shock • Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulopathy (International Normalised Ratio greater than 2.0) • Oliguria

		• Altered glucose homeostasis (hypoglycaemia or hyperglycaemia) • Metabolic acidosis (base deficit of 10 mmol/litre or greater) • Local signs of infection (for example, affecting the skin or eye) **Risk factors (prognostic)** • History of surgery (excluding surgical site infections) • Presence of a catheter (intravascular or urinary) or other indwelling device • Prematurity • Admission to neonatal unit • Prior Group B streptococcus (GBS) infection in the neonate • Colonisation with GBS or Methicillin-resistant Staphylococcus aureus (MRSA)
8.	Comparator/Reference standard/Confounding factors	• Culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days CGA (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given between 72 hours (where available) and 28 days of age (term babies) or 28 days CGA (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study
9.	Types of study to be included	• Diagnostic or predictive accuracy studies (cohort or cross sectional) reporting data from which a 2*2 contingency table can be calculated (True positives, false negatives, true negatives, false positives).

		• Multivariate association studies that report adjusted measures of association (adjusted risk ratios, odds ratios or hazard ratios) will be included only for risk factors or signs and symptoms where no accuracy (diagnostic or predictive) data is available. • Diagnostic or predictive accuracy studies were prioritised over multivariate association studies as they provide data that is more directly relatable to outcomes that are important to patients and their families. This approach is also consistent with the approach taken for a similar question on early onset infection in the 2012 version of the NICE guideline on Neonatal infection. • Systematic reviews of included studies types
10.	Other exclusion criteria	• Non-English language studies • Non-Organisation for Economic Cooperation and Development (OECD) countries • Conference abstracts, theses, dissertations • Case control studies
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question. Care is usually provided in hospitals with facilities to care for mothers and neonates. The question will also cover neonates admitted to hospital from home, and so will include risk factors identified in the community.
12.	Primary outcomes (critical outcomes)	Outcomes for diagnostic/prognostic accuracy studies: • Sensitivity • Specificity • Positive and negative likelihood ratios

		If association studies are included due to a lack of diagnostic or predictive accuracy data (see section 9 for details): • Adjusted risk ratios, odds ratios, hazard ratios
13.	Secondary outcomes (important outcomes)	Not applicable
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. Data will be extracted from the included studies into a standardised form for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed for diagnostic accuracy studies using the QUADAS-2 checklist and diagnostic association studies will be assessed using the Joanna Briggs institute checklist for cross sectional studies. Risk of bias for predictive accuracy studies and prognostic association (cohort) studies will be assessed using the QUIPs checklist.

		The ROBIS checklist will be used to assess systematic reviews.
16.	Strategy for data synthesis	Meta-analyses of predictive or diagnostic test accuracy data will be conducted for all factors that are reported by more than one study, with reference to the Cochrane Handbook for systematic reviews on diagnostic test accuracy (the same principles for meta-analysis of predictive test accuracy studies will be followed as for diagnostic test accuracy studies). Random-effects models will be fitted for all analyses. A bivariate model will be fitted when 5 or more studies are available to be meta-analysed. A univariate model will be fitted when there are fewer than 5 studies available. Bivariate meta-analyses will be performed in R using the 'mada' package Univariate meta-analysis will be performed in excel. Modified GRADE will be used to assess certainty in the evidence base. Heterogeneity will be assessed by considering whether studies are sufficiently similar in their populations, reference standards and adjustment for confounding factors to allow meaningful pooling of data to take place. If meta-analysis is conducted, I^2 will be used as a statistical measure of heterogeneity. In cases where heterogeneity make meta-analysis in appropriate, data for each study will be presented as separate lines in the GRADE profile. Meta-analysis will not be carried out for data from multivariate association studies as it is very unlikely that data from different studies will have adjusted for identical confounding factors as well as being heterogenous in terms of their population,
17.	Analysis of sub-groups	term babies and preterm babies age of the baby (72 hours - 6 days; 7+ days) admission to neonatal unit

		multiple births		
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/10/2019		
22.	Anticipated completion date	12/08/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		

		Data extraction		
		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: Dr Kathryn Hopkins Dr Clare Dadswell Mr Fadi Chehadah Mr Gabriel Rogers Mr Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from 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 advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10111
29.	Other registration details	None
30.	Reference/URL for published protocol	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	Late onset neonatal infection, neonate risk factors
33.	Details of existing review of same topic by same authors	None

34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

Appendix B – Literature search strategies

B.1 Clinical search: Clinical prediction models

The search was conducted on 14th August 2019. Given the broad range of publication types included in the review protocol, no in-house publication type filters were used. The following databases were searched: Medline, Medline In Process, Medline E-pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews, CENTRAL (all via the Wiley platform), and the DARE database (via the CRD platform).

Medline. Medline In Process, Medline E-pub

1 exp Infant, Newborn/

2 Term Birth/

3 Infant Care/

4 Perinatal Care/

5 Intensive Care Units, Neonatal/

6 Intensive Care, Neonatal/

7 Infant Health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp Bacterial Infections/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp Sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 or/11-15

17 exp Streptococcus/

18 exp Staphylococcus/

19 (streptococc* or staphylococc*).tw.

20 (GBS or MRSA or NRCS-A or MSSA).tw.

21 (met?icillin-resistant adj3 aureus).tw.

22 exp Escherichia coli/

23 ((Escheric* or E) adj2 coli).tw.

24 exp Listeria/

25 listeria*.tw.

26 exp Klebsiella/

27 klebsiella*.tw.

28 exp Pseudomonas/

29 (pseudomonas or chryseomonas or flavimonas).tw.

30 Enterobacteriaceae/

31 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

32 ((enteric or coliform) adj2 bac*).tw.

33 exp Neisseria/

34 neisseria*.tw.

35 exp Haemophilus influenzae/

36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

37 exp Serratia/

38 serratia*.tw.

39 exp Cronobacter/

40 (cronobact* or sakazaki* or malonatic*).tw.

41 exp Acinetobacter/

42 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

43 exp Fusobacterium/

44 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

45 exp Enterococcus/

46 enterococc*.tw.

47 or/17-46

48 16 or 47

49 10 and 48

50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

51 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

52 50 or 51

53 49 or 52

54 (bacter?emia* or bacill?emia*).tw.

55 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

56 54 or 55

57 10 and 56

58 53 or 57

59 Risk Assessment/mt [Methods]

60 ((risk* or predict* or probab* or prognos* or quantitativ*) adj2 (model* or tool* or algorithm* or rul*)).tw.

61 (diagnos* adj2 (model* or algorithm*)).tw.

62 ((sepsis* or septic* or Bayes* or EOS or LOS) adj4 calculator*).tw.

63 (NEOSC or EOSCAL* or SRC).tw.

64 (Kaiser adj2 Permanente).tw.

65 (Kaiser adj10 calculator*).tw.

66 ((sepsis or septic*) adj4 risk* adj4 scor*).tw.

67 SRS.tw.

68 ((sepsis* or septic*) adj4 (metascore* or meta-score*)).tw.

69 Diagnosis, Computer-Assisted/

70 Algorithms/

71 ((computer* or vital signs* or math* or manag* or clinic* or medic* or stratif* or prevent* or therap*) adj4 algorithm*).tw.

72 RALIS.tw.

73 (computer* adj4 (analys* or template*)).tw.

74 Decision Support Techniques/

75 (decision* adj4 (aid* or analys* or support* or assist*)).tw.

76 CDSS*.tw.

77 or/59-76

78 58 and 77

79 Animals/ not Humans/

80 78 not 79

81 limit 80 to english language

Embase

1 newborn/

2 term birth/

3 infant care/

4 perinatal care/

5 neonatal intensive care unit/

6 newborn intensive care/

7 child health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp bacterial infection/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 or/11-15

17 exp Streptococcus/

18 exp Staphylococcus/

19 (streptococc* or staphylococc*).tw.

20 (GBS or MRSA or NRCS-A or MSSA).tw.

21 (met?icillin-resistant adj3 aureus).tw.

22 exp Escherichia coli/

23 ((Escheric* or E) adj2 coli).tw.

24 exp Listeria/

25 listeria*.tw.

26 exp Klebsiella/

27 klebsiella*.tw.

28 exp Pseudomonas/

29 (pseudomonas or chryseomonas or flavimonas).tw.

30 Enterobacteriaceae/

31 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

32 ((enteric or coliform) adj2 bac*).tw.

33 exp Neisseria/

34 neisseria*.tw.

35 exp Haemophilus influenzae/

36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

37 exp Serratia/

38 serratia*.tw.

39 exp cronobacter/

40 (cronobact* or sakazaki* or malonatic*).tw.

41 exp Acinetobacter/

42 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

43 exp Fusobacterium/

44 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

45 exp Enterococcus/

46 enterococc*.tw.

47 or/17-46

48 16 or 47

49 10 and 48

50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. 51 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

52 50 or 51

53 49 or 52

54 (bacter?emia* or bacill?emia*).tw.

55 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

56 54 or 55

57 10 and 56

58 53 or 57

59 *risk assessment/

60 ((risk* or predict* or probab* or prognos* or quantitativ*) adj2 (model* or tool* or algorithm* or rul*)).tw.

61 (diagnos* adj2 (model* or algorithm*)).tw.

62 ((sepsis* or septic* or Bayes* or EOS or LOS) adj4 calculator*).tw.

63 (NEOSC or EOSCAL* or SRC).tw.

64 (Kaiser adj2 Permanente).tw.

65 (Kaiser adj10 calculator*).tw.

66 ((sepsis or septic*) adj4 risk* adj4 scor*).tw.

67 SRS.tw.

68 ((sepsis* or septic*) adj4 (metascore* or meta-score*)).tw.

69 computer assisted diagnosis/

70 algorithm/

71 ((computer* or vital signs* or math* or manag* or clinic* or medic* or stratif* or prevent* or therap*) adj4 algorithm*).tw.

72 RALIS.tw.

73 (computer* adj4 (analys* or template*)).tw.

74 exp decision support system/

75 (decision* adj4 (aid* or analys* or support* or assist*)).tw.

76 CDSS*.tw.

77 or/59-76

78 58 and 77

79 nonhuman/ not human/

80 78 not 79

81 limit 80 to english language

82 limit 81 to (conference abstract or conference paper or "conference review")

83 81 not 82

Cochrane Database of Systematic Reviews, CENTRAL

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Term Birth] this term only

#3 MeSH descriptor: [Infant Care] this term only

#4 MeSH descriptor: [Perinatal Care] this term only

#5 MeSH descriptor: [Intensive Care Units, Neonatal] this term only

#6 MeSH descriptor: [Intensive Care, Neonatal] this term only

#7 MeSH descriptor: [Infant Health] this term only

#8 ((newborn* or new born* or new-born or neonat* or neo-nat* or perinat* or peri-nat*)):ti,ab,kw

#9 ((premature or pre-mature* or preterm or pre-term) near/4 (child* or infant* or baby* or babies* or offspring)):ti,ab,kw

#10 {or #1-#9}

#11 MeSH descriptor: [Bacterial Infections] explode all trees

#12 ((bacter* or strep* or staph* or GNB) near/4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)):ti,ab,kw

#13 MeSH descriptor: [Sepsis] explode all trees

#14 ((sepsis or septic?emia* or py?emia* or pyho?emia*)):ti,ab,kw

#15 ((septic* near/4 shock*)):ti,ab,kw

#16 {or #11-#15}

#17 MeSH descriptor: [Streptococcus] explode all trees

#18 MeSH descriptor: [Staphylococcus] explode all trees

#19 ((streptococc* or staphylococc*)):ti,ab,kw

#20 ((GBS or MRSA or NRCS-A or MSSA)):ti,ab,kw

#21 ((met?icillin-resistant near/3 aureus)):ti,ab,kw

#22 MeSH descriptor: [Escherichia coli] explode all trees

#23 ((Escheric* or E) near/2 (coli)):ti,ab,kw

#24 MeSH descriptor: [Listeria] explode all trees

#25 (Listeria*):ti,ab,kw

#26 MeSH descriptor: [Klebsiella] explode all trees

#27 (klebsiella*):ti,ab,kw

#28 MeSH descriptor: [Pseudomonas] explode all trees

#29 ((pseudomonas or chryseomonas or flavimonas)):ti,ab,kw

#30 MeSH descriptor: [Enterobacteriaceae] this term only

#31 ((enterobact* or sodalis or paracolobactrum or ewingella or leclercia)):ti,ab,kw

#32 ((enteric or coliform) near/2 (bac*)):ti,ab,kw

#33 MeSH descriptor: [Neisseria] explode all trees

#34 (neisseria*):ti,ab,kw

#35 MeSH descriptor: [Haemophilus influenzae] explode all trees

#36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) near/2 (influenz* or pfeiffer* or meningitidis)):ti,ab,kw

#37 MeSH descriptor: [Serratia] explode all trees

#38 (serratia*):ti,ab,kw

#39 MeSH descriptor: [Cronobacter] explode all trees

#40 ((cronobact* or sakazaki* or malonatic*)):ti,ab,kw

#41 MeSH descriptor: [Acinetobacter] explode all trees

#42 ((acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*)):ti,ab,kw

#43 MeSH descriptor: [Fusobacterium] explode all trees

#44 ((fusobact* or sphaerophor* or necrophorum or nucleatum)):ti,ab,kw

#45 MeSH descriptor: [Enterococcus] explode all trees

#46 (enterococc*):ti,ab,kw

#47 {or #17-#46}

#48 #16 or #47

#49 #10 and #48

#50 ((newborn* or new born* or new-born* or neonat* or neo-nat* or perinat* or peri-nat*) near/4 (infect*)):ti,ab,kw

#51 ((premature or pre-mature* or preterm or pre-term) near/4 (child* or infant* or baby* or babies* or offspring) near/4 (infect*)):ti,ab,kw

#52 #50 or #51

#53 #49 or #52

#54 ((bacter?emia* or bacill?emia*)):ti,ab,kw

#55 ((blood*) near/4 (infect* or contamin* or invas* or invad*)):ti,ab,kw

#56 #54 or #55

#57 #10 and #56

#58 #53 or #57

#59 MeSH descriptor: [Risk Assessment] this term only and with qualifier(s): [methods - MT]

#60 ((risk* or predict* or probab* or prognos* or quantitativ*) near/2 (model* or tool* or algorithm* or rul*)):ti,ab,kw

#61 ((diagnos*) near/2 (model* or algorithm*)):ti,ab,kw

#62 ((sepsis* or septic* or Bayes* or EOS or LOS) near/4 (calculator*)):ti,ab,kw

#63 ((NEOSC or EOSCAL* or SRC)):ti,ab,kw

#64 ((Kaiser) near/2 (Permanente)):ti,ab,kw

#65 ((Kaiser) near/10 (calculator*)):ti,ab,kw

#66 ((sepsis or septic*) near/4 (risk*) near/4 (scor*)):ti,ab,kw

#67 (SRS):ti,ab,kw

#68 ((sepsis* or septic*) near/4 (metascore* or meta-score*)):ti,ab,kw

#69 MeSH descriptor: [Diagnosis, Computer-Assisted] this term only

#70 MeSH descriptor: [Algorithms] this term only

#71 ((computer* or vital signs* or math* or manag* or clinic* or medic* or stratif* or prevent* or therap*) near/4 (algorithm*)):ti,ab,kw

#72 (RALIS):ti,ab,kw

#73 ((computer*) near/4 (analys* or template*)):ti,ab,kw

#74 MeSH descriptor: [Decision Support Techniques] this term only

#75 ((decision*) near/4 (aid* or analys* or support* or assist*)):ti,ab,kw

#76 (CDSS*):ti,ab,kw

#77 {or #59-#76}

#78 #58 and #77

#79 (conference):pt

#80 ((clinicaltrials or trialsearch)):so

#81 #79 or #80

#82 #78 not #81

DARE

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES

2 MeSH DESCRIPTOR Term Birth

3 MeSH DESCRIPTOR Infant Care

4 MeSH DESCRIPTOR Perinatal Care

5 MeSH DESCRIPTOR Intensive Care Units, Neonatal

6 MeSH DESCRIPTOR Intensive Care, Neonatal

7 MeSH DESCRIPTOR Infant Health

8 (((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*)))

9 (((premature or pre-mature* or preterm or pre-term) NEAR4 (child* or infant* or baby* or babies* or offspring)))

10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

11 MeSH DESCRIPTOR Bacterial Infections EXPLODE ALL TREE

12 (((bacter* or strep* or staph* or GNB) NEAR4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)))

13 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES

14 (((sepsis or septic?emia* or py?emia* or pyho?emia*)))

15 (((septic* NEAR4 shock*)))

16 #11 OR #12 OR #13 OR #14 OR #15

17 MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES

18 MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES

19 (((streptococc* or staphylococc*)))

20 (((GBS or MRSA or NRCS-A or MSSA)))

21 (((met?icillin-resistant NEAR3 aureus)))

22 MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES

23 (((Escheric* or E) NEAR2 (coli)))

24 MeSH DESCRIPTOR Listeria EXPLODE ALL TREES

25 ((listeria*))

26 MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREES

27 ((klebsiella*))

28 MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES

29 ((pseudomonas or chryseomonas or flavimonas))

30 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES

31 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia)

32 ((enteric or coliform) NEAR2 (bac*))

33 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES

34 (neisseria*)

35 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES

36 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) NEAR2 (influenz* or pfeiffer* or meningitidis))

37 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES

38 (serratia*)

39 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES

40 (cronobact* or sakazaki* or malonatic*)

41 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES

42 ((acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*))

43 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES

44 ((fusobact* or sphaerophor* or necrophorum or nucleatum))

45 MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES

46 (enterococc*)

47 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46

48 #16 OR #47

49 #10 AND #48

50 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) NEAR4 (infect*))

51 ((premature or pre-mature* or preterm or pre-term) NEAR4 (child* or infant* or baby* or babies* or offspring) NEAR4 (infect*))

52 #50 OR #51

53 #49 OR #52

54 ((bacter?emia* or bacill?emia*))

55 ((blood*) NEAR4 (infect* or contamin* or invas* or invad*))

56 #54 OR #55

57 #10 AND #56

58 #53 OR #57

59 MeSH DESCRIPTOR Risk Assessment WITH QUALIFIER MT

60 ((risk* or predict* or probab* or prognos* or quantitativ*) NEAR2 (model* or tool* or algorithm* or rul*))

61 ((diagnos*) NEAR2 (model* or algorithm*))

62 ((sepsis* or septic* or Bayes* or EOS or LOS) NEAR4 (calculator*))

63 (NEOSC or EOSCAL* or SRC)

64 ((Kaiser) NEAR2 (Permanente))

65 ((Kaiser) NEAR10 (calculator*))

66 ((sepsis or septic*) NEAR4 (risk*) NEAR4 (scor*))

67 (SRS)

68 ((sepsis* or septic*) NEAR4 (metascore* or meta-score*))

69 MeSH DESCRIPTOR Diagnosis, Computer-Assisted

70 MeSH DESCRIPTOR Algorithms

71 ((computer* or vital signs* or math* or manag* or clinic* or medic* or stratif* or prevent* or therap*) NEAR4 (algorithm*))

72 (RALIS)

73 ((computer*) NEAR4 (analys* or template*))

74 MeSH DESCRIPTOR Decision Support Techniques

75 ((decision*) NEAR4 (aid* or analys* or support* or assist*))

76 (CDSS)

77 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76

78 #58 AND #77

79 * IN DARE

80 #78 AND #79

B.2 Clinical search: Maternal and neonatal risk factors

The search was conducted on 23rd September 2019. A single search strategy was developed for questions 5.1 and 5.2. The following databases were searched: Medline, Medline In Process, Medline E-pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews, (via the Wiley platform), and the DARE database (via the CRD platform).

Population and risk factor terms

The search terms used to identify information on population and risk factors are reproduced below for all databases. The population and risk factor terms were combined as 'And' to identify papers that discussed both.

Medline, Medline in Process & Medline E-pub Ahead of Print

1 exp Infant, Newborn/

2 Term Birth/

3 Infant Care/

4 Perinatal Care/

5 Intensive Care Units, Neonatal/

6 Intensive Care, Neonatal/

7 Infant Health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp Bacterial Infections/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp Sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 (bacter?emia* or bacill?emia*).tw.

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

18 or/11-17

19 exp Streptococcus/

20 exp Staphylococcus/

21 (streptococc* or staphylococc*).tw.

22 (GBS or MRSA or NRCS-A or MSSA).tw.

23 (met?icillin-resistant adj3 aureus).tw.

24 exp Escherichia coli/

25 ((Escheric* or E) adj2 coli).tw.

26 exp Listeria/

27 listeria*.tw.

28 exp Klebsiella/

29 klebsiella*.tw.

30 exp Pseudomonas/

31 (pseudomonas or chryseomonas or flavimonas).tw.

32 Enterobacteriaceae/

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

34 ((enteric or coliform) adj2 bac*).tw.

35 exp Neisseria/

36 neisseria*.tw.

37 exp Haemophilus influenzae/

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

39 exp Serratia/

40 serratia*.tw.

41 exp Cronobacter/

42 (cronobact* or sakazaki* or malonatic*).tw.

43 exp Acinetobacter/

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

45 exp Fusobacterium/

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

47 exp Enterococcus/

48 enterococc*.tw.

49 or/19-48

50 18 or 49

51 10 and 50

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

53 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

54 52 or 53

55 51 or 54

56 ((previous or preceding or earlier or prior or antecedent) adj4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries)).tw.

57 ((later or next or succeeding) adj4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries)).tw.

58 (Infectious Disease Transmission, Vertical/ or Carrier State/) and (Streptococcal Infections/ or Methicillin-Resistant Staphylococcus aureus/)

59 ((vertical* or maternal* or mother* or mum* or mom* or parental* or fetomaternal* or feto-maternal* or woman* or women* or pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r*) adj4 (GBS* or group B* or MRSA* or met?icillin-resist*) adj4 (transmission* or transmit* or transfer* or infect* or diseas* or contaminat* or coloni?ation* or contagio* or bacteriuria* or carrier* or carriage or heterozygo*)).tw.

60 exp Pregnancy, Multiple/

61 ((multiple or twin or triplet or quadruplet or quintuplet or superfetation) adj4 (pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r* or delivery or deliveries)).tw.

62 Wound Infection/

63 (wound* adj4 (infect* or diseas* or contaminat* or coloni?ation* or contagio* or sepsis)).tw.

64 Postpartum Period/

65 (postpartum or post-partum or puerperium or puerperal).tw.

66 ((perineal or perineum) adj4 (infect* or diseas* or contaminat* or coloni?ation* or contagio*)).tw.

67 exp Obesity/

68 ((obesity or obese or overweight or over-weight) adj8 risk*).tw.

69 exp Hygiene/

70 exp Sanitation/

71 (hygien* or saniti?e* or sanitation* or sanitary*).tw.

72 exp Maternal Behavior/

73 ((behavio?r* or attitud*) adj4 (factor* or aspect* or consider* or circumstanc* or component* or influenc* or feature*)).tw.

74 Illness Behavior/

75 ((alter* or chang* or illness*) adj4 (behavio?r* or respons* or feedback*) adj8 risk*).tw.

76 Muscle Hypotonia/

77 (flop* or flaccid* or hypoton* or hypomyotoni*).tw.

78 ((alter* or chang* or poor* or decreas* or atonic* or feeble or insuffic* or meag* or weak* or unsatisfact* or imperfect* or impair* or declin* or reduc* or diminish*) adj4 musc*).tw.

79 Feeding Behavior/

80 ((feed* or bottle* or breast*) adj4 (behavio?r* or difficult* or refus* or intoleran* or declin* or ignor* or withdraw* or problem*)).tw.

81 exp Vomiting/

82 (vomit* or emesis*).tw.

83 ((gastric* or nasogastric* or naso-gastric*) adj4 (aspirat* or suction*)).tw.

84 (abdom?n* adj4 disten*).tw.

85 Arrhythmias, Cardiac/ or Atrial Fibrillation/ or Atrial Flutter/ or Cardiac Complexes, Premature/ or Parasystole/ or Ventricular Fibrillation/ or Ventricular Flutter/

86 (arr?ythmia* or dysrhythmia*).tw.

87 ((abnormal* or anomal* or atypical* or irregular* or uncommon* or unexpect*) adj4 (heart* or cardiac* or vascular*) adj2 (rate* or pace* or measure* or rhythm* or beat*)).tw.

88 Bradycardia/ or Tachycardia/

89 (bradycardia* or bradyarrhythmia* or tachycardia* or tachyarrhythmia*).tw.

90 Respiratory Distress Syndrome, Newborn/

91 ((respirat* or breath*) adj4 (distres* or troubl* or discomfort*)).tw.

92 exp Hypoxia/

93 (hypoxia* or hypoxic* or hypoxem* or anoxia* or anoxem*).tw.

94 (oxygen* adj4 (deficien* or reduc* or suturat* or concentrat* or measur*)).tw.

95 exp Cyanosis/

96 exp Oximetry/

97 (cyanos?s* or cyanotic* or oximet*).tw.

98 exp Jaundice, Neonatal/

99 (jaundice* or icterus*).tw.

100 exp Apnea/

101 apn?ea*.tw.

102 Seizures/

103 ((seizure* or convuls* or paroxysm*) adj8 risk*).tw.

104 exp Cardiopulmonary Resuscitation/

105 (((cardiopulmon* or cardio-pulmon* or mouth-to-mouth*) adj4 resuscitat*) or CPR).tw.

106 exp Respiration, Artificial/

107 ((artificial* or mechanic* or automat* or machine* or control*) adj4 (respirat* or ventilat* or breath* or oxygenat*)).tw.

108 exp Body Temperature/

109 ((body* or organ* or skin* or high* or low* or excess* or reduc*) adj4 temperat*).tw.

110 (("36*" or "38*") adj2 (C or celsius)).tw.

111 (("96*" or "100*") adj2 (F or fahrenheit)).tw.

112 exp Shock/

113 (shock not (septic or sepsis)).tw.

114 (circulat* adj4 (collaps* or fail*)).tw.

115 ((pale* or cold* or clammy or chill* or blanch*) adj4 skin*).tw.

116 Sweat/ or Sweating/

117 (sweat* or perspir*).tw.

118 ((rapid* or shallow* or accelarat* or hollow* or flat*) adj4 (breath* or respirat*)).tw.

119 (weakness* or fragilit*).tw.

120 Dizziness/

121 (dizz* or orthostas* or lighthead* or light-head*).tw.

122 Thirst/

123 thirst*.tw.

124 Yawning/

125 (yawn* or sigh or sighs).tw.

126 exp Hemorrhage/

127 (bleed* or h?emorrhag*).tw.

128 (blood* adj4 (loss or effus* or excess*)).tw.

129 exp Thrombocytopenia/

130 (thrombocytop?enia* or thrombop?enia*).tw.

131 Blood Coagulation/

132 ((coagulat* or clot or clott*) adj8 risk*).tw.

133 Oliguria/

134 oliguria*.tw.

135 ((decreas* or diminish* or dwindl* or reduc* or wane) adj4 urin*).tw.

136 Homeostasis/

137 (homeostas* or homeostat* or autoregulat* or auto-regulat*).tw.

138 exp Hypoglycemia/

139 exp Hyperglycemia/

140 (hypoglyc?emi* or hyperglyc?emi*).tw.

141 ((low* or high*) adj4 blood* adj4 (sugar* or glucose*)).tw.

142 exp Acidosis/

143 acidos?s*.tw.

144 ((local* or region* or limit*) adj4 (infect* or contamin* or invas*)).tw.

145 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) adj4 (surg* or operat*)).tw.

146 exp Catheters/ or Catheterization/ or Catheterization, Central Venous/ or exp Catheterization, Peripheral/

147 ((catheter* or cannula*) adj4 (present* or presence* or exist* or attend* or current*)).tw.

148 ((indwell* or in-dwell*) adj4 (devic* or apparat* or applianc* or equip* or gadget* or machine* or mechanism*)).tw.

149 (prematur* adj8 risk*).tw.

150 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 (admiss* or admit*)).tw.

151 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) adj4 (GBS* or group B*) adj4 (infect* or contamin* or invas*)).tw.

152 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat* or infant* or baby* or babies*) adj4 (GBS* or group B* or MRSA* or met?icillin-resist*) adj4 (contaminat* or coloni?ation* or contagio*)).tw.

153 or/56-152

154 55 and 153

155 Animals/ not Humans/

156 154 not 155

157 limit 156 to english language

Embase

1 newborn/

2 term birth/

3 infant care/

4 perinatal care/

5 neonatal intensive care unit/

6 newborn intensive care/

7 child health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp bacterial infection/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 (bacter?emia* or bacill?emia*).tw.

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

18 or/11-17

19 exp Streptococcus/

20 exp Staphylococcus/

21 (streptococc* or staphylococc*).tw.

22 (GBS or MRSA or NRCS-A or MSSA).tw.

23 (met?icillin-resistant adj3 aureus).tw.

24 exp Escherichia coli/

25 ((Escheric* or E) adj2 coli).tw.

26 exp Listeria/

27 listeria*.tw.

28 exp Klebsiella/

29 klebsiella*.tw.

30 exp Pseudomonas/

31 (pseudomonas or chryseomonas or flavimonas).tw.

32 Enterobacteriaceae/

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

34 ((enteric or coliform) adj2 bac*).tw.

35 exp Neisseria/

36 neisseria*.tw.

37 exp Haemophilus influenzae/

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

39 exp Serratia/

40 serratia*.tw.

41 exp cronobacter/

42 (cronobact* or sakazaki* or malonatic*).tw.

43 exp Acinetobacter/

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw

45 exp Fusobacterium/

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

47 exp Enterococcus/

48 enterococc*.tw.

49 or/19-48

50 18 or 49

51 10 and 50

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

53 ((premature or pre-mature* or preterm or pre-term) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

54 52 or 53

55 51 or 54

56 ((previous or preceding or earlier or prior or antecedent) adj4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries)).tw.

57 ((later or next or succeeding) adj4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries)).tw.

58 (vertical transmission/ or heterozygote/) and (exp group B streptococcal infection/ or methicillin resistant Staphylococcus aureus/)

59 ((vertical* or maternal* or mother* or mum* or mom* or parental* or fetomaternal* or feto-maternal* or woman* or women* or pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r*) adj4 (GBS* or group B* or MRSA* or met?icillin-resist*) adj4 (transmission* or transmit* or transfer* or infect* or diseas* or contaminat* or coloni?ation* or contagio* or bacteriuria* or carrier* or carriage or heterozygo*)).tw.

60 exp multiple pregnancy/

61 ((multiple or twin or triplet or quadruplet or quintuplet or superfetation) adj4 (pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r* or delivery or deliveries)).tw.

62 wound infection/

63 (wound* adj4 (infect* or diseas* or contaminat* or coloni?ation* or contagio* or sepsis)).tw.

64 puerperium/

65 (postpartum or post-partum or puerperium or puerperal).tw.

66 ((perineal or perineum) adj4 (infect* or diseas* or contaminat* or coloni?ation* or contagio*)).tw.

67 exp obesity/

68 ((obesity or obese or overweight or over-weight) adj8 risk*).tw.

69 exp hygiene/

70 exp sanitation/

71 (hygien* or saniti?e* or sanitation* or sanitary*).tw.

72 maternal behavior/

73 ((behavio?r* or attitud*) adj4 (factor* or aspect* or consider* or circumstanc* or component* or influenc* or feature*)).tw.

74 illness behavior/

75 ((alter* or chang* or illness*) adj4 (behavio?r* or respons* or feedback*) adj8 risk*).tw.

76 exp muscle hypotonia/

77 (flop* or flaccid* or hypoton* or hypomyotoni*).tw.

78 ((alter* or chang* or poor* or decreas* or atonic* or feeble or insuffic* or meag* or weak* or unsatisfact* or imperfect* or impair* or declin* or reduc* or diminish*) adj4 musc*).tw.

79 feeding behavior/

80 ((feed* or bottle* or breast*) adj4 (behavio?r* or difficult* or refus* or intoleran* or declin* or ignor* or withdraw* or problem*)).tw.

81 exp vomiting/

82 (vomit* or emesis*).tw.

83 gastric suction/

84 ((gastric* or nasogastric* or naso-gastric*) adj4 (aspirat* or suction*)).tw.

85 abdominal distension/

86 (abdom?n* adj4 disten*).tw.

87 heart arrhythmia/ or heart atrium arrhythmia/ or heart fibrillation/ or heart palpitation/ or heart proarrhythmia/ or heart ventricle arrhythmia/ or parasystole/

88 (arr?ythmia* or dysrhythmia*).tw.

89 ((abnormal* or anomal* or atypical* or irregular* or uncommon* or unexpect*) adj4 (heart* or cardiac* or vascular*) adj2 (rate* or pace* or measure* or rhythm* or beat*)).tw.

90 exp bradycardia/ or exp tachycardia/

91 (bradycardia* or bradyarrhythmia* or tachycardia* or tachyarrhythmia*).tw.

92 neonatal respiratory distress syndrome/

93 ((respirat* or breath*) adj4 (distres* or troubl* or discomfort*)).tw.

94 exp hypoxia/

95 (hypoxia* or hypoxic* or hypoxem* or anoxia* or anoxem*).tw.

96 (oxygen* adj4 (deficien* or suturat* or concentrat* or measur* or reduc*)).tw.

97 exp cyanosis/

98 exp oximetry/

99 (cyanos?s* or cyanotic* or oximet*).tw.

100 newborn jaundice/

101 (jaundice* or icterus*).tw.

102 exp apnea/

103 apn?ea*.tw.

104 exp seizure/

105 ((seizure* or convuls* or paroxysm*) adj8 risk*).tw.

106 resuscitation/

107 (((cardiopulmon* or cardio-pulmon* or mouth-to-mouth*) adj4 resuscitat*) or CPR).tw.

108 exp artificial ventilation/

109 ((artificial* or mechanic* or automat* or machine* or control*) adj4 (respirat* or ventilat* or breath* or oxygenat*)).tw.

110 exp body temperature/

111 skin temperature/

112 ((body* or organ* or skin* or high* or low* or excess* or reduc*) adj4 temperat*).tw.

113 (("36*" or "38*") adj2 (C or celsius)).tw.

114 (("96*" or "100*") adj2 (F or fahrenheit)).tw.

115 exp shock/

116 (shock not (septic or sepsis)).tw.

117 (circulat* adj4 (collaps* or fail*)).tw.

118 ((pale* or cold* or clammy or chill* or blanch*) adj4 skin*).tw.

119 Sweat/ or exp Sweating/

120 (sweat* or perspir*).tw.

121 ((rapid* or shallow* or accelarat* or hollow* or flat*) adj4 (breath* or respirat*)).tw.

122 (weakness* or fragilit*).tw.

123 dizziness/

124 (dizz* or orthostas* or lighthead* or light-head*).tw.

125 thirst/

126 thirst*.tw.

127 yawning/

128 (yawn* or sigh or sighs).tw.

129 exp bleeding/

130 (bleed* or h?emorrhag*).tw.

131 (blood* adj4 (loss or effus* or excess*)).tw.

132 exp thrombocytopenia/

133 (thrombocytop?enia* or thrombop?enia*).tw.

134 exp blood clotting/

135 ((coagulat* or clot or clott*) adj8 risk*).tw.

136 oliguria/

137 oliguria*.tw.

138 ((decreas* or diminish* or dwindl* or reduc* or wane) adj4 urin*).tw.

139 homeostasis/

140 (homeostas* or homeostat* or autoregulat* or auto-regulat*).tw.

141 exp hypoglycemia/

142 exp hyperglycemia/

143 (hypoglyc?emi* or hyperglyc?emi*).tw.

144 ((low* or high*) adj4 blood* adj4 (sugar* or glucose*)).tw.

145 exp acidosis/

146 acidos?s*.tw.

147 ((local* or region* or limit*) adj4 (infect* or contamin* or invas*)).tw.

148 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) adj4 (surg* or operat*)).tw.

149 catheter/ or exp indwelling catheter/ or catheterization/ or central venous catheterization/

150 ((catheter* or cannula*) adj4 (present* or presence* or exist* or attend* or current*)).tw.

151 ((indwell* or in-dwell*) adj4 (devic* or apparat* or applianc* or equip* or gadget* or machine* or mechanism*)).tw.

152 (prematur* adj8 risk*).tw.

153 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 (admiss* or admit*)).tw.

154 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) adj4 (GBS* or group B*) adj4 (infect* or contamin* or invas*)).tw.

155 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat* or infant* or baby* or babies*) adj4 (GBS* or group B* or MRSA* or met?icillin-resist*) adj4 (contaminat* or coloni?ation* or contagio*)).tw.

156 or/56-155

157 55 and 156

158 nonhuman/ not human/

159 157 not 158

160 limit 159 to english language

CDSR

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Term Birth] this term only

#3 MeSH descriptor: [Infant Care] this term only

#4 MeSH descriptor: [Perinatal Care] this term only

#5 MeSH descriptor: [Intensive Care Units, Neonatal] this term only

#6 MeSH descriptor: [Intensive Care, Neonatal] this term only

#7 MeSH descriptor: [Infant Health] this term only

#8 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*)):ti,ab,kw

#9 ((premature* or pre-mature* or preterm* or pre-term*) near/4 (child* or infant* or baby* or babies* or offspring)):ti,ab,kw

#10 {or #1-#9}

#11 MeSH descriptor: [Bacterial Infections] explode all trees

#12 ((bacter* or strep* or staph* or GNB) near/4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)):ti,ab,kw

#13 MeSH descriptor: [Sepsis] explode all trees

#14 (sepsis or septic?emia* or py?emia* or pyho?emia*):ti,ab,kw

#15 (septic* near/4 shock*):ti,ab,kw

#16 (bacter?emia* or bacill?emia*):ti,ab,kw

#17 ((blood*) near/4 (infect* or contamin* or invas* or invad*)):ti,ab,kw

#18 {or #11-#17}

#19 MeSH descriptor: [Streptococcus] explode all trees

#20 MeSH descriptor: [Staphylococcus] explode all trees

#21 (streptococc* or staphylococc*):ti,ab,kw

#22 (GBS or MRSA or NRCS-A or MSSA):ti,ab,kw

#23 (met?icillin-resistant near/3 aureus):ti,ab,kw

#24 MeSH descriptor: [Escherichia coli] explode all trees

#25 ((Escheric* or E) near/2 (coli)):ti,ab,kw

#26 MeSH descriptor: [Listeria] explode all trees

#27 (listeria*):ti,ab,kw

#28 MeSH descriptor: [Klebsiella] explode all trees

#29 (klebsiella*):ti,ab,kw

#30 MeSH descriptor: [Pseudomonas] explode all trees

#31 (pseudomonas or chryseomonas or flavimonas):ti,ab,kw

#32 MeSH descriptor: [Enterobacteriaceae] explode all trees

#33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia):ti,ab,kw

#34 ((enteric or coliform) near/2 (bac*)):ti,ab,kw

#35 MeSH descriptor: [Neisseria] explode all trees

#36 (neisseria*):ti,ab,kw

#37 MeSH descriptor: [Haemophilus influenzae] explode all trees

#38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) near/2 (influenz* or pfeiffer* or meningitidis)):ti,ab,kw

#39 MeSH descriptor: [Serratia] explode all trees

#40 (serratia*):ti,ab,kw

#41 MeSH descriptor: [Cronobacter] explode all trees

#42 (cronobact* or sakazaki* or malonatic*):ti,ab,kw

#43 MeSH descriptor: [Acinetobacter] explode all trees

#44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*):ti,ab,kw

#45 MeSH descriptor: [Fusobacterium] explode all trees

#46 (fusobact* or sphaerophor* or necrophorum or nucleatum):ti,ab,kw

#47 MeSH descriptor: [Enterococcus] explode all trees

#48 (enterococc*):ti,ab,kw

#49 {or #19-#48}

#50 #18 or #49

#51 #10 and #50

#52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) near/4 (infect*)):ti,ab,kw

#53 ((premature or pre-mature* or "preterm" or "pre-term") near/4 (child* or infant* or baby* or babies* or offspring) near/4 (infect*)):ti,ab,kw

#54 #52 or #53

#55 #51 or #54

#56 ((previous or preceding or earlier or prior or antecedent) near/4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries)):ti,ab,kw

#57 ((later or "next" or succeeding) near/4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries)):ti,ab,kw

#58 MeSH descriptor: [Infectious Disease Transmission, Vertical] this term only

#59 MeSH descriptor: [Carrier State] this term only

#60 ((vertical* or maternal* or mother* or mum* or mom* or parental* or fetomaternal* or feto-maternal* or woman* or women* or pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r*) near/4 (GBS* or group B* or MRSA* or met?icillin-resist*) near/4 (transmission* or transmit* or transfer* or infect* or diseas* or contaminat* or coloni?ation* or contagio* or bacteriuria* or carrier* or carriage or heterozygo*)):ti,ab,kw

#61 MeSH descriptor: [Pregnancy, Multiple] explode all trees

#62 ((multiple or twin or triplet or quadruplet or quintuplet or superfetation) near/4 (pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r* or delivery or deliveries)):ti,ab,kw

#63 MeSH descriptor: [Wound Infection] this term only

#64 ((wound*) near/4 (infect* or diseas* or contaminat* or coloni?ation* or contagio* or sepsis)):ti,ab,kw

#65 MeSH descriptor: [Postpartum Period] this term only

#66 (postpartum or post-partum or puerperium or puerperal):ti,ab,kw

#67 ((perineal or perineum) near/4 (infect* or diseas* or contaminat* or coloni?ation* or contagio*)):ti,ab,kw

#68 MeSH descriptor: [Obesity] explode all trees

#69 ((obesity or obese or overweight or over-weight) near/8 (risk*)):ti,ab,kw

#70 MeSH descriptor: [Hygiene] explode all trees

#71 MeSH descriptor: [Sanitation] explode all trees

#72 (hygien* or saniti?e* or sanitation* or sanitary*):ti,ab,kw

#73 MeSH descriptor: [Maternal Behavior] explode all trees

#74 ((behavio?r* or attitud*) near/4 (factor* or aspect* or consider* or circumstanc* or component* or influenc* or feature*)):ti,ab,kw

#75 MeSH descriptor: [Illness Behavior] this term only

#76 ((alter* or chang* or illness*) near/4 (behavio?r* or respons* or feedback*) near/8 (risk*)):ti,ab,kw

#77 MeSH descriptor: [Muscle Hypotonia] this term only

#78 (flop* or flaccid* or hypoton* or hypomyotoni*):ti,ab,kw

#79 ((alter* or chang* or poor* or decreas* or atonic* or feeble or insuffic* or meag* or weak* or unsatisfact* or imperfect* or impair* or declin* or reduc* or diminish*) near/4 (musc*)):ti,ab,kw

#80 MeSH descriptor: [Feeding Behavior] this term only

#81 ((feed* or bottle* or breast*) near/4 (behavio?r* or difficult* or refus* or intoleran* or declin* or ignor* or withdraw* or problem)):ti,ab,kw

#82 MeSH descriptor: [Vomiting] explode all trees

#83 (vomit* or emesis*):ti,ab,kw

#84 ((gastric* or nasogastric* or naso-gastric*) near/4 (aspirat* or suction*)):ti,ab,kw

#85 ((abdom?n* near/4 disten*)):ti,ab,kw

#86 MeSH descriptor: [Arrhythmias, Cardiac] explode all trees

#87 (arr?ythmia* or dysrhythmia*):ti,ab,kw

#88 ((abnormal* or anomal* or atypical* or irregular* or uncommon* or unexpect*) near/4 (heart* or cardiac* or vascular*) near/2 (rate* or pace* or measure* or rhythm* or beat*)):ti,ab,kw

#89 (bradycardia* or bradyarrhythmia* or tachycardia* or tachyarrhythmia*):ti,ab,kw

#90 MeSH descriptor: [Respiratory Distress Syndrome, Newborn] this term only

#91 ((respirat* or breath*) near/4 (distres* or troubl* or discomfort*)):ti,ab,kw

#92 MeSH descriptor: [Hypoxia] explode all trees

#93 (hypoxia* or hypoxic* or hypoxem* or anoxia* or anoxem*):ti,ab,kw

#94 ((oxygen*) near/4 (deficien* or reduc* or suturat* or concentrat* or measur*)):ti,ab,kw

#95 MeSH descriptor: [Cyanosis] explode all trees

#96 MeSH descriptor: [Oximetry] explode all trees

#97 (cyanos?s* or cyanotic* or oximet*):ti,ab,kw

#98 MeSH descriptor: [Jaundice, Neonatal] explode all trees

#99 (jaundice* or icterus*):ti,ab,kw

#100 MeSH descriptor: [Apnea] explode all trees

#101 (apn?ea*):ti,ab,kw

#102 MeSH descriptor: [Seizures] this term only

#103 ((seizure* or convuls* or paroxysm*) near/8 (risk*)):ti,ab,kw 647

#104 MeSH descriptor: [Cardiopulmonary Resuscitation] explode all trees

#105 ((cardiopulmon* or cardio-pulmon* or mouth-to-mouth*) near/4 (resuscitat*)):ti,ab,kw

#106 (CPR):ti,ab,kw

#107 MeSH descriptor: [Respiration, Artificial] explode all trees

#108 ((artificial* or mechanic* or automat* or machine* or control*) near/4 (respirat* or ventilat* or breath* or oxygenat*)):ti,ab,kw

#109 MeSH descriptor: [Body Temperature] explode all trees

#110 ((body* or organ* or skin* or high* or low* or excess* or reduc*) near/4 (temperat*)):ti,ab,kw

#111 (("36*" or "38*") near/2 (C or celsius)):ti,ab,kw

#112 (("96*" or "100*") near/2 (F or fahrenheit)):ti,ab,kw

#113 MeSH descriptor: [Shock] explode all trees

#114 ((shock) not (septic or sepsis)):ti,ab,kw

#115 ((circulat*) near/4 (collaps* or fail*)):ti,ab,kw

#116 ((pale* or cold* or clammy or chill* or blanch*) near/4 (skin*)):ti,ab,kw

#117 MeSH descriptor: [Sweat] this term only

#118 MeSH descriptor: [Sweating] this term only

#119 (sweat* or perspir*):ti,ab,kw

#120 ((rapid* or shallow* or accelarat* or hollow* or flat*) near/4 (breath* or respirat*)):ti,ab,kw

#121 (weakness* or fragilit*):ti,ab,kw

#122 MeSH descriptor: [Dizziness] this term only

#123 (dizz* or orthostas* or lighthead* or light-head*):ti,ab,kw

#124 MeSH descriptor: [Thirst] this term only

#125 (thirst*):ti,ab,kw

#126 MeSH descriptor: [Yawning] this term only

#127 (yawn* or sigh or sighs):ti,ab,kw

#128 MeSH descriptor: [Hemorrhage] explode all trees

#129 (bleed* or h?emorrhag*):ti,ab,kw

#130 ((blood*) near/4 (loss or effus* or excess*)):ti,ab,kw

#131 MeSH descriptor: [Thrombocytopenia] explode all trees

#132 (thrombocytop?enia* or thrombop?enia*):ti,ab,kw

#133 MeSH descriptor: [Blood Coagulation] this term only

#134 ((coagulat* or clot or clott*) near/8 (risk*)):ti,ab,kw

#135 MeSH descriptor: [Oliguria] this term only

#136 (oliguria*):ti,ab,kw

#137 ((decreas* or diminish* or dwindl* or reduc* or wane) near/4 (urin*)):ti,ab,kw

#138 MeSH descriptor: [Homeostasis] this term only

#139 (homeostas* or homeostat* or autoregulat* or auto-regulat*):ti,ab,kw

#140 MeSH descriptor: [Hypoglycemia] explode all trees

#141 MeSH descriptor: [Hyperglycemia] explode all trees

#142 (hypoglyc?emi* or hyperglyc?emi*):ti,ab,kw

#143 ((low* or high*) near/4 (blood*) near/4 (sugar* or glucose*)):ti,ab,kw

#144 MeSH descriptor: [Acidosis] explode all trees

#145 (acidos?s*):ti,ab,kw

#146 ((local* or region* or limit*) near/4 (infect* or contamin* or invas*)):ti,ab,kw

#147 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) near/4 (surg* or operat*)):ti,ab,kw

#148 MeSH descriptor: [Catheters] explode all trees

#149 MeSH descriptor: [Catheterization] this term only

#150 MeSH descriptor: [Catheterization, Central Venous] this term only

#151 MeSH descriptor: [Catheterization, Peripheral] explode all trees

#152 ((catheter* or cannula*) near/4 (present* or presence* or exist* or attend* or current*)):ti,ab,kw

#153 ((indwell* or in-dwell*) near/4 (devic* or apparat* or applianc* or equip* or gadget* or machine* or mechanism*)):ti,ab,kw

#154 (prematur* near/8 risk*):ti,ab,kw

#155 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) near/4 (admiss* or admit*)):ti,ab,kw

#156 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) near/4 (GBS* or group B*) near/4 (infect* or contamin* or invas*)):ti,ab,kw

#157 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat* or infant* or baby* or babies*) near/4 (GBS* or group B* or MRSA* or met?icillin-resist*) near/4 (contaminat* or coloni?ation* or contagio*)):ti,ab,kw

#158 {or #56-#157}

#159 #55 and #158

DARE

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES

2 MeSH DESCRIPTOR Term Birth

3 MeSH DESCRIPTOR Infant Care

4 MeSH DESCRIPTOR Perinatal Care

5 MeSH DESCRIPTOR Intensive Care Units, Neonatal

6 MeSH DESCRIPTOR Intensive Care, Neonatal

7 MeSH DESCRIPTOR Infant Health

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*)

9 ((premature or pre-mature* or preterm or pre-term) NEAR4 (child* or infant* or baby* or babies* or offspring))

10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

11 MeSH DESCRIPTOR Bacterial Infections EXPLODE ALL TREES

12 ((bacter* or strep* or staph* or GNB) NEAR4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*))

13 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES

14 (sepsis or septic?emia* or py?emia* or pyho?emia*)

15 ((septic* NEAR4 shock*))

16 (bacter?emia* or bacill?emia)

17 ((blood*) NEAR4 (infect* or contamin* or invas* or invad*))

18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

19 MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES

20 MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES

21 (streptococc* or staphylococc*)

22 (GBS or MRSA or NRCS-A or MSSA)

23 ((met?icillin-resistant NEAR3 aureus))

24 MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES

25 ((Escheric* or E) NEAR2 (coli))

26 MeSH DESCRIPTOR Listeria EXPLODE ALL TREES

27 (listeria*)

28 MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREES

29 (klebsiella*)

30 MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES

31 (pseudomonas or chryseomonas or flavimonas)

32 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia)

34 ((enteric or coliform) NEAR2 (bac*))

35 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES

36 (neisseria*)

37 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) NEAR2 (influenz* or pfeiffer* or meningitidis))

39 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES

40 (serratia*)

41 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES

42 (cronobact* or sakazaki* or malonatic*)

43 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES

44 ((acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*))

45 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES

46 (fusobact* or sphaerophor* or necrophorum or nucleatum)

47 MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES

48 (enterococc*)

49 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48

50 #18 OR #49

51 #10 AND #50

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) NEAR4 (infect*))

53 ((premature or pre-mature* or preterm or pre-term) NEAR4 (child* or infant* or baby* or babies* or offspring) NEAR4 (infect*))

54 #52 OR #53

55 #51 OR #54

56 ((previous or preceding or earlier or prior or antecedent) NEAR4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries))

57 ((later or 'next' or succeeding) NEAR4 (child* or infant* or baby* or babies* or offspring or delivery or deliveries))

58 MeSH DESCRIPTOR Infectious Disease Transmission, Vertical EXPLODE ALL TREES

59 MeSH DESCRIPTOR Carrier State EXPLODE ALL TREES

60 ((vertical* or maternal* or mother* or mum* or mom* or parental* or fetomaternal* or feto-maternal* or woman* or women* or pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r*) NEAR4 (GBS* or group B* or MRSA* or met?icillin-resist*) NEAR4 (transmission* or transmit* or transfer* or infect* or diseas* or contaminat* or coloni?ation* or contagio* or bacteriuria* or carrier* or carriage or heterozygo))

61 MeSH DESCRIPTOR Pregnancy, Multiple EXPLODE ALL TREES

62 ((multiple or twin or triplet or quadruplet or quintuplet or superfetation) NEAR4 (pregnan* or gestat* or parturition* or birth* or childbirth* or labo?r* or delivery or deliveries)

63 MeSH DESCRIPTOR Wound Infection

64 ((wound*) NEAR4 (infect* or diseas* or contaminat* or coloni?ation* or contagio* or sepsis))

65 MeSH DESCRIPTOR Postpartum Period

66 (postpartum or post-partum or puerperium or puerperal)

67 ((perineal or perineum) NEAR4 (infect* or diseas* or contaminat* or coloni?ation* or contagio*))

68 MeSH DESCRIPTOR Obesity EXPLODE ALL TREES

69 ((obesity or obese or overweight or over-weight) NEAR8 (risk*))

70 MeSH DESCRIPTOR Hygiene EXPLODE ALL TREES

71 MeSH DESCRIPTOR Sanitation EXPLODE ALL TREES

72 (hygien* or saniti?e* or sanitation* or sanitary*)

73 MeSH DESCRIPTOR Maternal Behavior EXPLODE ALL TREES

74 ((behavio?r* or attitud*) NEAR4 (factor* or aspect* or consider* or circumstanc* or component* or influenc* or feature*))

75 MeSH DESCRIPTOR Illness Behavior

76 ((alter* or chang* or illness*) NEAR4 (behavio?r* or respons* or feedback*) NEAR8 (risk*))

77 MeSH DESCRIPTOR Muscle Hypotonia

78 (flop* or flaccid* or hypoton* or hypomyotoni*)

79 ((alter* or chang* or poor* or decreas* or atonic* or feeble or insuffic* or meag* or weak* or unsatisfact* or imperfect* or impair* or declin* or reduc* or diminish*) NEAR4 (musc*))

80 MeSH DESCRIPTOR Feeding Behavior

81 ((feed* or bottle* or breast*) NEAR4 (behavio?r* or difficult* or refus* or intoleran* or declin* or ignor* or withdraw* or problem*))

82 MeSH DESCRIPTOR Vomiting EXPLODE ALL TREES

83 (vomit* or emesis*)

84 ((gastric* or nasogastric* or naso-gastric*) NEAR4 (aspirat* or suction*)

85 ((abdom?n* NEAR4 disten*))

86 MeSH DESCRIPTOR Arrhythmias, Cardiac EXPLODE ALL TREES

87 (arr?ythmia* or dysrhythmia*)566 Delete

88 ((abnormal* or anomal* or atypical* or irregular* or uncommon* or unexpect*) NEAR4 (heart* or cardiac* or vascular*) NEAR2 (rate* or pace* or measure* or rhythm* or beat*)

89 (bradycardia* or bradyarrhythmia* or tachycardia* or tachyarrhythmia*)

90 MeSH DESCRIPTOR Respiratory Distress Syndrome, Newborn

91 ((respirat* or breath*) NEAR4 (distres* or troubl* or discomfort*))

92 MeSH DESCRIPTOR Hypoxia EXPLODE ALL TREES

93 (hypoxia* or hypoxic* or hypoxem* or anoxia* or anoxem*)

94 ((oxygen*) NEAR4 (deficien* or reduc* or suturat* or concentrat* or measur*))

95 MeSH DESCRIPTOR Cyanosis EXPLODE ALL TREES

96 MeSH DESCRIPTOR Oximetry EXPLODE ALL TREES

97 (cyanos?s* or cyanotic* or oximet*)

98 MeSH DESCRIPTOR Jaundice, Neonatal EXPLODE ALL TREES

99 (jaundice* or icterus*)

100 MeSH DESCRIPTOR Apnea EXPLODE ALL TREES

101 (apn?ea*)

102 MeSH DESCRIPTOR Seizures

103 ((seizure* or convuls* or paroxysm*) NEAR8 (risk*))

104 MeSH DESCRIPTOR Cardiopulmonary Resuscitation EXPLODE ALL TREES

105 ((cardiopulmon* or cardio-pulmon* or mouth-to-mouth*) NEAR4 (resuscitat*))

106 (CPR) 133

107 MeSH DESCRIPTOR Respiration, Artificial EXPLODE ALL TREES

108 ((artificial* or mechanic* or automat* or machine* or control*) NEAR4 (respirat* or ventilat* or breath* or oxygenat*))

109 MeSH DESCRIPTOR Body Temperature EXPLODE ALL TREES

110 ((body* or organ* or skin* or high* or low* or excess* or reduc*) NEAR4 (temperat*))

111 (('36*' or '38*') NEAR2 (C or celsius))

112 (('96*' or '100*') NEAR2 (F or fahrenheit))

113 MeSH DESCRIPTOR Shock EXPLODE ALL TREES

114 ((shock) NOT (septic or sepsis))

115 ((circulat*) NEAR4 (collaps* or fail*))

116 ((pale* or cold* or clammy or chill* or blanch*) NEAR4 (skin*))

117 MeSH DESCRIPTOR Sweat

118 MeSH DESCRIPTOR Sweating

119 (sweat* or perspir*)

120 ((rapid* or shallow* or accelarat* or hollow* or flat*) NEAR4 (breath* or respirat*))

121 (weakness* or fragilit*)

122 MeSH DESCRIPTOR Dizziness

123 (dizz* or orthostas* or lighthead* or light-head*)

124 MeSH DESCRIPTOR Thirst

125 (thirst*)

126 MeSH DESCRIPTOR Yawning

127 (yawn* or sigh or sighs)

128 MeSH DESCRIPTOR Hemorrhage EXPLODE ALL TREES

129 (bleed* or hemorrhag*)

130 ((blood*) NEAR4 (loss or effus* or excess*))

131 MeSH DESCRIPTOR Thrombocytopenia EXPLODE ALL TREES

132 (thrombocytop?enia* or thrombop?enia*)

133 MeSH DESCRIPTOR Blood Coagulation

134 ((coagulat* or clot or clott*) NEAR8 (risk*))

135 MeSH DESCRIPTOR Oliguria

136 (oliguria*)

137 ((decreas* or diminish* or dwindl* or reduc* or wane) NEAR4 (urin*))

138 MeSH DESCRIPTOR Homeostasis

139 (homeostas* or homeostat* or autoregulat* or auto-regulat*)

140 MeSH DESCRIPTOR Hypoglycemia EXPLODE ALL TREES

141 MeSH DESCRIPTOR Hyperglycemia EXPLODE ALL TREES

142 (hypoglyc?emi* or hyperglyc?emi*)

143 MeSH DESCRIPTOR Acidosis EXPlODE ALL TREES

144 (acidos?s*)

145 ((local* or region* or limit*) NEAR4 (infect* or contamin* or invas*))

146 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) NEAR4 (surg* or operat*))

147 MeSH DESCRIPTOR Catheters EXPLODE ALL TREES

148 MeSH DESCRIPTOR Catheterization

149 MeSH DESCRIPTOR Catheterization, Central Venous

150 MeSH DESCRIPTOR Catheterization, Peripheral EXPLODE ALL TREES

151 ((catheter* or cannula*) NEAR4 (present* or presence* or exist* or attend* or current*))

152 ((indwell* or in-dwell*) NEAR4 (devic* or apparat* or applianc* or equip* or gadget* or machine* or mechanism*))

153 ((prematur* NEAR8 risk*))

154 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) NEAR4 (admiss* or admit*))

155 ((previous* or preced* or earlier or prior* or anteceden* or histor* or past*) NEAR4 (GBS* or group B*) NEAR4 (infect* or contamin* or invas*))

156 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat* or infant* or baby* or babies*) NEAR4 (GBS* or group B* or MRSA* or met?icillin-resist*) NEAR4 (contaminat* or coloni?ation* or contagio*))

157 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156

158 #55 AND #157

Search Filters

The following search filters were combined as 'And' with the population and risk factor terms for the Medline databases and Embase. CDSR and DARE are systematic review databases so did not require the addition of a filter.

The Medline versions of the filters are reproduced below. Embase has validated translations of these that were used in the search.

Systematic Review

1 MEDLINE or pubmed).tw.

2 systematic review.tw.

3 systematic review.pt.

4 meta-analysis.pt.

5 intervention$.ti.

6 or/1-5

Observational studies

The in-house observational studies filter was adapted to focus on cross-sectional studies this was then supplemented with the McMaster diagnostic and prognostic filters.

1 Cohort Studies/

2 Prospective Studies/

3 Retrospective Studies/

4 Cross-Sectional Studies/

5 cohort:.mp.

6 predictor:.tw.

7 cross sectional.tw.

8 prospective*.tw.

9 retrospective*.tw.

10 sensitiv:.mp.

11 predictive value:.mp.

12 accurac:.tw.

13 prognosis.sh.

14 diagnosed.tw.

15 death.tw.

16 exp models, statistical/

17 or/1-16

Risk terms

Following combination of population, risk factor and filter terms (if an appropriate database) the number of results were still considered too high. Additional risk terms were combined as 'And' with the other sections of the search strategy to reduce numbers.

The Medline risk terms are listed below. These were translated across all databases used in the search:

1 exp Risk/

2 exp Risk Management/

3 Pregnancy, High Risk/

4 risk*.tw.

5 exp Health Status Indicators/

6 ((health* or illness* or wellness* or wellbeing* or well-being*) adj4 (indicat* or index* or indices* or apprais* or barometer* or gaug* or mark* or warn* or ratio or ratios)).tw.

7 (sever* adj4 illness*).tw.

8 exp "Signs and Symptoms"/

9 ((symptom* or sign or signs or manifest* or phenomenon*) adj8 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

10 or/1-9

Virus terms

The following terms were combined as 'Not' with the other sections of the search strategy to remove any papers focused on viral illness.

The Medline virus terms are listed below. These were translated across all databases used in the search:

1 exp Virus Diseases/

2 exp Viruses/

3 (virus* or viral* or retrovir* or arbovir* or lentivir* or deltaretrovir*).tw.

4 HIV*.tw.

5 (cytomegalovir* or CMV*).tw.

6 herpes*.tw.

7 (papillomavir* or HPV*).tw.

8 ((hepatitis* or hepatitid*) adj2 (A or B or C or D or E)).tw.

9 (parechovir* or echovir*).tw.

10 (yellow* adj2 fever*).tw.

11 rhinovir*.tw.

12 (coronavir* or deltacoronavir*).tw.

13 rotavir*.tw.

14 (enterovir* or coxsackie*).tw.

15 exp Malaria/

16 (malaria* or paludism*).tw.

17 exp Syphilis/

18 (syphili* or neurosyphili* or neuro-syphili*).tw.

19 or/1-18

B.3 Economics search: Health Economics literature search strategy

Sources searched to identify economic evaluations

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- Medline E-pubs (Ovid)
- Embase (Ovid)
- EconLit (Ovid)

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update in July 2019. Search filters to retrieve economic evaluations and quality of life papers were appended to the population and intervention terms to identify relevant evidence. Searches were not undertaken for qualitative RQs. Searches were re-run in July 2020 where the filters were added to the population terms.

Health economics search strategy

Database: Medline (Ovid)
1 exp Infant, Newborn/ (607120)
2 Term Birth/ (2958)
3 Infant Care/ (9209)
4 Perinatal Care/ (4613)
5 Intensive Care Units, Neonatal/ (14748)
6 Intensive Care, Neonatal/ (5673)
7 Infant Health/ (783)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (394580)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (50922)
10 or/1-9 (791905)
11 exp Bacterial Infections/ (886598)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (148920)
13 exp Sepsis/ (123123)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (100090)

15 (septic* adj4 shock*).tw. (19697)

16 (bacter?emia* or bacill?emia*).tw. (26877)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (38725)

18 or/11-17 (1097119)

19 exp Streptococcus/ (78627)

20 exp Staphylococcus/ (104852)

21 (streptococc* or staphylococc*).tw. (206696)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (27020)

23 (met?icillin-resistant adj3 aureus).tw. (23563)

24 exp Escherichia coli/ (278943)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (289781)

26 exp Listeria/ (15143)

27 listeria*.tw. (18688)

28 exp Klebsiella/ (19836)

29 klebsiella*.tw. (26962)

30 exp Pseudomonas/ (71592)

31 (pseudomonas or chryseomonas or flavimonas).tw. (85911)

32 Enterobacteriaceae/ (18945)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (30291)

34 ((enteric or coliform) adj2 bac*).tw. (5982)

35 exp Neisseria/ (20482)

36 neisseria*.tw. (18785)

37 exp Haemophilus influenzae/ (13731)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (19500)

39 exp Serratia/ (6599)

40 serratia*.tw. (8439)

41 exp Cronobacter/ (655)

42 (cronobact* or sakazaki* or malonatic*).tw. (958)

43 exp Acinetobacter/ (9822)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (15154)

45 exp Fusobacterium/ (3796)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (5425)

47 exp Enterococcus/ (19718)

48 enterococc*.tw. (26150)

49 or/19-48 (765874)

50 18 or 49 (1614537)

51 10 and 50 (65444)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (16079)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (946)

54 52 or 53 (16770)

55 51 or 54 (74853)

56 Economics/ (27206)

57 exp "Costs and Cost Analysis"/ (237006)

58 Economics, Dental/ (1911)

59 exp Economics, Hospital/ (24558)

60 exp Economics, Medical/ (14206)

61 Economics, Nursing/ (3999)

62 Economics, Pharmaceutical/ (2941)

63 Budgets/ (11315)

64 exp Models, Economic/ (15053)

65 Markov Chains/ (14321)

66 Monte Carlo Method/ (28322)

67 Decision Trees/ (11133)

68 econom$.tw. (238765)

69 cba.tw. (9764)

70 cea.tw. (20532)

71 cua.tw. (999)

72 markov$.tw. (17997)

73 (monte adj carlo).tw. (29925)

74 (decision adj3 (tree$ or analys$)).tw. (13431)

75 (cost or costs or costing$ or costly or costed).tw. (460618)

76 (price$ or pricing$).tw. (33468)

77 budget$.tw. (23716)

78 expenditure$.tw. (49355)

79 (value adj3 (money or monetary)).tw. (2096)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3485)

81 or/56-80 (926379)

82 "Quality of Life"/ (194718)

83 quality of life.tw. (229884)

84 "Value of Life"/ (5706)

85 Quality-Adjusted Life Years/ (12284)

86 quality adjusted life.tw. (10842)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (8901)

88 disability adjusted life.tw. (2741)

89 daly$.tw. (2486)

90 Health Status Indicators/ (23409)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (22454)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1323)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4902)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (29)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (381)
96 (euroqol or euro qol or eq5d or eq 5d).tw. (9001)
97 (qol or hql or hqol or hrqol).tw. (44126)
98 (hye or hyes).tw. (60)
99 health$ year$ equivalent$.tw. (38)
100 utilit$.tw. (171457)
101 (hui or hui1 or hui2 or hui3).tw. (1304)
102 disutili$.tw. (396)
103 rosser.tw. (94)
104 quality of wellbeing.tw. (14)
105 quality of well-being.tw. (381)
106 qwb.tw. (190)
107 willingness to pay.tw. (4500)
108 standard gamble$.tw. (783)
109 time trade off.tw. (1037)
110 time tradeoff.tw. (238)
111 tto.tw. (899)
112 or/82-111 (493012)
113 81 or 112 (1350947)
114 55 and 113 (3480)
115 limit 114 to ed=20190716-20200724 (226)
116 animals/ not humans/ (4686781)
117 115 not 116 (213)
118 limit 117 to english language (208)

Database: MiP (Ovid)
1 exp Infant, Newborn/ (0)

2 Term Birth/ (0)

3 Infant Care/ (0)

4 Perinatal Care/ (0)

5 Intensive Care Units, Neonatal/ (0)

6 Intensive Care, Neonatal/ (0)

7 Infant Health/ (0)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (32462)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (4347)

10 or/1-9 (34405)

11 exp Bacterial Infections/ (0)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (17517)

13 exp Sepsis/ (0)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (12331)

15 (septic* adj4 shock*).tw. (2749)

16 (bacter?emia* or bacill?emia*).tw. (2792)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (4519)

18 or/11-17 (35377)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

21 (streptococc* or staphylococc*).tw. (22112)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (4384)

23 (met?icillin-resistant adj3 aureus).tw. (3264)

24 exp Escherichia coli/ (0)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (21337)

26 exp Listeria/ (0)

27 listeria*.tw. (2351)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (4101)

30 exp Pseudomonas/ (0)

31 (pseudomonas or chryseomonas or flavimonas).tw. (10779)

32 Enterobacteriaceae/ (0)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (4282)

34 ((enteric or coliform) adj2 bac*).tw. (585)

35 exp Neisseria/ (0)

36 neisseria*.tw. (1256)

37 exp Haemophilus influenzae/ (0)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (1064)

39 exp Serratia/ (0)

40 serratia*.tw. (829)

41 exp Cronobacter/ (0)

42 (cronobact* or sakazaki* or malonatic*).tw. (168)

43 exp Acinetobacter/ (0)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2747)

45 exp Fusobacterium/ (0)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (821)

47 exp Enterococcus/ (0)

48 enterococc*.tw. (3589)

49 or/19-48 (59520)

50 18 or 49 (83682)

51 10 and 50 (2543)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (1246)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (81)

54 52 or 53 (1309)

55 51 or 54 (3367)

56 Economics/ (0)

57 exp "Costs and Cost Analysis"/ (0)

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (1)

66 Monte Carlo Method/ (2)

67 Decision Trees/ (0)

68 econom$.tw. (47080)

69 cba.tw. (456)

70 cea.tw. (2004)

71 cua.tw. (198)

72 markov$.tw. (5795)

73 (monte adj carlo).tw. (17215)

74 (decision adj3 (tree$ or analys$)).tw. (2609)

75 (cost or costs or costing$ or costly or costed).tw. (99726)

76 (price$ or pricing$).tw. (6047)

77 budget$.tw. (5074)

78 expenditure$.tw. (6509)

79 (value adj3 (money or monetary)).tw. (364)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (502)

81 or/56-80 (172313)

82 "Quality of Life"/ (0)

83 quality of life.tw. (40043)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (1728)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (1455)

88 disability adjusted life.tw. (523)

89 daly$.tw. (479)

90 Health Status Indicators/ (0)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2735)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (779)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (773)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (5)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (20)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (1711)

97 (qol or hql or hqol or hrqol).tw. (7636)

98 (hye or hyes).tw. (8)

99 health$ year$ equivalent$.tw. (2)

100 utilit$.tw. (32031)

101 (hui or hui1 or hui2 or hui3).tw. (203)

102 disutili$.tw. (60)

103 rosser.tw. (4)

104 quality of wellbeing.tw. (9)

105 quality of well-being.tw. (29)

106 qwb.tw. (13)

107 willingness to pay.tw. (957)

108 standard gamble$.tw. (62)

109 time trade off.tw. (119)

110 time tradeoff.tw. (11)

111 tto.tw. (145)

112 or/82-111 (74419)

113 81 or 112 (236895)

114 55 and 113 (231)

115 limit 114 to dt=20190716-20200724 (89)

116 animals/ not humans/ (1)

117 115 not 116 (89)

118 limit 117 to english language (89)

Database: Medline E-pubs (Ovid)

1 exp Infant, Newborn/ (0)

2 Term Birth/ (0)

3 Infant Care/ (0)

4 Perinatal Care/ (0)

5 Intensive Care Units, Neonatal/ (0)

6 Intensive Care, Neonatal/ (0)

7 Infant Health/ (0)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (6371)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (1421)

10 or/1-9 (6871)

11 exp Bacterial Infections/ (0)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (2219)

13 exp Sepsis/ (0)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (1706)

15 (septic* adj4 shock*).tw. (361)

16 (bacter?emia* or bacill?emia*).tw. (347)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (688)

18 or/11-17 (4700)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

21 (streptococc* or staphylococc*).tw. (2264)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (468)

23 (met?icillin-resistant adj3 aureus).tw. (345)

24 exp Escherichia coli/ (0)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (2275)

26 exp Listeria/ (0)

27 listeria*.tw. (198)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (476)

30 exp Pseudomonas/ (0)

31 (pseudomonas or chryseomonas or flavimonas).tw. (1004)

32 Enterobacteriaceae/ (0)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (460)

34 ((enteric or coliform) adj2 bac*).tw. (64)

35 exp Neisseria/ (0)

36 neisseria*.tw. (177)

37 exp Haemophilus influenzae/ (0)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (149)

39 exp Serratia/ (0)

40 serratia*.tw. (72)

41 exp Cronobacter/ (0)

42 (cronobact* or sakazaki* or malonatic*).tw. (14)

43 exp Acinetobacter/ (0)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (290)

45 exp Fusobacterium/ (0)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (112)

47 exp Enterococcus/ (0)

48 enterococc*.tw. (403)

49 or/19-48 (6238)

50 18 or 49 (9619)

51 10 and 50 (455)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (255)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (16)

54 52 or 53 (268)

55 51 or 54 (651)

56 Economics/ (0)

57 exp "Costs and Cost Analysis"/ (0)

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (0)

66 Monte Carlo Method/ (0)

67 Decision Trees/ (0)

68 econom$.tw. (6645)

69 cba.tw. (61)

70 cea.tw. (331)

71 cua.tw. (17)

72 markov$.tw. (718)

73 (monte adj carlo).tw. (1219)

74 (decision adj3 (tree$ or analys$)).tw. (519)

75 (cost or costs or costing$ or costly or costed).tw. (13246)

76 (price$ or pricing$).tw. (954)

77 budget$.tw. (555)

78 expenditure$.tw. (1143)

79 (value adj3 (money or monetary)).tw. (65)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (51)

81 or/56-80 (21922)

82 "Quality of Life"/ (0)

83 quality of life.tw. (7520)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (388)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (329)

88 disability adjusted life.tw. (101)

89 daly$.tw. (88)

90 Health Status Indicators/ (0)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (479)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (50)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (180)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (1)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (4)
96 (euroqol or euro qol or eq5d or eq 5d).tw. (407)
97 (qol or hql or hqol or hrqol).tw. (1460)
98 (hye or hyes).tw. (1)
99 health$ year$ equivalent$.tw. (0)
100 utilit$.tw. (4989)
101 (hui or hui1 or hui2 or hui3).tw. (18)
102 disutili$.tw. (12)
103 rosser.tw. (0)
104 quality of wellbeing.tw. (0)
105 quality of well-being.tw. (9)
106 qwb.tw. (3)
107 willingness to pay.tw. (184)
108 standard gamble$.tw. (7)
109 time trade off.tw. (20)
110 time tradeoff.tw. (2)
111 tto.tw. (18)
112 or/82-111 (12826)
113 81 or 112 (32909)
114 55 and 113 (55)
115 limit 114 to english language (55)

Database: Embase (Ovid)
1 newborn/ (526097)
2 term birth/ (3569)

3 infant care/ (1049)

4 perinatal care/ (14198)

5 neonatal intensive care unit/ (10192)

6 newborn intensive care/ (26405)

7 child health/ (27137)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (536460)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (68782)

10 or/1-9 (841089)

11 exp bacterial infection/ (838120)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (208658)

13 exp sepsis/ (263922)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (168012)

15 (septic* adj4 shock*).tw. (36223)

16 (bacter?emia* or bacill?emia*).tw. (40194)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (61015)

18 or/11-17 (1201558)

19 exp Streptococcus/ (128274)

20 exp Staphylococcus/ (209430)

21 (streptococc* or staphylococc*).tw. (262126)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (46092)

23 (met?icillin-resistant adj3 aureus).tw. (34157)

24 exp Escherichia coli/ (361361)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (339772)

26 exp Listeria/ (24096)

27 listeria*.tw. (22102)

28 exp Klebsiella/ (59561)

29 klebsiella*.tw. (42289)

30 exp Pseudomonas/ (144052)

31 (pseudomonas or chryseomonas or flavimonas).tw. (118130)

32 Enterobacteriaceae/ (23812)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (42447)

34 ((enteric or coliform) adj2 bac*).tw. (7285)

35 exp Neisseria/ (32218)

36 neisseria*.tw. (22936)

37 exp Haemophilus influenzae/ (29007)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (24329)

39 exp Serratia/ (14280)

40 serratia*.tw. (10397)

41 exp cronobacter/ (817)

42 (cronobact* or sakazaki* or malonatic*).tw. (1214)

43 exp Acinetobacter/ (27955)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (23888)

45 exp Fusobacterium/ (7678)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (7403)

47 exp Enterococcus/ (49841)

48 enterococc*.tw. (37571)

49 or/19-48 (967441)

50 18 or 49 (1894492)

51 10 and 50 (70672)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (21945)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1283)

54 52 or 53 (22885)

55 51 or 54 (83775)

56	exp Health Economics/ (845404)
57	exp "Health Care Cost"/ (290992)
58	exp Pharmacoeconomics/ (202216)
59	Monte Carlo Method/ (40279)
60	Decision Tree/ (13001)
61	econom$.tw. (368838)
62	cba.tw. (12788)
63	cea.tw. (34786)
64	cua.tw. (1498)
65	markov$.tw. (30389)
66	(monte adj carlo).tw. (48341)
67	(decision adj3 (tree$ or analys$)).tw. (23602)
68	(cost or costs or costing$ or costly or costed).tw. (772396)
69	(price$ or pricing$).tw. (57398)
70	budget$.tw. (38616)
71	expenditure$.tw. (74588)
72	(value adj3 (money or monetary)).tw. (3455)
73	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8625)
74	or/56-73 (1760062)
75	"Quality of Life"/ (469927)
76	Quality Adjusted Life Year/ (26663)
77	Quality of Life Index/ (2774)
78	Short Form 36/ (29036)
79	Health Status/ (127411)
80	quality of life.tw. (439622)
81	quality adjusted life.tw. (19747)
82	(qaly$ or qald$ or qale$ or qtime$).tw. (20178)
83	disability adjusted life.tw. (4103)

84 daly$.tw. (4016)

85 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (41434)

86 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2420)

87 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (9462)

88 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (61)

89 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (455)

90 (euroqol or euro qol or eq5d or eq 5d).tw. (20619)

91 (qol or hql or hqol or hrqol).tw. (97056)

92 (hye or hyes).tw. (135)

93 health$ year$ equivalent$.tw. (41)

94 utilit$.tw. (289831)

95 (hui or hui1 or hui2 or hui3).tw. (2300)

96 disutili$.tw. (924)

97 rosser.tw. (124)

98 quality of wellbeing.tw. (42)

99 quality of well-being.tw. (486)

100 qwb.tw. (253)

101 willingness to pay.tw. (8837)

102 standard gamble$.tw. (1104)

103 time trade off.tw. (1708)

104 time tradeoff.tw. (291)

105 tto.tw. (1683)

106 or/75-105 (989974)

107 74 or 106 (2593254)

108 55 and 107 (5731)

109 limit 108 to dc=20190716-20200724 (558)
110 nonhuman/ not human/ (4649157)
111 109 not 110 (522)
112 limit 111 to english language (510)
113 limit 112 to (conference abstract or conference paper or "conference review") (113)
114 112 not 113 (397)

Database: Econlit (Ovid)
1 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (732)
2 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (45)
3 1 or 2 (767)
4 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (49)
5 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (17)
6 (septic* adj4 shock*).tw. (1)
7 (bacter?emia* or bacill?emia*).tw. (3)
8 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (17)
9 (streptococc* or staphylococc*).tw. (18)
10 (GBS or MRSA or NRCS-A or MSSA).tw. (40)
11 (met?icillin-resistant adj3 aureus).tw. (8)
12 (((Escheric* or E) adj2 coli) or ecoli*).tw. (47)
13 listeria*.tw. (6)
14 klebsiella*.tw. (0)
15 (pseudomonas or chryseomonas or flavimonas).tw. (6)
16 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (1)
17 ((enteric or coliform) adj2 bac*).tw. (0)
18 neisseria*.tw. (1)

19 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (14)

20 serratia*.tw. (0)

21 (cronobact* or sakazaki* or malonatic*).tw. (1)

22 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2)

23 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (0)

24 enterococc*.tw. (5)

25 or/4-24 (194)

26 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (11)

27 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1)

28 26 or 27 (12)

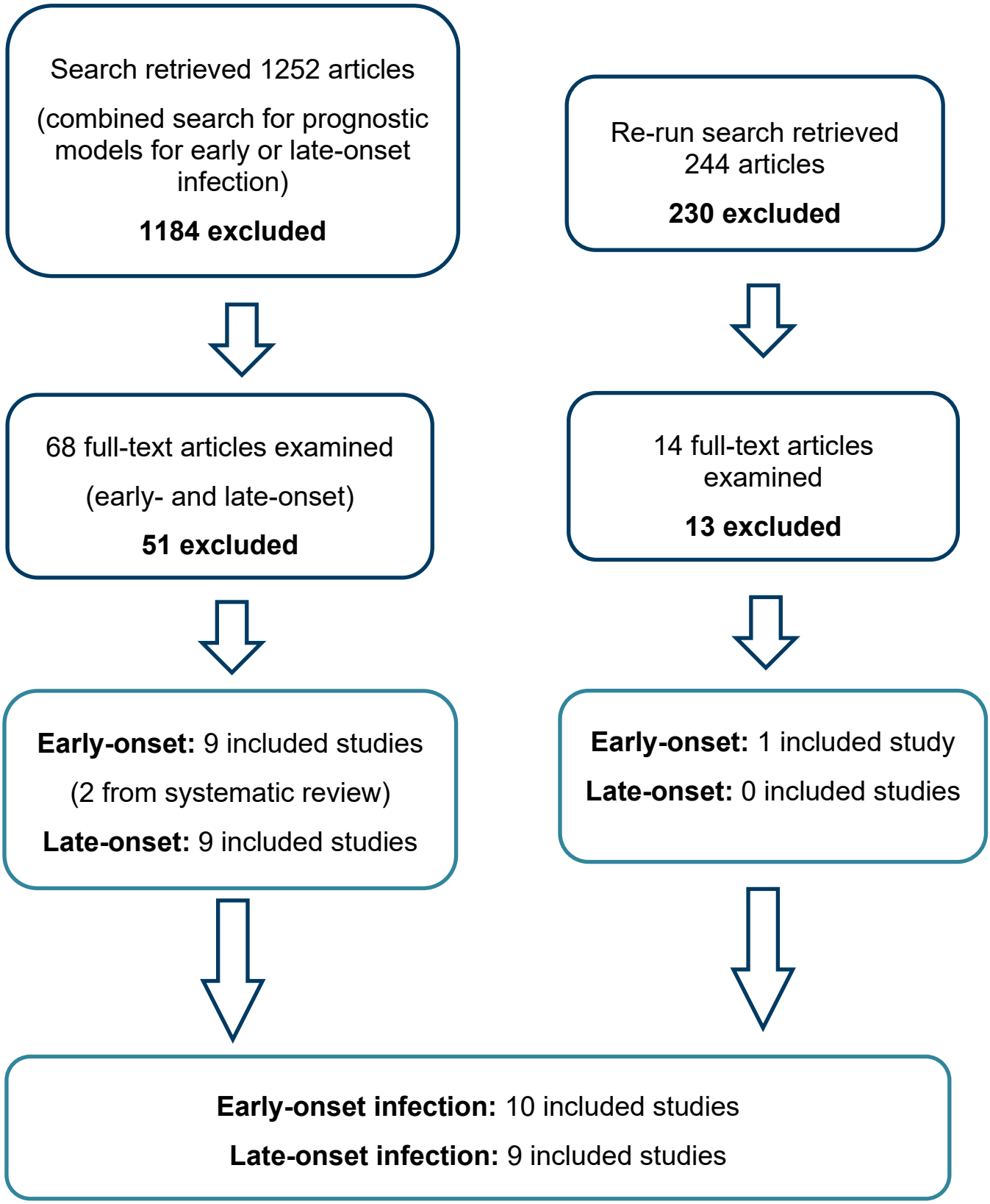
29 25 or 28 (205)

30 3 and 29 (15)

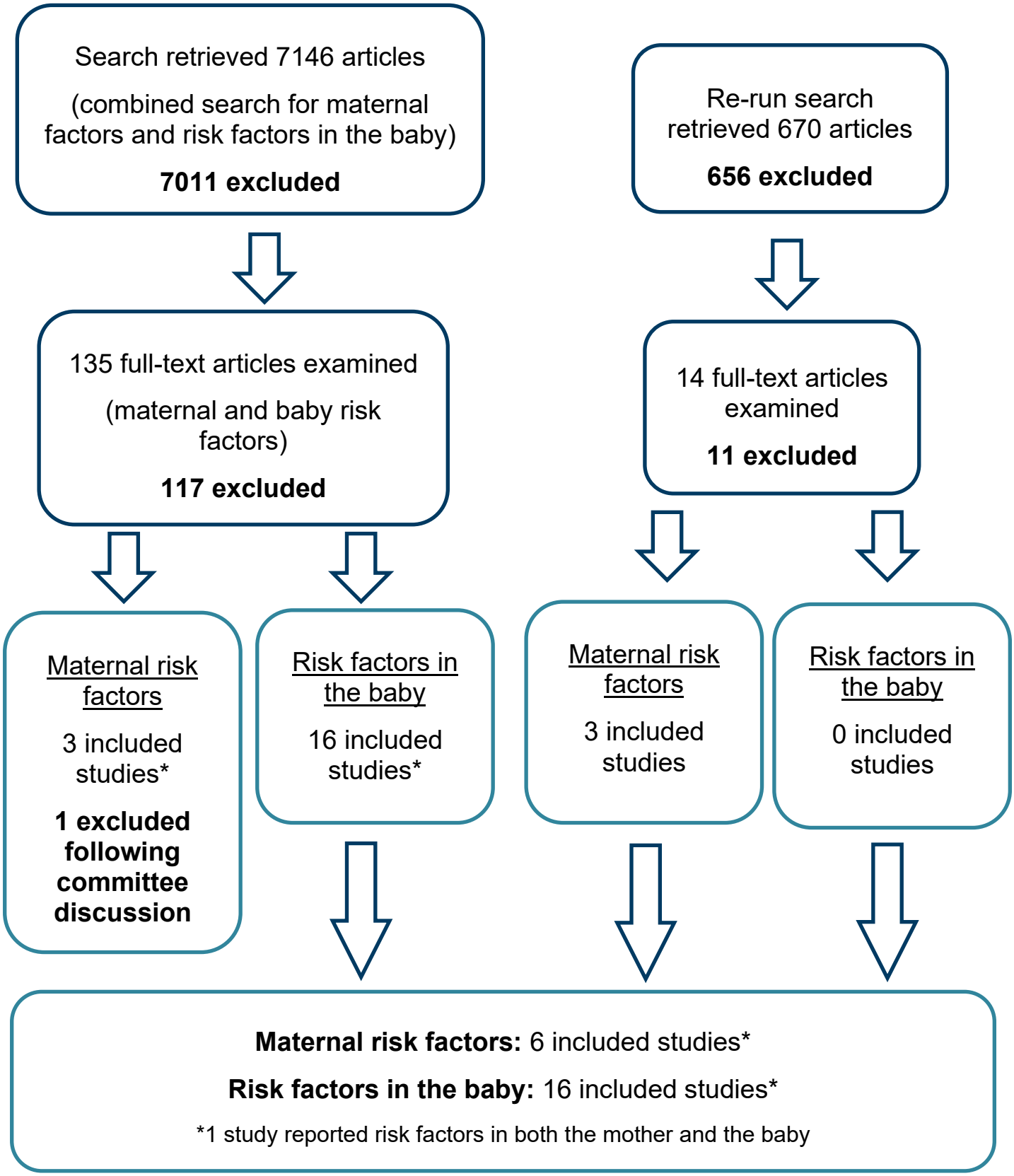
31 limit 30 to yr="2019 -Current" (1)

Appendix C –Prognostic and diagnostic evidence study selection

C.1 Clinical prediction models



C.2 Maternal and neonatal risk factors



Appendix D –Prognostic and diagnostic evidence

D.1 Clinical prediction models

Celik, 2013

Bibliographic Reference	Celik, I H; Demirel, G; Sukhachev, D; Erdeve, O; Dilmen, U; Neutrophil volume, conductivity and scatter parameters with effective modeling of molecular activity statistical program gives better results in neonatal sepsis.; International journal of laboratory hematology; 2013; vol. 35 (no. 1); 82-7

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Turkey Study setting Zekai Tahir Burak Maternity Teaching Hospital Study dates October 2010 - April 2011 Duration of follow-up Not reported but examines late-onset neonatal sepsis
Inclusion criteria	Not reported Potentially all babies in the neonatal intensive care unit of Zekai Tahir Burak Maternity Teaching Hospital between October 2010 and April 2011

Exclusion criteria	Not reported
Sample characteristics	Sample size 304 Female Proven sepsis 47%; Clinical sepsis 48%; Control 49% Mean gestational age (SD) Proven sepsis 30 (5); Clinical sepsis 33 (4); Control 30 (4) Gestational age ≤32 weeks Proven sepsis 75%; Clinical sepsis 52%; Control 75% Birth weight (g) Proven sepsis 1423 (828); Clinical sepsis 1967 (1035); Control 1571 (626) % with late-onset infection Proven sepsis 89.5%; Clinical sepsis 63.5%; Control 0
Prognostic models	Combined neutrophil VCS parameters, interleukin-6 and C-reactive protein models

Study arms

Model 1 (N = 304) C-reactive protein & mean neutrophil volume parameters
Model 2 (N = 304) C-reactive protein, mean neutrophil volume & volume distribution width parameters

Model 3 (N = 304)

Interleukin-6, C-reactive protein & mean neutrophil volume parameters

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes

	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	No information
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes *(> N = 100 with sepsis.)*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	Yes

	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Limited information about analysis methods)*
	Concerns for applicability	Low

Griffin, 2003

Bibliographic Reference	Griffin, M Pamela; O'Shea, T Michael; Bissonette, Eric A; Harrell, Frank E Jr; Lake, Douglas E; Moorman, J Randall; Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness.; Pediatric research; 2003; vol. 53 (no. 6); 920-6

Study Characteristics

Study design	Prospective cohort study
Study details	Study location USA Study setting University of Virginia and Wake Forest University NICUs

	Study dates September 1999 - March 2001 Duration of follow-up Neonatal sepsis after 7 days of age
Inclusion criteria	All infants admitted to NICUs at University of Virginia (UVA) and Wake Forest University (WFU)
Exclusion criteria	None reported
Sample characteristics	Sample size 633 Birth weight (g) UVA: 1746 (1102, 2852); WFU: 1790 (890, 2751) Mean gestational age (weeks; IQR) UVA: 32 (28, 37); WFU: 33 (27, 37) % with positive blood cultures UVA: 21%; WFU: 23%
Prognostic models	Demographics and heart rate monitoring model

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Prospective cohort)*

Section	Question	Answer
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information

Section	Question	Answer
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	No information
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	Yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable

Section	Question	Answer
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Gur, 2014

Bibliographic Reference Gur, Ilan; Markel, Gal; Nave, Yaron; Vainshtein, Igor; Eisenkraft, Arik; Riskin, Arieh; A mathematical algorithm for detection of late-onset sepsis in very-low birth weight infants: a preliminary diagnostic test evaluation.; Indian pediatrics; 2014; vol. 51 (no. 8); 647-50

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Israel Study setting NICU of Bikur Holim hospital, Jerusalem Study dates January 2006 - December 2008 Duration of follow-up 10 days

Inclusion criteria	Preterm infants <33 weeks gestation Birthweight <1500 g
Exclusion criteria	Early-onset sepsis Gestational age>33 weeks
Sample characteristics	Sample size 46 Female Proven sepsis: 25%; No sepsis: 41% Mean age (SD) Proven sepsis: 9.2 days (6.2); No sepsis: 7.6 days (1.8) Mean gestational age (SD) Proven sepsis: 27.7 weeks (2.3); No sepsis: 29.5 weeks (2.1) Birth weight (g) Proven sepsis: 930 (217); No sepsis: 1135 (213)
Prognostic models	RALIS model

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Retrospective study (diagnostic evaluation))*

Section	Question	Answer
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Probably yes *(Unclear whether blood cultures were taken before initiation of antibiotics)*
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes

Section	Question	Answer
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	No information
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	No *(N = 24 'proven sepsis')*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No information
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable

Section	Question	Answer
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information *(Unclear how many were given antibiotics initially)*
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Unclear *(Moderate - Unclear how many were given antibiotics initially. Unclear whether blood cultures were taken before initiation of antibiotics)*
	Concerns for applicability	Unclear *(Moderate - unclear whether blood cultures were taken before initiation of antibiotics. No information on how many were given antibiotics under standard practice)*

Gur, 2015

Bibliographic Reference	Gur, Ilan; Riskin, Arieh; Markel, Gal; Bader, David; Nave, Yaron; Barzilay, Bernard; Eyal, Fabien G; Eisenkraft, Arik; Pilot study of a new mathematical algorithm for early detection of late-onset sepsis in very low-birth-weight infants.; American journal of perinatology; 2015; vol. 32 (no. 4); 321-30

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Israel Study setting NICUs of 3 hospitals in Israel (1 hospital later excluded for policy of wide use of antimicrobials) Study dates June 2009 - March 2011 Duration of follow-up 21 days
Inclusion criteria	Preterm infants <33 weeks gestation Birthweight <1500 g
Exclusion criteria	Preterm infants with congenital malformations or who did not survive for more than 3 days
Sample characteristics	Sample size 118 Mean gestational age (SD) 28.1 weeks (2.2)

	Birth weight (g) 1056 (292) % with culture proven sepsis 37%
Prognostic models	RALIS model

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Prospective cohort)*
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes *(1 hospital was excluded as it reported no positive cases in NICU.)*
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes *('RALIS' algorithm.)*
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Probably yes *(No information about standard clinical practice (how many were given antibiotics and why))*
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	No information
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	No *(N = 44 positive sepsis)*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes

Section	Question	Answer
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	No information
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Unclear *(Moderate - No information about standard clinical practice (how many were given antibiotics and why))*
	Concerns for applicability	Low

Mahieu, 2002

Bibliographic Reference	Mahieu LM; De Dooy JJ; Cossey VR; Goossens LL; Vrancken SL; Jespers AY; Vandeputte CT; De Muynck AO; Internal and external validation of the NOSEP prediction score for nosocomial sepsis in neonates.; Critical care medicine; 2002; vol. 30 (no. 7)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Belgium Study setting Internal validation: University Hospital of Antwerp; External validation: 6 hospitals in Belgium Study dates Internal validatoin: December 1995 - November 1996; External validation: September 1998 - January 1999
Inclusion criteria	Infants admitted to the NICU Internal: University Hospital of Antwerp; External: 5 regional centres in Belgium
Exclusion criteria	Blood cultures not drawn before starting antibiotics
Sample characteristics	Sample size Internal validation: 62; External validation; 93 Female Internal validation: 68%; External validation; 46% Mean gestational age (weeks; range) Internal validation: 29.4 (25-40); External validation; 32 (24-41) Birth weight (g; range)

	Internal validation: 1277 (400-3800); External validation; 1728 (520-3866) Birth weight <1500 g Internal validation: 75%; External validation; 58%
Prognostic models	NOSEP-1 score NOSEP-New-1 score NOSEP-New-2 score

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Prospective cohort study.)*
	1.2 Were all inclusions and exclusions of participants appropriate?	Probably yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	No information
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	No *(N = 20 of suspected sepsis were positive.)*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes

Section	Question	Answer
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Mahieu, 2000

Bibliographic Reference	Mahieu LM; De Muynck AO; De Dooy JJ; Laroche SM; Van Acker KJ; Prediction of nosocomial sepsis in neonates by means of a computer-weighted bedside scoring system (NOSEP score); Critical care medicine; 2000; vol. 28 (no. 6)

Study Characteristics

Study design	Prospective cohort study Prospective: Derivation cohort; Retrospective: Validation cohort
Study details	Study location Belgium Study setting NICU of the University Hospital of Antwerp Study dates Derivation cohort: November 1993 - December 1995; validation cohort: December 1995 - November 1996 Duration of follow-up Not reported. Proven sepsis had to be >48 hours after admission
Inclusion criteria	Infants admitted to the NICU University Hospital of Antwerp
Exclusion criteria	Blood cultures not drawn before starting antibiotics
Sample characteristics	Sample size Derivation: 80; Validation: 50 Female Derivation: Screened for sepsis 57%; Not screened 48% Mean gestational age (SD) Derivation: Screened for sepsis 30.8 (4.9); Not screened 34 (14.6)

	Birth weight (g) Derivation: Screened for sepsis 1550 (883); Not screened 2188 (910) Gestational age <30 weeks Derivation: Screened for sepsis 40%; Not screened 54%
Prognostic models	NOSEP-1 score

Section	**Question**	**Answer**
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Prospective cohort (derivation) and retrospective cohort (validation cohort))*
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes *(NOSEP model)*
	2.2 Were predictor assessments made without knowledge of outcome data?	Yes *(Paediatrician blinded to culture result.)*

Section	Question	Answer
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	Probably yes
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Probably yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.2 Were continuous and categorical predictors handled appropriately?	No *(N=43 proven sepsis)*

Section	Question	Answer
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Mani, 2014

Bibliographic Reference	Mani, Subramani; Ozdas, Asli; Aliferis, Constantin; Varol, Huseyin Atakan; Chen, Qingxia; Carnevale, Randy; Chen, Yukun; Romano-Keeler, Joann; Nian, Hui; Weitkamp, Jorn-Hendrik; Medical decision support using machine learning for early detection of late-onset neonatal sepsis.; Journal of the American Medical Informatics Association : JAMIA; 2014; vol. 21 (no. 2); 326-36

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting NICU in the Monroe Carell Jr. Children's Hospital at Vanderbilt University Study dates January 2006 - June 2007 Duration of follow-up 60 h (starting 48 h before and finishing 12 h after the first blood culture test) Sources of funding National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health through Grant Number UL1 TR000041
Inclusion criteria	Infants evaluated for late-onset sepsis defined as neonatal sepsis occurring over 72 h after birth
Exclusion criteria	None reported
Sample characteristics	Sample size 299

	Female 44$ % with culture proven sepsis 32% Birth weight (g) (median; IQR) 1400 (865, 2424) Gestational age (weeks) (median, 25th - 75th percentiles) 30 (27-36)
Prognostic models	Machine learning models

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Retrospective cohort.)*
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information

Section	Question	Answer
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Probably yes *(No information on whether blood cultures were taken before initiation of antibiotics)*
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Probably yes *(N = 209 sepsis positive, N = 95 culture positive sepsis)*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Unclear *(Moderate - no information on whether blood cultures were taken before initiation of antibiotics)*

Section	Question	Answer
	Concerns for applicability	Low

Mithal, 2016

Bibliographic Reference Mithal, Leena Bhattacharya; Yogev, Ram; Palac, Hannah; Gur, Ilan; Mestan, Karen K; Computerized vital signs analysis and late onset infections in extremely low gestational age infants.; Journal of perinatal medicine; 2016; vol. 44 (no. 5); 491-7

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Prentice Women's Hospital Chicago Study dates 2008 - 2011 Sources of funding National Heart, Lung, and Blood Institute, (Grant/Award Number: “K23 HL093302”). Northwestern Memorial Foundation Friends of Prentice Grants Initiative
Inclusion criteria	Preterm infants <28 weeks gestation Complete vital signs data from birth to 28 days of life

Exclusion criteria	Early-onset sepsis <72 hours Infants who died within first 28 days of life Congenital syndromes or multiple anomalies Infants requiring high frequency oscillator ventilation
Sample characteristics	Sample size 73 Female Control 48%; Late-onset infection 35%; Culture-negative sepsis 57%; False-positive culture 38% Mean gestational age (SD) Control 28 weeks (1); Late-onset infection 26 weeks (2); Culture-negative sepsis 27 weeks (1); False-positive culture 27 weeks (1) Birth weight (g) Control 1083 (151); Late-onset infection 874 (198); Culture-negative sepsis 856 (133); False-positive culture 977 (241) Number of women with prolonged rupture of membranes Control 32%; Late-onset infection 32%; Culture-negative sepsis 43%; False-positive culture 31%
Prognostic models	RALIS model

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Retrospective cohort.)*
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes

Section	Question	Answer
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes
	2.2 Were predictor assessments made without knowledge of outcome data?	No information
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	No information

Section	Question	Answer
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	No *(N = 34 late onset infection)*
	4.2 Were continuous and categorical predictors handled appropriately?	Yes
	4.3 Were all enrolled participants included in the analysis?	Yes
	4.4 Were participants with missing data handled appropriately?	No information
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	No information
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable

Section	Question	Answer
	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Xiao, 2010

Bibliographic Reference Xiao, Yuping; Griffin, M Pamela; Lake, Douglas E; Moorman, J Randall; Nearest-neighbor and logistic regression analyses of clinical and heart rate characteristics in the early diagnosis of neonatal sepsis.; Medical decision making : an international journal of the Society for Medical Decision Making; 2010; vol. 30 (no. 2); 258-66

Study Characteristics

Study design	Prospective cohort study
Study details	Study location USA Study setting University of Virginia NICU
Inclusion criteria	Infants admitted to the NICU University of Virginia NICU Age >7 days

Sample characteristics	Sample size 676 Birth weight <1500 g 47% % with culture proven sepsis 18% Birth weight (g) (median; IQR) 1581 (974, 2700) Gestational age (weeks) (median, 25th - 75th percentiles) 31 (27, 36)
Prognostic models	Nearest neighbour model - physiological and demographic monitoring

Risk of bias

Section	Question	Answer
Selection of participants	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Yes *(Prospective cohort.)*
	1.2 Were all inclusions and exclusions of participants appropriate?	Yes
	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	2.1 Were predictors defined and assessed in a similar way for all participants?	Yes

Section	Question	Answer
	2.2 Were predictor assessments made without knowledge of outcome data?	Yes
	2.3 Are all predictors available at the time the model is intended to be used?	Yes
	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	3.1 Was the outcome determined appropriately?	Yes
	3.2 Was a pre-specified or standard outcome definition used?	Yes
	3.3 Were predictors excluded from the outcome definition?	Yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	Yes
	3.5 Was the outcome determined without knowledge of predictor information?	Probably yes
	3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Yes
	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	4.1 Were there a reasonable number of participants with the outcome?	No information *(Study does not report number of true positives.)*
	4.2 Were continuous and categorical predictors handled appropriately?	Probably yes
	4.3 Were all enrolled participants included in the analysis?	Probably yes
	4.4 Were participants with missing data handled appropriately?	Probably yes
	4.5 Was selection of predictors based on univariable analysis avoided? - Development studies	Not applicable
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?	Yes
	4.7 Were relevant model performance measures evaluated appropriately?	Yes
	4.8 Were model overfitting and optimism in model performance accounted for? - Development studies	Not applicable
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	Not applicable
	Overall risk of bias for analysis domain	Unclear *(Unclear risk as unable to assess number of people with late onset infection.)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Unclear
	Concerns for applicability	Low

D.2 Maternal risk factors

Garcia-Munoz Rodrigo, 2014

Bibliographic Reference **Garcia-Munoz Rodrigo, Fermin; Galan Henriquez, Gloria; Figueras Aloy, Josep; Garcia-Alix Perez, Alfredo; Outcomes of very-low-birth-weight infants exposed to maternal clinical chorioamnionitis: a multicentre study.; Neonatology; 2014; vol. 106 (no. 3); 229-34**

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Spain Study setting Multicentre: 53 neonatal intensive care units Study dates 2008-2011 Duration of follow-up Not reported - likely to be duration of admission Sources of funding Spanish society of neonatology
Inclusion criteria	Birthweight <1500g

	Gestational age <32 weeks Admitted to a neonatal unit
Exclusion criteria	Incomplete data available from medical records
Sample characteristics	Sample size 8330 Female 47.9% Mean gestational age (weeks) (SD) With chorioamnionitis: 27.1 (2.3) weeks Wtihout chorioamnionitis: 28.8 (2.3) weeks Caesarian delivery (%) 68.4% (calculated from table 1) Mean birthweight (SD) With chorioamnionitis: 1016 (278.2) g Without chorioamnionitis: 1101.4 (267.5) g Multiple births (%)
Prognostic/diagnostic factors	Maternal chorioamnionitis
Reference Factor (s)	Late-onset neonatal sepsis bacterial infection documented by a positive blood culture after 72 h of life, and with clinical symptoms: apnoea, temperature instability, feeding intolerance, worsening respiratory distress or hemodynamic instability.

Study arms

Very-low birthweight infants with gestational age <32 weeks (N = 8330)

Retrospective study. All neonates admitted to collaborating units with complete data who met inclusion criteria were included (83.1% of total eligible had complete data). Multivariate logistic regression was performed to assess the impact of maternal chorioamnionitis on late-onset sepsis with adjustment for gestational age, birth weight, maternal hypertension, antenatal steroids, infant sex, multiplicity (2 or more fetuses), type of delivery, necessity of advanced cardiopulmonary resuscitation (CPR), and stability after admission based on the Clinical Risk Index for Babies 1 (CRIB 1) score.

Risk of bias

Section	Question	Answer
Study participation	**Summary Study participation**	Low risk of bias *(Appropriate recruitment method and adequate description of sample.)*
Study Attrition	**Study Attrition Summary**	Low risk of bias *(82.3% of eligible neonates had complete data sets and were included. Attrition unlikely to be important as data recorded during stay on neonatal unit,)*
Prognostic factor measurement	**Prognostic factor Measurement Summary**	Low risk of bias *(Definition of maternal chorioamnionitis was reported and was unambiguous.)*
Outcome Measurement	**Outcome Measurement Summary**	Low risk of bias
Study Confounding	**Study Confounding Summary**	Low risk of bias *(Adjustment for confounding factors was reported and appears adequate.)*
Statistical Analysis and Reporting	**Statistical Analysis and Presentation Summary**	Moderate risk of bias *(Strategy for model development and criteria for including confounding factors for adjustment was not reported.)*

Overall risk of bias and directness	**Risk of Bias**	**Moderate** ***(Strategy for model development and criteria for including confounding factors for adjustment was not reported.)***
	Directness	**Directly applicable**

Lee, 2019

Bibliographic Reference	Lee, H.-S.; Kim, S.Y.; Histological chorioamnionitis, antenatal steroids, and neonatal outcomes in very low birth weight infants: A nationwide study; PLoS ONE; 2019; vol. 14 (no. 10); e0224450

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location South Korea Study setting 60 NICUs Study dates January 2013 - December 2015 Sources of funding Research of Korea Centers for Disease Control and Prevention.
Inclusion criteria	Very low birthweight <1500 g

	<34 weeks' gestational age
Exclusion criteria	Infants with insufficient placental histopathology data Major congenital malformations Multiple gestation
Sample characteristics	Sample size 2900
Length of follow-up	From 8 days onwards
Outcome(s) of interest	Positive blood culture for neonatal sepsis from 8 days of life onwards
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Antenatal steroids (receipt of at least one dose of any corticosteroid during pregnancy)
Covariates adjusted for in the multivariable regression modelling	Chorioamnionitis, antenatal steroids, maternal age, gravidity, parity, maternal hypertension, maternal diabetes, rupture of membranes > 18 h, caesarean delivery, gestational age, birth weight, infant sex, and small for gestational age

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias

Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low
	Directness	Directly applicable

Njagu, 2020

Bibliographic Reference	**Njagu, R.; Adkins, L.; Tucker, A.; Gatta, L.; Brown, H.L.; Reiff, E.; Dotters-Katz, S.; Maternal weight gain and neonatal outcomes in women with class III obesity; Journal of Maternal-Fetal and Neonatal Medicine; 2020**

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA

	Study setting Single tertiary care center Study dates July 2013 - Deccember 2017 Sources of funding None reported
Inclusion criteria	Women with class III obesity Body mass index >40 kg/m2. Women delivered at term >37 weeks
Exclusion criteria	Multiple gestation Pre-term delivery Fetal anomalies Missing data related to maternal weight, height, or delivery timings
Sample characteristics	Sample size 374 (Weight gain <20 lbs: 230; Weight gain >20 lbs: 144 Mean maternal age (IQR) Weight gain <20 lbs: 29.3 years (25.4, 34.7) Weight gain >20 lbs: 30.0 years (26.5, 33.6) Mean maternal BMI (IQR) Weight gain <20 lbs: 44.7 (41.6, 49.4) Weight gain >20 lbs: 43.7 (41.5, 48.0)
Length of follow-up	Not reported

Outcome(s) of interest	Confirmed neonatal sepsis
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Gestational weight gain (women who gained <20 lbs vs women who gained >20 lbs)
Covariates adjusted for in the multivariable regression modelling	Delivery BMI, tobacco use, chorioamnionitis and mode of delivery

Risk of bias

Section	Question	Answer
Study participation	**Summary Study participation**	Low risk of bias
Study Attrition	**Study Attrition Summary**	Low risk of bias
Prognostic factor measurement	**Prognostic factor Measurement Summary**	Low risk of bias
Outcome Measurement	**Outcome Measurement Summary**	Moderate risk of bias *(Confirmed neonatal sepsis - no further definition)*
Study Confounding	**Study Confounding Summary**	Low risk of bias
Statistical Analysis and Reporting	**Statistical Analysis and Presentation Summary**	Low risk of bias

Overall risk of bias and directness	**Risk of Bias**	Moderate *(Limited definition of neonatal sepsis)*
	Directness	Partially applicable *(Neonatal sepsis outcome may include babies with early- and late-onset infection. Results not reported separately)*

Olivier, 2016

Bibliographic Reference Olivier, F; Bertelle, V; Shah, P S; Drolet, C; Piedboeuf, B; Association between birth route and late-onset sepsis in very preterm neonates.; Journal of perinatology : official journal of the California Perinatal Association; 2016; vol. 36 (no. 12); 1083-1087

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Canada Study setting Study dates 2010-2014 Duration of follow-up Not reported - likely to be duration of admission to neonatal unit. Sources of funding

	Not reported.
Inclusion criteria	Admitted to a neonatal unit Gestational age 22 - 32 weeks
Exclusion criteria	Incomplete data available from medical records Death or sepsis within 72 hours of birth Major congenital abnormalities Moribund on admission
Sample characteristics	Sample size 20038 % babies with sepsis 13.2% Caesarian delivery (%) 59% Mean birthweight (SD) 1334 (453) g Multiple births (%) 32% Gestational age (groups, %) 22-25 weeks: 12% 26-28 weeks: 26% 29-30 weeks: 26% 31-32 weeks 37%
Prognostic/diagnostic factors	Mode of delivery Vaginal or caesarian section

Reference Factor (s)	Late-onset neonatal sepsis Positive blood or CSF culture or pathogenic organisms after 2 days of age in a symptomatic neonate. Data was coded by trained abstractors at each site.

Study arms

Very Pre-term neonates (22-32 weeks) (N = 20038)

Retrospective study including all eligible individuals admitted to participating neonatal units in study period. Very few neonates excluded because of missing data relative to sample size (188). Multivariate logistic regression was used to account for clustering within sites and to adjust for the following confounding factors: Gestational age, sex, small for gestational age, Apgar score 7 at 5 min, singleton, prolonged rupture of membranes exceeding 24 h, maternal systemic antibiotic use and initiation of labor.

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias *(Low proportion of eligible individuals excluded. Method for identifying individuals appears robust.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Attrition unlikely to have an impact as data recorded for duration of neonatal stay.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Definition of mode of delivery is unambiguous and low rate of data not available.)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Insufficient details reported on development of statistical model, including selection of variables to be adjusted for.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Insufficient details reported on development of statistical model, including selection of variables to be adjusted for.)*
	Directness	Directly applicable

Ward, 2020

Bibliographic Reference Ward, C.; Caughey, A.B.; Does the presence of epidural analgesia reduce the risk of neonatal sepsis in the setting of an intrapartum fever?; Journal of Maternal-Fetal and Neonatal Medicine; 2020

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting University of California, San Francisco Study dates

	Not reported Sources of funding None reported
Inclusion criteria	All women with preterm and term singleton pregnancies All deliveries for which data on gestational age and epidural status at delivery were available
Exclusion criteria	Multiple gestation Women who did not attempt labour Still births Delivery <24 weeks' gestation
Sample characteristics	Sample size 34,371 (Epidural: 16,917; No epidural: 17,454) Mean maternal age >35 years Epidural: 54% ; No epidural: 46%
Length of follow-up	Not reported
Outcome(s) of interest	Neonatal sepsis
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Women given an epidural
Covariates adjusted for in the	Maternal age, race/ethnicity, parity, and gestational age

multivariable regression modelling	

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Limited definition of neonatal sepsis)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(States what model was adjusted for but no justification for the choice of these factors)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Limited information about statistical analysis)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Limited defintion of the outcome and no justification of choice of factors to adjust for in the analysis)*
	Directness	Partially applicable *(Neonatal sepsis outcome may include early- and late-onset. Results not reported separately)*

D.3 Neonatal risk factors

Auriti, 2003

Bibliographic Reference	Auriti, C; Maccallini, A; Di Liso, G; Di Ciommo, V; Ronchetti, M P; Orzalesi, M; Risk factors for nosocomial infections in a neonatal intensive-care unit.; The Journal of hospital infection; 2003; vol. 53 (no. 1); 25-30

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Italy Study setting NICU at the Children's Hospital Bambino GesuÁ of Rome Study dates 1 year (dates not specified) Duration of follow-up Not reported Sources of funding None reported
Inclusion criteria	All consecutive infants admitted to the NICU during one year and discharged after a hospital stay of at least 48 h
Exclusion criteria	Patient records with missing information

Sample characteristics	Sample size 280 Female 47% Gestational age weeks (SD) 47 (SD not reported) Twin births (%) 11% Caesarean delivery (%) 60%
Prognostic/diagnostic factors	Gestational age Presence of a central venous catheter
Reference Factor (s)	Hospital acquired infection If the patient had positive symptoms and bacteriologic cultures at least after 48 h after admission to the NICU, the infection was defined as HAI

Study arms

Risk factors for hospital acquired infection (N = 280)

Included a review of various risk factors including initial clinical risk and illness severity (measured by the APGAR score or the clinical risk index for babies (CRIB) for very low birthweight infants within the first 12 h of birth. Association with infection examined using adjusted risk ratios calculated from multivariate logistic regression analysis (no information about model adjustment provided).

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information on multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Only significant results from the model are reported)*
Overall risk of bias and directness	Risk of Bias	High *(No information on model adjustment and only significant results from the model are reported)*
	Directness	Directly applicable

Babazono, 2008

Bibliographic Reference Babazono, Akira; Kitajima, Hiroyuki; Nishimaki, Shigeru; Nakamura, Tomohiko; Shiga, Seigo; Hayakawa, Masahiro; Tanaka, Tahei; Sato, Kazuo; Nakayama, Hideki; Ibara, Satoshi; Une, Hiroshi; Doi, Hiroyuki; Risk factors for nosocomial infection in the neonatal intensive care unit by the Japanese Nosocomial Infection Surveillance (JANIS).; Acta medica Okayama; 2008; vol. 62 (no. 4); 261-8

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Japan Study setting 7 NICUs Study dates June 2002 - January 2003 Duration of follow-up Not reported Sources of funding Ministry of Health, Labor and Welfare of Japan
Inclusion criteria	Participation in the Japanese nosocomial infection surveillance (JANIS)
Exclusion criteria	Data from 2 institutions was excluded because of limited data
Sample characteristics	Sample size 871 Female 47%
Prognostic/diagnostic factors	Presence of a central venous catheter Gender Birth weight

	Artificial ventilation Presence of a catheter in the bladder Umblical artery catheterisation Umbilical venous catheterisation
Reference Factor (s)	Noscomial infection Defined according to the national nosocomial infection surveillance (NNIS) system. If the patient had positive symptoms and bacteriologic cultures at least after 48 h after admission to the NICU, the infection was defined as HAI

Study arms

Risk factors for noscomial infection (N = 871) Risk factors included gender, birth weight, artificial ventilation, CVC, catheterization in the umbilical cord artery or vein, and catheter indwelling in the bladder. Association with noscomial infection examined using adjusted odds ratio calculated from multiple logistic regression analysis (no information provided about model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about multivariate model adjustment)*
	Directness	Directly applicable

Bekhof, 2013

Bibliographic Reference Bekhof, Jolita; Reitsma, Johannes B; Kok, Joke H; Van Straaten, Irma H L M; Clinical signs to identify late-onset sepsis in preterm infants.; European journal of pediatrics; 2013; vol. 172 (no. 4); 501-8

Study Characteristics

Study design	Prospective cohort study
Study details	Study location The Netherlands Study setting Level III NICU in Zwolle

	Study dates July 2005 - November 2007 Duration of follow-up Until a corrected gestational age of 35 weeks or until discharge to other hospitals before 35 weeks Sources of funding None reported
Inclusion criteria	Gestational age <34 weeks More than 72 hours of age Not on antibiotic therapy for the previous 24 hours
Exclusion criteria	None reported
Sample characteristics	Sample size 142 Female 44% Gestational age weeks (SD) 29+6 (2+1) Age at onset of suspected infection (median, IQR) 10 (7-15) Mean birth weight (SD) 1207 g (351)
Prognostic/diagnostic factors	Presence of a central venous catheter Pallor/grey skin colour

	Increased respiratory support Lethargy Capillary refill >2s Weight at episode <1200g
Reference Factor (s)	Late-onset sepsis Positive blood culture with skin commensals was defined as proven sepsis when the same organism was found in at least two blood cultures and/or signs of catheter-related sepsis were present (i.e. inflammation of the skin at the site of line insertion)

Study arms

Pre-term infants (N = 142)

Risk factors included pallor or grey skin colour, capillary refill time >2 s [20], dyspnoea (grunting, nasal flaring and/or chest retractions), tachypnoea (respiratory rate >60/min during >1 h), need for increased respiratory support (intensifying the modus, i.e. low flow, CPAP or endotracheal ventilation and/or degree of respiratory support), increasing need or supplemental oxygen, tachycardia (pulse >180/min during >1 h), temperature instability (difference in body temperature >0.5 °C within 24 h), hyperthermia (rectal temperature >38.0 °C), hypothermia (rectal temperature <36.0 °C), feeding difficulties (vomiting or gastric aspirates >50 % of feed volume), increasing frequency of apnoea, bradycardia and/or cyanotic spells, lethargy and irritability. Association with neonatal infection examined using adjusted odds ratios calculated from a multivariable model (no information provided about model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about multivariate model adjustment)*
	Directness	Directly applicable

Boghossian, 2013

Bibliographic Reference Boghossian, Nansi S; Page, Grier P; Bell, Edward F; Stoll, Barbara J; Murray, Jeffrey C; Cotten, C Michael; Shankaran, Seetha; Walsh, Michele C; Laptook, Abbot R; Newman, Nancy S; Hale, Ellen C; McDonald, Scott A; Das, Abhik; Higgins, Rosemary D; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research, Network; Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births.; The Journal of pediatrics; 2013; vol. 162 (no. 6); 1120-1124e1

Study Characteristics

Study design	Retrospective cohort study Not stated in study. Appears to be retrospective
Study details	Study location USA Study setting National Institute of Child Health and Human Development Neonatal Research Network clinical centres Study dates January 2002 - December 2008 Duration of follow-up Not reported Sources of funding National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child and Human Development
Inclusion criteria	Birth weight 401-1500 g Gestational age 22-28+6 weeks Inclusion criteria changed to include this in January 2008 (final year of study)
Exclusion criteria	Infants whose cultures grew unclassified bacteria or who had no recorded organisms Positive blood cultures due to organisms considered to be contaminants, including Corynebacterium, Propionibacterium, and Penicillium species and diphtheroids Infants with blood cultures that grew multiple organisms in the first LOS event
Sample characteristics	Sample size 15178 singleton babies, 5294 babies from multiple births % with late-onset infection 25% singleton babies, 23% babies from multiple births

Prognostic/diagnostic factors	Gestational age Gender Duration of mechanical ventilation History of surgery Length of stay Age when full feeds acheived Small for gestational age Parenteral nutrition
Reference Factor (s)	Late-onset sepsis I the infant had a positive blood culture due to an identified bacterial (including coagulasenegative staphylococcus) or fungal organism, treated with antibiotics for 5 days or more or treated for a shorter duration if the infant died during treatment

Study arms

Very low birth weight infants from singleton and multiple births (N = 20472)

Risk factors included maternal factors and neonatal factors (intrauterine infection, sex, gestational age, small for gestational age, rectal or axillary temperature at birth above 38°C, total duration of assisted ventilation, duration of conventional ventilation, duration of high-frequency ventilation, duration of supplemental oxygen, parenteral nutritional support, major surgery, length of hospital stay, age when birth weight was regained, age at first parenteral feeding, age when full feedings were achieved, and postnatal corticosteroid use. Association between with neonatal infection examined using adjusted odds ratios calculated from logistic regression (no information provided about model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(6 year study - study inclusion criteria changed in the final year but results not reported separately)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about multivariate model adjustment and study inclusion criteria changed in the final year)*
	Directness	Directly applicable

Garland, 2017

Bibliographic Reference	Garland, J S; Kanneberg, S; Mayr, K A; Porter, D M; Vanden Heuvel, A; Kurziak, J; McAuliffe, T L; Risk of morbidity following catheter removal among neonates with catheter associated bloodstream infection.; Journal of neonatal-perinatal medicine; 2017; vol. 10 (no. 3); 291-299

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Four community level III neonatal intensive care units in Milwaukee Study dates January 2000 - November 2010 Duration of follow-up Not reported Sources of funding Wheaton Franciscan Foundation-St Joseph Foundation
Inclusion criteria	PICC in place for >72 hours
Exclusion criteria	Major congenital abnormalities
Sample characteristics	Sample size 2913 Female Without infection: 45%, With infection: 45%

	Gestational age weeks (SD) 29.5 (4.0) Mean birth weight (SD) 1330 g (769) % with late-onset infection 10% Multiple births (%) Without infection: 24%, With infection: 27%
Prognostic/diagnostic factors	Gestational age Patent ductus arteriosus Catheter related infection during initial catheterisation
Reference Factor (s)	Catheter associated bloodstream infection The presence of bacteria or fungus from one or more peripheral blood cultures obtained from a symptomatic neonate without an identifiable source who was treated with at least 6 days of systemic antibiotics. Infection must have occurred during the time a PICC was in situ, or within 24 hours of a PICC removal.

Study arms

Neonates with peripherally inserted central catheters (N = 2913)

Risk factors included year of birth, gender, race, location of birth, antenatal steroid treatment, route of birth, birth weight gestational age, Apgar scores, Score for Neonatal Acute Physiology, presence of respiratory distress syndrome at birth, surfactant treatment, presence of documented early onset septicemia, severity of intracranial hemorrhage and days of antibiotic treatment prior to the initial PICC placement. Associations with neonatal infection examined using adjusted odds ratios calculated from multiple logistic regression controlling for potential confounders (no further information about potential confounders)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(States that multivariate model was adjusted for confounding variables but no details of what the confounding factors are)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Limited information on multivariate model adjustment)*
	Directness	Directly applicable

Hylander, 1998

Bibliographic Reference	Hylander, M A; Strobino, D M; Dhanireddy, R; Human milk feedings and infection among very low birth weight infants.; Pediatrics; 1998; vol. 102 (no. 3); e38

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Georgetown University Medical Center NICU Study dates January 1992 - September 1993 Duration of follow-up Until discharge Sources of funding Medela Incorporated, McHenry, IL
Inclusion criteria	All preterm infants weighing up to 1500 g at birth and hospitalized in the NICU from January 1992–September 1993

Exclusion criteria	Infants who died before the start of enteral feedings Infants whose medical records were not available from the medical records department
Sample characteristics	Sample size 212 Gestational age weeks (SD) Human milk: 28.2 (2.3) Formula: 27.8 (2.4) Mean birth weight (SD) Human milk: 1061 g (251) Formula: 988 g (242) % with late-onset infection Human milk: 19.5% Formula: 32.6%
Prognostic/diagnostic factors	Type of feeding Human milk vs formula
Reference Factor (s)	Late-onset sepsis Sepsis/meningitis: presence of clinical signs of sepsis and by positive cultures for pathogenic organisms in blood or spinal fluid.

Study arms

Human milk (N = 123) Babies who received milk from their own mothers with supplemental formula feedings when human milk was not available. Expressed human milk was provided fresh or frozen for future use at 220°C. Frozen milk was thawed for each use. Human milk was fortified with Human Milk Fortifier, Polycose, or MCT oil, as clinically indicated.
Formula (N = 89) Babies who were only fed formula milk.

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Retrospective study but outcome was taken from clinical records so diagnosis of different babies may have been made by different clinicians)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Outcome was adjusted by potential confounding factors, based on the results of regression models. No information about how the initial variables were selected to determine if they were confounding factors)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Retrospective study so outcome could vary between clinicians. No information about how variables were selected for analysis, or how it was decided which would be investigated as potential confounding factors.)*
	Directness	Directly applicable

Kim, 2018

Bibliographic Reference	Kim, J.K.; Chang, Y.S.; Sung, S.; Ahn, S.Y.; Park, W.S.; Trends in the incidence and associated factors of late-onset sepsis associated with improved survival in extremely preterm infants born at 23-26 weeks' gestation: A retrospective study; BMC Pediatrics; 2018; vol. 18 (no. 1); 172

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location

	Korea Study setting Study dates Duration of follow-up Sources of funding
Inclusion criteria	Admitted to neonatal unit
Exclusion criteria	None reported
Sample characteristics	Sample size 364 Female Not reported Gestational age weeks (SD) Late onset sepsis: 25.4 (0.5) weeks No late-onset sepsis: 25.5 (0.5 weeks)
Prognostic/diagnostic factors	Intubation duration Necrotising enterocolitis >= stage 2b
Reference Factor (s)	Late-onset sepsis Positive blood cultures in symptomatic patients after 72 h of life with concurrent use of antibiotics for more than 5 days, or those treated for a shorter period if the patient died.

Study arms

Preterm neonates (23-26 weeks) (N = 154)

Retrospective study examing the medical records of neonates with gestational ages between 23 and 26 weeks in a single centre were examined. The study period was long (11 years) and was split into 2 for the purpose of the analysis. Multivariate logistic regression was used to control for 'all variable's but specific variables that were controlled for are not reported. Only statistically significant results appear to be reported for the multivariate analysis, though this is not clear.

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Moderate risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Confounding factors that were adjusted for were not reported.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Inadequate description of statistical model, including how factors were selected for inclusion. Appears that only significant results were reported for the multivariate analysis.)*
Overall risk of bias and directness	Risk of Bias	High *(Proportion of participants excluded due to incomplete outcome data was not reported. Details of statistical model development not included and list of confounders adjusted for is unknown)*

Section	Question	Answer
	Directness	Directly applicable

Leal, 2012

Bibliographic Reference	Leal, Yelda A; Alvarez-Nemegyei, Jose; Velazquez, Juan R; Rosado-Quiab, Ulises; Diego-Rodriguez, Nidia; Paz-Baeza, Etna; Davila-Velazquez, Jorge; Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up.; BMC pregnancy and childbirth; 2012; vol. 12; 48

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Mexico Study setting Neonatology wards Study dates 2004-2007 Duration of follow-up 4.2 (±14.6) days per patient (range 1-142 days) Sources of funding None reported

Inclusion criteria	Newborns
Exclusion criteria	None reported
Sample characteristics	Sample size 11790 Female 49% % with late-onset infection 1%
Prognostic/diagnostic factors	Gestational age Birth weight Artificial ventilation Apgar score <5 Perinatal asphyxia Surgical procedure required Invasive medical procedure required
Reference Factor (s)	Late-onset sepsis The microbial isolation of any biological sample. Diagnosis after 72 hours from birth

Study arms

Risk factors for late-onset neonatal sepsis (N = 11790)

Risk factors included gender, gestational age, birth weight, height, prematurity, postmaturity, product of multiple pregnancy, Apgar score ≤5 and fetal distress. Associations with neonatal infection were examined using adjusted hazard ratios calculated from multivariable analysis (no information provided on multivariable analysis or model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about the multivariate model in the methods)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Only significant results from the model reported)*
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about the multivariate model and only significant results reported from the model)*
	Directness	Directly applicable

Makhoul, 2006

Bibliographic Reference	Makhoul, Imad R; Yacoub, Afeefi; Smolkin, Tatiana; Sujov, Polo; Kassis, Imad; Sprecher, Hannah; Values of C-reactive protein, procalcitonin, and Staphylococcus-specific PCR in neonatal late-onset sepsis.; Acta paediatrica (Oslo, Norway : 1992); 2006; vol. 95 (no. 10); 1218-23

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Israel Study setting neonatal intensive care unit at Meyer Children's Hospital, Rambam Medical Center Study dates Not reported Duration of follow-up Not reported Sources of funding A. & E. Blum Medical Research Fund
Inclusion criteria	Neonates who developed clinically suspected late-onset sepsis beyond 3 d of age
Exclusion criteria	None

Sample characteristics	Sample size 111 Age at onset of suspected infection (mean, SD) (range) 17.3 (18.7) (4-105)
Prognostic/diagnostic factors	Artificial ventilation
Reference Factor (s)	Late-onset sepsis Clinical features of sepsis along with positive blood culture obtained at the start of event

Study arms

Risk factors for late-onset sepsis (N = 111)

Risk factors included hypotension, mechanical ventilation, immature/total neutrophil ratio, C-Reactive protein levels and small for gestational age. Associations with neonatal infection were examined using adjusted risk ratios calcualted from multivariate analysis (states that controlled for other variables, but specific variables that are controlled for are not stated)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Only significant results from the model reported)*
Overall risk of bias and directness	Risk of Bias	High *(No information about multivariate model adjustment and only significant results from the model reported)*
	Directness	Directly applicable

Nayeri, 2018

Bibliographic Reference Nayeri, Unzila Ali; Buhimschi, Catalin S; Zhao, Guomao; Buhimschi, Irina A; Bhandari, Vineet; Components of the antepartum, intrapartum, and postpartum exposome impact on distinct short-term adverse neonatal outcomes of premature infants: A prospective cohort study.; PloS one; 2018; vol. 13 (no. 12); e0207298

Study Characteristics

Study design	Prospective cohort study

Study details	Study location USA Study setting YNHH Newborn Intensive Care Unit Study dates Not reported (60 months data collection) Duration of follow-up Until death or discharge Sources of funding National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development
Inclusion criteria	378 consecutive preterm singleton newborns born to mothers who delivered preterm between 23–34 weeks of gestation
Exclusion criteria	None reported
Sample characteristics	Sample size 378
Prognostic/diagnostic factors	Gestational age Intrauterine infection
Reference Factor (s)	Late-onset sepsis Positive blood cultures >72 h after birth

Study arms

Risk factors for late-onset sepsis (N = 378)

Risk factors included GA at birth, route of delivery, sex, steroids, exposure to magnesium for neuroprotection, and need for surfactant. Associations with neonatal infection examined using adjusted odds ratios calculated from multivariable logistic regression analysis (no information provided on model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about multivariate model adjustment)*

Section	Question	Answer
	Directness	Directly applicable

Padula, 2014

Bibliographic Reference Padula, Michael A; Dewan, Maya L; Shah, Samir S; Padula, Amy M; Srinivasan, Lakshmi; McGowan, Karin L; Mahoney, Kaitilin R; Harris, Mary C; Risk factors associated with laboratory-confirmed bloodstream infections in a tertiary neonatal intensive care unit.; The Pediatric infectious disease journal; 2014; vol. 33 (no. 10); 1027-32

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Study setting Single centre: tertiary neonatal unit Study dates Duration of follow-up Not reported but likely to be duration of admission. Sources of funding None
Inclusion criteria	Blood culture drawn for suspected bloodstream infection

	Admitted to neonatal unit >3 days of age
Exclusion criteria	None
Sample characteristics	Sample size Female Median birth weight 1980 (IQR 850-3025) Gestational age weeks (median, IQR) 34 (IQR 27-38)
Prognostic/diagnostic factors	Presence of a central venous catheter Apnea Hypotension Enteral contrast within 48 hours
Reference Factor (s)	Late-onset sepsis At least 1 positive blood culture. Note that inclusion criteria for study was neonates >3 days with suspected sepsis. Episodes within 7 days of a previous episode were excluded from the analysis.

Study arms

Neonates with suspected sepsis (N = 409)

Prospective study on 409 neonates admitted to a neonatal unit with suspected sepsis who had a blood culture. Data on clinical signs was recorded prospectively at the time of blood culture. A multivariate regression analysis was conducted with stepwise model selection. Only factors which were significant in a univariate analysis were considered for inclusion in the model, and only factors which were significant predictors were retained in the final model. The unit of analysis in the model was the number of blood stream infections - each participant could contribute more than one episode.

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(No indication on proportion of eligible neonates who were included in the study.)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Information was recorded prospectively.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No particular consideration of adjustment for known confounding factors.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Factors were included in the model based on signficant association in univariate model.)*

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Factors were included in the model based on signficant association in univariate model and there was no specific consideration of adjustment for known confounders. Only significant factors were retained in final multivariate model.)*
	Directness	Directly applicable

Sanderson, 2017

Bibliographic Reference	Sanderson, E; Yeo, K T; Wang, A Y; Callander, I; Bajuk, B; Bolisetty, S; Lui, K; NICUS, Network; Dwell time and risk of central-line-associated bloodstream infection in neonates.; The Journal of hospital infection; 2017; vol. 97 (no. 3); 267-274

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Australia Study setting 10 NICUs Study dates January 2007 - December 2009

	Duration of follow-up Not reported Sources of funding None reported
Inclusion criteria	Babies who had an umbilical venous catheter or central venous catheter inserted
Exclusion criteria	None reported
Sample characteristics	Sample size 3985 Median age of catheter insertion (25%, 75%) UVC: 0.13 days (0.0, 0.5), PICC: 4.15 days (2.1, 8.3)
Prognostic/diagnostic factors	Gestational age History of surgery Presence of a catheter UVC vs PICC Congenital abnormality Age of catheter insertion
Reference Factor (s)	Central line-associated bloodstream infection Infection after 48 hours from birth, with a positive blood culture, clinical symptoms, and signs of sepsis and clinician decision to treat with antibiotics for >5 days

Study arms

Neonates with a central line (UVC or PICC) (N = 3985)

Risk factors included catheter type, gestational age, congenital abnormalities, major surgery and age of catheter insertion. Association with sepsis examined using adjusted hazard ratios calculated from multivariate Cox regression analysis (no information provided about model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate (*No information about model adjustment)*
	Directness	Partially applicable *(Age range for infection >48 hours.)*

Smith, 2008

Bibliographic Reference	Smith, P Brian; Benjamin, Daniel K Jr; Cotten, C Michael; Schultz, Eric; Guo, Rose; Nowell, Lisa; Smithwick, Mary Laura; Thornburg, Courtney D; Is an increased dwell time of a peripherally inserted catheter associated with an increased risk of bloodstream infection in infants?.; Infection control and hospital epidemiology; 2008; vol. 29 (no. 8); 749-53

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Duke University Medical Center NICU Study dates August 2002 - November 2005 Duration of follow-up Not reported Sources of funding NIH T32, HD044799-01 and the Thrasher Research Fund
Inclusion criteria	Babies who had a PICC inserted
Exclusion criteria	None reported

Sample characteristics	Sample size 882 Female 41% Gestational age weeks (SD) 31 weeks (5.1) Mean birth weight (SD) 1749 g (1033) % with late-onset infection 8.8% Median age of catheter insertion (25%, 75%) 8 days (mean: 12.2 days) Age at onset of suspected infection (median) 17 days
Prognostic/diagnostic factors	Presence of a central venous catheter Compared with peripheral cannula Age of catheter insertion Duration of catheter insertion
Reference Factor (s)	Catheter associated bloodstream infection First positive blood culture noted in the period of time from 24 hours after catheter insertion until 72 hours after removal

Study arms

Catheter associated-bloodstream infection (N = 882)

Risk factors included adjusted gestational age, gestational age at birth, peripheral vs central PICC, duration of catheter insertion and adjusted gestational age at insertion. Association with neonatal infection examined using adjusted odds ratios calculated from multivariate analysis (no information provided for model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Only significant results from the model reported)*
Overall risk of bias and directness	Risk of Bias	High *(Multivariate model and only significant results from the model reported)*
	Directness	Directly applicable

Stoll, 1996

Bibliographic Reference	Stoll, B J; Gordon, T; Korones, S B; Shankaran, S; Tyson, J E; Bauer, C R; Fanaroff, A A; Lemons, J A; Donovan, E F; Oh, W; Stevenson, D K; Ehrenkranz, R A; Papile, L A; Verter, J; Wright, L L; Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network.; The Journal of pediatrics; 1996; vol. 129 (no. 1); 63-71

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Study setting Multicentre study: tertiary neonatal units Study dates 1991-1993 Duration of follow-up Not reported but likely to be duration of stay on neonatal unit. Sources of funding Not reported
Inclusion criteria	Birth weight 401-1500 g Admitted to neonatal unit
Exclusion criteria	Neonates who died or were discharged within 72 hours from birth

Sample characteristics	Sample size 6911 Female Not reported Gestational age weeks (SD) Not reported Mean birth weight (SD) Not reported. Birth weight of 401-1500g was inclusion criteria for study
Prognostic/diagnostic factors	Respiratory distress syndrome Duration of mechanical ventilation Intubation Bronchopulmonary dysplasia Steroids for brochopulmonary dysplasia Patent ductus arteriosus Intraventricular haemorrhage (grade 3-4) Proven Necrotising enterocolitis Bell stage HA or greater
Reference Factor (s)	Late-onset sepsis Positive results on one or more blood cultures obtained after 72 hours of life, in the presence of clinical signs or symptoms suggestive of infection

Study arms

Very-low birthweight neonates (N = 6911)

Retrospective study using data recorded in a registry on all neonates who were admitted to participating neonatal units and met the inclusion criteria. Multivaraite logistic regression was used to examine the relation between risk factors and late-onset infection. The model was adjusted for the following confounding factors: Gestational age, centre differences.

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(No description of number of eligible participants who were not included (e.g. due to missing data).)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Attrition not likely to be an issue in this population.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(Adjustment for confounding factors is described.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Insufficient details on how model was developed and factos to be included were selected.)*

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Insufficient details on how model was developed. Factors were only included in the multivariate analysis if significant predictor in a univariate analysis. Only significant results were reported.)*
	Directness	Directly applicable

Troger, 2014

Bibliographic Reference Troger, Birte; Gopel, Wolfgang; Faust, Kirstin; Muller, Thilo; Jorch, Gerhard; Felderhoff-Muser, Ursula; Gortner, Ludwig; Heitmann, Friedhelm; Hoehn, Thomas; Kribs, Angela; Laux, Reinhard; Roll, Claudia; Emeis, Michael; Mogel, Michael; Siegel, Jens; Vochem, Matthias; von der Wense, Axel; Wieg, Christian; Herting, Egbert; Hartel, Christoph; German Neonatal, Network; Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network.; The Pediatric infectious disease journal; 2014; vol. 33 (no. 3); 238-43

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Germany Study setting 46 NICUs Study dates 2003-2011

	Duration of follow-up Not reported Sources of funding None reported
Inclusion criteria	Birth weight <1500 g Gestational age ≤36+6 weeks
Exclusion criteria	Infants with lethal abnormalities Infants with early-onset sepsis (<72 hours of age)
Sample characteristics	Sample size 5886 Female Birth weight 10th percentile: 48% Gestational age weeks (SD) Birth weight 10th percentile: 28.2 (2.6) Caesarean delivery (%) Birth weight 10th percentile: 81% Mean birth weight (SD) Birth weight 10th percentile: 1073g (266) Multiple births (%) Birth weight 10th percentile: 34%
Prognostic/diagnostic factors	Gestational age Duration of total parental nutrition

	Small for gestational age Treatment with antinatal steriods German descendence
Reference Factor (s)	Late-onset sepsis Blood-culture–confirmed clinical sepsis (2 clinical signs, according to NEO-KISS criteria and microbiologically confirmed bloodstream infection)15,16 occurring ≥ 72 hours of age

Study arms

Late-onset sepsis (N = 5886)

Risk factors included gestational age, treatment with antenatal steroids, German descendance, treatment with prophylactic glycopeptide antibiotics, duration of parenteral nutrition and small for gestational age. Associations with neonatal infection were examined using adjusted odds ratios calculated from multivariate logistic regression analysis with stepwise conditional exclusion of nonsignificant parameters (no information provided for model adjustment)

Risk of bias

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No information about multivariate model adjustment)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	High *(No information about multivariate model adjustment and only significant results reported)*
	Directness	Directly applicable

Yapicioglu, 2011

Bibliographic Reference	Yapicioglu, H.; Ozcan, K.; Sertdemir, Y.; Mutlu, B.; Satar, M.; Narli, N.; Tasova, Y.; Healthcare-associated infections in a Neonatal Intensive Care Unit in Turkey in 2008: Incidence and risk factors, a prospective study; Journal of Tropical Pediatrics; 2011; vol. 57 (no. 3); 157-164

Study Characteristics

Study design	Prospective cohort study

Study details	Study location Study setting Study dates Duration of follow-up Sources of funding Not reported
Inclusion criteria	All babies admitted to the NICU
Exclusion criteria	Neonates who died or were discharged within 72 hours from birth
Sample characteristics	Sample size 413 Female 41.3% Gestational age weeks (SD) 35.1 weeks (3.84) Mean birth weight (SD) 2470 g (905) % with late-onset infection 16%
Prognostic/diagnostic factors	Duration of mechanical ventilation Hood oxygen use

	Total parenteral nutrition
Reference Factor (s)	Late-onset sepsis

Study arms

Neonates admitted to neonatal unit (N = 413)

Prospective single centre study. All neonates who were admitted to a tertiary neonatal unit during the study period who met the inclusion criteria were included. Multivariate logistic regression was used to assess risk factors. Inclusion of factors was based on significance in univariate analysis. Only statistically significant results are reported. There are no details on additional adjustment for confounding factors such as gestational age.

Risk of bias

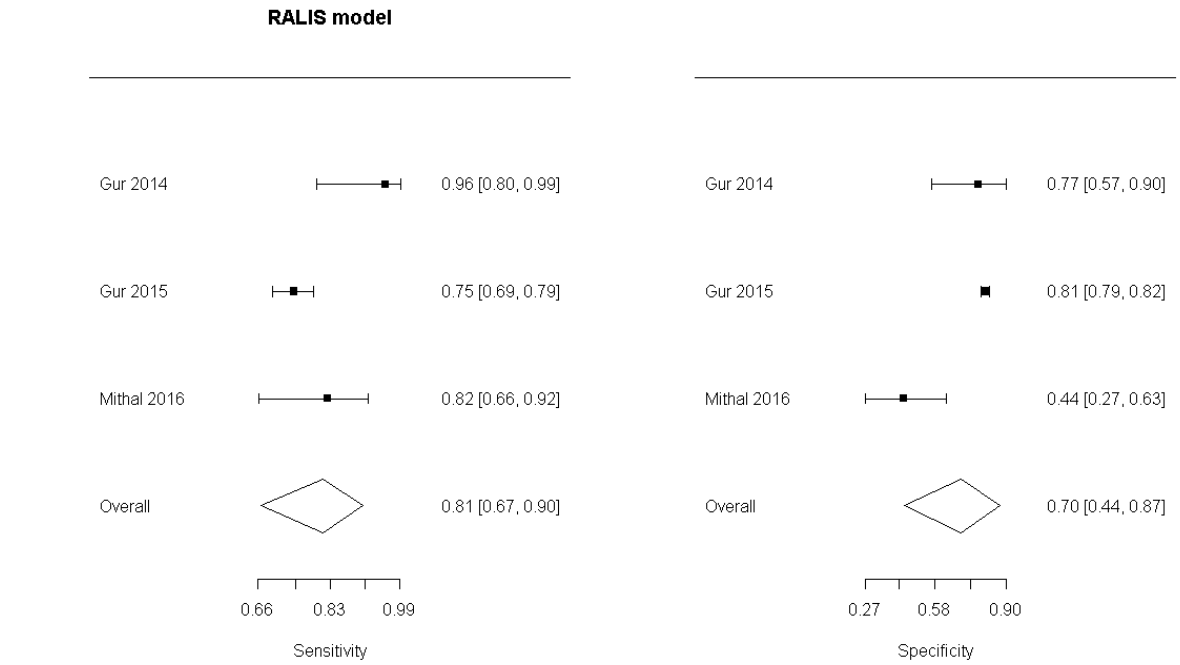
Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(No details of adjustment for confounding factors such as gestational age.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Insufficient details of model design. Inclusion in the multivariate model was based on significance of univariate results. Only significant results are reported.)*
Overall risk of bias and directness	Risk of Bias	High *(Insufficient details of model design. Inclusion in the multivariate model was based on significance of univariate results. Only significant results are reported. No details of adjustment for confounding factors such as gestational age.)*
	Directness	Partially applicable *(Definition of blood stream infection was 'positive blood culture with no significant focus'. The absence of significant focus was not a criterion specified in the review protocol.)*

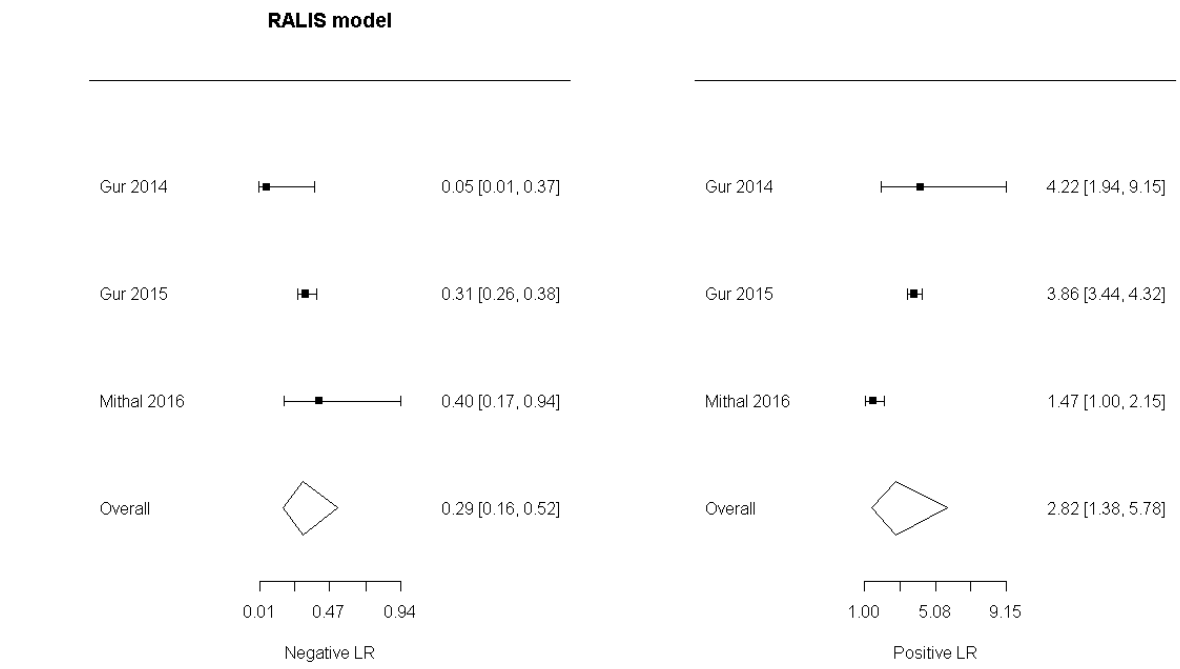
Appendix E – Forest plots and ROC curves

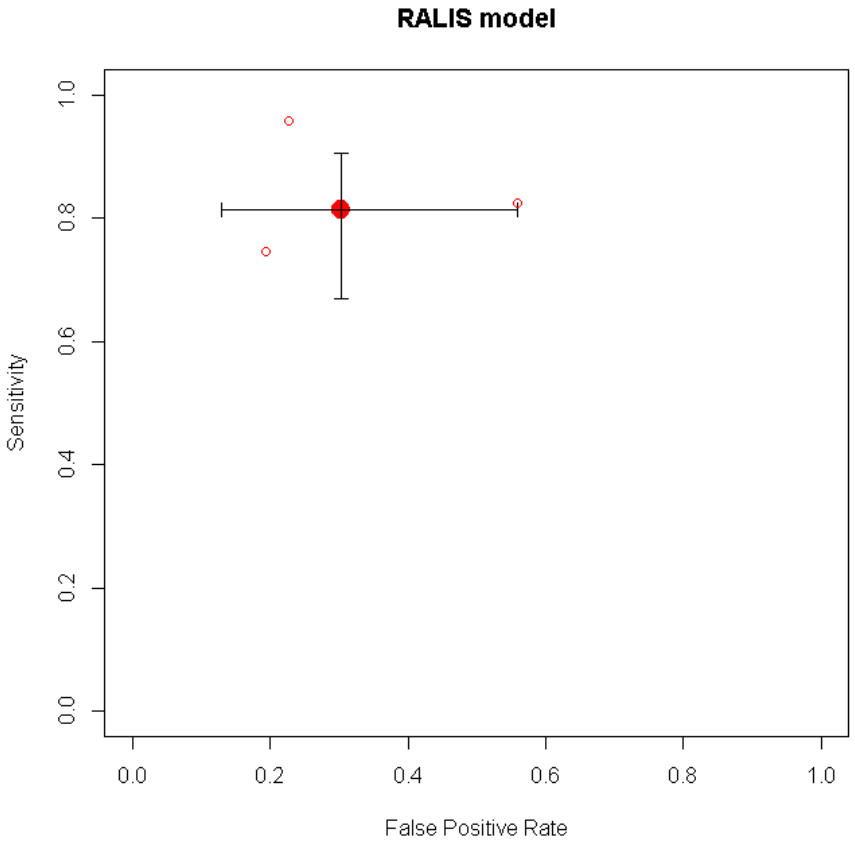
RALIS model

Sensitivity and specificity



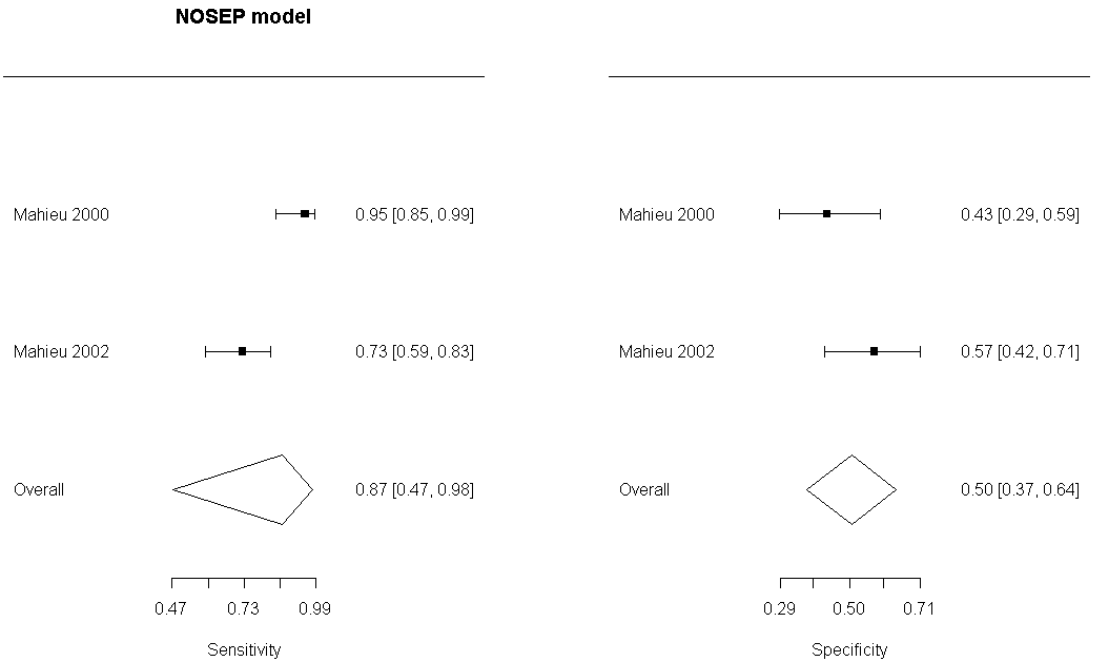
Likelihood ratios


RALIS model
Gur 2014
0.05 [0.01, 0.37]
Gur 2015
0.31 [0.26, 0.38]
Mithal 2016
0.40 [0.17, 0.94]
Overall
0.29 [0.16, 0.52]
0.01
0.47
0.94
Negative LR
Gur 2014
4.22 [1.94, 9.15]
Gur 2015
3.86 [3.44, 4.32]
Mithal 2016
1.47 [1.00, 2.15]
Overall
2.82 [1.38, 5.78]
1.00
5.08
9.15
Positive LR

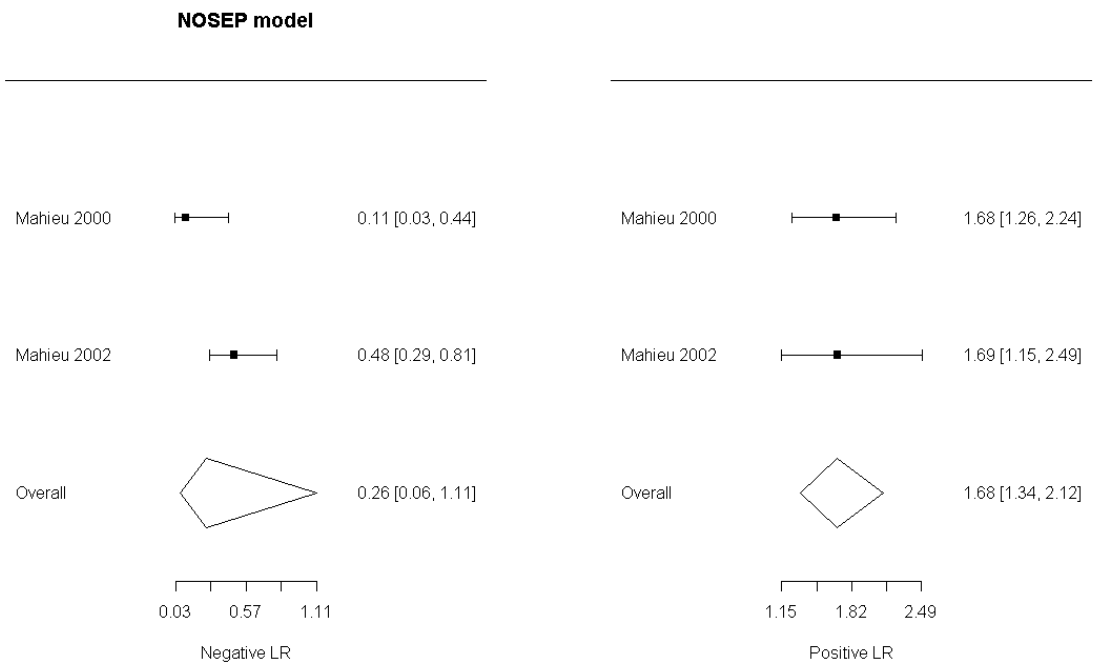

RALIS model
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate

NOSEP model

Sensitivity and specificity

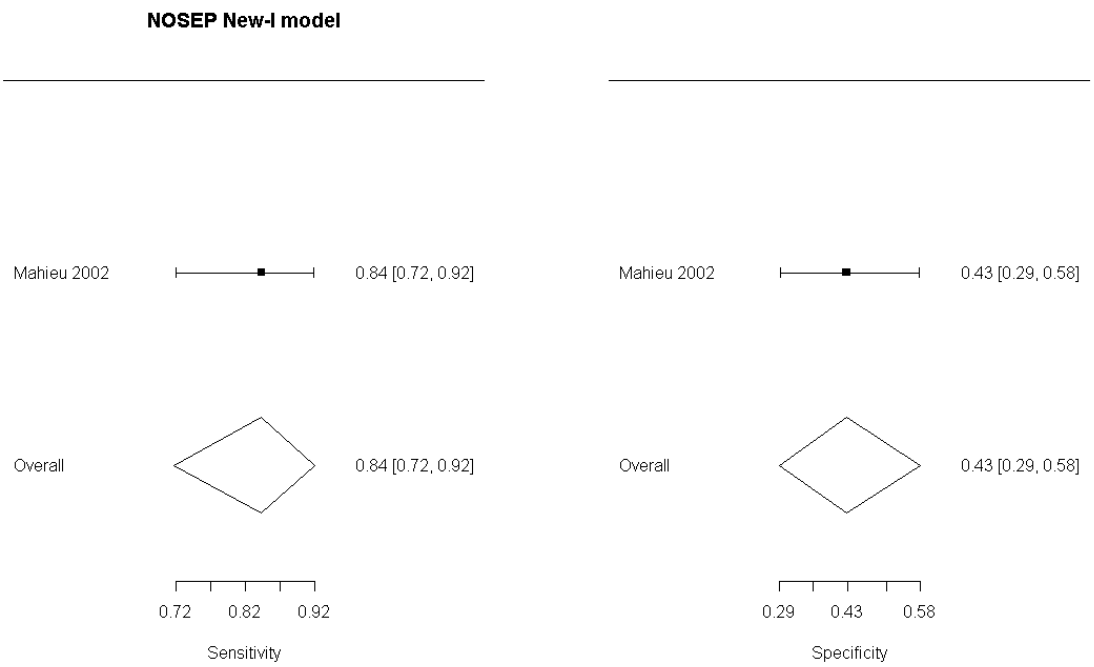


Likelihood ratios

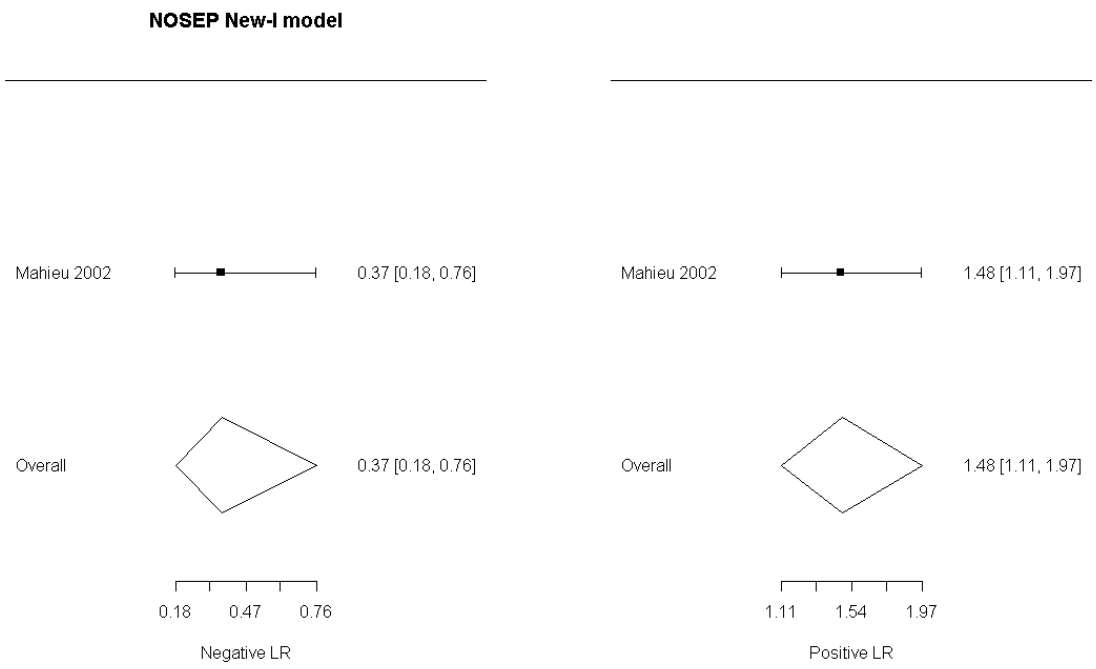


NOSEP-New-I model

Sensitivity and specificity

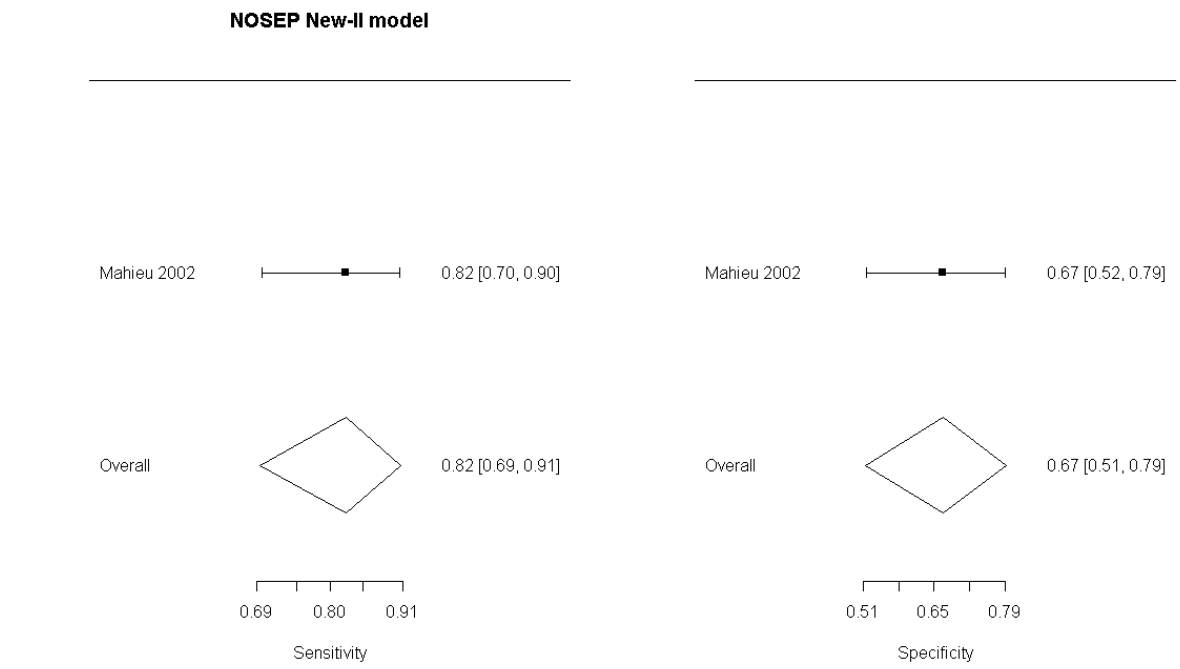


Likelihood ratios

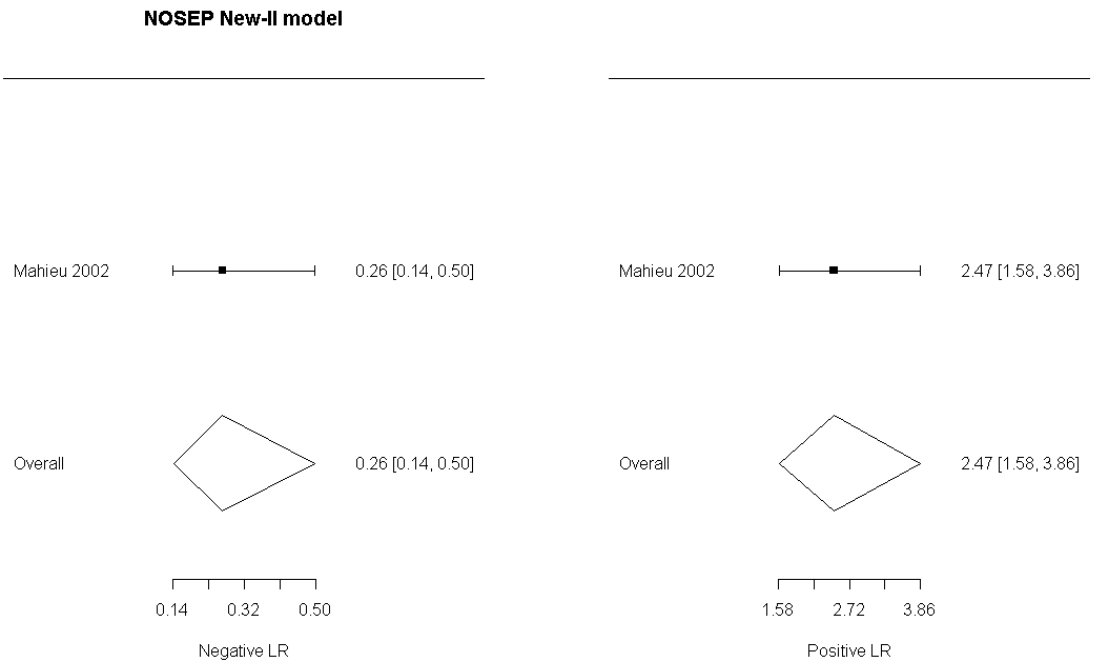


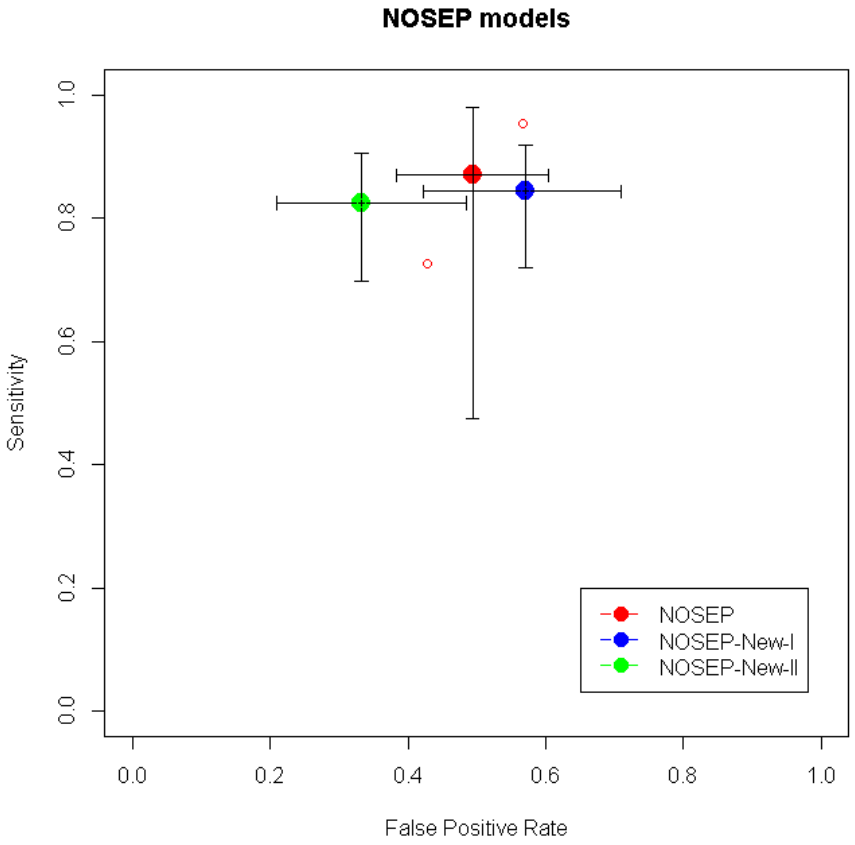
NOSEP-New-II model

Sensitivity and specificity



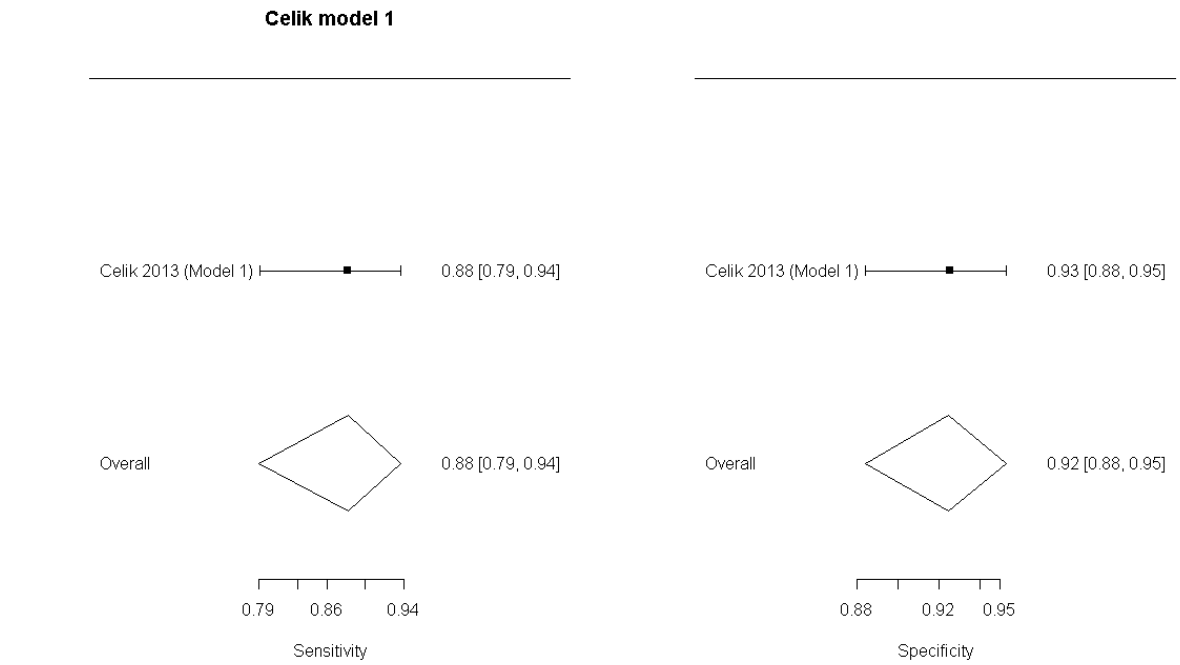
Likelihood ratios


NOSEP New-II model
Mahieu 2002
0.26 [0.14, 0.50]
Overall
0.26 [0.14, 0.50]
0.14
0.32
0.50
Negative LR
Mahieu 2002
2.47 [1.58, 3.86]
Overall
2.47 [1.58, 3.86]
1.58
2.72
3.86
Positive LR

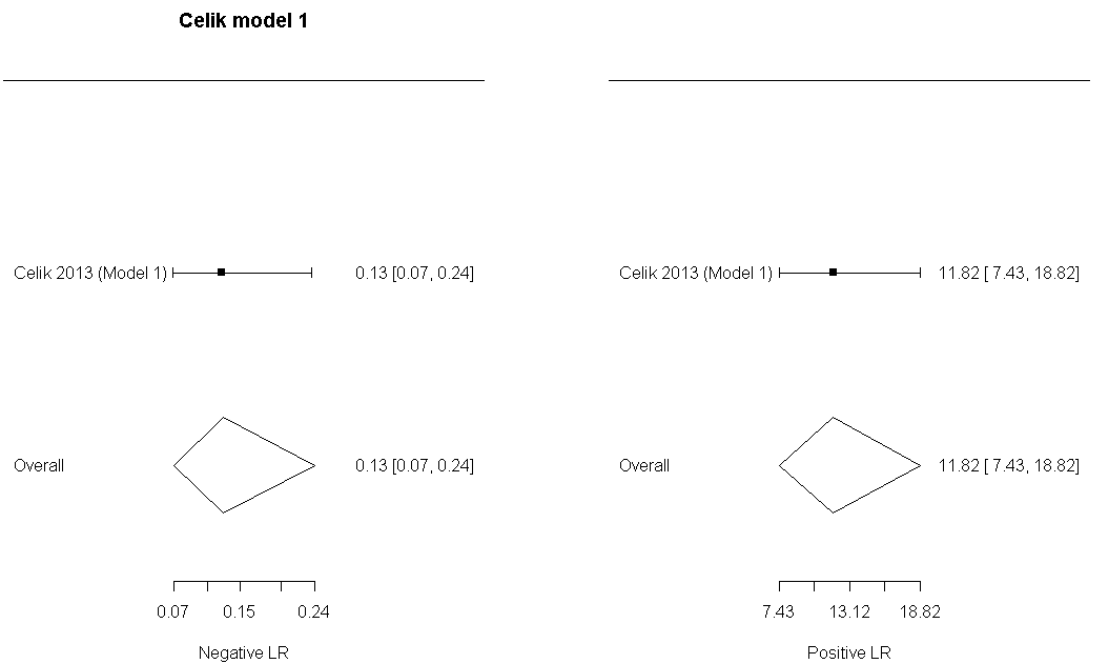

NOSEP models
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
NOSEP
NOSEP-New-I
NOSEP-New-II

Celik 2013 (Model 1)

Sensitivity and specificity

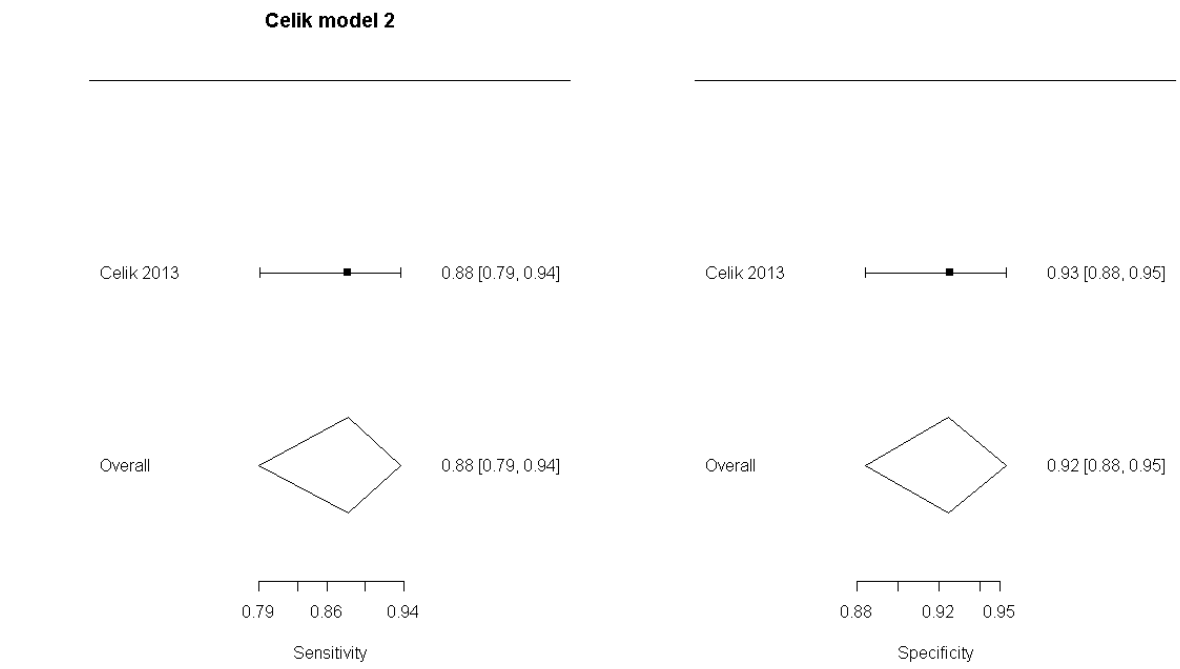


Likelihood ratios

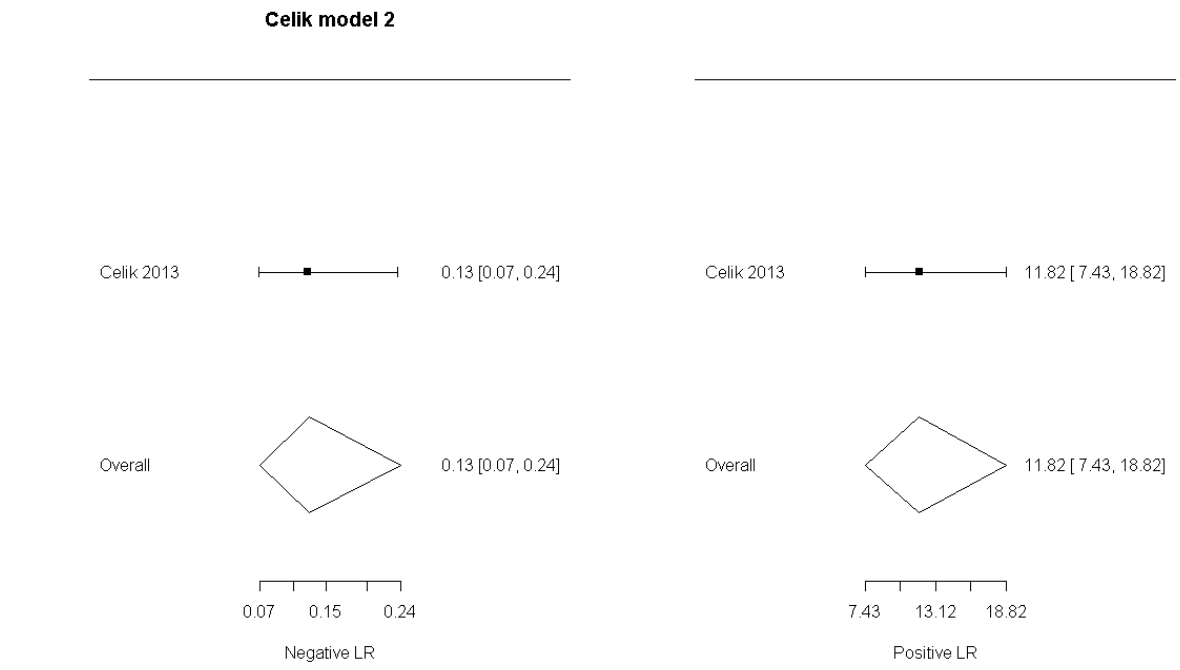


Celik 2013 (Model 2)

Sensitivity and specificity

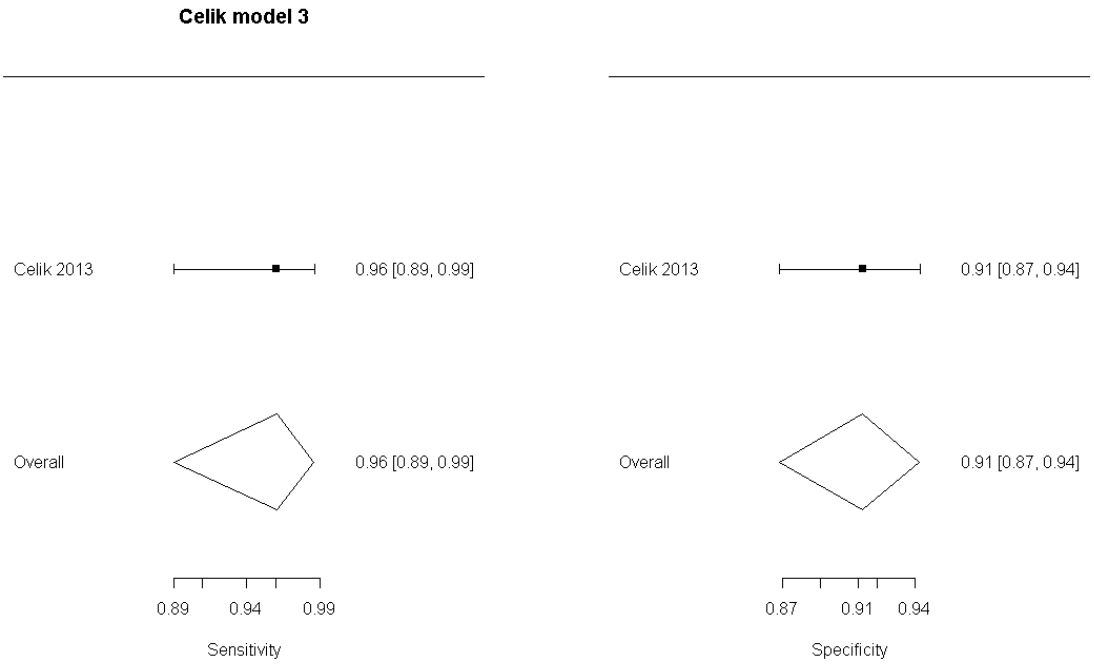


Likelihood ratios

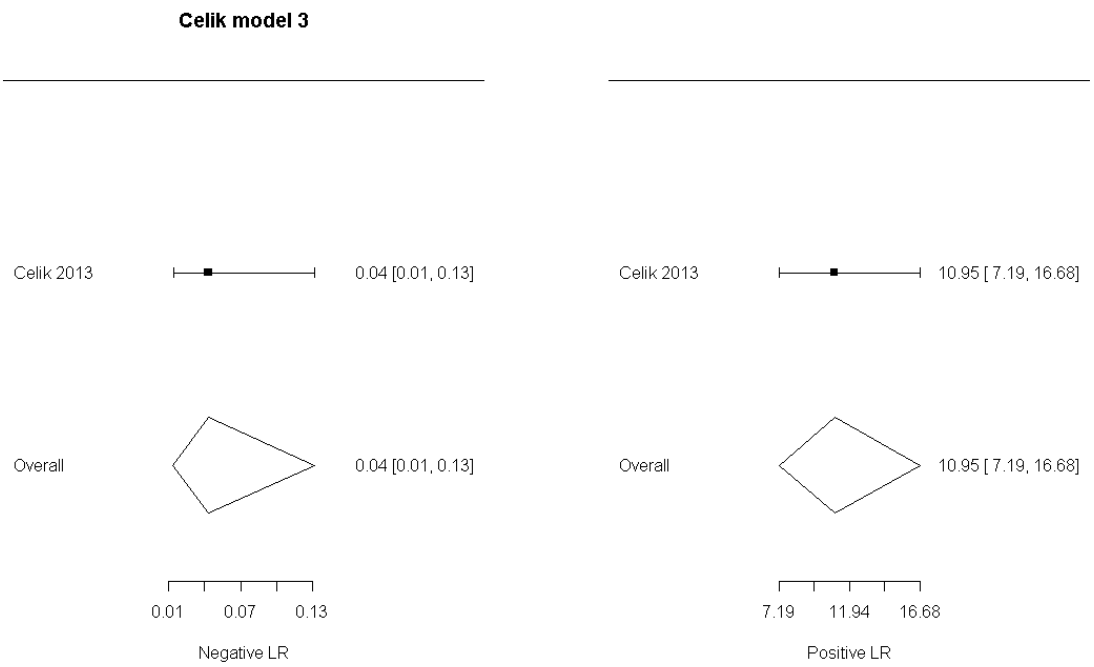


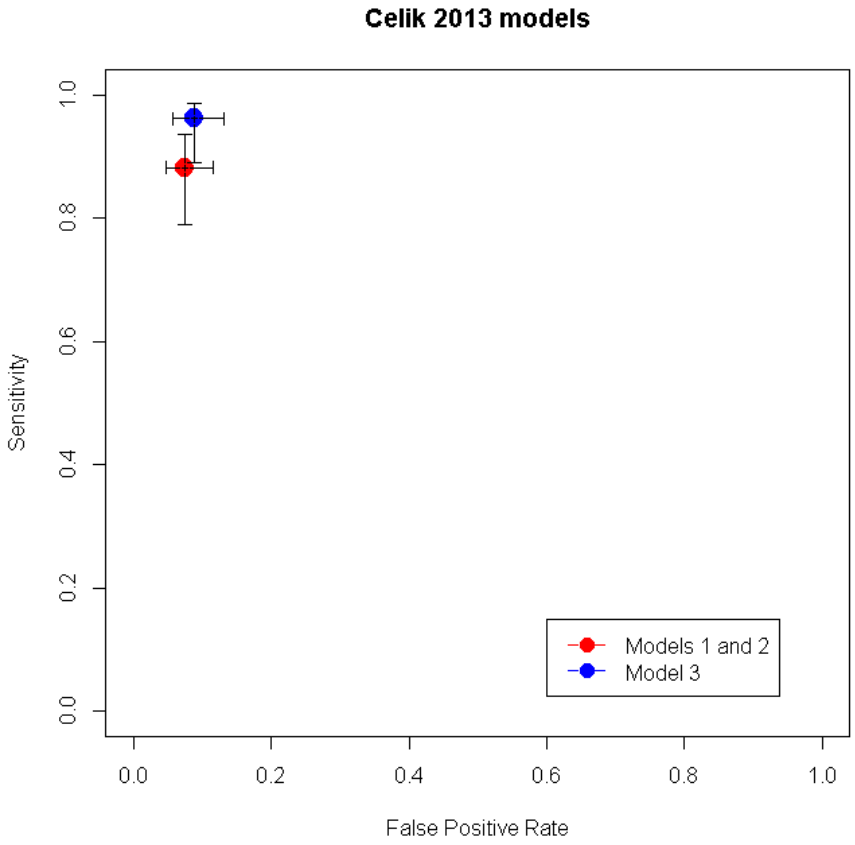
Celik 2013 (Model 3)

Sensitivity and specificity



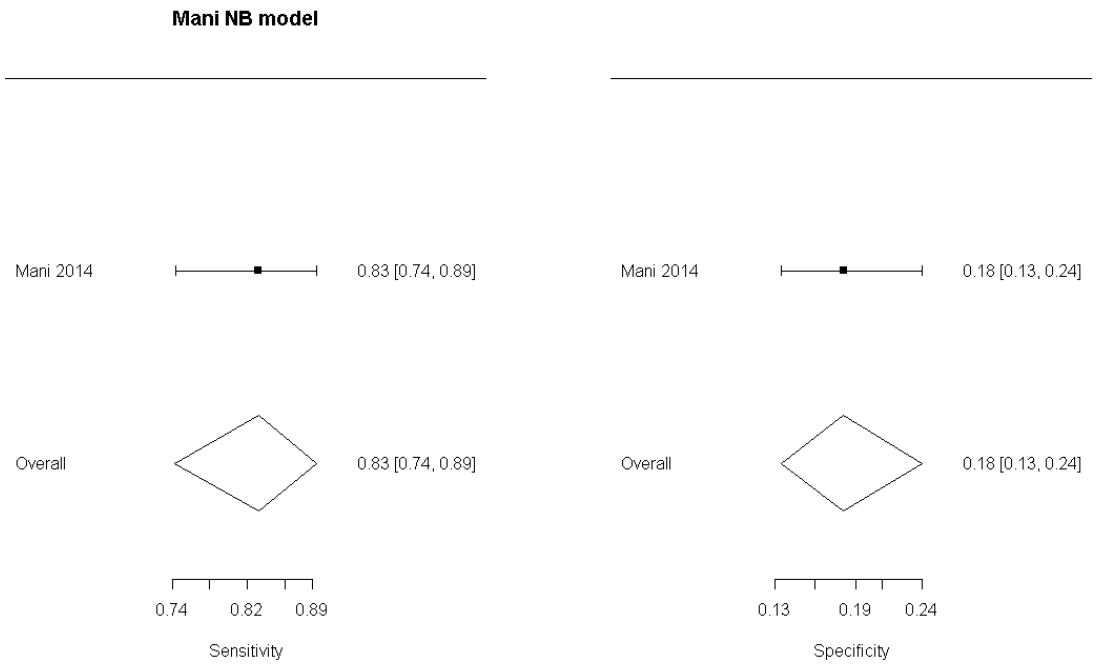
Likelihood ratios


Celik model 3
Celik 2013
0.04 [0.01, 0.13]
Overall
0.04 [0.01, 0.13]
0.01
0.07
0.13
Negative LR
Celik 2013
10.95 [7.19, 16.68]
Overall
10.95 [7.19, 16.68]
7.19
11.94
16.68
Positive LR

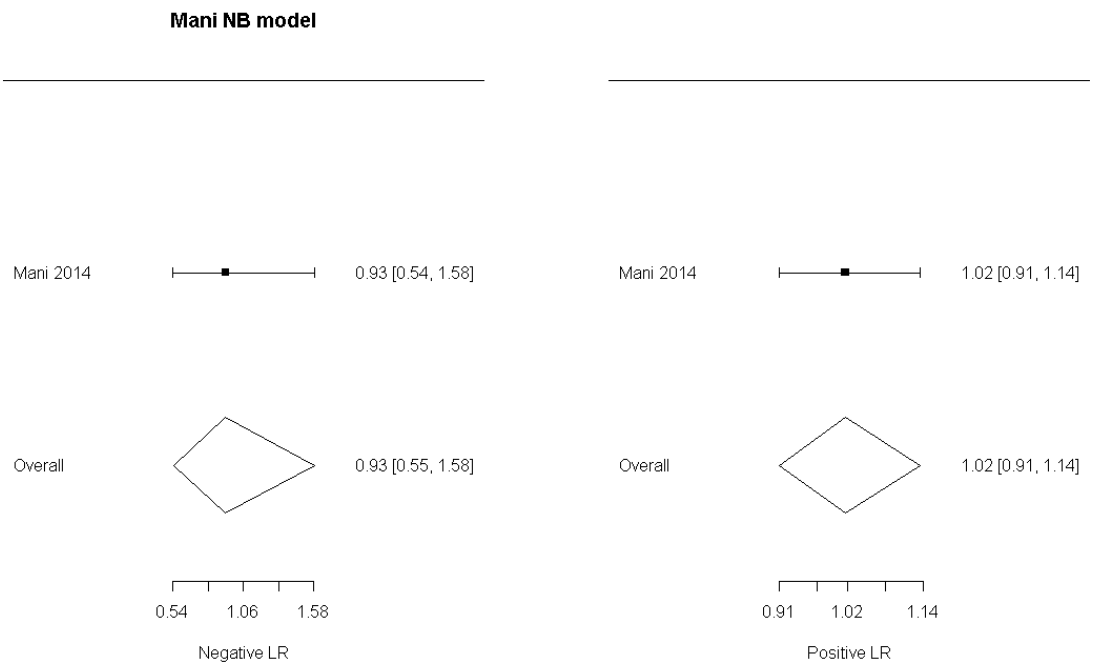

Celik 2013 models
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
Models 1 and 2
Model 3

Mani 2014 (NB model)

Sensitivity and specificity

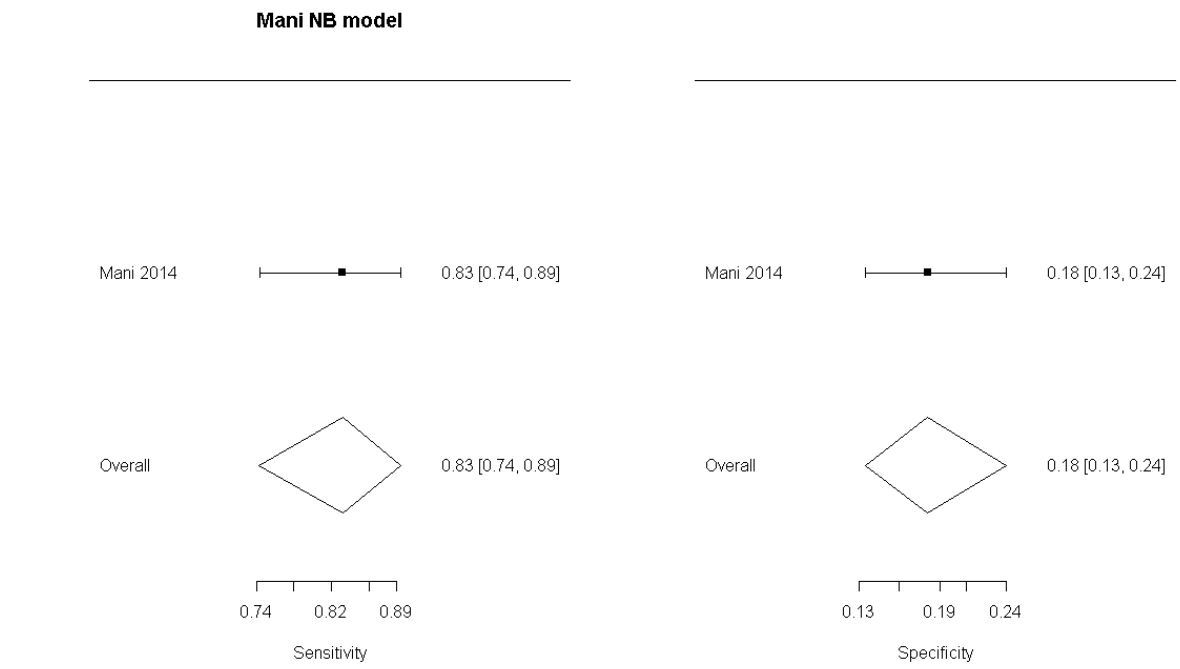


Likelihood ratios

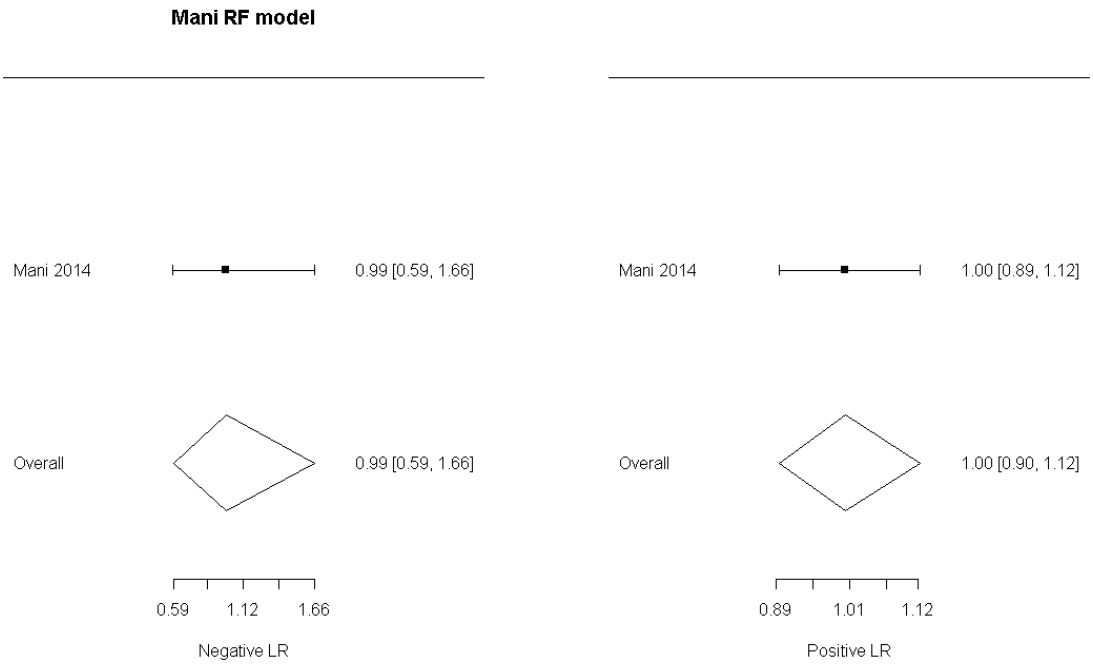


Mani 2014 (RF model)

Sensitivity and specificity

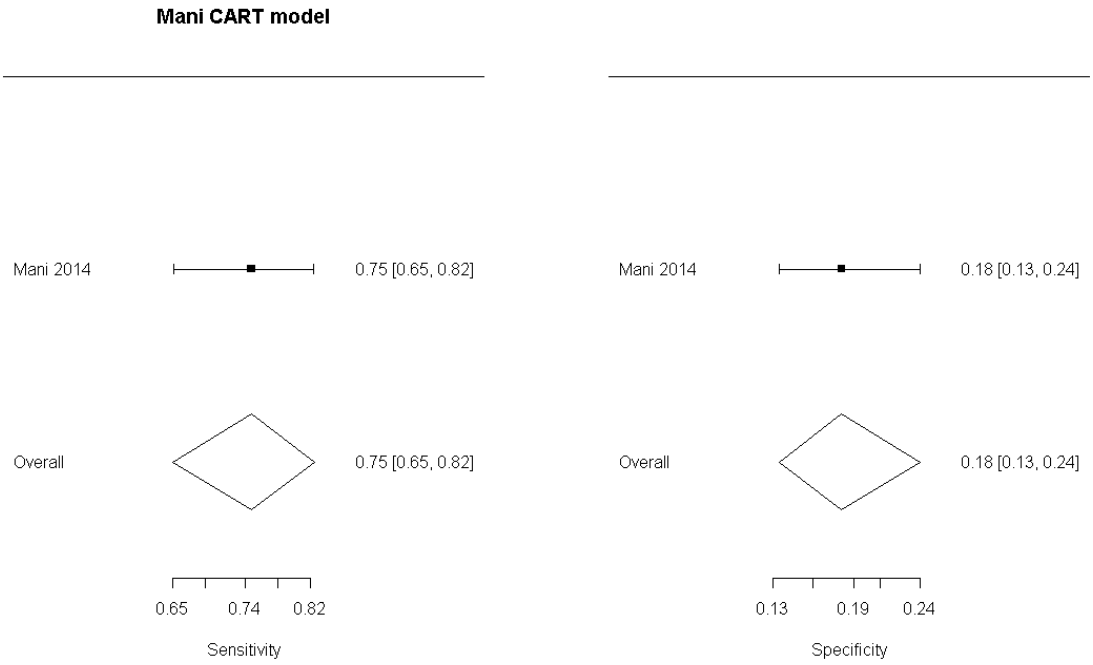


Likelihood ratios

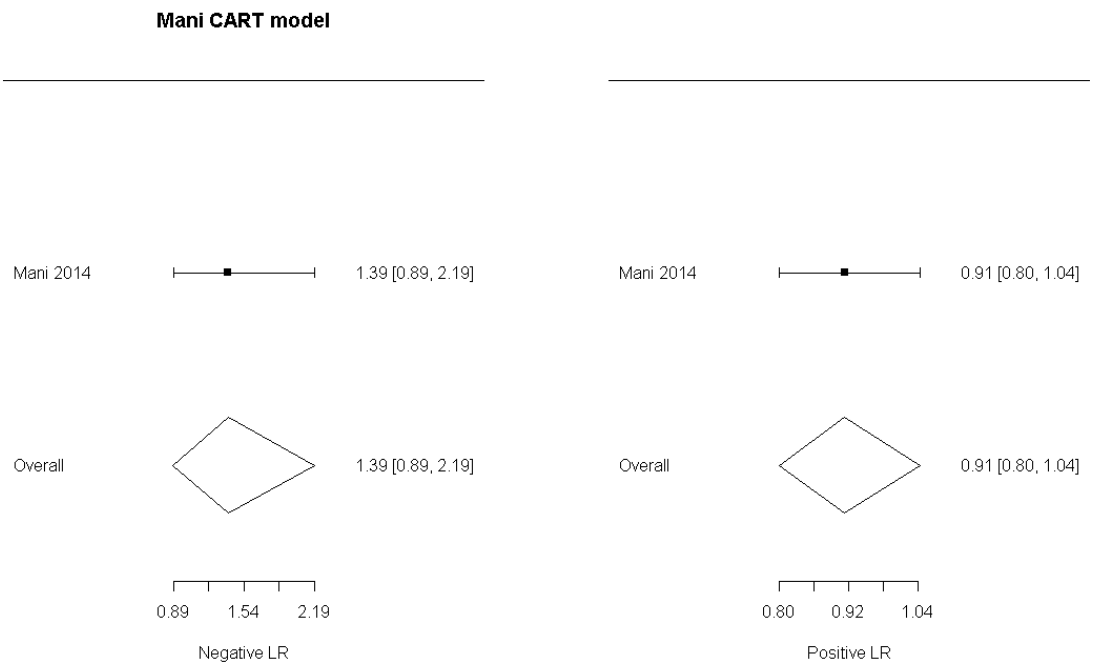


Mani 2014 (CART model)

Sensitivity and specificity

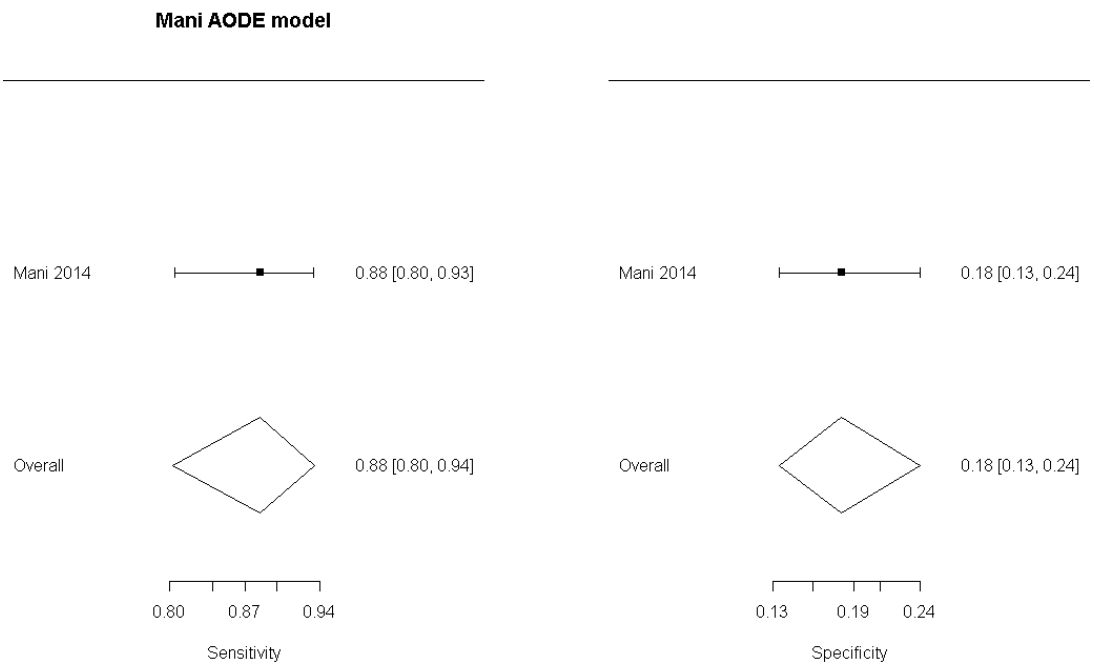


Likelihood ratios

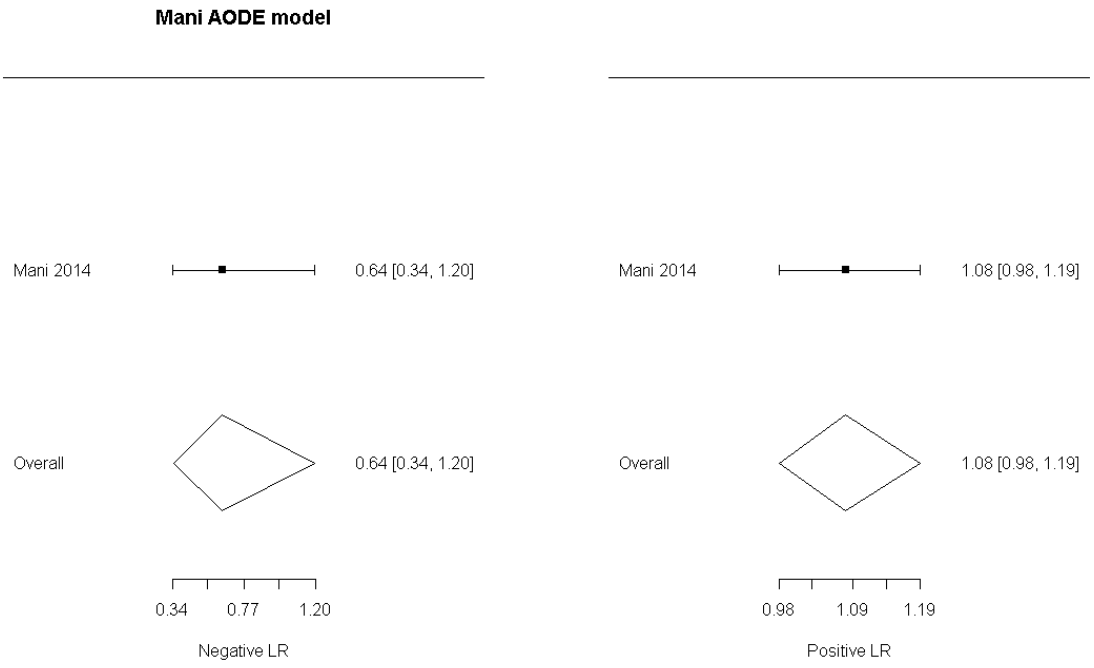


Mani 2014 (AODE model)

Sensitivity and specificity

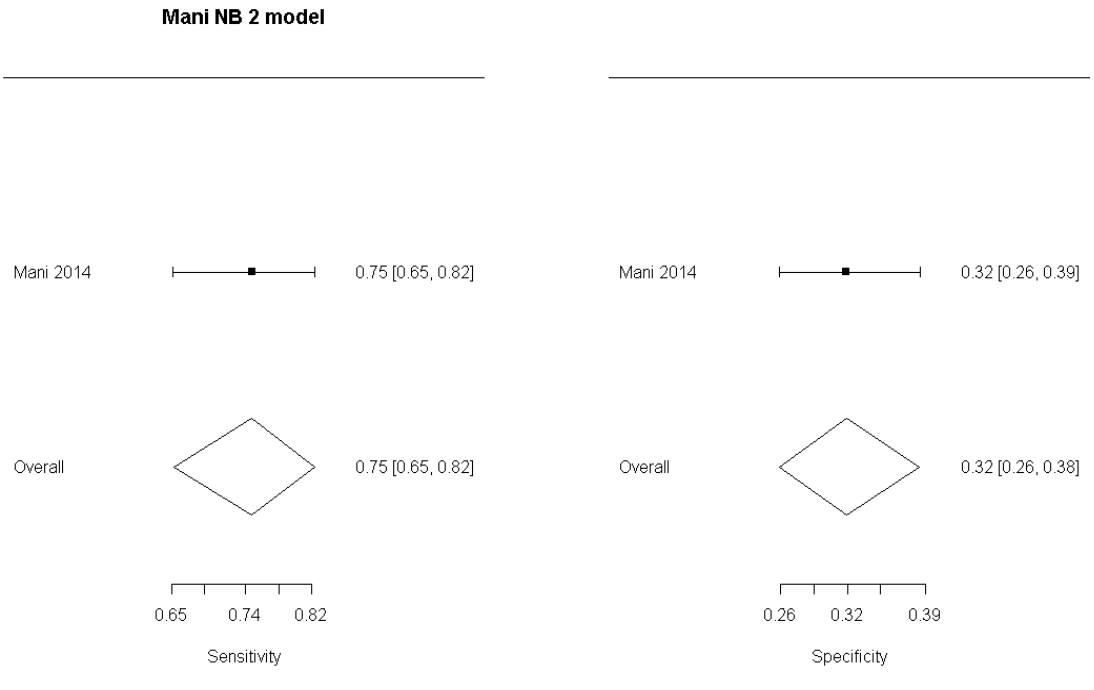


Likelihood ratios

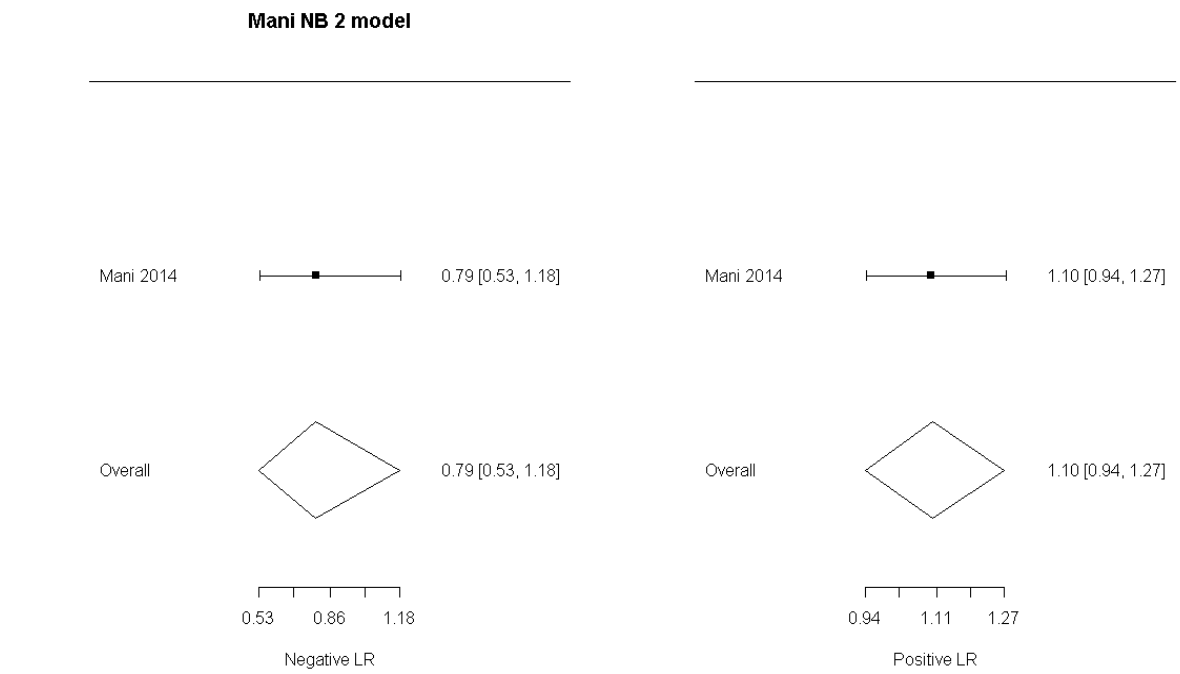


Mani 2014 (NB model 2)

Sensitivity and specificity

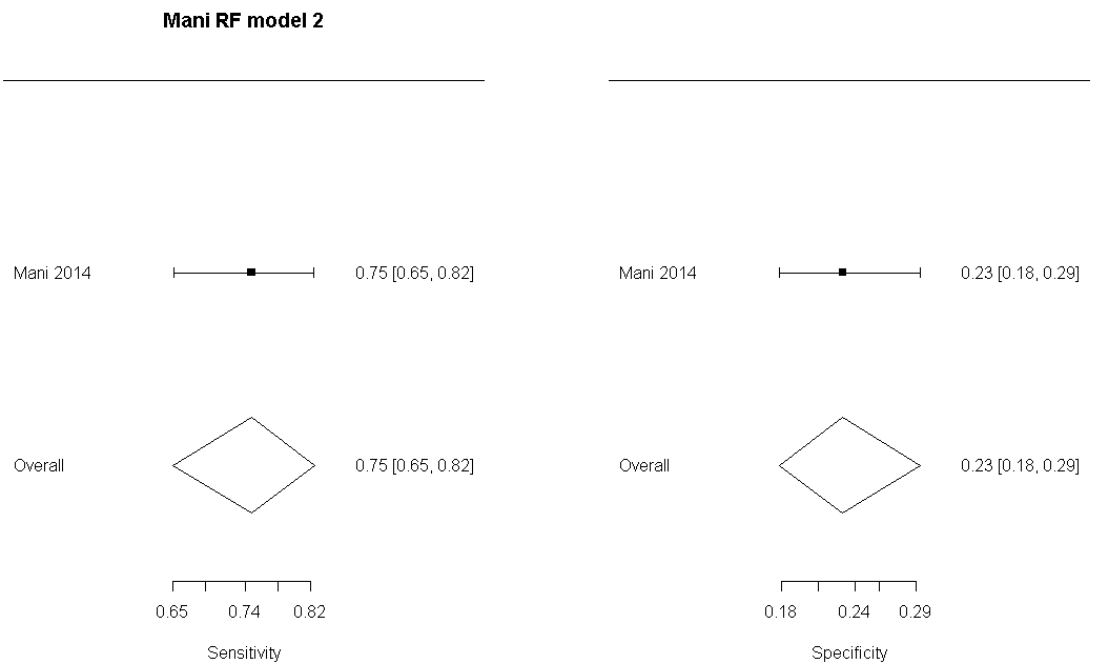


Likelihood ratios

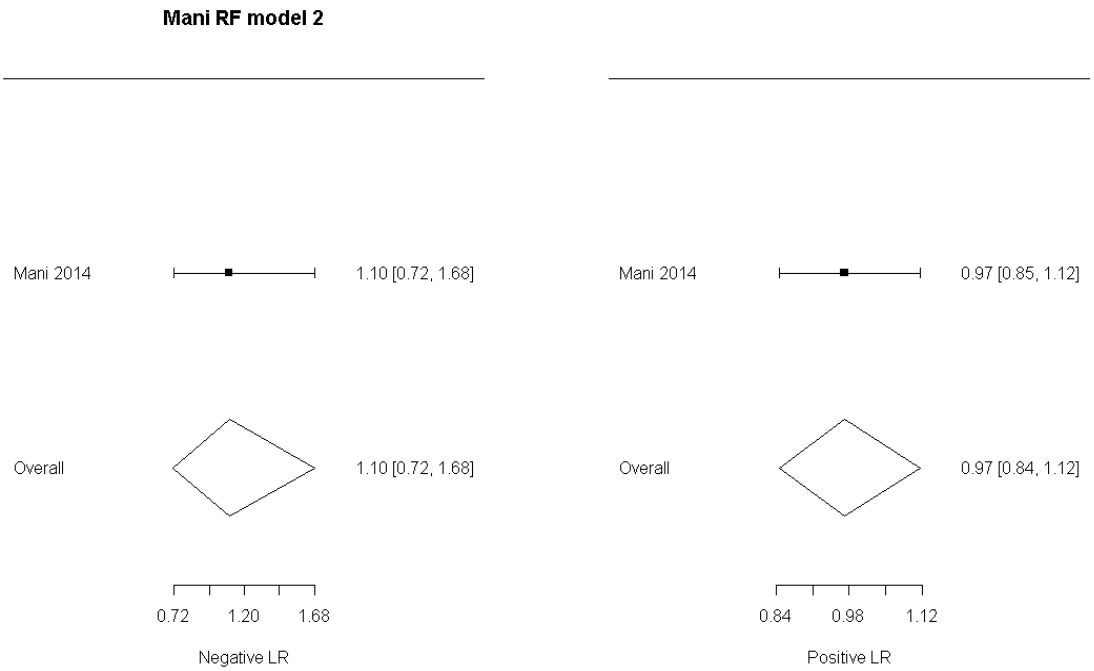


Mani 2014 (RF model 2)

Sensitivity and specificity

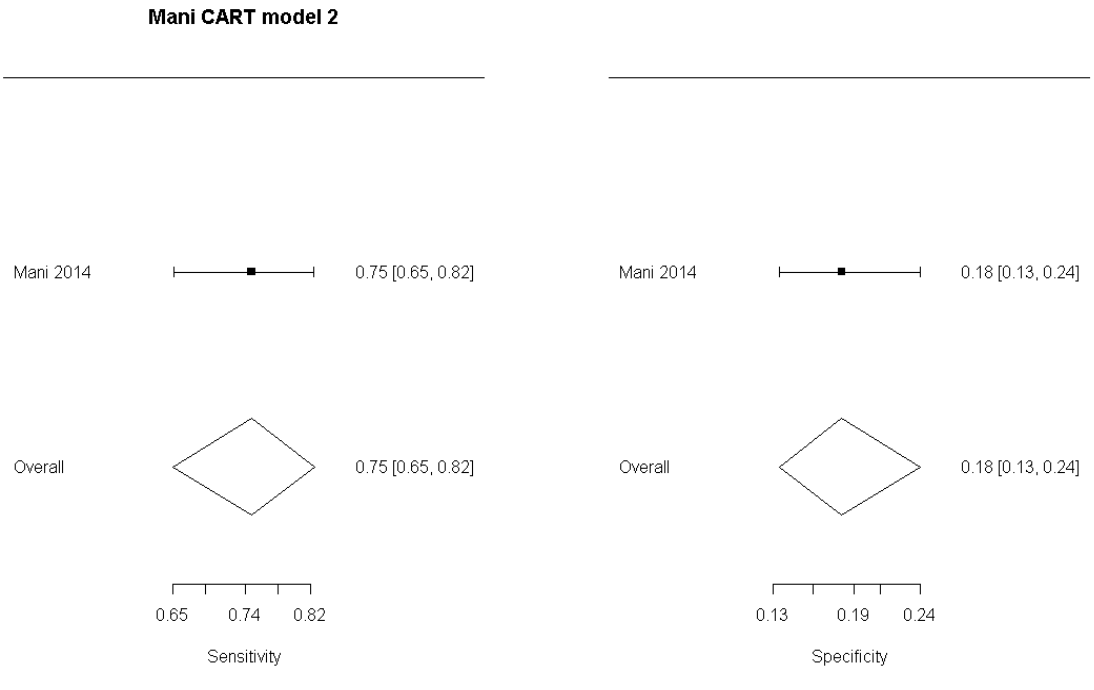


Likelihood ratios

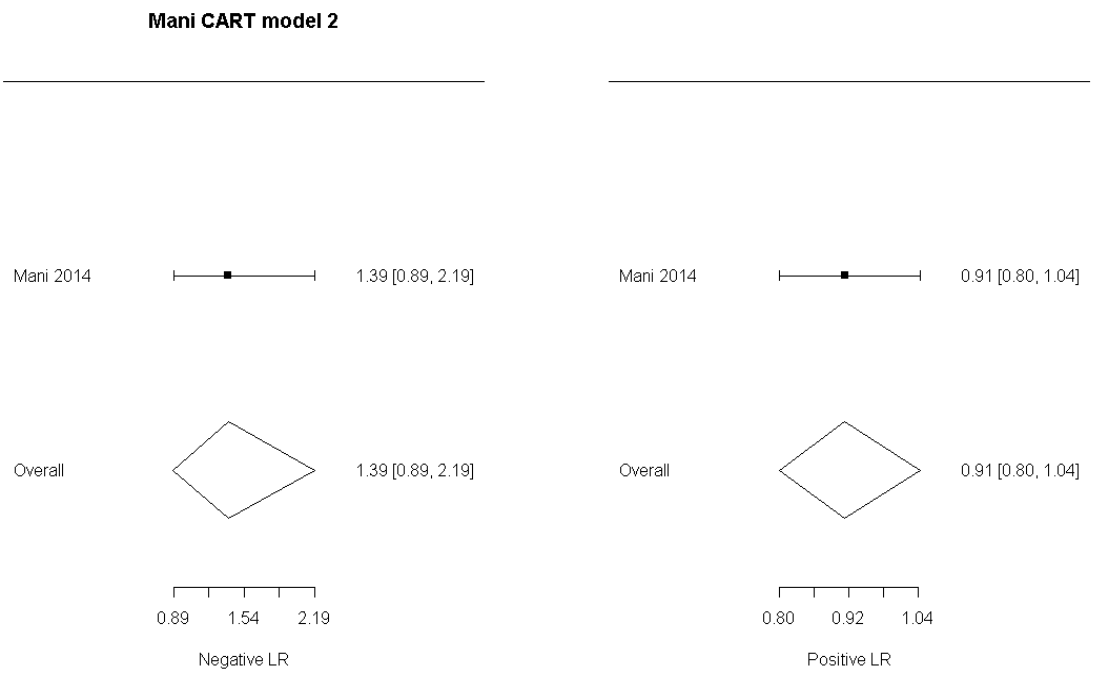


Mani 2014 (CART model 2)

Sensitivity and specificity

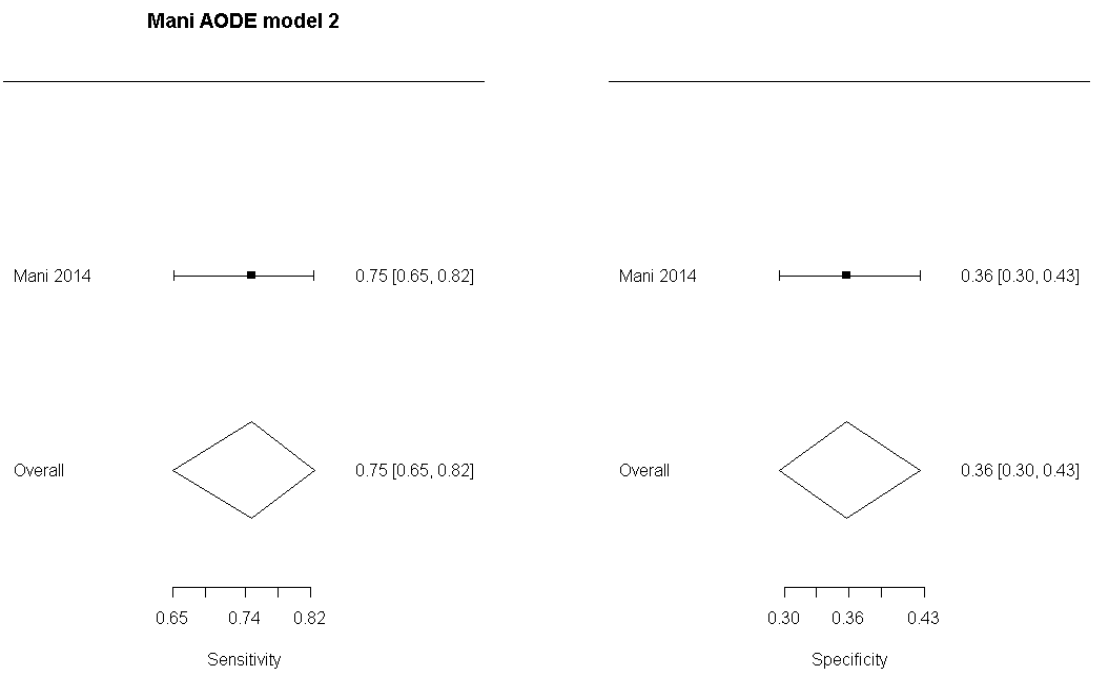


Likelihood ratios

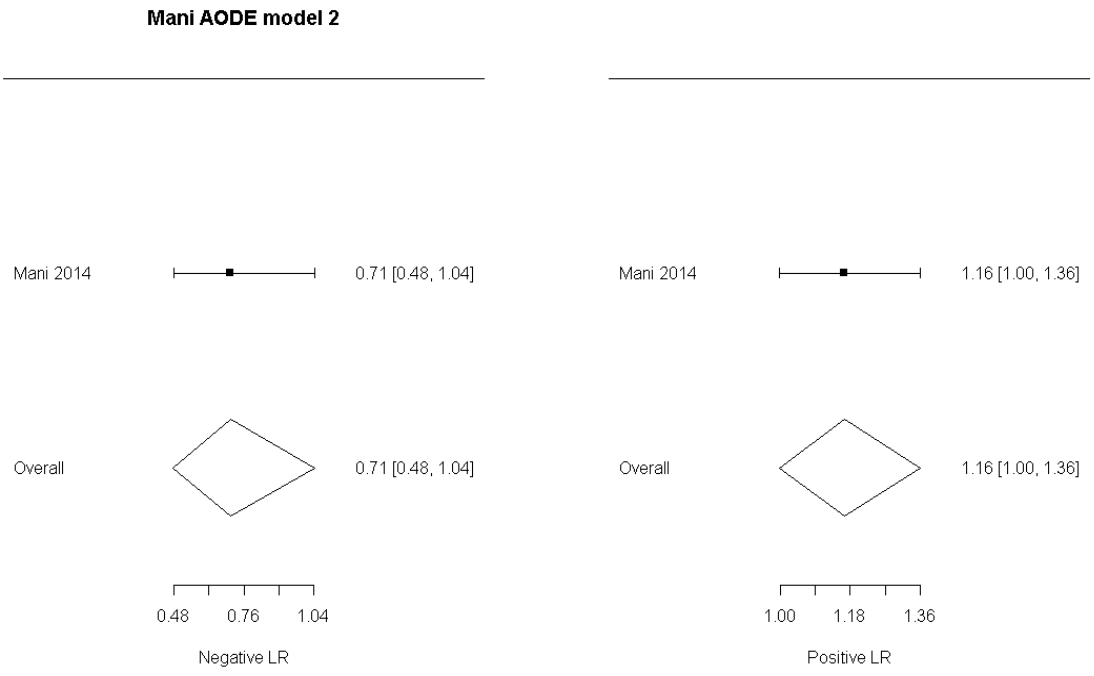


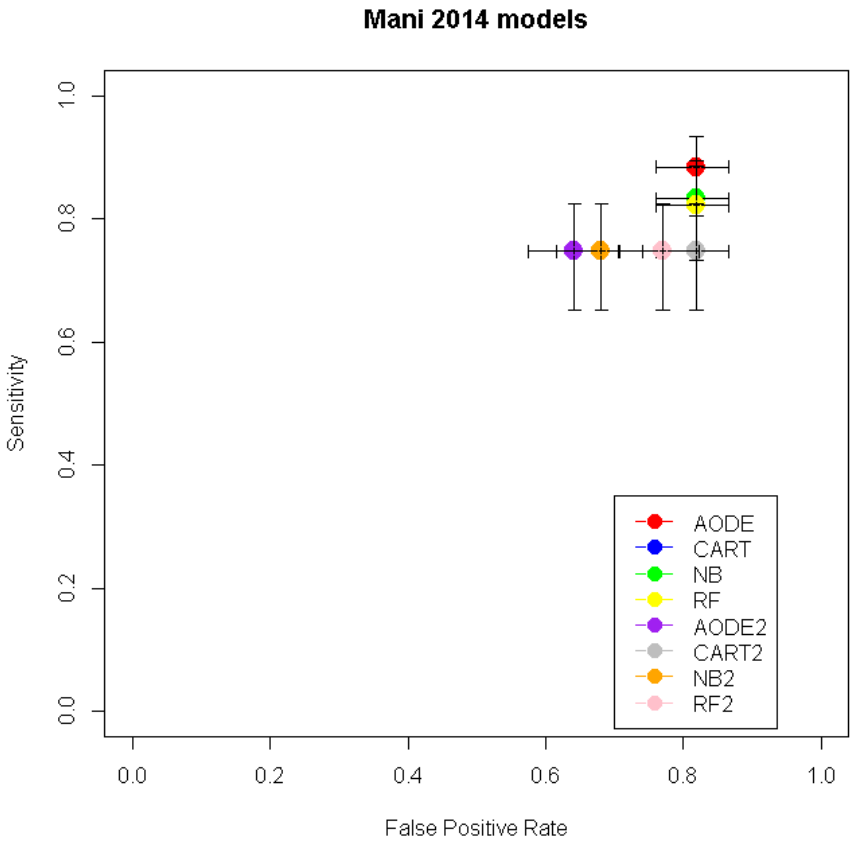
Mani 2014 (AODE model 2)

Sensitivity and specificity



Likelihood ratios




Mani 2014 models
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
AODE
CART
NB
RF
AODE2
CART2
NB2
RF2

Appendix F – GRADE tables

F.1.1 Clinical prediction models

F.1.2 Sensitivity, specificity and likelihood ratios

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
RALIS model										
3	Cohort studies (1 prospective, 2 retrospective)	2279	0.81 (0.67, 0.90)	0.70 (0.44, 0.87)	LR+ 2.82 (1.38, 5.78)	Serious[6]	Not serious	Very serious[1]	Serious[3]	Very low
					LR- 0.29 (0.16, 0.52)	Serious[6]	Not serious	Not serious	Serious[4]	Low
NOSEP model										
2	2 prospective cohort studies	173	0.87 (0.47, 0.98)	0.50 (0.37, 0.64)	LR+ 1.68 (1.34, 2.12)	Not serious	Not serious	Not serious	Serious[3]	Moderate
					LR- 0.26 (0.06, 1.11)	Not serious	Not serious	Very serious[1]	Very serious[7]	Very low
NOSEP New-I model										
1 (Mahieu 2002)	Prospective cohort study	93	0.84 (0.72, 0.92)	0.43 (0.29, 0.58)	LR+ 1.48 (1.11, 1.97)	Not serious	Not serious	N/A[2]	Not serious	High
					LR- 0.37 (0.18, 0.76)	Not serious	Not serious	N/A[2]	Serious[4]	Moderate
NOSEP New-II model										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Mahieu 2002)	Prospective cohort study	93	0.82 (0.69, 0.91)	0.67 (0.51, 0.79)	LR+ 2.47 (1.58, 3.86)	Not serious	Not serious	N/A[2]	Serious[3]	Moderate
					LR- 0.26 (0.14, 0.50)	Not serious	Not serious	N/A[2]	Serious[4]	Moderate
Celik 2013 (Model 1)										
1 (Celik 2013)	Retrospective cohort study	304	0.88 (0.79, 0.94)	0.92 (0.88, 0.95)	LR+ 11.82 (7.43, 18.82)	Not serious	Not serious	N/A[2]	Not serious	Moderate
					LR- 0.13 (0.07, 0.24)	Not serious	Not serious	N/A[2]	Not serious	Moderate
Celik 2013 (Model 2)										
1 (Celik 2013)	Retrospective cohort study	304	0.88 (0.79, 0.94)	0.92 (0.88, 0.95)	LR+ 11.82 (7.43, 18.82)	Not serious	Not serious	N/A[2]	Not serious	Moderate
					LR- 0.13 (0.07, 0.24)	Not serious	Not serious	N/A[2]	Not serious	Moderate
Celik 2013 (Model 3)										
1 (Celik 2013)	Retrospective cohort study	304	0.96 (0.89, 0.99)	0.91 (0.87, 0.94)	LR+ 10.95 (7.19, 16.68)	Not serious	Not serious	N/A[2]	Not serious	Moderate
					LR- 0.04 (0.01, 0.13)	Not serious	Not serious	N/A[2]	Not serious	Moderate
Mani 2014 (NB model – specificity fixed at 0.18)										
1 (Mani 2014)	Retrospective cohort study	299	0.83 (0.74, 0.89)	0.18 (0.13, 0.24)	LR+ 1.02 (0.91, 1.14)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 0.93 (0.55, 1.58)	Serious[5]	Not serious	N/A[2]	Serious[4]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Mani 2014 (RF model – specificity fixed at 0.18)										
1 (Mani 2014)	Retrospective cohort study	299	0.83 (0.74, 0.89)	0.18 (0.13, 0.24)	LR+ 1.00 (0.90, 1.12)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 0.99 (0.59, 1.66)	Serious[5]	Not serious	N/A[2]	Serious[4]	Low
Mani 2014 (CART model – specificity fixed at 0.18)										
1 (Mani 2014)	Retrospective cohort study	299	0.75 (0.65, 0.82)	0.18 (0.13, 0.24)	LR+ 0.91 (0.80, 1.04)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 1.39 (0.89, 2.19)	Serious[5]	Not serious	N/A[2]	Very serious[8]	Very low
Mani 2014 (AODE model – specificity fixed at 0.18)										
1 (Mani 2014)	Retrospective cohort study	299	0.88 (0.80, 0.94)	0.18 (0.13, 0.24)	LR+ 1.08 (0.98, 1.19)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 0.64 (0.34, 1.20)	Serious[5]	Not serious	N/A[2]	Very serious[7]	Very low
Mani 2014 (NB model 2 – sensitivity fixed at 0.75)										
1 (Mani 2014)	Retrospective cohort study	299	0.75 (0.65, 0.82)	0.32 (0.26, 0.38)	LR+ 1.10 (0.94, 1.27)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 0.79 (0.53, 1.18)	Serious[5]	Not serious	N/A[2]	Serious[4]	Low
Mani 2014 (RF model 2 – sensitivity fixed at 0.75)										
1 (Mani 2014)	Retrospective cohort study	299	0.75 (0.65, 0.82)	0.23 (0.18, 0.29)	LR+ 0.97 (0.84, 1.12)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 1.10	Serious[5]	Not serious	N/A[2]	Serious[4]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
					(0.72, 1.68)					
Mani 2014 (CART model 2 – sensitivity fixed at 0.75)										
1 (Mani 2014)	Retrospective cohort study	299	0.75 (0.65, 0.82)	0.18 (0.13, 0.24)	LR+ 0.91 (0.80, 1.04)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 1.39 (0.89, 2.19)	Serious[5]	Not serious	N/A[2]	Very serious[8]	Very low
Mani 2014 (AODE model 2 – sensitivity fixed at 0.75)										
1 (Mani 2014)	Retrospective cohort study	299	0.75 (0.65, 0.82)	0.36 (0.30, 0.43)	LR+ 1.16 (1.00, 1.36)	Serious[5]	Not serious	N/A[2]	Serious[3]	Low
					LR- 0.71 (0.48, 1.04)	Serious[5]	Not serious	N/A[2]	Very serious[7]	Very low

1. I^2 >66.7%. Quality downgraded 2 levels
2. Single study. Inconsistency not applicable
3. Positive likelihood ratio crossed 1 end of the defined MIDs (1 or 2). Quality downgraded 1 level
4. Negative likelihood ratio crossed 1 end of the defined MIDs (0.5 or 1). Quality downgraded 1 level
5. Single study at serious risk of bias. Quality downgraded 1 level
6. >33.3% of weight of meta-analysis at serious risk of bias. Quality downgraded 1 level
7. Negative likelihood ratio crossed both ends of the defined MIDs (0.5 and 1). Quality downgraded 2 levels
8. Negative likelihood ratio crossed both ends of the defined MIDs for positive likelihood ratio (1 and 2). Quality downgraded 2 levels

F.1.3 c-statistics

No. of studies	Study design	Sample size	Effect size (95% CI) (or SD if stated)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
NOSEP model								
1 (Mahieu 2000)	Prospective cohort study	80	0.82 (SD ±0.04)	Not serious	N/A[3]	Not serious	Very serious[2]	Low
1 (Mahieu 2002)	Prospective cohort study	93	0.66 (SD ±0.06)	Not serious	N/A[3]	Not serious	Very serious[2]	Low
NOSEP-New-I model								
1 (Mahieu 2002)	Prospective cohort study	93	0.71 (SD ±0.05)	Not serious	N/A[3]	Not serious	Very serious[2]	Low
NOSEP-New-II model								
1 (Mahieu 2002)	Prospective cohort study	93	0.82 (SD ±0.04)	Not serious	N/A[3]	Not serious	Very serious[2]	Low
Celik 2013 (Model 1)								
1 (Celik 2013)	Ret]rospective cohort study	304	0.95 (0.92, 0.98)	Not serious	N/A[3]	Not serious	Not serious	High
Celik 2013 (Model 2)								
1 (Celik 2013)	Retrospective cohort study	304	0.95 (0.91, 0.97)	Not serious	N/A[3]	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI) (or SD if stated)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Celik 2013 (Model 3)								
1 (Celik 2013)	Retrospective cohort study	304	0.98 (0.95, 0.99)	Not serious	N/A[3]	Not serious	Not serious	High
Mani 2014 (NB model – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.64 (0.51, 0.79)	Serious[4]	N/A[3]	Not serious	Serious[1]	Low
Mani 2014 (RF model – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.57 (0.50, 0.73)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low
Mani 2014 (CART model – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.65 (0.53, 0.77)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low
Mani 2014 (AODE model – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.61 (0.51, 0.75)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low
Mani 2014 (NB model 2 – sensitivity fixed at 0.75)								
1 (Mani 2014)	Retrospective cohort study	299	0.64 (0.51, 0.79)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI) (or SD if stated)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mani 2014 (RF model 2 – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.57 (0.50,0.73)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low
Mani 2014 (CART model 2 – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.65 (0.53, 0.77)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low
Mani 2014 (AODE model 2 – specificity fixed at 0.18)								
1 (Mani 2014)	Retrospective cohort study	299	0.61 (0.51, 0.75)	Serious[4]	N/A[3]	Not serious	Very serious[6]	Very low
Demographics and heart rate monitoring models: demographics and HR characteristics								
1 (Griffin 2003)	Prospective cohort study	633	0.72 CI not reported	Not serious	N/A[3]	Not serious	Serious[5]	Moderate
Demographics and heart rate monitoring models: demographics and HR characteristics index								
1 (Griffin 2003)	Prospective cohort study	633	0.77 CI not reported	Not serious	N/A[3]	Not serious	Serious[5]	Moderate
Nearest neighbour model (optimal model: HRC index, WBC, I:T ratio, HCO3)								
1 (Xiao 2010)	Prospective cohort study	676	0.86 CI not reported	Not serious	N/A[3]	Not serious	Serious[5]	Moderate

1. Confidence interval crosses 2 categories of test classification accuracy. Quality downgraded 1 level
2. Confidence intervals not reported for c-statistic in a study with a sample size <250. Quality downgraded 2 levels
3. Single study. Inconsistency not applicable
4. Single study at serious risk of bias. Quality downgraded 1 level
5. Confidence intervals not reported for c-statistic in a study with a sample size >250. Quality downgraded 1 level
6. Confidence interval crosses 3 categories of test classification accuracy. Quality downgraded 2 levels

F.2 Maternal factors

F.2.1 Sensitivity and specificity

See 'neonatal factors' for evidence table for Nayeri 2018

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Maternal chorioamnionitis										
1 (Garcia-Munoz 2014)	Retrospective cohort study	8330	0.196 (0.181, 0.211)	0.831 (0.821, 0.841)	LR+ 1.16 (1.06, 1.28)	Serious[1]	Not serious	N/A[2]	Not Serious	Moderate
					LR- 0.96(0.95, 0.99)	Serious[1]	Not serious	N/A[2]	Not Serious	Moderate
Intra-amniotic infection										
1 (Nayeri 2018)	Retrospective cohort stud	378	0.50 (0.23, 0.78)	0.53 (0.47, 0.59)	LR+ 1.07 (0.57, 2.0)	Serious[1]	Not serious	N/A[2]	Very serious[4]	Very low
					LR- 0.94 (0.5, 1.77)	Serious[1]	Not serious	N/A[2]	Very serious[5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Vaginal mode of delivery (vs caesarean)										
1 (Olivier 2016)	Prospective cohort study	20038	0.5 (0.32, 0.68)	0.59 (0.57, 0.63)	LR+ 1.23 (0.83, 1.8)	Serious[1]	Not serious	N/A[2]	Serious[3]	Low
					LR- 0.84 (0.57, 1.45)	Serious[1]	Not serious	N/A[2]	Serious[3]	Low

1. Single study at moderate risk of bias. Quality downgraded 1 level
2. Single study. Inconsistency not applicable
3. Confidence intervals cross 1 clinical decision threshold (LR of 1). Quality downgraded 1 level
4. Positive likelihood ratio crossed both ends of the defined MIDs for positive likelihood ratio (1 and 2). Quality downgraded 2 levels
5. Negative likelihood ratio crossed both ends of the defined MIDs for positive likelihood ratio (0.5 and 1). Quality downgraded 2 levels

F.2.2 Association studies

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Antenatal steroids (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Lee 2019)	Retrospective cohort study	2900	Adjusted OR 1.13 (0.87, 1.47)	Not serious	Not serious	N/A[3]	Serious[4]	Moderate
Gestational weight gain for women with BMI ≥40 mg/kg^2 (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Njagu 2020)	Retrospective cohort study	374	Adjusted OR 2.85	Serious[1]	Serious[2]	N/A[3]	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			(1.06, 7.67)					
Epidural (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Ward 2020)	Retrospective cohort study	34,371	Adjusted OR 0.53 (0.29, 0.98)	Serious[1]	Serious[2]	N/A[3]	Not serious	Low

1. Single study at moderate risk of bias. Quality downgraded 1 level
2. Single study which is partially directly applicable. Quality downgraded 1 level
3. Single study. Inconsistency not applicable
4. Confidence intervals cross line of no effect. Quality downgraded 1 level

F.3 Neonatal factors

F.3.1 Risk factors

Gestational age

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Gestational age (extremely pre-term) (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017) *22-25 weeks vs 26-27 weeks*	Retrospective cohort study	3985	Adjusted HR 1.58 (1.23, 2.04)	Serious[2]	Not serious	N/A[1]	Not serious	Low
Gestational age (extremely pre-term vs pre-term) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Garland 2017) *<25 weeks vs >32 weeks*	Retrospective cohort study	2913	Adjusted OR 4.40 (2.50, 7.80)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Garland 2017) *25-28 weeks vs >32 weeks*	Retrospective cohort study	2913	Adjusted OR 2.20 (1.30, 3.70)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Gestational age (extremely pre-term vs pre-term) (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017) *22-25 weeks vs 28-31 weeks*	Retrospective cohort study	3985	Adjusted HR 3.57 (2.70, 4.76)	Not serious	Not serious	N/A[1]	Not serious	Moderate
1 (Sanderson 2017) *22-25 weeks vs 32-36 weeks*	Retrospective cohort study	3985	Adjusted HR 6.67 (4.34, 10.0)	Not serious	Not serious	N/A[1]	Not serious	Moderate
Gestational age (very pre-term vs term) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Garland 2017) *29-32 weeks vs >32 weeks*	Retrospective cohort study	2913	Adjusted OR 2.04 (1.11, 3.70)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Gestational age (very pre-term vs term) (RR >1 indicates risk factor of late-onset neonatal infection)								
1 (Auriti 2003) *<32 weeks vs >32 weeks*	Retrospective cohort study	280	Adjusted RR 3.58 (No CI provided)	Very serious[3]	Not serious	N/A[1]	Serious[4]	Very low
Gestational age (pre-term vs term) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Leal 2012) *<37 weeks vs >37 weeks*	Retrospective cohort study	11,790	Adjusted HR 1.08 (1.03, 1.14)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Gestational age (OR >1 indicates risk factor of late-onset neonatal infection)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Nayeri 2018)	Prospective cohort study	378	Adjusted OR 1.42 (1.25, 1.66)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
1 (Smith 2008)	Retrospective cohort study	882	Adjusted OR 1.25 (1.32, 1.19)	Serious[2]	Not serious	N/A[1]	Not serious	Low
1 (Troger 2014)	Prospective cohort study	5886	Adjusted OR 1.33 (1.28, 1.39)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Gestational age (singleton birth subgroup) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013) *Weeks (from <25 to >32)*	Retrospective cohort study	15,178	Adjusted OR 1.23 (1.20, 1.27)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Gestational age (multiple births subgroup) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013) *Weeks (from <25 to >32)*	Retrospective cohort study	5294	Adjusted OR 1.20 (1.15, 1.27)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Single study at high risk of bias. Quality downgraded 2 levels
4. No confidence intervals provided. Quality downgraded 1 level

History of surgery

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
History of surgery (single births only) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20,472	Adjusted OR 1.43 (1.26, 1.61)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
History of surgery (single births only) (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 1.00 (0.77, 1.29)	Serious[2]	Not serious	N/A[1]	Serious[3]	Very low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Confidence interval crossed the line of no effect. Quality downgraded 1 level

Presence of a catheter

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Central venous catheter (RR >1 indicates risk factor of late-onset neonatal infection)								
1 (Auriti 2003)	Retrospective cohort study	280	Adjusted RR 3.61 (No CI reported)	Very serious[3]	Not serious	N/A[1]	Serious[5]	Very low
Central venous catheter (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 2.27 (1.28, 4.02)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Bekhof 2013)	Prospective cohort study	142	Adjusted OR 7.13 (3.15, 16.16)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
1 (Padula 2014)	Retrospective cohort study	409	OR 2.52 (1.44, 4.38)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Umbilical catheter (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 0.87 (0.34, 2.56)	Serious[2]	Not serious	N/A[1]	Serious[4]	Low
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 1.46 (0.60, 3.54)	Serious[2]	Not serious	N/A[1]	Serious[4]	Low
Urinary catheter (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 1.34 (0.69, 2.60)	Serious[2]	Not serious	N/A[1]	Serious[4]	Low
PICC vs UVC (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 0.51 (0.40, 0.66)	Serious[2]	Not serious	N/A[1]	Not serious	Low
Peripheral cannula vs central PICC (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Smith 2008)	Retrospective cohort study	882	Adjusted OR 0.50 (0.26, 0.96)	Serious[2]	Not serious	N/A[1]	Not serious	Low

1. Single study. Inconsistency not applicable

2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Single study at high risk of bias. Quality downgraded 2 levels
4. Confidence interval crossed the line of no effect. Quality downgraded 1 level
5. No confidence intervals provided. Quality downgraded 1 level

Other catheter related factors

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Catheter related infection during initial catheterisation – refers to infections after catheter removal (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Garland 2017)	Retrospective cohort study	2913	Adjusted OR 2.0 (1.06, 3.79)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Catheter dwell time (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Smith 2008)	Retrospective cohort study	882	Adjusted OR 0.98 (0.96, 0.99)	Serious[2]	Not serious	N/A[1]	Not serious	Low
Age at central venous catheter insertion 7-13 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 0.8 (0.56, 1.15)	Serious[2]	Not serious	N/A[1]	Serious[3]	Very low
Age at central venous catheter insertion 14-20 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 0.92 (0.57, 1.5)	Serious[2]	Not serious	N/A[1]	Serious[3]	Very low
Age at central venous catheter insertion 21-27 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 0.28 (0.1, 0.75)	Serious[2]	Not serious	N/A[1]	Not serious	Very low
Age at central venous catheter insertion >=28 days vs <7days (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 0.53 (0.33, 0.85)	Serious[2]	Not serious	N/A[1]	Not serious	Very low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Confidence interval crossed the line of no effect. Quality downgraded 1 level

Weight

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Birthweight <1000g vs =>1500g (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 8.82 (4.8, 16.21)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Birthweight 1000g-1499g vs =>1500g (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 2.35 (1.02, 5.38)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Birthweight =< 2500g (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Leal 2012)	Retrospective cohort study	11790	HR 1.04 (1.01, 1.08)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Small for gestational age – singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 1.22 (1.06, 1.43)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Small for gestational age (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Troger 2016)	Retrospective cohort study	5886	Adjusted OR 1.31 (1.02, 1.68)	Serious[2]	Not serious	N/A[1]	Not serious	Low
Weight at episode <1200g (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Bekhof 2013)	Retrospective cohort study	142	Adjusted OR 1.72 (0.87, 3.4)	Serious[2]	Not serious	N/A[1]	Serious[3]	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Confidence interval crossed the line of no effect. Quality downgraded 1 level

Parenteral nutrition

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Parenteral nutrition – singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 7.66 (3.1, 19.1)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Duration of parenteral nutrition (per day)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Troger 2016)	Retrospective cohort study	5886	Adjusted OR 1.02 (1.01, 1.02)	Serious[2]	Not serious	N/A[1]	Not serious	Low
Duration of total parenteral nutrition (per day)								
1 (Yapicioglu 2011)	Prospective cohort study	378	OR 1.09 (1.06, 1.14)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Human milk

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Human milk vs formula (OR <1 indicates risk factor of late-onset neonatal infection)								
1 (Hylander 1998)	Retrospective cohort study	212	Adjusted OR 0.50 (0.25, 1.02)	Serious[2]	Not serious	N/A[1]	Serious[3]	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Confidence intervals crossed the line of no effect, Quality downgraded 1 level

Gender

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Female gender- singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 0.89 (0.81, 0.98)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Male gender (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babazono 2008)	Retrospective cohort study	871	Adjusted OR 1.86 (1.04, 3.35)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Length of hospital stay

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Length of hospital stay, per day – singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 1.003 (1.002, 1.004)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Length of hospital stay, per day – multiple pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 1.005 (1.002, 1.009)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Age when full feeds achieved

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Age when full feeds achieved (per day)- singleton pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 1.04 (1.03, 1.05)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Age when full feeds achieved (per days) - multiple pregnancies (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Boghossian 2013)	Retrospective cohort study	20038	Adjusted OR 0.83 (0.79, 0.87)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Patent ductus arteriosus

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Patent ductus arteriosus – relates specifically to infections following catheter removal (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Garland 2017)	Retrospective cohort study	2913	Adjusted OR 0.49 (0.27, 0.9)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
1 (Stoll 1996)	Retrospective cohort study	6911	OR 2.03 (1.33, 2.3)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Surgical procedure required

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Surgical procedure required (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Leal 2012)	Retrospective cohort study	11790	HR 2.85 (1.49, 5.46)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Invasive medical procedure required

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Invasive medical procedure required (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Leal 2012)	Retrospective cohort study	11790	HR 2.07 (1.63, 2.62)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Enteral contrast in previous 48hrs

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Enteral contrast in previous 48hrs (OR >1 indicates risk factor of late-onset neonatal infection)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Padula 2014)	Retrospective cohort study	409	OR 9.58 (2.03, 45.2)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Congenital abnormality

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Congenital abnormality (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Sanderson 2017)	Retrospective cohort study	3985	Adjusted HR 1.45 (1.11, 1.89)	Serious[2]	Not serious	N/A[1]	Not serious	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Treatment with antenatal steroids

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Treatment with antenatal steroids (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Troger 2016)	Retrospective cohort study	5886	Adjusted OR 0.7 (0.53, 0.92)	Serious[2]	Not serious	N/A[1]	Not serious	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

German descendance

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
German descendance (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Troger 2016)	Retrospective cohort study	5886	Adjusted OR 0.76 (0.63, 0.91)	Serious[2]	Not serious	N/A[1]	Not serious	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

F.3.2 Signs and symptoms

Assisted ventilation

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Need for mechanical ventilation (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Babanoza 2008)	Retrospective cohort study	871	Adjusted OR 1.49 (0.82, 2.72)	Serious[2]	Not serious	N/A[1]	Serious[4]	Low
Need for mechanical ventilation (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Leal 2012)	Retrospective cohort study	11,790	Adjusted HR 1.60 (1.19, 2.40)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Need for mechanical ventilation (RR >1 indicates risk factor of late-onset neonatal infection)								
1 (Makhoul 2006)	Prospective cohort study	111	Adjusted RR 2.37 (1.36, 4.15)	Very serious[3]	Not serious	N/A[1]	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Intubation (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Stoll 1996)	Retrospective cohort study	6911	OR 1.52 (1.31, 1.78)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Duration of ventilation (per day) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Yapicioglu 2011)	Prospective cohort study	378	OR 0.96 (0.94, 0.99)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Duration of intubation (per week) (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Kim 2018)	Retrospective cohort study	364	OR 1.12 (1.05, 1.18)	Very serious[3]	Not serious	N/A[1]	Not serious	Low
Hood O2 Use (per day) OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Yapicioglu 2011)	Prospective cohort study	378	OR 1.13 (1.06, 1.2)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Single study at high risk of bias. Quality downgraded 2 levels
4. Confidence interval crosses line of no effect. Quality downgraded 1 level

Altered behaviour or responsiveness

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Lethargy (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Bekhof 2013)	Prospective cohort study	142	Adjusted OR 2.61 (1.14, 6.01)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Capillary refill >2s

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Capillary refill >2 s (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Bekhof 2013)	Prospective cohort study	142	Adjusted OR 2.32 (1.00, 5.37)	Serious[2]	Not serious	N/A[1]	Serious[3]	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Confidence interval crosses line of no effect. Quality downgraded 1 level

Pallor/grey skin

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Pallor/grey skin (OR >1 indicates risk factor of late-onset neonatal infection)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Bekhof 2013)	Prospective cohort study	142	Adjusted OR 1.25 (0.52, 2.97)	Serious[2]	Not serious	N/A[1]	Serious[3]	Low

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level
3. Confidence interval crosses line of no effect. Quality downgraded 1 level

Apgar score=<5

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Apgar score=<5 (HR >1 indicates risk factor of late-onset neonatal infection)								
1 (Leal 2012)	Retrospective cohort study	11790	HR 1.4 (1.19, 1.76)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Respiratory difficulties

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Apnoea (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Padula 2014)	Retrospective cohort study	409	OR 2.86 (1.43, 5.73)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Respiratory distress syndrome (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Stoll 1996)	Retrospective cohort study	6911	OR 1.52 (1.31, 1.78)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Bronchopulmonary dysplasia (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Stoll 1996)	Retrospective cohort study	6911	OR 2.2 (1.91, 2.55)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate
Steroids for bronchopulmonary dysplasia (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Stoll 1996)	Retrospective cohort study	6911	OR 1.59 (1.81, 2.48)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Necrotising enterocolitis

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
NEC stage 2A or greater (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Stoll 1996)	Retrospective cohort study	6911	OR 4.58 (3.63, 5.66)	Serious4	Not serious	N/A[1]	Not serious	Moderate
NEC stage 2B or greater at 23-26 weeks' gestational age (OR >1 indicates risk factor of late-onset neonatal infection)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Kim 2018)	Retrospective cohort study	364	OR 3.38 (1.51, 7.55)	Very serious[2]	Not serious	N/A[1]	Not serious	Low

1. Single study. Inconsistency not applicable
2. Single study at high risk of bias. Quality downgraded 2 levels

Hypotension

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Hypotension (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Padula 2014)	Retrospective cohort study	409	OR 2.64 (1.26, 5.5)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

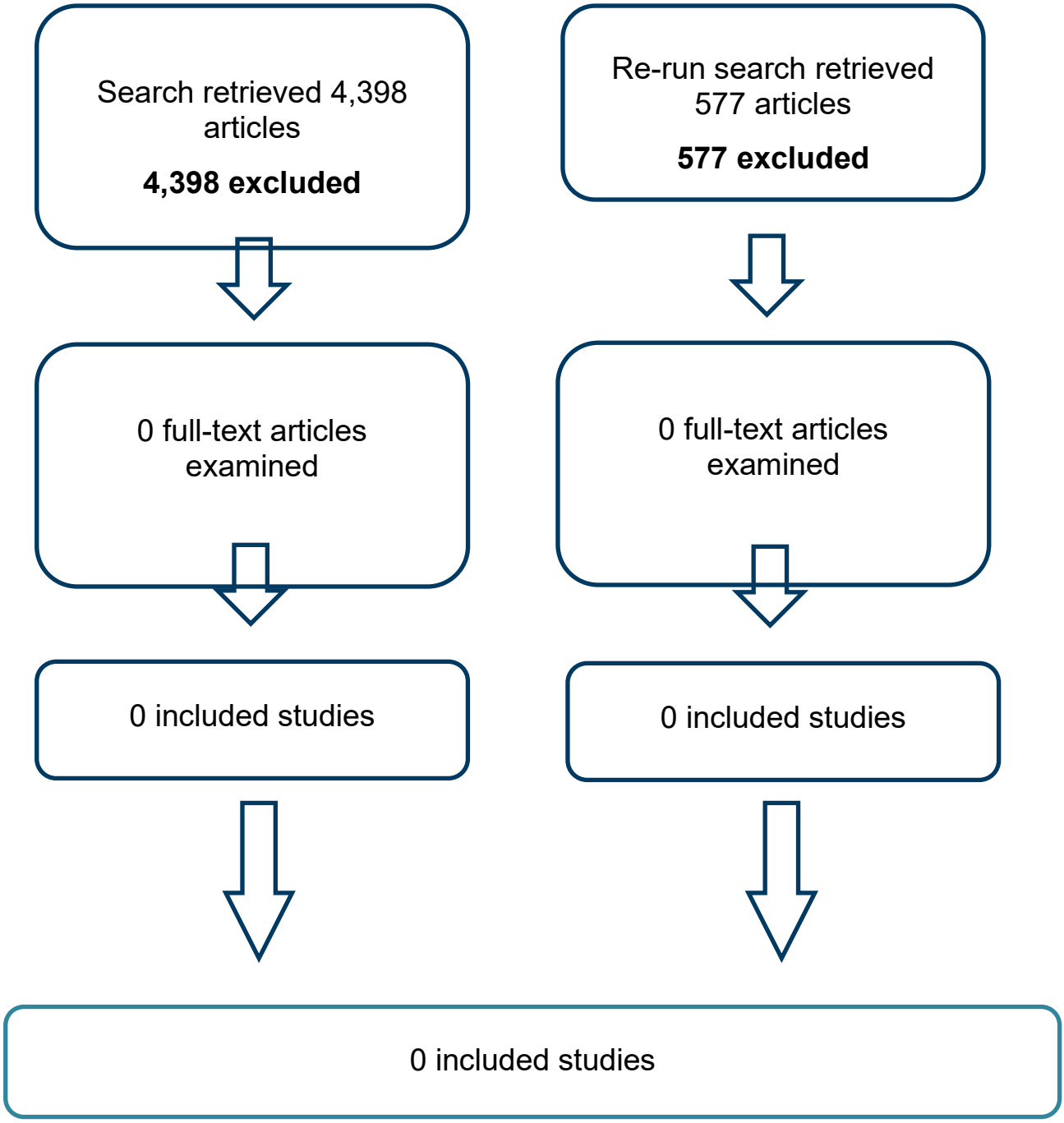
1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Intraventricular haemorrhage

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
IVH grade 3/4 (OR >1 indicates risk factor of late-onset neonatal infection)								
1 (Stoll 1996)	Retrospective cohort study	6911	OR 1.27 (1.08, 1.52)	Serious[2]	Not serious	N/A[1]	Not serious	Moderate

1. Single study. Inconsistency not applicable
2. Single study at moderate risk of bias. Quality downgraded 1 level

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence is available as none of the studies in the economic search results were found to be relevant.

Appendix I – Health economic model

This question was not prioritised for original economic analysis.

Appendix J – Excluded studies

J.1 Clinical prediction models

Clinical studies

Study	Reason for exclusion
Achten N.B., Zonneveld R., Tromp E. et al. (2017) Association between sepsis calculator and infection parameters for newborns with suspected early onset sepsis. Journal of Clinical Neonatology 6(3): 159-162	- Does not contain outcomes of interest
Achten, Niek B, Dorigo-Zetsma, J Wendelien, van der Linden, Paul D et al. (2018) Sepsis calculator implementation reduces empiric antibiotics for suspected early-onset sepsis.. European journal of pediatrics 177(5): 741-746	- Not possible to calculate a contingency table from the data specified in the protocol
Achten, N.B., Klingenberg, C., Benitz, W.E. et al. (2019) Association of Use of the Neonatal Early-Onset Sepsis Calculator with Reduction in Antibiotic Therapy and Safety: A Systematic Review and Meta-analysis. JAMA Pediatrics 173(11): 1032-1040	- Systematic review. Reference list checked for possible includes
Achten, N.B., Visser, D.H., Tromp, E. et al. (2020) Early onset sepsis calculator implementation is associated with reduced healthcare utilization and financial costs in late preterm and term newborns. European Journal of Pediatrics 179(5): 727-734	- Outcome to be predicted does not match that specified in the protocol *Health economics analysis*
Achten, Niek B, Dorigo-Zetsma, J Wendelien, van Rossum, Annemarie M C et al. (2020) Risk-based maternal group B streptococcus screening strategy is compatible with neonatal early onset sepsis calculator implementation. Clinical and experimental pediatrics	- End point does not match that specified in the protocol *Effects of known vs unknown maternal GBS status*
Aghai, Zubair H (2018) Is early-onset sepsis risk calculator safe for the management of neonates born to mothers with chorioamnionitis?.. Journal of perinatology : official journal of the California Perinatal Association 38(6): 769-770	- Article correspondence
Akangire, G., Simpson, E., Weiner, J. et al. (2020) Implementation of the Neonatal Sepsis Calculator in Early-Onset Sepsis and Maternal Chorioamnionitis. Advances in neonatal care : official journal of the National Association of Neonatal Nurses 20(1): 25-32	- Outcome to be predicted does not match that specified in the protocol *Comparison between clinician and calculator outcomes*
Anonymous (1999) Conclusions from the WHO multicenter study of serious infections in young infants. The WHO Young Infants Study Group.. The Pediatric infectious disease journal 18(10suppl): 32-4	- End point do not match that specified in the protocol

Anonymous (1999) Clinical prediction of serious bacterial infections in young infants in developing countries. The WHO Young Infants Study Group.. The Pediatric infectious disease journal 18(10suppl): 23-31	- Outcome to be predicted does not match that specified in the protocol [Bacterial infection in infants aged up to 90 days. Results for neonates not presented separately]
Bachur, R G and Harper, M B (2001) Predictive model for serious bacterial infections among infants younger than 3 months of age.. Pediatrics 108(2): 311-6	- Outcomes to be predicted do not match that specified in the protocol [Bacterial infection in infants less than 3 months. Data for neonates not presented separately]
Baizat, Melinda, Zaharie, Gabriela, Iancu, Mihaela et al. (2019) Potential Clinical Predictors of Suspected Early and Late Onset Sepsis (EOS and LOS) in Preterm Newborns: a Single Tertiary Center Retrospective Study. Clinical laboratory 65(7)	- Non-OECD country
Barbadoro, Pamela, Marigliano, Anne, D'Errico, Marcello Mario et al. (2011) Gestational age as a single predictor of health care-associated bloodstream infections in neonatal intensive care unit patients.. American journal of infection control 39(2): 159-62	- Assessment tool does not match that specified in the protocol [Suggests single predictor for neonatal infection]
Benaim, E.H.; Upadhyay, K.; Talati, A.J. (2020) Comparison of institutional guidelines with established early onset sepsis risk calculator in reducing antibiotic use in an inner-city NICU in US. Journal of Global Antimicrobial Resistance 21: 124-129	- End point does not match that specified in the protocol
Berger, R M, Berger, M Y, van Steensel-Moll, H A et al. (1996) A predictive model to estimate the risk of serious bacterial infections in febrile infants.. European journal of pediatrics 155(6): 468-73	- Study does not contain the population of interest [Excluded babies with gestational age <37 weeks. Included children aged 2 weeks - 1 year but results not separated by age]
Bressan, Silvia, Gomez, Borja, Mintegi, Santiago et al. (2012) Diagnostic performance of the lab-score in predicting severe and invasive bacterial infections in well-appearing young febrile infants.. The Pediatric infectious disease journal 31(12): 1239-44	- Outcomes to be predicted do not match that specified in the protocol [Bacterial infection in infants up to 1 year. Results for neonates not presented separately]
Bridges M., Pesek E., McRae M. et al. (2019) Use of an Early Onset-Sepsis Calculator to Decrease Unnecessary NICU Admissions and Increase Exclusive Breastfeeding. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 48(3): 372-382	- Does not contain outcomes of interest
Cabaret B., Laurans C., Launay E. et al. (2013) Diagnostic value of a new procalcitonin cord sample-guided algorithm to manage newborns suspected of early-onset infection. Archives de Pediatrie 20(9): 954-962	- Study not reported in English
Chen, Chun-Jen, Lo, Yu-Fang, Huang, Miao-Chiu et al. (2009) A model for predicting risk of serious bacterial infection in febrile infants younger than 3 months of age.. Journal of the Chinese Medical Association : JCMA 72(10): 521-6	- Study does not contain the population of interest [Excludes babies <36 weeks gestation. Includes infants up to 3

	months but results not separated by age]
Chiu, C H and Lin, T Y (1998) Application of the Rochester Criteria in febrile neonates.. The Pediatric infectious disease journal 17(3): 267-9	- Article correspondence
Degraeuwe, Pieter (2018) Applying the neonatal Early-Onset Sepsis calculator in cases of clinical chorioamnionitis at or after 34 weeks of gestation.. The Journal of pediatrics 203: 463-464	- Article correspondence
Deshmukh, Mangesh; Mehta, Shailender; Patole, Sanjay (2019) Sepsis calculator for neonatal early onset sepsis - a systematic review and meta-analysis.. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians: 1-9	- Systematic review. Reference list was checked for additional articles
Despins, Laurel A (2017) Automated Detection of Sepsis Using Electronic Medical Record Data: A Systematic Review.. Journal for healthcare quality : official publication of the National Association for Healthcare Quality 39(6): 322-333	- Systematic review. Reference list was checked for additional articles
Eason, J., Ward, H., Danko, O. et al. (2019) Early-onset sepsis: Can we screen fewer babies safely?. Archives of Disease in Childhood	- End point does not match that specified in the protocol
Escobar, Gabriel J, Puopolo, Karen M, Wi, Soora et al. (2014) Stratification of risk of early-onset sepsis in newborns >= 34 weeks' gestation.. Pediatrics 133(1): 30-6	- Not possible to calculate a contingency table from the data specified in the protocol
Fairchild, Karen D, Lake, Douglas E, Kattwinkel, John et al. (2017) Vital signs and their cross-correlation in sepsis and NEC: a study of 1,065 very-low-birth-weight infants in two NICUs.. Pediatric research 81(2): 315-321	- Outcomes to be predicted do not match that specified in the protocol [Sepsis in neonates, results not separated by early- and late-onset]
Fowler, Nyles T; Garcia, Michael; Hankins, Cynthia (2019) Impact of Integrating a Neonatal Early-Onset Sepsis Risk Calculator into the Electronic Health Record. Pediatric quality & safety 4(6): e235	- Outcome to be predicted does not match that specified in the protocol *Only reports true positives*
Fowlie, P W, Gould, C R, Parry, G J et al. (1996) CRIB (clinical risk index for babies) in relation to nosocomial bacteraemia in very low birthweight or preterm infants.. Archives of disease in childhood. Fetal and neonatal edition 75(1): f49-52	- Study does not contain any relevant index tests
Franz, Axel R, Bauer, Karl, Schalk, Andreas et al. (2004) Measurement of interleukin 8 in combination with C-reactive protein reduced unnecessary antibiotic therapy in newborn infants: a multicenter, randomized, controlled trial.. Pediatrics 114(1): 1-8	- Assessment tool do not match that specified in the protocol [Individual predictors of infection, not a model]
Garra, Gregory; Cunningham, Sandra J; Crain, Ellen F (2005) Reappraisal of criteria used to predict serious bacterial illness in febrile infants less than 8 weeks of age.. Academic	- Study does not contain the population of interest

emergency medicine : official journal of the Society for Academic Emergency Medicine 12(10): 921-5	[Infants. Results for neonates not reported separately]
Gievers L.L., Sedler J., Phillipi C.A. et al. (2018) Implementation of the sepsis risk score for chorioamnionitis-exposed newborns. Journal of Perinatology 38(11): 1581-1587	- Study design does not match protocol
Good, Pamela I and Hooven, Thomas A (2019) Evaluating Newborns at Risk for Early-Onset Sepsis.. Pediatric clinics of North America 66(2): 321-331	- Review article but not a systematic review
Griffin, M Pamela; Lake, Douglas E; Moorman, J Randall (2005) Heart rate characteristics and laboratory tests in neonatal sepsis.. Pediatrics 115(4): 937-41	- Assessment tool do not match that specified in the protocol
Gupta, R; Sachdev, H P; Shah, D (2000) Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the ages of one week to two months.. Indian pediatrics 37(4): 383-90	- End point do not match that specified in the protocol [No information about the model and primarily predicting hospitalisation]
Harrell, F E Jr, Margolis, P A, Gove, S et al. (1998) Development of a clinical prediction model for an ordinal outcome: the World Health Organization Multicentre Study of Clinical Signs and Etiological agents of Pneumonia, Sepsis and Meningitis in Young Infants. WHO/ARI Young Infant Multicentre Study Group.. Statistics in medicine 17(8): 909-44	- Study does not contain the population of interest [Sepsis in infants but not specifically neonatal sepsis]
He, Yi, Chen, Jie, Liu, Zhenqiu et al. (2019) Efficacy and safety of applying a neonatal early-onset sepsis risk calculator in China.. Journal of paediatrics and child health	- Set in non-OECD country
Helmbrecht A.R.; Marfurt S.; Chaaban H. (2019) Systematic Review of the Effectiveness of the Neonatal Early-Onset Sepsis Calculator. The Journal of perinatal & neonatal nursing 33(1): 82-88	- Systematic review. Reference list was checked for additional articles
Huang, Yuejun, Yu, Xiaochan, Li, Weidong et al. (2020) Development and validation of a nomogram for predicting late-onset sepsis in preterm infants on the basis of thyroid function and other risk factors: Mixed retrospective and prospective cohort study. Journal of advanced research 24: 43-51	- Non-OECD country
Ji H., Bridges M., Pesek E. et al. (2019) Acute Funisitis Correlates With the Risk of Early-Onset Sepsis in Term Newborns Assessed Using the Kaiser Sepsis Calculator. Pediatric and Developmental Pathology	- End point do not match that specified in the protocol
Kerste, Marleen, Corver, Jellina, Sonnevelt, Martine C et al. (2016) Application of sepsis calculator in newborns with suspected infection.. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(23): 3860-5	- Not possible to calculate a contingency table from the data specified in the protocol
Klingenberg C. (2018) Early-onset sepsis risk calculator reduces empiric antibiotic use. Journal of Pediatrics 192: 266-269	- Conference abstract
Kordek, Agnieszka; Halasa, Maciej; Podraza, Wojciech (2008) Early detection of an early onset infection in the neonate based on measurements of procalcitonin and C-reactive	- Not possible to calculate a contingency table from the data specified in the protocol

protein concentrations in cord blood.. Clinical chemistry and laboratory medicine 46(8): 1143-8	
Kuzniewicz, Michael W, Puopolo, Karen M, Fischer, Allen et al. (2017) A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis.. JAMA pediatrics 171(4): 365-371	- Not possible to calculate a contingency table from the data specified in the protocol
Kuzniewicz, Michael W, Walsh, Eileen M, Li, Sherian et al. (2016) Development and Implementation of an Early-Onset Sepsis Calculator to Guide Antibiotic Management in Late Preterm and Term Neonates.. Joint Commission journal on quality and patient safety 42(5): 232-9	- Prediction model tutorial paper
Labenne, Marc, Lizard, Gerard, Ferdynus, Cyril et al. (2011) A clinic-biological score for diagnosing early-onset neonatal infection in critically ill preterm infants.. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 12(2): 203-9	- Study design does not match protocol
Lake, Douglas E; Fairchild, Karen D; Moorman, J Randall (2014) Complex signals bioinformatics: evaluation of heart rate characteristics monitoring as a novel risk marker for neonatal sepsis.. Journal of clinical monitoring and computing 28(4): 329-39	- Assessment tool do not match that specified in the protocol
Leonardi, Bianca M, Binder, Margaret, Griswold, Katherine J et al. (2019) Utilization of a Neonatal Early-Onset Sepsis Calculator to Guide Initial Newborn Management. Pediatric quality & safety 4(5): e214	- Outcome to be predicted does not match that specified in the protocol
Loughlin, L., Knowles, S., Twomey, A. et al. (2020) The Neonatal Early Onset Sepsis Calculator; in Clinical Practice. Irish medical journal 113(4): 57	- Outcome to be predicted does not match that specified in the protocol
Modi, N, Dore, C J, Saraswatula, A et al. (2009) A case definition for national and international neonatal bloodstream infection surveillance.. Archives of disease in childhood. Fetal and neonatal edition 94(1): f8-12	- End point do not match that specified in the protocol [Used to produce definition of infection rather than a model for wider use]
Moorman, J Randall, Delos, John B, Flower, Abigail A et al. (2011) Cardiovascular oscillations at the bedside: early diagnosis of neonatal sepsis using heart rate characteristics monitoring.. Physiological measurement 32(11): 1821-32	- Assessment tool do not match that specified in the protocol
Morris, R., Jones, S., Banerjee, S. et al. (2020) Comparison of the management recommendations of the Kaiser Permanente neonatal early-onset sepsis risk calculator (SRC) with NICE guideline CG149 in infants >=34 weeks' gestation who developed early-onset sepsis. Archives of Disease in Childhood: Fetal and Neonatal Edition: 2019317165	- Outcome to be predicted does not match that specified in the protocol *All babies have confirmed infection - not possible to calculate specificity*
Okascharoen, C, Hui, C, Cairnie, J et al. (2007) External validation of bedside prediction score for diagnosis of late-	- Set in non-OECD country

onset neonatal sepsis.. Journal of perinatology : official journal of the California Perinatal Association 27(8): 496-501	
Okascharoen, Chusak, Sirinavin, Sayomporn, Thakkinstian, Ammarin et al. (2005) A bedside prediction-scoring model for late-onset neonatal sepsis.. Journal of perinatology : official journal of the California Perinatal Association 25(12): 778-83	- Set in non-OECD country
Puopolo, Karen M and Escobar, Gabriel J (2013) Early-onset sepsis: a predictive model based on maternal risk factors.. Current opinion in pediatrics 25(2): 161-6	- Review article but not a systematic review
Rosenberg, Rebecca E, Ahmed, A S M Nawshad U, Saha, Samir K et al. (2010) Nosocomial sepsis risk score for preterm infants in low-resource settings.. Journal of tropical pediatrics 56(2): 82-9	- Set in non-OECD country
Singh SA; Dutta S; Narang A (2003) Predictive clinical scores for diagnosis of late onset neonatal septicemia.. Journal of tropical pediatrics 49(4): 235-239	- Assessment tool do not match that specified in the protocol [Individual factors rather than combined predictor model]
Stipelman, Carole H, Smith, Elizabeth R, Diaz-Ochu, Margarita et al. (2019) Early-Onset Sepsis Risk Calculator Integration Into an Electronic Health Record in the Nursery. Pediatrics 144(2)	- Outcome to be predicted does not match that specified in the protocol *Frequency of calculator use*
Thakur J.; Pahuja S.K.; Pahuja R. (2019) Performance comparison of prediction models for neonatal sepsis using logistic regression, multiple discriminant analysis and artificial neural network. Biomedical Physics and Engineering Express 5(3): 035013	- Outcomes to be predicted do not match that specified in the protocol [Overall neonatal sepsis risk. Results not separated by early- and late-onset neonatal infection]
Thakur J.; Pahuja S.K.; Pahuja R. (2019) Non-invasive prediction model for developing countries to predict sepsis in neonates. Biomedical Engineering - Applications, Basis and Communications 31(1): 1950001	- Outcomes to be predicted do not match that specified in the protocol [Overall neonatal sepsis risk. Results not separated by early- and late-onset neonatal infection]
Tzialla, Chryssoula, Manzoni, Paolo, Achille, Cristian et al. (2018) New Diagnostic Possibilities for Neonatal Sepsis.. American journal of perinatology 35(6): 575-577	- Review article but not a systematic review
Verstraete, Evelien Hilde, Blot, Koen, Mahieu, Ludo et al. (2015) Prediction models for neonatal health care-associated sepsis: a meta-analysis.. Pediatrics 135(4): e1002-14	- Systematic review used as source of primary studies
Vujevic, Matea; Benzon, Benjamin; Markic, Josko (2017) New prediction model for diagnosis of bacterial infection in febrile infants younger than 90 days.. The Turkish journal of pediatrics 59(3): 261-268	- Study does not contain the population of interest [Excludes babies <37 weeks gestation. Includes infants age 0-90 days but results not separated by age]
Walker, Sandra A N, Cormier, Melanie, Elligsen, Marion et al. (2019) Development, evaluation and validation of a screening	- Study design does not match protocol

tool for late onset bacteremia in neonates - a pilot study.. BMC pediatrics 19(1): 253	
Warren, S; Garcia, M; Hankins, C (2017) Impact of neonatal early-onset sepsis calculator on antibiotic use within two tertiary healthcare centers.. Journal of perinatology : official journal of the California Perinatal Association 37(4): 394-397	- Study design does not match protocol
Young, Paul C (2014) A data-based approach to evaluation and empiric treatment of newborn sepsis.. The Journal of pediatrics 165(3): 640-1	- Conference abstract

J.2 Maternal and neonatal risk factors

Clinical studies

Study	Code [Reason]
Ajayi, O A and Mokuolu, O A (1997) Evaluation of neonates with risk for infection/suspected sepsis: is routine lumbar puncture necessary in the first 72 hours of life?. Tropical medicine & international health : TM & IH 2(3): 284-8	- Considered under investigations for late-onset sepsis review question
Akturk, Hacer, Sutcu, Murat, Somer, Ayper et al. (2016) Vancomycin-resistant enterococci colonization in a neonatal intensive care unit: who will be infected?. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(21): 3478-82	- Outcome to be predicted do not match that specified in the protocol [Was concerned with predicting vancomycin resistant infection]
Al-Mouqdad, M.M., Aljobair, F., Alaklobi, F.A. et al. (2018) The consequences of prolonged duration of antibiotics in premature infants with suspected sepsis in a large tertiary referral hospital: a retrospective cohort study. International Journal of Pediatrics and Adolescent Medicine 5(3): 110-115	- Based in non-OECD country
Alexander, J M, Gilstrap, L C, Cox, S M et al. (1998) Clinical chorioamnionitis and the prognosis for very low birth weight infants. Obstetrics and gynecology 91(5pt1): 725-9	- Outcome to be predicted do not match that specified in the protocol [Unclear whether early or late-onset infection]
Alexander, J M; McIntire, D M; Leveno, K J (1999) Chorioamnionitis and the prognosis for term infants. Obstetrics and gynecology 94(2): 274-8	- Outcome to be predicted do not match that specified in the protocol [Unclear whether early or late-onset infection]
Alshaikh, Belal, Dharel, Dinesh, Yusuf, Kamran et al. (2019) Early total enteral feeding in stable preterm infants: a systematic review and meta-analysis. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the	- Systematic review. Checked for possible includes

Study	Code [Reason]
Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians: 1-8	
Apostolopoulou, E.; Lambridou, M.; Lambadaridis, I. (2004) Nosocomial bloodstream infections in a neonatal intensive care unit. British journal of nursing (Mark Allen Publishing) 13(13): 806-812	- Not a multivariate analysis
Appelgren, P., Hellstrom, I., Weitzberg, E. et al. (2001) Risk factors for nosocomial intensive care infection: A long-term prospective analysis. Acta Anaesthesiologica Scandinavica 45(6): 710-719	- Population does not match the protocol [Infection in adults]
Arayici, Sema, Kadioglu Simsek, Gulsum, Oncel, Mehmet Yekta et al. (2014) The effect of histological chorioamnionitis on the short-term outcome of preterm infants <=32 weeks: a single-center study. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 27(11): 1129-33	- Statistical outcomes do not match those specified in the protocol
Baizat, M., Zaharie, G., Iancu, M. et al. (2019) Potential clinical predictors of suspected early and late onset sepsis (EOS and LOS) in preterm newborns: A single tertiary center retrospective study. Clinical Laboratory 65(7): 1299-1308	- Based in non-OECD country
Balagtas, R C, Bell, C E, Edwards, L D et al. (1971) Risk of local and systemic infections associated with umbilical vein catheterization: a prospective study in 86 newborn patients. Pediatrics 48(3): 359-67	- Outcome to be predicted do not match that specified in the protocol
Baltimore, R.S. (1998) Neonatal nosocomial infections. Seminars in Perinatology 22(1): 25-32	- Review article but not a systematic review
Barcaite, E., Bartusevicius, A., Tameliene, R. et al. (2012) Group B streptococcus and Escherichia coli colonization in pregnant women and neonates in Lithuania. International Journal of Gynecology and Obstetrics 117(1): 69-73	- Reference standard in study does not match that specified in protocol [Not blood culture]
Bastek, J.A., Sammel, M.D., Pare, E. et al. (2008) Adverse neonatal outcomes: examining the risks between preterm, late preterm, and term infants. American Journal of Obstetrics and Gynecology 199(4): 367	- Not a multivariate analysis
Benitz, W E; Gould, J B; Druzin, M L (1999) Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 103(6): e77	- Systematic review. Reference list checked for possible includes

Study	Code [Reason]
Berardi, Alberto, Lugli, Licia, Baronciani, Dante et al. (2007) Group B streptococcal infections in a northern region of Italy. Pediatrics 120(3): e487-93	- Statistical outcomes do not match those specified in the protocol
Berardi, Alberto, Rossi, Cecilia, Guidotti, Isotta et al. (2014) Factors associated with intrapartum transmission of group B Streptococcus. The Pediatric infectious disease journal 33(12): 1211-5	- Outcome to be predicted do not match that specified in the protocol [Neonatal colonisation but not infection]
Berlak, Neta, Shany, Eilon, Ben-Shimol, Shalom et al. (2018) Late onset sepsis: comparison between coagulase-negative staphylococci and other bacteria in the neonatal intensive care unit. Infectious diseases (London, England) 50(10): 764-770	- Late-onset definition included sepsis beyond 28 days of age/corrected gestational age [Definition includes infection up to 90 days] - Outcome to be predicted do not match that specified in the protocol [Multivariate model predicted CONS vs non-CONS sepsis]
Bizzarro, Matthew J, Jiang, Yuan, Hussain, Naveed et al. (2011) The impact of environmental and genetic factors on neonatal late-onset sepsis. The Journal of pediatrics 158(2): 234-8e1	- Statistical outcomes do not match those specified in the protocol [Model coefficients but not odds/risk ratios]
Bizzarro, Matthew J, Raskind, Craig, Baltimore, Robert S et al. (2005) Seventy-five years of neonatal sepsis at Yale: 1928-2003. Pediatrics 116(3): 595-602	- Statistical outcomes do not match those specified in the protocol
Bonadio, W A, Lehrmann, M, Hennes, H et al. (1991) Relationship of temperature pattern and serious bacterial infections in infants 4 to 8 weeks old 24 to 48 hours after antibiotic treatment. Annals of emergency medicine 20(9): 1006-8	- Statistical outcomes do not match those specified in the protocol
Bonifacio, Lea, Petrova, Anna, Nanjundaswamy, Shakuntala et al. (2007) Thrombocytopenia related neonatal outcome in preterms. Indian journal of pediatrics 74(3): 269-74	- Study design does not match the protocol
Braun, D., Bromberger, P., Ho, N.J. et al. (2015) Low Rate of Perinatal Sepsis in Term Infants of Mothers with Chorioamnionitis. American Journal of Perinatology 33(2): 143-150	- Statistical outcomes do not match those specified in the protocol
Braye, Kathryn, Ferguson, John, Davis, Deborah et al. (2018) Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B Streptococcal infection: An integrative review. Women and birth : journal of the Australian College of Midwives 31(4): 244-253	- Systematic review. Reference list checked for possible includes
Brigtsen, Anne Karin, Jacobsen, Anne Flem, Dedi, Lumnije et al. (2015) Maternal Colonization with Group B Streptococcus Is Associated with an Increased Rate of Infants	- Reference standard in study does not match that specified in protocol [Probable early-onset infection]

Study	Code [Reason]
Transferred to the Neonatal Intensive Care Unit. Neonatology 108(3): 157-63	
Brooker, R W and Keenan, W J (2007) Catheter related bloodstream infection following PICC removal in preterm infants. Journal of perinatology : official journal of the California Perinatal Association 27(3): 171-4	- Statistical outcomes do not match those specified in the protocol
Buhimschi, Catalin S, Abdel-Razeq, Sonya, Cackovic, Michael et al. (2008) Fetal heart rate monitoring patterns in women with amniotic fluid proteomic profiles indicative of inflammation. American journal of perinatology 25(6): 359-72	- Predictive factors do not match the protocol [Heart rate in the foetus, not the baby]
Cairns, P A, Wilson, D C, McClure, B G et al. (1995) Percutaneous central venous catheter use in the very low birth weight neonate. European journal of pediatrics 154(2): 145-7	- Article does not distinguish between early and late-onset infections
Cantey, Joseph B, Anderson, Kelsey R, Kalagiri, Ram R et al. (2018) Morbidity and mortality of coagulase-negative staphylococcal sepsis in very-low-birth-weight infants. World journal of pediatrics : WJP 14(3): 269-273	- Outcome to be predicted do not match that specified in the protocol
Cantey, Joseph B, Pyle, Alaina K, Wozniak, Phillip S et al. (2018) Early Antibiotic Exposure and Adverse Outcomes in Preterm, Very Low Birth Weight Infants. The Journal of pediatrics 203: 62-67	- Outcome to be predicted do not match that specified in the protocol
Casner, Michael, Hoesli, Sandra J, Slaughter, James C et al. (2014) Incidence of catheter-related bloodstream infections in neonates following removal of peripherally inserted central venous catheters. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 15(1): 42-8	- Not a multivariate analysis
Chan, Grace J, Lee, Anne C C, Baqui, Abdullah H et al. (2015) Prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonization: a systematic review and meta-analysis. BMC infectious diseases 15: 118	- Systematic review. Checked for possible includes
Chapman Evelina, Reveiz Ludovic, Illanes Eduardo, Bonfill Cosp Xavier (2014) Antibiotic regimens for management of intra-amniotic infection. Cochrane Database of Systematic Reviews: Reviews issue12	- Review protocol
Chen, Z., Wu, C., Cao, X. et al. (2018) Risk factors for neonatal group B streptococcus vertical transmission: a prospective cohort study of 1815 mother-baby pairs. Journal of Perinatology 38(10): 1309-1317	- Based in non-OECD country

Study	Code [Reason]
Cheng, Hao-Yuan, Lu, Chun-Yi, Huang, Li-Min et al. (2016) Increased frequency of peripheral venipunctures raises the risk of central-line associated bloodstream infection in neonates with peripherally inserted central venous catheters. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi 49(2): 230-6	- Study design does not match the protocol
Cheng, Y W, Kaimal, A J, Bruckner, T A et al. (2011) Perinatal morbidity associated with late preterm deliveries compared with deliveries between 37 and 40 weeks of gestation. BJOG : an international journal of obstetrics and gynaecology 118(12): 1446-54	- Outcome to be predicted do not match that specified in the protocol
Chien, Li-Yin, Macnab, Ying, Aziz, Khalid et al. (2002) Variations in central venous catheter-related infection risks among Canadian neonatal intensive care units. The Pediatric infectious disease journal 21(6): 505-11	- Statistical outcomes do not match those specified in the protocol
Churgay, C A; Smith, M A; Blok, B (1994) Maternal fever during labor--what does it mean?. The Journal of the American Board of Family Practice 7(1): 14-24	- Reference standard in study does not match that specified in protocol
Colicchia, L C, Lauderdale, D S, Du, H et al. (2015) Recurrence of group B streptococcus colonization in successive pregnancies. Journal of perinatology : official journal of the California Perinatal Association 35(3): 173-6	- Outcome to be predicted do not match that specified in the protocol
Cuna, Alain, Hakima, Laleh, Tseng, Yun-An et al. (2014) Clinical dilemma of positive histologic chorioamnionitis in term newborn. Frontiers in pediatrics 2: 27	- Outcome to be predicted do not match that specified in the protocol [Combination of confirmed and suspected infection]
da Silva, H.D. and Kretli Winkelstroter, L. (2019) Universal gestational screening for Streptococcus agalactiae colonization and neonatal infection - A systematic review and meta-analysis. Journal of Infection and Public Health 12(4): 479-481	- Systematic review. Reference list checked for possible includes
Daniels, J., Gray, J., Pattison, H. et al. (2009) Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness. Health technology assessment (Winchester, England) 13(42)	- Outcome to be predicted do not match that specified in the protocol
Davis, J. and Lehman, E. (2019) Fever Characteristics and Risk of Serious Bacterial Infection in Febrile Infants. Journal of Emergency Medicine 57(3): 306-313	- Study does not contain statistical outcomes of interest *Odds ratios not adjusted for confounding variables*

Study	Code [Reason]
Demir, Nihat, Peker, Erdal, Gulsen, Ismail et al. (2015) Factors affecting infection development after meningomyelocele repair in newborns and the efficacy of antibiotic prophylaxis. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery 31(8): 1355-9	- Outcome to be predicted do not match that specified in the protocol
Dior, Uri P, Kogan, Liron, Calderon-Margalit, Ronit et al. (2014) The association of maternal intrapartum subfebrile temperature and adverse obstetric and neonatal outcomes. Paediatric and perinatal epidemiology 28(1): 39-47	- Early-onset neonatal infection
Erdemir, Gulin, Kultursay, Nilgun, Calkavur, Sebnem et al. (2013) Histological chorioamnionitis: effects on premature delivery and neonatal prognosis. Pediatrics and neonatology 54(4): 267-74	- Statistical outcomes do not match those specified in the protocol
Eriksen, N.L. and Blanco, J.D. (1995) Group B streptococcus in pregnancy. Female Patient - OB/GYN Edition 20(10): 25-33	- Review article but not a systematic review
Escalante, Maria Jose, Ceriani-Cernadas, Jose Maria, D'Apremont, Ivonne et al. (2018) Late Onset Sepsis in Very Low Birth Weight Infants in the South American NEOCOSUR Network. The Pediatric infectious disease journal 37(10): 1022-1027	- Based in non-OECD country
Fajardo, C.; Alshaikh, B.; Harabor, A. (2019) Prolonged use of antibiotics after birth is associated with increased morbidity in preterm infants with negative cultures. Journal of Maternal-Fetal and Neonatal Medicine 32(24): 4060-4066	- Outcome to be predicted do not match that specified in the protocol
Fanaroff, A A, Korones, S B, Wright, L L et al. (1998) Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. The National Institute of Child Health and Human Development Neonatal Research Network. The Pediatric infectious disease journal 17(7): 593-8	- Late-onset definition included sepsis beyond 28 days of age/corrected gestational age [LOS defined from 96 days from birth]
Femitha, P and Bhat, B Vishnu (2012) Early neonatal outcome in late preterms. Indian journal of pediatrics 79(8): 1019-24	- Based in non-OECD country
Foglia, E.; Meier, M.D.; Elward, A. (2007) Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients. Clinical Microbiology Reviews 20(3): 409-425	- Review article but not a systematic review
Fortunov, Regine M, Hulten, Kristina G, Hammerman, Wendy A et al. (2006) Community-acquired Staphylococcus aureus infections in term and near-term previously healthy neonates. Pediatrics 118(3): 874-81	- Outcome to be predicted do not match that specified in the protocol [Predicted localised infections]

Study	Code [Reason]
Fraser, D; Picard, R; Picard, E (1991) Factors associated with neonatal problems in twin gestations. Acta geneticae medicae et gemellologiae 40(2): 193-200	- Outcome to be predicted do not match that specified in the protocol
Frohlicher, Simone, Reichen-Fahrni, Gabriela, Muller, Martin et al. (2014) Serotype distribution and antimicrobial susceptibility of group B streptococci in pregnant women: results from a Swiss tertiary centre. Swiss medical weekly 144: w13935	- Outcome to be predicted do not match that specified in the protocol
Fryklund, B.; Tullus, K.; Burman, L.G. (1993) Relation between nursing procedures, other local characteristics and transmission of enteric bacteria in neonatal wards. Journal of Hospital Infection 23(3): 199-210	- Study design does not match the protocol
Furman, B, Shoham-Vardi, I, Bashiri, A et al. (2000) Clinical significance and outcome of preterm prelabor rupture of membranes: population-based study. European journal of obstetrics, gynecology, and reproductive biology 92(2): 209-16	- Outcome to be predicted do not match that specified in the protocol
Gagliardi, Luigi, Rusconi, Franca, Bellu, Roberto et al. (2014) Association of maternal hypertension and chorioamnionitis with preterm outcomes. Pediatrics 134(1): e154-61	- Outcome to be predicted do not match that specified in the protocol
Galanakis, Emmanouil, Krallis, Nikolaos, Levidiotou, Stamatia et al. (2002) Neonatal bacteraemia: a population-based study. Scandinavian journal of infectious diseases 34(8): 598-601	- Not a multivariate analysis [Insufficient data reported for results of multivariate analysis]
Garland, S M; Kelly, N; Ugoni, A M (2000) Is antenatal group B streptococcal carriage a predictor of adverse obstetric outcome?. Infectious diseases in obstetrics and gynecology 8(34): 138-42	- Study design does not match the protocol
Geslain, G., Guellec, I., Guedj, R. et al. (2018) Incidence and risk factors of ventilator-associated pneumonia in neonatal intensive care unit: A first French study. Minerva Anestesiologica 84(7): 829-835	- Outcome to be predicted do not match that specified in the protocol
Giapros, Vasileios, Drougia, Aikaterini, Krallis, Nikolaos et al. (2012) Morbidity and mortality patterns in small-for-gestational age infants born preterm. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 25(2): 153-7	- Outcome to be predicted do not match that specified in the protocol
Gilbert, G L, Hewitt, M C, Turner, C M et al. (2002) Epidemiology and predictive values of	- Outcome to be predicted do not match that specified in the protocol

Study	Code [Reason]
risk factors for neonatal group B streptococcal sepsis. The Australian & New Zealand journal of obstetrics & gynaecology 42(5): 497-503	[Maternal outcomes not neonatal infection]
Gowda, Harsha, Norton, Robert, White, Andrew et al. (2017) Late-onset Neonatal Sepsis-A 10-year Review From North Queensland, Australia. The Pediatric infectious disease journal 36(9): 883-888	- Statistical outcomes do not match those specified in the protocol
Gupta, P, Faridi, M M, Goel, N et al. (2014) Reappraisal of twinning: epidemiology and outcome in the early neonatal period. Singapore medical journal 55(6): 310-7	- Based in non-OECD country
Haase, R, Worlitzsch, D, Schmidt, F et al. (2014) Colonization and infection due to multi-resistant bacteria in neonates: a single center analysis. Klinische Padiatrie 226(1): 8-12	- Reference standard in study does not match that specified in protocol
Hall, S.L. (1991) Coagulase-negative staphylococcal infections in neonates. Pediatric Infectious Disease Journal 10(1): 57-67	- Review article but not a systematic review
Haque, K.N., Khan, A., Kerry, S. et al. (2004) Pattern of culture-proven neonatal sepsis in a district general hospital in the United Kingdom. Infection Control and Hospital Epidemiology 25(9): 759-764	- Statistical outcomes do not match those specified in the protocol [Not multivariate analysis]
Hiersch, Liran, Krispin, Eyal, Linder, Nehama et al. (2017) Meconium-Stained Amniotic Fluid and Neonatal Morbidity in Low-Risk Pregnancies at Term: The Effect of Gestational Age. American journal of perinatology 34(2): 183-190	- Predictive factors do not match the protocol
Holmes, A, Dore, C J, Saraswatula, A et al. (2008) Risk factors and recommendations for rate stratification for surveillance of neonatal healthcare-associated bloodstream infection. The Journal of hospital infection 68(1): 66-72	- Statistical outcomes do not match those specified in the protocol [Incidence rate ratios not specified in protocol]
Holmgren, P A and Hogberg, U (2001) The very preterm infant - a population-based study. Acta obstetricia et gynecologica Scandinavica 80(6): 525-31	- Outcome to be predicted do not match that specified in the protocol
Hufnagel, Markus, Liese, Cathrin, Loescher, Claudia et al. (2007) Enterococcal colonization of infants in a neonatal intensive care unit: associated predictors, risk factors and seasonal patterns. BMC infectious diseases 7: 107	- Reference standard in study does not match that specified in protocol
Hung, Po-Pin, Lin, Yu-Hui, Lin, Chin-Fu et al. (2008) Chryseobacterium meningosepticum infection: antibiotic susceptibility and risk factors for mortality. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi 41(2): 137-44	- Based in non-OECD country

Study	Code [Reason]
Itakura, A, Kurauchi, O, Morikawa, S et al. (1996) A prospective study on the relationship between intrapartum maternal group-B streptococcal concentration and signs of infection in neonates. The journal of obstetrics and gynaecology research 22(2): 101-5	- Statistical outcomes do not match those specified in the protocol
Jaiswal, Ashish, Murki, Srinivas, Gaddam, Pramod et al. (2011) Early neonatal morbidities in late preterm infants. Indian pediatrics 48(8): 607-11	- Based in non-OECD country
Jimenez-Truque, N., Tedeschi, S., Saye, E.J. et al. (2012) Relationship between maternal and neonatal Staphylococcus aureus colonization. Pediatrics 129(5): e1252-e1259	- Outcome to be predicted do not match that specified in the protocol
Kilic, A., Okulu, E., Kocabas, B.A. et al. (2019) Health care-associated infection surveillance: A prospective study of a tertiary neonatal intensive care unit. Journal of Infection in Developing Countries 13(3): 181-187	- Reference standard in study does not match that specified in protocol [Excluded following discussion with committee]
Kim, S.J., Kim, G.E., Park, J.H. et al. (2019) Clinical features and prognostic factors of early-onset sepsis: A 7.5-year experience in one neonatal intensive care unit. Korean Journal of Pediatrics 62(1): 36-41	- Outcome to be predicted do not match that specified in the protocol [Early-onset mortality]
Klinger, G, Osovsky, M, Boyko, V et al. (2016) Risk factors associated with post-hemorrhagic hydrocephalus among very low birth weight infants of 24-28 weeks gestation. Journal of perinatology : official journal of the California Perinatal Association 36(7): 557-63	- Outcome to be predicted do not match that specified in the protocol
Ko, H.S., Jang, Y.-R., Yun, H. et al. (2019) Late-preterm infants, early-term infants, and timing of elective deliveries; current status in a Korean medical center. Journal of Maternal-Fetal and Neonatal Medicine 32(8): 1267-1274	- Includes suspected and proved infections. Results not reported separately
Kojima, Katsuaki, Tanaka, Ryuma, Nakajima, Keisuke et al. (2014) Predicting outcomes of neonates born to GBS-positive women who received inadequate intrapartum antimicrobial prophylaxis. The Turkish journal of pediatrics 56(3): 238-42	- Statistical outcomes do not match those specified in the protocol [Does not include multivariate analysis]
Lee, Soon Min; Chang, Meayoung; Kim, Ki-Soo (2015) Blood Culture Proven Early Onset Sepsis and Late Onset Sepsis in Very-Low-Birth-Weight Infants in Korea. Journal of Korean medical science 30suppl1: 67-74	- Statistical outcomes do not match those specified in the protocol
LeFlore, Judy L and Engle, William D (2007) Comparison of nonelective removal of percutaneously versus surgically placed central venous catheters in high-risk neonates. Journal	- Reference standard in study does not match that specified in protocol

Study	Code [Reason]
of the American Academy of Nurse Practitioners 19(3): 111-5	
Levit, Orly, Bhandari, Vineet, Li, Fang-Yong et al. (2014) Clinical and laboratory factors that predict death in very low birth weight infants presenting with late-onset sepsis. The Pediatric infectious disease journal 33(2): 143-6	- Outcome to be predicted do not match that specified in the protocol
Li, R., Cao, X., Shi, T. et al. (2019) Application of peripherally inserted central catheters in critically ill newborns experience from a neonatal intensive care unit. Medicine (United States) 98(32): e15837	- Outcome to be predicted do not match that specified in the protocol
Li, Shunming, Huang, Jingya, Chen, Zhiyao et al. (2017) Antibiotic Prevention for Maternal Group B Streptococcal Colonization on Neonatal GBS-Related Adverse Outcomes: A Meta-Analysis. Frontiers in microbiology 8: 374	- Systematic review. Checked for possible includes
Lieu, T.A., Mohle-Boetani, J.C., Ray, G.T. et al. (1998) Neonatal group B streptococcal infection in a managed care population. Obstetrics and Gynecology 92(1): 21-27	- Statistical outcomes do not match those specified in the protocol
Lin, Y.-W.; Tsao, L.-Y.; Chen, H.-N. (2001) Neonatal group B streptococcal infection: An 11-year retrospective study. Clinical Neonatology 8(2): 13-17	- Full text paper not available
Linder, N, Hiersch, L, Fridman, E et al. (2015) The effect of gestational age on neonatal outcome in low-risk singleton term deliveries. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 28(3): 297-302	- Outcome to be predicted do not match that specified in the protocol [No information on timing of sepsis]
Lindquist, Simon, Hentz, Elisabet, Tessin, Ingemar et al. (2016) Very low birthweight infants face an increased risk of bloodstream infections following the removal of umbilical catheters. Acta paediatrica (Oslo, Norway : 1992) 105(4): 391-6	- Not a multivariate analysis
Liston, T E, Harris, R E, Foshee, S et al. (1979) Relationship of neonatal pneumonia to maternal urinary and neonatal isolates of group B streptococci. Southern medical journal 72(11): 1410-2	- Early-onset neonatal infection - Reference standard in study does not match that specified in protocol [Positive culture from blood, CSF, urine, throat or gastric aspirate]
Mahieu, L M, De Muynck, A O, Ieven, M M et al. (2001) Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. The Journal of hospital infection 48(2): 108-16	- Article does not distinguish between early and late-onset infections

Study	Code [Reason]
Malik, R.K., Montecalvo, M.A., Reale, M.R. et al. (1999) Epidemiology and control of vancomycin-resistant enterococci in a regional neonatal intensive care unit. Pediatric Infectious Disease Journal 18(4): 352-356	- Outcome to be predicted do not match that specified in the protocol
Maraqa, Nizar F, Aigbivbalu, Lemuel, Masnita-Iusan, Carmen et al. (2011) Prevalence of and risk factors for methicillin-resistant Staphylococcus aureus colonization and infection among infants at a level III neonatal intensive care unit. American journal of infection control 39(1): 35-41	- Statistical outcomes do not match those specified in the protocol
Marostica, P J; Raskin, S; Abreu-e-Silva, F A (1998) Analysis of the delta F508 mutation in a Brazilian cystic fibrosis population: comparison of pulmonary status of homozygotes with other patients. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 31(4): 529-32	- Population does not match the protocol
Martin, Camilia R, Dasilva, Deborah A, Cluette-Brown, Joanne E et al. (2011) Decreased postnatal docosahexaenoic and arachidonic acid blood levels in premature infants are associated with neonatal morbidities. The Journal of pediatrics 159(5): 743-2	- Outcome to be predicted do not match that specified in the protocol
Martius, J A, Roos, T, Gora, B et al. (1999) Risk factors associated with early-onset sepsis in premature infants. European journal of obstetrics, gynecology, and reproductive biology 85(2): 151-8	- Reference standard in study does not match that specified in protocol [Does not include blood culture]
McKenna, D.S. and Iams, J.D. (1998) Group B streptococcal infections. Seminars in Perinatology 22(4): 267-276	- Review article but not a systematic review
Milstone, Aaron M, Reich, Nicholas G, Advani, Sonali et al. (2013) Catheter dwell time and CLABSIs in neonates with PICCs: a multicenter cohort study. Pediatrics 132(6): e1609-15	- Outcome to be predicted do not match that specified in the protocol
Miyazaki, Ken, Furuhashi, Madoka, Ishikawa, Kaoru et al. (2016) Impact of chorioamnionitis on short- and long-term outcomes in very low birth weight preterm infants: the Neonatal Research Network Japan. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(2): 331-7	- Outcome to be predicted do not match that specified in the protocol [No information on timing of infection]
Moffa, Michelle, Guo, Wilson, Li, Trudy et al. (2017) A systematic review of nosocomial waterborne infections in neonates and mothers.	- Systematic review. Checked for possible includes

Study	Code [Reason]
International journal of hygiene and environmental health 220(8): 1199-1206	
Money, D. and Allen, V.M. (2018) No. 298-The Prevention of Early-Onset Neonatal Group B Streptococcal Disease. Journal of Obstetrics and Gynaecology Canada 40(8): e665-e674	- Review article but not a systematic review
Mount, V., Burton, C., Jackson, C. et al. (2017) Neonatal invasive pneumococcal disease: New Zealand experience in the era of pneumococcal vaccination. Australian and New Zealand Journal of Obstetrics and Gynaecology 57(3): 280-285	- Statistical outcomes do not match those specified in the protocol
Mulloy, R H; Jadavji, T; Russell, M L (1991) Tunneled central venous catheter sepsis: risk factors in a pediatric hospital. JPEN. Journal of parenteral and enteral nutrition 15(4): 460-3	- Population does not match the protocol [Paediatrics up to 18 years of age]
Negara, K.T., Ryan, S.M., Endang, W. et al. (2017) Chorioamnionitis and funisitis increase the risk of preterm labor and early onset neonatal sepsis. Biomedical and Pharmacology Journal 10(2): 767-772	- Outcome to be predicted do not match that specified in the protocol [Criteria for infection not defined]
Ogunyemi, D, Murillo, M, Jackson, U et al. (2003) The relationship between placental histopathology findings and perinatal outcome in preterm infants. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 13(2): 102-9	- Reference standard in study does not match that specified in protocol [Positive culture from blood, cerebrospinal fluid, urine or tracheal aspirates]
Ohlsson, Arne; Shah, Vibhuti S; Stade, Brenda C (2014) Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. The Cochrane database of systematic reviews: cd003520	- Study design does not match the protocol
Olsen, Anne L, Reinholdt, Jes, Jensen, Anders Morup et al. (2009) Nosocomial infection in a Danish Neonatal Intensive Care Unit: a prospective study. Acta paediatrica (Oslo, Norway : 1992) 98(8): 1294-9	- Statistical outcomes do not match those specified in the protocol [Insufficient information provided for multivariate model results] - Reference standard in study does not match that specified in protocol [Included non-culture proven infections]
Olukman, Ozgur, Ozdemir, Rahmi, Karadeniz, Cem et al. (2017) Is there a relationship between platelet parameters and patency of ductus arteriosus in preterm infants?. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 28(1): 8-13	- Outcome to be predicted do not match that specified in the protocol

Study	Code [Reason]
Ono, Y., Takagi, K., Seki, H. et al. (2013) Neonatal outcome in infants of chronically hypertensive mothers. Journal of Obstetrics and Gynaecology Research 39(6): 1142-1146	- Outcome to be predicted do not match that specified in the protocol
Ovalle, A., Kakarieka, E., Rencoret, G. et al. (2012) Risk factors for preterm deliveries in a public hospital. Revista Medica de Chile 140(1): 19-29	- Study not reported in English
Pappas, Athina, Kendrick, Douglas E, Shankaran, Seetha et al. (2014) Chorioamnionitis and early childhood outcomes among extremely low-gestational-age neonates. JAMA pediatrics 168(2): 137-47	- Outcome to be predicted do not match that specified in the protocol
Parea, M., Goglio, A., Natale, N. et al. (1994) Neonatal early-onset Streptococcus agalactiae disease and maternal risk factors: A six-year retrospective study. Alpe Adria Microbiology Journal 3(3): 187-193	- Study design does not match the protocol
Parente, V, Clark, R H, Ku, L et al. (2017) Risk factors for group B streptococcal disease in neonates of mothers with negative antenatal testing. Journal of perinatology : official journal of the California Perinatal Association 37(2): 157-161	- Reference standard in study does not match that specified in protocol [Positive blood, CSF or urine culture]
Pass, M.A., Gray, B.M., Khare, S. et al. (1979) Prospective studies of group B streptococcal infections in infants. Journal of Pediatrics 95(3): 437-443	- Statistical outcomes do not match those specified in the protocol
Patel, A and Musoke, R N (1987) Risk of infections associated with umbilical vein catheterisation in newborn patients. East African medical journal 64(3): 232-6	- Based in non-OECD country
Perez-Moreno, Mar Olga, Pico-Plana, Ester, Grande-Armas, Jesus et al. (2017) Group B streptococcal bacteriuria during pregnancy as a risk factor for maternal intrapartum colonization: a prospective cohort study. Journal of medical microbiology 66(4): 454-460	- Outcome to be predicted do not match that specified in the protocol
Perlman, Sharon E; Saiman, Lisa; Larson, Elaine L (2007) Risk factors for late-onset health care-associated bloodstream infections in patients in neonatal intensive care units. American journal of infection control 35(3): 177-82	- Not a multivariate analysis
Pessoa-Silva, Carmem Lucia, Hugonnet, Stephane, Pfister, Riccardo et al. (2007) Reduction of health care associated infection risk in neonates by successful hand hygiene promotion. Pediatrics 120(2): e382-90	- Conference abstract

Study	Code [Reason]
Petrova, A., Demissie, K., Rhoads, G.G. et al. (2001) Association of maternal fever during labor with neonatal and infant morbidity and mortality. Obstetrics and Gynecology 98(1): 20-27	- Outcome to be predicted do not match that specified in the protocol
Ponnusamy, Vennila, Perperoglou, Aris, Venkatesh, Vidheya et al. (2014) Skin colonisation at the catheter exit site is strongly associated with catheter colonisation and catheter-related sepsis. Acta paediatrica (Oslo, Norway : 1992) 103(12): 1233-8	- Considered under invesigations for late-onset sepsis review question
Puopolo, Karen M, Mukhopadhyay, Sagori, Hansen, Nellie I et al. (2017) Identification of Extremely Premature Infants at Low Risk for Early-Onset Sepsis. Pediatrics 140(5)	- Reference standard in study does not match that specified in protocol
Rabier, V, Bataillon, S, Jolivet-Gougeon, A et al. (2008) Hand washing soap as a source of neonatal Serratia marcescens outbreak. Acta paediatrica (Oslo, Norway : 1992) 97(10): 1381-5	- Study design does not match the protocol
Ran, N.C.; van den Hoogen, A.; Hemels, M.A.C. (2019) Gram-negative Late-onset Sepsis in Extremely Low Birth Weight Infants Is Emerging in The Netherlands Despite Quality Improvement Programs and Antibiotic Stewardship!. The Pediatric infectious disease journal 38(9): 952-957	- Statistical outcomes do not match those specified in the protocol
Rangel, U.V., Gomes Junior, S.C., Costa, A.M. et al. (2014) Variables associated with peripherally inserted central catheter related infection in high risk newborn infants. Revista latino-americana de enfermagem 22(5): 842-847	- Based in non-OECD country
Regan, J A, Klebanoff, M A, Nugent, R P et al. (1996) Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. American journal of obstetrics and gynecology 174(4): 1354-60	- Outcome to be predicted do not match that specified in the protocol
Rosado, Viviane, Camargos, Paulo A M, Anchieta, Leni M et al. (2018) Risk factors for central venous catheter-related infections in a neonatal population - systematic review. Jornal de pediatria 94(1): 3-14	- Based in non-OECD country
Rosenstein, N E and Schuchat, A (1997) Opportunities for prevention of perinatal group B streptococcal disease: a multistate surveillance analysis. The Neonatal Group B Streptococcal Disease Study Group. Obstetrics and gynecology 90(6): 901-6	- Statistical outcomes do not match those specified in the protocol
Roy, K K, Baruah, Jinee, Kumar, Sunesh et al. (2006) Maternal antenatal profile and immediate	- Based in non-OECD country

Study	Code [Reason]
neonatal outcome in VLBW and ELBW babies. Indian journal of pediatrics 73(8): 669-73	
Saiman, L. (2002) Risk factors for hospital-acquired infections in the neonatal intensive care unit. Seminars in Perinatology 26(5): 315-321	- Review article but not a systematic review
Sengupta, Arnab, Lehmann, Christoph, Diener-West, Marie et al. (2010) Catheter duration and risk of CLA-BSI in neonates with PICCs. Pediatrics 125(4): 648-53	- Statistical outcomes do not match those specified in the protocol [Incidence rate ratio not specified in protocol]
Sensini, A., Tissi, L., Verducci, N. et al. (1997) Carriage of group B streptococcus in pregnant women and newborns: A 2-year study at Perugia General Hospital. Clinical Microbiology and Infection 3(3): 324-328	- Statistical outcomes do not match those specified in the protocol
Seo, K; McGregor, J A; French, J I (1992) Preterm birth is associated with increased risk of maternal and neonatal infection. Obstetrics and gynecology 79(1): 75-80	- Population does not match the protocol
Seybold, Ulrich, Halvosa, J Sue, White, Nancy et al. (2008) Emergence of and risk factors for methicillin-resistant Staphylococcus aureus of community origin in intensive care nurseries. Pediatrics 122(5): 1039-46	- Outcome to be predicted do not match that specified in the protocol
Shah, Jyotsna, Jefferies, Ann L, Yoon, Eugene W et al. (2015) Risk Factors and Outcomes of Late-Onset Bacterial Sepsis in Preterm Neonates Born at < 32 Weeks' Gestation. American journal of perinatology 32(7): 675-82	- Outcome to be predicted do not match that specified in the protocol [Considers how late-onset infection predicts other outcomes rather than factors that predict infection]
Shakil, S, Ali, S Z, Akram, M et al. (2010) Risk factors for extended-spectrum beta-lactamase producing Escherichia coli and Klebsiella pneumoniae acquisition in a neonatal intensive care unit. Journal of tropical pediatrics 56(2): 90-6	- Based in non-OECD country
Shalabi, Mohamed, Adel, Mohamed, Yoon, Eugene et al. (2015) Risk of Infection Using Peripherally Inserted Central and Umbilical Catheters in Preterm Neonates. Pediatrics 136(6): 1073-9	- Study design does not match the protocol
Shariati, M.K., Karimi, Z., Rezaienejad, M. et al. (2015) Perinatal complications associated with preterm deliveries at 24 to 33 weeks and 6 days gestation (2011-2012): A hospital-based retrospective study. International Journal of Reproductive BioMedicine 13(11): 697-702	- Based in non-OECD country
Sharma, Deepak, Kumar, Chetan, Pandita, Aakash et al. (2016) Bacteriological profile and clinical predictors of ESBL neonatal sepsis. The journal of maternal-fetal & neonatal medicine :	- Based in non-OECD country

Study	Code [Reason]
the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(4): 567-70	
Shete, Vishal B, Ghadage, Dnyaneshwari P, Muley, Vrishali A et al. (2009) Acinetobacter septicemia in neonates admitted to intensive care units. Journal of laboratory physicians 1(2): 73-6	- Based in non-OECD country
Simarojana, N. and Pataradool, K. (2019) Effect of mode of delivery on neonatal outcomes of appropriately grown preterm infants. Journal of the Medical Association of Thailand 102(9): 49-53	- Non-OECD country
Singh, S Amuchou; Dutta, Sourabh; Narang, Anil (2003) Predictive clinical scores for diagnosis of late onset neonatal septicemia. Journal of tropical pediatrics 49(4): 235-9	- Based in non-OECD country
Skworc, Aneta; Marciniak, Sylwia; Slawska, Helena (2020) Influence of infections on the quality of general movements in premature infants. Early human development 148: 105118	- Study does not contain outcomes of interest
Smulian, J C, Shen-Schwarz, S, Vintzileos, A M et al. (1999) Clinical chorioamnionitis and histologic placental inflammation. Obstetrics and gynecology 94(6): 1000-5	- Reference standard in study does not match that specified in protocol
Soares, Beatriz Nicolau, Pissarra, Susana, Rouxinol-Dias, Ana Lidia et al. (2018) Complications of central lines in neonates admitted to a level III Neonatal Intensive Care Unit. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 31(20): 2770-2776	- Outcome to be predicted do not match that specified in the protocol
Steele, R.W. (1993) Control of neonatal group B streptococcal infection. Journal of the Royal Society of Medicine 86(12): 712-715	- Article commentary
Steiner, L.; Diesner, S.C.; Voitl, P. (2019) Risk of infection in the first year of life in preterm children: An Austrian observational study. PLoS ONE 14(12): e0224766	- Study does not contain statistical outcomes of interest
Stoll, Barbara J, Hansen, Nellie, Fanaroff, Avroy A et al. (2002) Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 110(2pt1): 285-91	- Not a multivariate analysis

Study	Code [Reason]
Strus, M., Pawlik, D., Brzychczy-Wloch, M. et al. (2009) Group B streptococcus colonization of pregnant women and their children observed on obstetric and neonatal wards of the University hospital in krakow, Poland. Journal of Medical Microbiology 58(2): 228-233	- Outcome to be predicted do not match that specified in the protocol [GBS colonisation not infection]
Sullivan, Brynne A, McClure, Christina, Hicks, Jamie et al. (2016) Early Heart Rate Characteristics Predict Death and Morbidities in Preterm Infants. The Journal of pediatrics 174: 57-62	- Early-onset neonatal infection
Tabib, M.S., Nili, F., Nayeri, F. et al. (2008) Risk factors in neonatal anaerobic infections. Acta Medica Iranica 46(3): 245-248	- Not a multivariate analysis
Tafari, N. and Ljungh-Wadstrom, A. (1979) Consequences of amniotic fluid infections: early neonatal septicaemia. Ciba Foundation symposium: 55-67	- Statistical outcomes do not match those specified in the protocol
Tairy, D., Gluck, O., Tal, O. et al. (2019) Amniotic fluid transitioning from clear to meconium stained during labor-prevalence and association with adverse maternal and neonatal outcomes. Journal of Perinatology 39(10): 1349-1355	- Study does not contain outcomes of interest *Association with composite outcome which included sepsis. Association with sepsis not reported separately*
Thatrimontrichai, A., Rujeerapaiboon, N., Janjindamai, W. et al. (2017) Outcomes and risk factors of ventilator-associated pneumonia in neonates. World Journal of Pediatrics 13(4): 328-334	- Based in non-OECD country
Thompson, P.J., Greenough, A., Hird, M.F. et al. (1992) Nosocomial bacterial infections in very low birth weight infants. European Journal of Pediatrics 151(6): 451-454	- Study design does not match the protocol
Torres, D., Munoz, T., Bancalari, A. et al. (2018) Prolonged initial empirical antibiotic treatment and the risk of morbidity and mortality in very low birthweight infants. Revista Chilena de Pediatria 89(5): 600-605	- Not a multivariate analysis
Turner, J.; Flatley, C.; Kumar, S. (2020) Epidural use in labour is not associated with an increased risk of maternal or neonatal morbidity when the second stage is prolonged. Australian and New Zealand Journal of Obstetrics and Gynaecology 60(3): 336-343	- Study does not contain outcomes of interest *Does not report neonatal infection*
Venkatesh, Kartik K, Jackson, Wesley, Hughes, Brenna L et al. (2019) Association of chorioamnionitis and its duration with neonatal morbidity and mortality. Journal of perinatology : official journal of the California Perinatal Association 39(5): 673-682	- Study does not contain outcomes of interest *Association with composite neonatal outcome which included sepsis. Association with sepsis not reported separately*

Study	Code [Reason]
Vergnano, S, Embleton, N, Collinson, A et al. (2010) Missed opportunities for preventing group B streptococcus infection. Archives of disease in childhood. Fetal and neonatal edition 95(1): f72-3	- Statistical outcomes do not match those specified in the protocol
Videholm, S.; Silfverdal, S.-A.; Reniers, G. (2019) Maternal weight and infections in early childhood: A cohort study. Archives of Disease in Childhood 104(1): 58-63	- Population does not match the protocol [Children up to 5 years. Neonates not reported separately]
Viscomi, C M and Manullang, T (2000) Maternal fever, neonatal sepsis evaluation, and epidural labor analgesia. Regional anesthesia and pain medicine 25(5): 549-53	- Review article but not a systematic review
Vivian Ukah, U., Bayrampour, H., Sabr, Y. et al. (2019) Association between gestational weight gain and severe adverse birth outcomes in Washington State, US: A population-based retrospective cohort study, 2004-2013. PLoS Medicine 16(12): e1003009	- Study does not contain outcomes of interest
von Dadelszen, Peter, Kives, Sari, Delisle, Marie-France et al. (2003) The association between early membrane rupture, latency, clinical chorioamnionitis, neonatal infection, and adverse perinatal outcomes in twin pregnancies complicated by preterm prelabour rupture of membranes. Twin research : the official journal of the International Society for Twin Studies 6(4): 257-62	- Reference standard in study does not match that specified in protocol [Definition of infection includes many reference standards other than positive blood culture]
Voskamp, Bart Jan, Peelen, Myrthe J C S, Ravelli, Anita C J et al. (2020) Association between fetal sex, birthweight percentile and adverse pregnancy outcome. Acta obstetricia et gynecologica Scandinavica 99(1): 48-58	- Study does not contain statistical outcomes of interest
Wang, Joanna, Kortsalioudaki, Christina, Heath, Paul T et al. (2019) Epidemiology and healthcare factors associated with neonatal enterococcal infections. Archives of disease in childhood. Fetal and neonatal edition 104(5): f480-f485	- Reference standard in study does not match that specified in protocol [Reference standard was blood culture, cerebrospinal fluid culture or urine culture]
Wang, Li, Du, Ke-Ning, Zhao, Yan-Ling et al. (2019) Risk Factors of Nosocomial Infection for Infants in Neonatal Intensive Care Units: A Systematic Review and Meta-Analysis. Medical science monitor : international medical journal of experimental and clinical research 25: 8213-8220	- Systematic review. Reference list checked for possible includes
Werawatakul, Y., Wilailuckana, C., Taksaphan, S. et al. (2001) Prevalence and risk factors of Streptococcus agalactiae (group B) colonization	- Based in non-OECD country

Study	Code [Reason]
in mothers and neonatal contamination at Srinagarind Hospital. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 84(10): 1422-1429	
Wertheimer, A., Shemer, A., Hadar, E. et al. (2020) The effect of meconium-stained amniotic fluid on perinatal outcome in pregnancies complicated by preterm premature rupture of membranes. Archives of Gynecology and Obstetrics 301(5): 1181-1187	- Not a relevant study design *Case-control study*
Wilson, D; Verklan, M T; Kennedy, K A (2007) Randomized trial of percutaneous central venous lines versus peripheral intravenous lines. Journal of perinatology : official journal of the California Perinatal Association 27(2): 92-6	- Study design does not match the protocol
Xiao, Z., Li, Z., Zhong, Q. et al. (2013) 116 cases of neonatal early-onset or late-onset sepsis: A single center retrospective analysis on pathogenic bacteria species distribution and antimicrobial susceptibility. International Journal of Clinical and Experimental Medicine 6(8): 693-699	- Based in non-OECD country
Yalaz, Mehmet, Altun-Koroglu, Ozge, Ulusoy, Behiye et al. (2012) Evaluation of device-associated infections in a neonatal intensive care unit. The Turkish journal of pediatrics 54(2): 128-35	- Statistical outcomes do not match those specified in the protocol
Yancey, M K, Duff, P, Kubilis, P et al. (1996) Risk factors for neonatal sepsis. Obstetrics and gynecology 87(2): 188-94	- Outcome to be predicted do not match that specified in the protocol
Yumani, Dana F J; van den Dungen, Frank A M; van Weissenbruch, Mirjam M (2013) Incidence and risk factors for catheter-associated bloodstream infections in neonatal intensive care. Acta paediatrica (Oslo, Norway : 1992) 102(7): e293-8	- Statistical outcomes do not match those specified in the protocol [Rate ratios not specified in the protocol]
Zingg, Walter, Posfay-Barbe, Klara M, Pfister, Riccardo E et al. (2011) Individualized catheter surveillance among neonates: a prospective, 8-year, single-center experience. Infection control and hospital epidemiology 32(1): 42-9	- Reference standard in study does not match that specified in protocol [Included 'clinical sepsis']
Zonnenberg, I.A., van Dijk, J., van den Dungen, F.A.M. et al. (2019) The prognostic value of NIRS in preterm infants with (suspected) late-onset sepsis in relation to long term outcome: A pilot study. PLoS ONE 14(7): e0220044	- Outcome to be predicted do not match that specified in the protocol

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the accuracy of new or existing clinical prediction models for late-onset neonatal infection in the UK and what is their effectiveness in guiding management?

- for babies already on a neonatal unit
- for babies admitted from home

K.1.2 Why this is important

Eight studies were identified which evaluated the accuracy of clinical prediction models for late-onset neonatal infection, none of which were based in the UK and none which provided evidence of external validation. There was no evidence for the use of clinical prediction models for babies who were admitted to hospital from home.

Further research is needed using a robust study design such as prospective cohort studies, parallel RCTs or cluster RCTs to either examine the effectiveness of existing clinical prediction models for late-onset neonatal infection, or to develop new clinical prediction models designed for use in UK clinical practice. Research in this area is essential to help develop accurate methods of identifying babies most at risk of developing late-onset neonatal infection whilst avoiding over-prescribing of antibiotics.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Neonatal infection can have serious consequences if left untreated but can be difficult to diagnose. There are currently no prognostic tools validated for use in the UK to predict which babies are at high risk of late-onset neonatal infection. Consequently, many babies are being given antibiotic treatment while waiting for a culture result, and treatment is stopped if the culture result is negative. This results in some babies who do not have late-onset neonatal infection being given unnecessary antibiotic treatment. The development of a tool that can predict a babies' risk of late-onset neonatal infection will mean that decisions about whether a baby needs treatment can be made more quickly than waiting for a blood culture. This will ensure that those who need antibiotics will receive them quickly while reducing the number of babies who receive unnecessary antibiotics.
Relevance to NICE guidance	The committee were unable to make recommendations based on the current evidence for predictor tools for late-onset

	neonatal infection. Future research will help to develop validated risk prediction tools suitable for use in the UK.
Relevance to the NHS	The outcome would help to identify any prognostic models that can accurately predict a baby's risk of developing late-onset infection. This would help to ensure that babies who need antibiotic treatment receive this as quickly as possible, reducing potential side effects. This will also help to reduce the treatment costs associated with any side effects. Babies at low risk of infection would also be less likely to receive unnecessary treatment, which will help to reduce the issues of increasing antibiotic resistance.
National priorities	Medium
Current evidence base	This review identified 8 studies reporting data on 13 different prognostic models to predict late-onset neonatal infection. None have been externally validated. There is currently no evidence for prognostic models designed for use in babies who are admitted to hospital from home.
Equality considerations	No specific equality concerns are relevant to this research recommendation

K.1.4 Modified PICO table (Part A – prognostic accuracy)

PICO	**Population:** Babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age Pregnant women **Risk tool:** Any new or validated risk tool using multiple predictors to predict the risk of development or the presence of late-onset neonatal infection **Reference standard:** Culture-proven infection from a sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). **Outcomes:** Predictive accuracy measures, for example: • Model fit, including discrimination (C statistic, area under ROC curve) and calibration (r squared) • Sensitivity, specificity, positive and negative predictive values
Current evidence base	8 observational studies
Study design	Prospective cohort studies

Other comments	Study should be adequately powered, could link with local audits, and should collect data on resource-use and cost

K.1.5 Modified PICO table (Part B – clinical effectiveness)

PICO	**Population:** Babies from 72 hours up to 28 days of age and preterm babies up to 28 days corrected gestational age Pregnant women **Intervention:** Any validated risk tool for early-onset neonatal infection that meets the criteria for Part A of the protocol **Comparator:** • Standard care: treatment based on clinician experience or existing clinical protocols (for example, existing NICE guidance) • Comparisons between risk tools **Outcomes:** Neonatal outcomes: • Culture-proven infection from sample taken between 72 hours of birth and 28 days of age (or 28 days corrected gestational age for preterm babies) • Suspected bloodstream infection based on clinical symptoms • Mortality from 72 hours of birth onwards • Health-related quality of life, measured using a validated tool • Hospital length of stay • Number of babies prescribed antibiotic treatment Family outcomes: • Psychological distress in baby's family, measured using a validated scale
Current evidence base	No evidence
Study design	Test and treat RCTs
Other comments	Study should be adequately powered