National Institute for Health and Care Excellence

Final

Neonatal infection: antibiotics for prevention and treatment

[D] Evidence reviews for maternal and neonatal risk factors for early-onset neonatal infection

NICE guideline NG195

Evidence reviews underpinning recommendations 1.3.1-1.3.9 and research recommendations in the NICE guideline

April 2021

Final

These evidence reviews were developed by NICE Guideline Updates Team

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ISBN: 978-1-4731-4080-6

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1.1 Review question

What is the accuracy of clinical prediction models for early-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. Early-onset neonatal infection is typically defined as infection that occurs within 72 hours of birth.

Predicting which babies are most at risk of early-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 early-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 the development of antimicrobial resistance. The aim of this review is therefore to evaluate existing clinical prediction models for early-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 early 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	• Unborn or newborn babies under 72 hours • Pregnant women
Interventions	Any validated risk tool using multiple predictors to predict the risk of development or the presence of early-onset neonatal infection. For example: the neonatal early-onset sepsis calculator (Kaiser Permanente)
Reference standard	• culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate)
Outcome Measures	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

Part B

Population	• Unborn or newborn babies under 72 hours • Pregnant women
Interventions	Any validated risk tool using multiple predictors to predict the risk of development or the presence of early-onset neonatal infection. For example: the neonatal early-onset sepsis calculator (Kaiser Permanente)
Comparators	• 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 within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection • antibiotics for suspected bloodstream infection (within 72 hours of birth or within the study-defined period for early-onset neonatal infection) • mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth) • respiratory distress within 72 hours of birth or within the study-defined period for early-onset neonatal infection • health-related quality of life, measured using a validated tool (during the neonatal period and at the latest time point reported in study) • hospital length of stay • number of babies 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 time point 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 in this review, 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 of these study types. The review protocols specified that, where possible, subgroup analyses would be conducted for gestational age of the baby (preterm vs term). However, this was not possible as most studies included both preterm and term babies, and the results were not separated by gestational age. Results were stratified by population where the models were evaluated on different cohorts, such as mothers with chorioamnionitis.

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 late-onset infection (for details, see evidence review E – Risk factors for late 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 7 met the inclusion criteria for the review. Two additional studies were included from a systematic review making 9 included references in total.

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, 13 were excluded. The one included study examined the use of a clinical prediction model for early-onset infection. In total there were therefore 10 studies which met the inclusion criteria for this review (5 prospective cohort studies, 5 retrospective cohort studies).

The majority of the evidence (9 studies) investigated the use of the Kaiser Permanente neonatal sepsis calculator, including one study that compared the prognostic accuracy of the calculator against the recommendations from the 2012 version of this guideline. One study examined the use of a different model, based on various demographic and clinical factors. Studies reported the information needed to calculate prognostic outcomes for sensitivity, specificity and likelihood ratios. Only one study reported model fit statistics (c-statistic), and none reported hazard or odds ratios. No studies matched the protocol for Part B of the review (RCTs for different risk predictor tools).

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
Carola 2018 (n=896)	• Retrospective cohort • Follow-up time not reported but study investigated early-onset infection	• Newborn babies with a gestational age ≥35 weeks • Born to mothers with clinical chorioamnionitis *diagnosis of chorioamnionitis was made by an obstetrician based on intrapartum fever (temperature ≥38°C) alone or in conjunction with maternal leukocytosis, uterine tenderness, foul-smelling amniotic fluid, and maternal or fetal tachycardia*	• Kaiser Permanente neonatal sepsis calculator *Background incidence of early-onset infection set at 0.5/1000 live births (CDC national incidence)*

Study	Study type and follow-up time	Population	Prediction model
Dhudasia 2018 (n=6090)	• Retrospective cohort • 72 hour follow-up	• Neonates with gestational age ≥36 weeks gestation	• Kaiser Permanente neonatal sepsis calculator *Background incidence of early-onset infection set at 0.5/1000 live births (CDC national incidence)*
Goel 2020 (n=3593)	• Prospective cohort • 72 hour follow-up	• Newborn babies with a gestational age ≥34 weeks	• Kaiser Permanente neonatal sepsis calculator *Background incidence for early-onset infection set at 0.5/1000 live births (closest estimated incidence from studies of term and near-term infants in high-income countries including the UK)* • Current 2012 NICE guidelines
Hershkovich-Shporen 2019 (n=1341)	• Prospective cohort • Duration of follow-up not reported	• Gestational age of 35 weeks or more • Risk factors for early-onset neonatal sepsis • Receiving antibiotics in the first 72 hours of life • Symptoms of suspected early-onset sepsis • Proven sepsis	• Kaiser Permanente neonatal sepsis calculator • *Background incidence for early-onset infection set at 0.6/1000 live births (based on incidence in the centre between January 2008 - January 2015)*
Joshi 2019 (n=319)	• Prospective cohort • 72 hour follow-up	• Born to mothers with clinical chorioamnionitis *diagnosed by the obstetric team and is treated with intravenous broad-spectrum antibiotics* • Neonates with gestational age ≥34 weeks • Well-appearing infants	• Kaiser Permanente neonatal sepsis calculator *Background incidence for early-onset infection set at 0.6/1000 live births*
Money 2017 (n=362)	• Retrospective cohort • Duration of follow-up not reported but study investigated early-onset infection	• Well-appearing infants • Born to mothers with clinical chorioamnionitis *According to maternal ICD-9 codes*	• Kaiser Permanente neonatal sepsis calculator *Baseline incidence of early-onset infection set at 0.5/1000 (based on CDC national incidence)*
Popowski 2011 (n=399)	• Prospective cohort	• Women with prolonged rupture of membranes at ≥34 weeks gestation	• Predictive model (unnamed)

Study	Study type and follow-up time	Population	Prediction model
	• 72 hour follow-up	• Singleton pregnancies	• *Based on predictive factors: maternal white blood cell count, C-reactive protein concentration, pathogenic genital bacteria. Includes potential confounding factors: gestational age, antibiotic prescription at admission, type of management (expectant or active)*
Shakib 2015 (n=698)	• Retrospective cohort • Duration of follow-up not reported but study investigated early-onset infection	• Newborn babies with a gestational age ≥34 weeks • Born to mothers with clinical chorioamnionitis *based on a discharge ICD-9 diagnosis code of 762.7, 658.40, 658.41, or 658.43*	• Kaiser Permanente neonatal sepsis calculator *No information on baseline incidence of infection*
Sloane 2019 (n=896) *Follow-up study from Carola 2018*	• Retrospective cohort • Follow-up time not reported but study investigated early-onset infection	• Newborn babies with a gestational age ≥34 weeks • Born to mothers with clinical chorioamnionitis *diagnosis made by an obstetrician based on intrapartum fever (temperature of 38°C) alone or in conjunction with maternal leukocytosis, uterine tenderness, foul-smelling amniotic fluid, and maternal or fetal tachycardia*	• Kaiser Permanente neonatal sepsis calculator *Baseline incidence of infection set at 4/1000 live births. Based on the EOS incidence of 4.3/1000 live births in the population of infants exposed to chorioamnionitis in the NICU in the study*
Strunk 2018 (n=1732)	• Prospective cohort • Follow-up from birth to 1688 hours of life (separated into <24 hours and >24 hours after birth)	• Newborn babies with a gestational age ≥35 weeks	• Kaiser Permanente neonatal sepsis calculator *Baseline incidence of infection set at 0.44/1000 live births (based on local 2005-2014 rate)*

See appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

1.1.6.1 Model summaries

Kaiser Permanente neonatal sepsis model

The Kaiser Permanente neonatal sepsis model was developed in the USA and is designed to predict the risk of early-onset neonatal infection for any baby born at or after 34 weeks' gestational age. The model was developed from data that can be obtained from a patient's electronic medical record and requires a clinician to enter information on the local incidence of early-onset infection, gestational age of the baby, highest maternal antepartum temperature, duration of rupture of membranes, maternal group B streptococcal (GBS) status and the type and duration of intrapartum antibiotics given to the mother. This information is used to calculate a baby's risk of infection at birth. The clinician then determines whether the baby is well appearing, equivocal or has clinical illness and this information is used to provide guidance on how the baby should be treated. The calculator produces three recommendations depending on the baby's risk of infection; if a baby is at low risk then 'no culture or antibiotics' are recommended, if they are at moderate risk of infection then 'blood culture' is recommended alongside vitals every 4 hours for 24 hours and if the baby is at high risk then the recommendation is for 'empiric antibiotics'.

Popowski 2011 model

The model reported by Popowski was developed in France and designed for babies born at or after 34 weeks' gestational age whose mothers had prelabour rupture of membranes. The model was developed from information from serum samples and vaginal swabs at admission and data that could be obtained from a patient's electronic medical record. The final model includes white blood cell count and C-reactive protein levels. The study reported information on the algorithms used for the model but there is no evidence of a web-based tool or software that can be used directly by a clinician.

1.1.6.2 Summary of clinical findings included in the evidence review

Sensitivity, specificity and likelihood ratios

Comparison	No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
Current NICE 2012 guidelines						
Overall analysis	1	3588	0.60 (0.23, 0.88)	0.84 (0.83, 0.85)	LR+ 3.80 (1.80, 7.70)	Moderate
					LR- 0.48 (0.16, 1.39)	Low
Kaiser Permanente neonatal sepsis calculator: babies recommended antibiotic treatment						
Overall analysis	9	16697	0.56 (0.37, 0.73)	0.90 (0.81, 0.95)	LR+ 6.07 (2.84, 11.70)	Very low
					LR- 0.50 (0.31, 0.70)	Very low
Lower baseline incidence of sepsis (0.44-0.6/1000 live births)	8	16583	0.47 (0.29, 0.65)	0.94 (0.90, 0.97)	LR+ 8.57 (4.36, 15.10)	Very low
					LR- 0.56 (0.37, 0.75)	Very low
Higher baseline incidence of sepsis (4.0/1000 live births)	1	896	1.00 (0.57, 1.00)	0.41 (0.38, 0.44)	LR+ 1.69 (1.60, 1.78)	Moderate
					LR- *not calculable*	N/A
Babies born to mothers with chorioamnionitis	4	5552	0.48 (0.21, 0.77)	0.95 (0.79, 0.99)	LR+ 6.82 (2.20, 21.08)	Very low
					LR- 0.75 (0.51, 1.11)	Very low

Comparison	No. studies	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95% CI)	Quality
Current NICE 2012 guidelines						
Overall analysis	1	3588	0.60 (0.23, 0.88)	0.84 (0.83, 0.85)	LR+ 3.80 (1.80, 7.70)	Moderate
					LR- 0.48 (0.16, 1.39)	Low
Kaiser Permanente neonatal sepsis calculator: babies recommended either antibiotic treatment and blood culture or blood culture and vital sign monitoring every 4 hours						
Overall analysis	5	5354	0.73 (0.40, 0.92)	0.66 (0.27, 0.91)	LR+ 2.44 (1.05, 6.24)	Very low
					LR- 0.47 (0.16, 0.92)	Very low
Lower baseline incidence of sepsis (0.44-0.5/1000 live births)	4	4458	0.69 (0.34, 0.90)	0.81 (0.72, 0.87)	LR+ 3.38 (2.13, 5.39)	Low
					LR- 0.64 (0.33, 1.25)	Very low
Higher baseline incidence of sepsis (4.0/1000 live births)	1	896	1.00 (0.57, 1.00)	0.07 (0.06, 0.09)	LR+ 1.07 (1.06, 1.09)	Moderate
					LR- *not calculable*	N/A
Babies born to mothers with chorioamnionitis	3	1956	0.67 (0.30, 0.91)	0.81 (0.65, 0.91)	LR+ 3.32 (1.65, 6.70)	Very low
					LR- 0.68 (0.34, 1.37)	Very low
Popowski 2011 model – mothers with premature rupture of membranes (based on C-reactive protein and white blood cell count)						
Overall analysis	1	399	0.94 (0.73, 0.99)	0.43 (0.38, 0.48)	LR+ 1.6 (1.4, 1.9)	High
					LR- 0.1 (0.02, 0.92)	Moderate

C-statistics

Comparison	No. studies	Sample size	c-statistic (95%CI)	Quality
Popowski 2011 model – mothers with premature rupture of membranes (based on C-reactive protein and white blood cell count)				
Overall analysis	1	399	0.82 (0.72, 0.92)	Moderate

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 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, as none of them were found to be relevant.

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.

1.1.8 Economic model

This question was not prioritised for original economic analysis

2.1 Review question

Which maternal and fetal risk factors for early-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 in newborn babies. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. For the purpose of this guideline, early-onset neonatal infection is defined as infection which occurs in babies up to 72 hours of age (corrected for gestational age).

Predicting which babies are most at risk of early-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 the fetus and determine how well they can guide management of the baby.

2.1.2 Summary of the protocol

Population	• Unborn or newborn babies under 72 hours • Pregnant women
Risk factors	• Behavioural and hygienic factors (for example adherence to infection control measures by medical professionals and parents/carers) • Gestational age • Intrapartum antibiotic prophylaxis (including the time before birth that it is received) • Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis • Invasive group B streptococcal (GBS) infection in a previous baby • Maternal carriage of Methicillin-resistant Staphylococcus aureus (MRSA) • Maternal GBS colonisation, bacteriuria, detection (including vaginal or rectal swab) or infection in the current pregnancy • Maternal GBS colonisation, bacteriuria, detection (including vaginal or rectal swab) or infection in a previous pregnancy (including where the baby was well) • Maternal obesity • Maternal perineal infections • Maternal suspected bacterial infection in the puerperium period • Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth [This does not refer to intrapartum antibiotic prophylaxis] • Preterm prelabour rupture of membranes • Suspected or confirmed infection in another baby in the case of a multiple pregnancy

	• Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth
Reference standard	• culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given within 72 hours of birth where available or within the study-defined period for early onset neonatal infection
Outcomes	Outcomes for predictive accuracy studies: • Sensitivity • Specificity • Positive and negative predictive values • 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 in this review, 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) and multiple births. Some evidence was available for single and multiple births, and where studies have included babies of different gestational ages this has been highlighted in the results.

Some studies reported outcomes that matched the protocol but were only reported as part of univariate analysis and not included in multivariate analysis. These outcomes are stated in the clinical evidence tables (Appendix D) but not reported in the analysis as they did not meet the criteria for multivariate analyses.

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 early-onset infection (for details, see section 3.1 of this evidence review). This returned a total of 1,825 results, of which 55 were identified as potential included studies. Full text articles were ordered and reviewed against the inclusion criteria, of which 11 met the inclusion criteria for this review.

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 late-onset maternal and fetal risk factors and risk factors in the baby returned a total of 143 results, of which 3 were identified as possible included studies. After full text review, all 3 were excluded. In total there were therefore 11 studies which met the inclusion criteria for this review (3 prospective cohort

studies, 8 retrospective cohort studies). No studies reported predictive accuracy data and so prognostic association data was considered instead.

Most of the multivariate cohort studies identified reported on the association between early-onset neonatal infection and chorioamnionitis (6 studies) or singleton births (3 studies). One study reported on the association between maternal obesity and early-onset infection and another examined the effects of intrapartum fever.

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

Study	Study type and follow-up time	Population	Predictive factors
Dempsey 2005 (n=392)	• Retrospective cohort • 72 hour follow-up	• All singleton neonates delivered at <30 weeks gestational age	• Chorioamnionitis
Dior 2016 (n=46,560)	• Retrospective cohort • 72 hour follow-up	• Women in labour who had a singleton live birth • <50 years old • Had a term pregnancy (≥ 37 weeks' gestation) • Baby with a birth weight <5000 g • Spent >1 hour in the delivery room	• Intrapartum fever
Garcia-Munoz 2014a (n=451)	• Prospective cohort • 72 hour follow up	• Born in maternity unit or admitted to Neonatal Intensive Care Unit in the first 28 days of life • Birth weight <1500 g • or <30 weeks' gestational age	• Chorioamnionitis
Garcia-Munoz 2014b (n=8330)	• Retrospective cohort • Duration of follow-up not reported	• Birth weight <1500 g • <32 weeks' gestational age • Admitted to a neonatal unit	• Chorioamnionitis
Hakansson 2008 (n=344,127)	• Retrospective cohort • Follow-up for rfirst 27 days of life	• Gestational age >22 weeks • Vaginal birth or emergency caesarean section	• Maternal BMI (weight grouped by BMI. Obesity classified as BMI ≥30.0)
Klinger 2009* (n=15,839)	• Retrospective cohort • Duration of follow up unclear	• Infants whose data was collected by the Israel Neonatal Network on very low birth weight newborn infants (BW <1500 g)	• Chorioamnionitis • Maternal fever • Single/multiple birth
Mularoni 2014 (n=14,719)	• Prospective cohort • 72 hour follow-up	• Babies weighing 401 - 1500 g • Babies with a positive blood culture and clinical signs of	• Twin/singleton births

Study	Study type and follow-up time	Population	Predictive factors
		sepsis during the first 72 hours of life	
Ofman 2016* (n=2192)	• Retrospective cohort • 72 hour follow-up	• Moderately preterm infants	• Chorioamnionitis
Ronnestad 2005 (n=462)	• Prospective cohort • Follow-up for first week of life	• Birth weight <1000 g	• Chorioamnionitis • Gestational age
Soraisham 2009 (n=3094)	• Retrospective cohort • Follow-up for first 48 hours after birth	• All singleton infants with birth gestational age <33 weeks • No congenital anomalies	• Chorioamnionitis

*Also included in review question on risk factors in the baby for neonatal infection

See appendix D for full evidence tables.

2.1.6 Summary of the prognostic evidence for predicting the development of early-onset neonatal infection

Risk factor	No. studies	Sample size	Effect size (95% CI)	Quality
Chorioamnionitis				
Histological chorioamnionitis (babies <30 weeks' gestational age)	1 (Dempsey 2005)	392	Adjusted OR 6.9 (2.2, 20.0)	Moderate
Clinical chorioamnionitis in very low birth weight babies	1 (Garcia-Munoz 2014a)	451	Adjusted RR 6.13 (1.67, 22.58)	Moderate
	1 (Garcia-Munoz 2014b)	8330	Adjusted OR 3.10 (2.31-4.17)	Moderate
Clinical chorioamnionitis in preterm babies	1 (Soraisham 2009)	3094	Adjusted OR 5.54 (2.87-10.69)	Moderate
Clinical chorioamnionitis in moderately preterm babies	1 (Ofman 2016)	2192	Adjusted OR 4.1 (2.83-5.30)	Low
Clinical chorioamnionitis in extremely preterm babies	1 (Ronnestad 2005)	451	Adjusted OR 10.5 (3.3-33.4)	Moderate
Intrapartum fever				
Low febrile fever (38.0-38.9◦C)	1 (Dior 2016)	43,560	Adjusted OR 7.44 (3.29, 16.85)	Moderate

Risk factor	No. studies	Sample size	Effect size (95% CI)	Quality
High febrile fever (>39◦C)	1 (Dior 2016)	43,560	Adjusted OR 16.08 (2.15, 120.3)	Moderate
Maternal obesity				
Overweight mothers (BMI 25-29.9)	1 (Hakansson 2008)	344,127	Adjusted OR 1.3 (0.9, 2.0)	Low
Obese mothers (BMI 30.0)	1 (Hakansson 2008)	344,127	Adjusted OR 1.8 (1.1, 3.0)	Moderate
Single vs multiple births				
Very low birth weight babies	1 (Mularoni 2014)	14,719	Adjusted OR 1.4 (1.1, 1.8)	Moderate
	1 (Klinger 2009)	15,839	Adjusted OR 1.4 (1.1, 1.8)	Moderate
Babies born ≥22 weeks' gestational age	1 (Hakansson 2006)	319	Adjusted OR 1.1 (0.6, 2.0)	Moderate

See appendix F for full GRADE tables.

2.1.7 Economic evidence

2.1.7.1 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, as none of them were found to be relevant.

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 early-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, early-onset neonatal infection is defined as infection which occurs within 72 hours of birth (corrected for gestational age).

Predicting which babies are most at risk of early-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. These factors can either be diagnostic, such as the signs and symptoms that babies commonly display when they have an infection, or prognostic, such as factors that are commonly associated with babies subsequently developing an 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	• Newborn babies under 72 hours, or study definition for 'early onset' infection
Risk factors	**Signs and symptoms (diagnostic)** • Abnormal heart rate (bradycardia or tachycardia) • Altered behaviour or responsiveness • Altered glucose homeostasis (hypoglycaemia or hyperglycaemia) • Altered muscle tone (for example, floppiness) • Apnoea • Feed intolerance, including vomiting, excessive gastric aspirates and abdominal distension • Feeding difficulties (for example, feed refusal) • Jaundice • Local signs of infection (for example, affecting the skin or eye) • Metabolic acidosis (base deficit of 10 mmol/litre or greater) • Need for cardio-pulmonary resuscitation • Need for mechanical ventilation • Oliguria • Reduced oxygen saturation level • Seizures • Signs of neonatal encephalopathy • Signs of respiratory distress • Signs of shock • Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors

	• Unexplained excessive bleeding, thrombocytopenia, or abnormal coagulopathy (International Normalised Ratio greater than 2.0) **Risk factors (prognostic)** • Gestational age • Colonisation with Group B streptococcus (GBS) or Methicillin-resistant Staphylococcus aureus (MRSA) in the baby • Persistent fetal circulation (persistent pulmonary hypertension)
Reference standard	• culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given within 72 hours of birth where available or within the study-defined period for early onset neonatal infection
Outcomes	Outcomes for diagnostic/predictive accuracy studies: • Sensitivity • Specificity • Positive and negative predictive values • 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 in Appendix A. For full details of the methods used in this review, 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 and babies who have been admitted to hospital from home. Data was available for gestational age, but no data was reported for babies admitted to hospital from home. Some evidence was available for multiple births, and this was reported as part of the maternal risk factors review (for details, see section 2.1). Evidence was separated by those which reported prognostic (risk factors for infection) and diagnostic (signs and symptoms of infection) factors.

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 and fetal risk factors for early-onset infection (for details, see section 2.1). This returned a total of 1,825 results, of which 55 were identified as potential included studies. Full text articles were ordered and reviewed against the inclusion criteria, of which 4 met the inclusion criteria for this review. No studies reported diagnostic or predictive accuracy data.

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 late-onset maternal and fetal risk factors, and risk factors in the baby returned a total of 143 results, of which 3 were identified as possible included studies. After full text review, all 3 were excluded. In total there were therefore 4 studies which met the inclusion criteria for this review (1 prospective cohort study, 3 retrospective cohort studies). No studies reported predictive accuracy data and so prognostic and diagnostic association data was considered instead.

Of the 4 multivariate cohort studies identified, most were prognostic and reported on the association between early-onset neonatal infection and gestational age (3 studies). One diagnostic study reported on the association between respiratory distress syndrome and early-onset infection.

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 and diagnostic evidence

Study	Study type and follow-up time	Population	Predictive factors
Hakansson 2006 (n=319)	• Retrospective cohort (prognostic) • Follow-up for first 27 days of life	• Gestational age >21 weeks	• Gestational age • Twin/singleton births (subgroup analysis)
Klinger 2009* (n=15,839)	• Retrospective cohort (prognostic) • Duration of follow up unclear	• Infants whose data was collected by the Israel Neonatal Network on very low birth weight newborn infants (BW <1500 g)	• Single/multiple birth • Gestational age
Ofman 2016* (n=2192)	• Retrospective cohort (diagnostic) • 72 hour follow-up	• Moderately preterm infants	• Respiratory distress syndrome
Ronnestad 2005* (n=462)	• Prospective cohort (prognostic) • Follow-up for first week of life	• Birth weight <1000 g	• Gestational age

*Also included in review question on maternal and fetal risk factors for neonatal infection

See appendix D for full evidence tables.

3.1.6 Summary of the prognostic evidence for predicting the development of early-onset neonatal infection

3.1.6.1 Risk factors

Risk factor	No. studies	Sample size	Effect size (95% CI)	Quality
Gestational age				

Risk factor	No. studies	Sample size	Effect size (95% CI)	Quality
Very early onset infection in extremely premature babies	1 (Ronnestad 2005)	462	Adjusted OR[1] 1.1 (0.4, 3.6)	Low
Early onset infection in extremely premature babies	1 (Ronnestad 2005)	462	Adjusted OR[1] 3.0 (0.6, 14.9)	Low
Very low birthweight babies (1-week increase)	1 (Klinger 2009)	15,839	Adjusted OR[1] 0.98 (0.94, 1.03)	Low
Babies born ≥22 weeks' gestational age (<28 weeks vs 40 weeks)	1 (Hakansson 2006)	319	Adjusted OR[1] 22.1 (8.5, 57.4)	Moderate
Babies born ≥22 weeks' gestational age (28-31 weeks vs 40 weeks)	1 (Hakansson 2006)	319	Adjusted OR[1] 34.1 (18.6, 62.7)	Moderate
Babies born ≥22 weeks' gestational age (32-34 weeks vs 40 weeks)	1 (Hakansson 2006)	319	Adjusted OR[1] 11.2 (6.0, 21.0)	Moderate
Babies born ≥22 weeks' gestational age (35-36 weeks vs 40 weeks)	1 (Hakansson 2006)	319	Adjusted OR[1] 4.7 (2.5, 8.9)	Moderate
Babies born ≥22 weeks' gestational age (37 weeks vs 40 weeks)	1 (Hakansson 2006)	319	Adjusted OR[1] 3.5 (1.8, 6.5)	Moderate
Babies born ≥22 weeks' gestational age (≥42 weeks vs 40 weeks)	1 (Hakansson 2006)	319	Adjusted OR[1] 1.9 (0.9, 3.7)	Low

3.1.6.2 Signs and symptoms

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality
Respiratory distress syndrome in moderately preterm babies	1 (Ofman 2016)	2192	Adjusted OR 2.05 (1.62-3.14)	Low

See appendix F for full GRADE tables.

3.1.7 Economic evidence

3.1.7.1 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, as none of them were found to be relevant.

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.

3.1.8 Economic model

This question was not prioritised for original economic analysis.

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 a baby's risk of early-onset 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 issue when evaluating neonatal infection as it can be difficult to diagnose and can therefore result in many babies being prescribed antibiotics to avoid any infections being missed and 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 either admission to hospital or prolonged admission in hospital will lead to separation of the mother and baby, potentially causing anxiety and distress to the family. The mother may also have to remain in hospital for longer than she otherwise would. This has an impact on the family as well as the increasing costs of a longer hospital stay. False positives can also 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. The committee therefore discussed how negative likelihood ratios should be prioritised over positive likelihood ratios as they believed that it was important that negative test results were accurate, and that neonatal infection was not incorrectly ruled out. As a result, the committee used a combination of likelihood ratios, sensitivity and specificity to examine the effectiveness of each clinical prediction model. Some studies also reported c-statistics. 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.

The committee highlighted that while babies tend to be discharged between 6-12 hours after birth if they appear healthy, there are often no follow-up observations in the community during the first 72 hours of life. It is therefore important for any prognostic model or risk factor tool to avoid false negative results, thereby ensuring that any babies at high risk of infection remain in the hospital for treatment and monitoring.

The committee were also interested in the diagnostic accuracy of risk factors and signs and symptoms for early-onset infection. No studies reported sensitivity, specificity, predictive values or likelihood ratios for these outcomes. Instead, studies reported adjusted odds ratios, and risk ratios. These do not provide an indication of how well each risk factor or symptom can correctly identify a baby with or without early-onset neonatal infection. However, the committee were interested in these outcomes as they indicate which factors have the strongest association with infection. This helped them to decide which were the most important risk factors and signs to include in the risk factor and clinical indicators boxes in the recommendations. As the committee only wanted to consider the factors which were most relevant to early-onset infection, studies were only included if they had used a multivariate analysis which had adjusted for other potential risk factors for infection.

4.1.2 The quality of the evidence

4.1.2.1 Clinical prediction models

The outcomes from the evidence for prognostic models ranged from high to very low quality, with most outcomes either low or very-low quality. The quality of outcomes were commonly downgraded for imprecision in the results and for including studies at moderate risk of bias. All of the studies were directly applicable to the research question. Most of the evidence examined the use of the Kaiser Permanente neonatal sepsis calculator, with only one study reporting the details of a different prognostic model. One other study also compared the use of the calculator to the NICE recommendations. The committee therefore decided that only the neonatal sepsis calculator had sufficient evidence to be considered as an alternative to the NICE risk factors and clinical indicators.

Four studies examined the use of the Kaiser Permanente neonatal sepsis calculator in all babies over 34-, 35- or 36-weeks' gestational age. Five studies examined the use of the calculator specifically for babies who were born to mothers with chorioamnionitis. The committee discussed whether the results from the chorioamnionitis studies could be applied to all babies but, as the results did not differ greatly from the three studies that included all babies, the committee thought that the results could be generalised. Six of the studies in the review were based in the USA where the calculator was developed. Only one study (Goel 2020) examined the use of the calculator in the UK. The committee discussed whether differences in the demographics of the population, in addition to differences in group B streptococcal (GBS) screening policies, could mean that the outcomes of the calculator may differ between the UK and the USA. GBS status is one of the factors in the neonatal sepsis calculator and the committee were unsure whether the unknown status in the UK would make assumptions about the mother that might change the outcome of the neonatal sepsis calculator. However, GBS status only contributes approximately 2% to the predictive weight of the model. This, in addition to the similarities in results between the UK study and the USA validation studies, meant that the committee did not feel it should recommend against the use of the neonatal sepsis calculator based on GBS status.

An important aspect of the neonatal sepsis calculator is the need for clinicians to enter a background rate for the incidence of early-onset neonatal infection. Further research is needed in the UK to identify what rate should be applied to reflect the local prevalence of neonatal infection, and whether this should be a single rate that is used across the UK or if it should vary by hospital. The committee did not feel that this should be a reason to recommend against the use of the neonatal sepsis calculator but potential differences in the incidence rate of infection between the UK and the USA, and the differences in GBS screening policies, meant that the studies that reported on the use of the calculator in the USA were downgraded as being partially applicable to the research question. The committee decided that the rate of infection should be considered as part of future research into the use of the neonatal sepsis calculator in the UK. This will help to ensure the accuracy of the outcomes of the calculator when used in NHS practice. For clinicians who are currently using the calculator, the committee decided to recommend that they should use either the national or local rate of infection, whichever is higher. This will help to increase the sensitivity of the calculator, thereby reducing the risk of a baby who has infection not being recommended for antibiotic treatment.

The imprecision of some of the results from the neonatal sepsis calculator studies was discussed, particularly when comparing the overall results of the calculator to the NICE guidelines. The neonatal sepsis calculator identified a slightly lower number of true positives to the NICE guidelines, and the likelihood ratios indicated that a positive outcome with the neonatal sepsis calculator would indicate a slightly higher chance of a baby having infection than a positive test from the NICE guidelines. However, the wide confidence intervals suggested variation in the results. This was particularly evident for the negative likelihood ratio for the NICE guidelines, which suggested that a negative outcome would indicate

anything between a large decrease in the probability of a baby having infection to a slight increase in their chance of having infection. This made it difficult for the committee to decide on recommendations based on likelihood ratios alone. This imprecision in the results may be due to the very low incidence of culture-confirmed early-onset neonatal infection in the studies, with many studies reporting only one baby with a confirmed infection. Given that both the NICE recommendations and the neonatal sepsis calculator were associated with a wide degree of imprecision, the committee did not think this should be a reason against recommending the neonatal sepsis calculator. Instead, they decided to recommend that the risk factors specified in boxes 1 and 2 is used to identify babies at risk of early-onset infection, but also stated that if the calculator is being used in clinical practice it should be used as part of a clinical audit. This will help give a clearer understanding of its effectiveness. Examples of the outcomes that should be collected in an audit (number of babies assessed using the calculator and number of true positive, false positive and false negative results when using the calculator) were included in the recommendation to ensure that the most relevant information on effectiveness is available. These outcomes were chosen as the ones needed to form a 2 x 2 table to examine the effectiveness of a prognostic tool. This information will be useful in future updates of this guideline to decide whether a stronger recommendation can be made in favour of the use of the Kaiser Permanente neonatal sepsis calculator.

Given the issues discussed above, the committee agreed that more evidence is needed before it could recommend the Kaiser Permanente neonatal sepsis calculator as the sole option for predicting risk of early-onset neonatal infection in the UK. More research is particularly important for babies born before 34 weeks' gestational age, as the neonatal sepsis calculator is only designed for babies born at a gestational age of 34 weeks or above. As such, the committee could not recommend the use of the calculator for this group of babies and this was stated as part of the calculator recommendations. Instead, a research recommendation relating to prognostic models was made which did not specify gestational age (Appendix K). This should help to ensure that the most effective prognostic tool can be determined for all babies, and not just those covered by the calculator.

4.1.2.2 Maternal and neonatal risk factors and clinical indicators

The evidence for risk factors and signs and symptoms ranged from high to low quality and most studies were directly applicable to the research question. Each of the studies reported the use of a multivariate model but there was a wide range in the factors that the models were adjusted for, and most studies did not explain why those particular factors were chosen. The committee agreed that this could affect the validity of the data and so the quality of the outcomes from these studies were downgraded for risk of bias. However, the factors that were highlighted as potential risks for infection were consistent with their clinical experience. As such, they decided that they could still be identified as risk factors in the recommendations.

There was also variation in the populations that were included in each study, with some basing the inclusion criteria on gestational age or birthweight while other studies included all babies born in a particular setting. Consequently, the results were presented by individual study outcomes rather than pooled effect estimates. An additional issue was that many studies only reported the significant results from the models. This means that while one study may have reported an association between a particular factor and neonatal infection, it is unclear how many other studies also investigated that risk factor but found non-significant results. Where studies only reported significant results, they were therefore downgraded for risk of bias. The committee decided that risk factors would only be included as part of the recommendations if the evidence corresponded with their clinical experience.

Only one study examined the effects of maternal obesity on the risk of early-onset neonatal infection. The committee questioned the applicability of this research as mothers who were included in the analysis were grouped by the World Health Organisation definition of obesity

(BMI of 30.0 and above). It was highlighted that in clinical practice maternal obesity is now often defined as women with a BMI of 35 and above. Due to these differences in classification, this study was graded as partially applicable to the research question and the quality of the outcomes were downgraded. With such limited and partially applicable evidence, the committee decided that more relevant research was needed before recommendations could be made on maternal obesity and neonatal infection. A research recommendation was therefore made to reflect this (Appendix K).

The committee discussed the criteria for chorioamnionitis that was used in the research. Many studies used the Gibbs criteria or similar, and this is known to have relatively low sensitivity. It was raised that these criteria do not reflect the complexities of diagnosing chorioamnionitis in clinical practice where clinicians tend to look for more subtle signs to enable earlier diagnosis and treatment. These differences in definition may change the association between chorioamnionitis and neonatal infection. However, the committee was confident that its clinical experience supported the findings that chorioamnionitis is a risk factor for neonatal infection. They therefore agreed that these studies should remain applicable to the research question and that chorioamnionitis should remain part of the maternal risk factors table.

The studies which examined individual risk factors examined a wider range of populations, including babies born before 34 weeks' gestational age. As a result, the risk factor tables and their accompanying recommendations can be used for babies of any gestational age, including the population that are not covered by the neonatal sepsis calculator.

4.1.3 Benefits and harms

4.1.3.1 Clinical prediction models

The main concern of the committee in relation to any prognostic model or management tool for neonatal infection was the trade-off between the potential issues associated with over-treatment versus the risks from lack of treatment where a baby does have infection. Although there are harms associated with unnecessary antibiotic treatment, such as the potential for nephrotoxicity when a baby is given gentamicin, and increased length of stay in hospital, the committee decided that these were smaller than the risk of a baby not receiving treatment when they do have infection. It is therefore important that any clinical prediction model or framework can maximise the number of babies that are correctly identified as needing treatment, while minimising the number who are given antibiotics unnecessarily.

Most of the data on clinical prediction models was for the Kaiser Permanente neonatal sepsis calculator. The committee agreed that overall pooled results from 9 studies showed that the tool had good specificity, but that there was substantial uncertainty about the sensitivity, with wide confidence intervals in the results. The positive likelihood ratio was above the clinical decision threshold, suggesting that a positive test result from the neonatal sepsis calculator indicated a large to very large increase in the probability of a baby having infection. However, the negative likelihood ratio was on the clinical decision threshold, and so the committee thought that more research was needed before the calculator could be considered as the sole option for predicting a baby's risk of infection. One UK study compared the predictive accuracy of the Kaiser Permanente neonatal sepsis calculator with the recommendations in the 2012 guideline on neonatal infection, and the committee placed particular weight on this study when making recommendations. This study showed that both tools had similar sensitivity, but that the specificity of the neonatal sepsis calculator was higher, suggesting that using the neonatal sepsis calculator may result in fewer babies being treated with antibiotics who do not have infection. However, data on sensitivity were very uncertain because of the low number of cases of culture confirmed early-onset neonatal infection. This was particularly the case for the framework outlined in the 2012 NICE guideline which had data from only a single study with just 6 cases of confirmed neonatal infection. Given the uncertainties in the evidence, the committee decided that a recommendation for a framework

based on individual factors was appropriate, with an option for obstetric or paediatric centres to consider the Kaiser Permanente neonatal sepsis calculator as part of an audit which assesses and manages the risk of neonatal infection. The committee thought that using a framework based on individual risk factors (described in more detail in the section below) was likely to be a conservative approach which would result in more antibiotics being prescribed that the neonatal sepsis calculator, but might also identify more true cases of infection. However, as the evidence did not show one option to be clearly better than the other, and as the neonatal sepsis calculator is already used in some centres in the UK, the committee decided that the recommendation to use the calculator in the context of an audit was appropriate, as long as this was for babies with a gestational age of 34 weeks and above. In situations where the Kaiser Permanente neonatal sepsis calculator is used, the committee decided that clinicians should use the recommendations within the tool to decide whether to treat with antibiotics or monitor further, as the evidence included as part of this review is based on these categorisations.

An additional aspect of the recommendation for use of the Kaiser Permanente calculator is that is should only be used for babies who are being cared for in a neonatal unit (neonatal intensive care units, local neonatal units and special care units), transitional care or postnatal ward. The committee did not think the calculator should be recommended for use in the emergency department or other settings, as babies who are brought in from home are likely to already be showing signs of being unwell and therefore need more immediate treatment than babies who are being assessed for risk of infection in a neonatal unit. In these cases, waiting to consult the calculator could instead delay treatment.

Given the limited evidence on clinical prediction models in the UK (including the Kaiser Permanente neonatal sepsis calculator as well as the framework set out by NICE), the committee decided that a research recommendation was needed for the use of prognostic tools for early-onset neonatal infection specifically in the UK. This recommendation was for any prognostic model, meaning that other models can be designed and evaluated, which may be particularly important for specific populations, such as babies born before 34 weeks gestational age (Appendix K).

4.1.3.2 Individual risk factors and clinical indicators

The committee decided that current evidence was not sufficient to make recommendations based only on clinical prediction models, so they also reviewed the evidence on individual risk factors and signs and symptoms of early-onset neonatal infection. The committee agreed that the structure of the recommendations outlined in the 2012 version of this guideline was still appropriate, with tables of risk factors and clinical indicators, some of which were designated as ‘red flag’ indicators. Red flag indicators were selected based on committee experience and are those thought to be the most high risk factors that require immediate treatment. Non-red flag indicators are those that can have causes other than neonatal infection and therefore do not always signal the need for immediate treatment. They decided that the recommendations in the 2012 version of this guideline on when to start antibiotic treatment or carry out further monitoring based on the number of indicators and red flag indicators met were still appropriate, and so made recommendations that were very similar to those made previously.

The committee thought it was important to retain the separate tables for risk factors and for clinical indicators that were used in the 2012 version of the guideline. The risk factors list (Box 1) gives an indication of the factors that a clinician should be aware of before the birth and the clinical indicators list (Box 2) highlights the signs and symptoms to look for in the baby after birth. Separating risk factors and clinical indicators should make it clearer for clinicians when they are trying to make important decisions about whether a baby should be treated for neonatal infection. Although the committee decided to keep the format of the recommendations the same as the previous version of the guideline, they made some

changes to the risk factors and clinical indicators based on the updated evidence and their knowledge and experience. These changes are outlined in the sections below.

4.1.3.3 Maternal risk factors

When presented with the evidence for maternal risk factors, the committee decided to use a modified version of the risk factors table used in the 2012 version of the guideline (Box 1), as the main factors identified as risks for neonatal infection in the evidence review (intrapartum fever and chorioamnionitis) were already included in the table. Intrapartum fever and chorioamnionitis were a single risk factor in the 2012 guideline but, based on their clinical experience, the committee decided to separate these into two risk factors, as fever can also indicate other bacterial infections that are not chorioamnionitis. However, it specified that fever should only be considered a risk factor when there is suspected bacterial infection. This will avoid women who have a high temperature for other reasons, such as the side-effects of an epidural, receiving antibiotics unnecessarily. The committee also discussed how a woman can have chorioamnionitis without having fever, and this should be considered a risk factor for infection. There was discussion about whether this separation of fever and chorioamnionitis into separate risk factors would result in an increase in the number of women prescribed antibiotics. However, as women with both chorioamnionitis and fever would generally be given antibiotics in practice, the committee did not think this would result have a big impact on antibiotic prescription or resistance. The committee also updated the terminology for chorioamnionitis from suspected or confirmed chorioamnionitis to clinical chorioamnionitis, as a diagnosis during the intrapartum period is usually based on clinical signs rather than a histological diagnosis.

The committee decided to remove parenteral antibiotic treatment from the list of risk factors. This decision was made based on changes in obstetric practice since the previous guideline update, meaning that the threshold for diagnosing a mother with septicaemia is now lower. This means that many babies are now receiving antibiotics based on this red flag risk factor alone. This is considered to be an issue for the overprescribing of antibiotics.

The committee combined the risk factors ‘Invasive group B streptococcal infection in a previous baby’ and ‘maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy’ into a single item in the list because they considered that these items relate to the same risk factor. Having a previous baby with invasive group B streptococcal infection does not increase the risk of neonatal infection further if a mother is known to have group B streptococcal colonisation, bacteriuria or infection in her current pregnancy, and so this should not be considered an additional risk factor.

The committee revised the table to make the sections on rupture of membranes at term and preterm clearer, and to reflect current NICE guidance in this area. Confirmed pre-labour rupture of membranes at term for more than 24 hours was included to correspond with the recommendations in the intrapartum care guideline (NICE clinical guideline 190, recommendation 1.11.6). However, the committee decided that the time period for confirmed rupture of membranes for more than 18 hours in a preterm birth should be retained (as in the 2012 version of the guideline) because there was no new evidence available in relation to this risk factor. Confirmed prelabour rupture of membranes was removed from the table because the committee felt that it is now covered by other risk factors in the table (preterm birth and confirmed rupture of membranes in a preterm or term birth). Consequently, they agreed that babies born to these mothers would still receive treatment when using the updated version of the NICE guidelines.

One other factor (single compared to multiple births) was identified in the evidence review. However, the committee did not think that it would be useful to highlight single births as a risk factor for infection, as this could result in most babies being identified as at higher risk of infection. It decided that there were other factors in the review that were more important to identify as potential risks for infection.

4.1.3.4 Neonatal risk factors and clinical indicators

The committee also reviewed the risk factors and clinical indicators in the baby for early-onset infection. They decided to recommend a modified version of the risk factors (Box 1) and clinical indicators (Box 2) tables used in the 2012 version of the guideline as a starting point to modify based on new evidence as appropriate.

One of the most common risk factors identified in the evidence review was low gestational age. The committee discussed whether this should be an additional risk factor but agreed that this is already covered by the preterm birth risk factor. It was highlighted that while there are a number of risk factors in the baby, many of these are as a result of low gestational age. The evidence suggested that babies born at less than 32 weeks' gestational age are at greater risk of developing infection than those born at 32 weeks or greater. The committee discussed whether this should be added as additional information to the preterm birth factor, but it was deemed unnecessary as it would still count as one risk factor in the table. It was highlighted that babies who are slightly preterm and on a postnatal ward might be more at risk of an infection being missed because they might not be considered a high-risk group. The inclusion of babies born before 37 weeks' gestation as a risk factor should therefore highlight to clinicians that these babies should be monitored for other signs of infection.

There was very little evidence on clinical indicators for early-onset infection and so the committee decided to base their recommendations on the table of clinical indicators in the 2012 version of the NICE guideline on neonatal infection. They made changes to this table based on their knowledge and experience and to make the table applicable to current practice (Box 2).

The committee decided to remove respiratory distress starting 4 hours after birth from the table of risk factors because they agreed that they would not want clinicians to wait 4 hours for treatment on the basis of this recommendation. Instead, they chose to retain 'signs of respiratory distress' as a factor in the table as this would include the group of babies who have symptoms beyond 4 hours after birth and should ensure that any babies who have infection will still receive the necessary treatment. The 2012 recommendations also had two recommendations for need for mechanical ventilation; one for preterm babies which was not a red flag risk factor and one for term babies which was a red flag. The committee agreed that mechanical ventilation is a risk factor for infection regardless of prematurity and so they decided to merge these into one recommendation which did not refer to whether a baby was born pre-term or at term for simplicity. They decided that this should be a red flag indicator.

For signs and symptoms in the baby, the committee decided to remove oliguria and local signs of infection from the recommendations table. Oliguria persisting beyond 24 hours after birth was removed because there is no clear definition of this risk factor, and the 24-hour time point is beyond the time when babies typically present with early-onset infection. The committee also considered oliguria to be a poor indicator of early-onset sepsis. The committee felt that local signs of infection should be removed because such infections are very common in newborn babies and including 'local infection' in the table may result in overprescribing antibiotics. Many local infections also require different management pathways to sepsis, such as oral or topical antibiotics.

4.1.3.5 Management of babies at increased risk of infection

The committee made recommendations based on their knowledge and experience that were consistent with the recommendations from the 2012 version of this guideline and current best practice. These recommendations were designed to direct clinicians to other, evidence-based, sections of the guideline where they could receive guidance when deciding whether a baby should be given antibiotic treatment, what antibiotics should be given, or what to do when discharging the baby if there are no further concerns.

The committee discussed how the recommendations for the use of the NICE risk factors and clinical indicators, or the neonatal sepsis calculator may result in some babies beginning to receive treatment when they do not have an infection. However, this risk is mitigated by clear recommendations in other sections of the guideline (recommendations 1.9.1-1.9.4) on when clinicians should stop giving antibiotics. This will minimise the time that a baby receives treatment if a negative blood culture result is returned. Recommendations on duration of antibiotics for early-onset infection were from the previous version of the guideline, and were thought to be appropriate in ensuring that babies receive necessary and timely treatment as well as making sure that treatment is stopped as soon as it is safe to do so. As such, the committee did not think that these needed to be changed.

4.1.4 Cost effectiveness and resource use

The committee were mindful that, as well as having potentially catastrophic consequences for the neonate, any infection that is missed can generate very substantial costs for the health and care system. They noted the clinical evidence, including one UK-based study suggesting that the neonatal sepsis calculator results in a similar number of false negatives as the NICE guidelines. However, the same study suggests that the calculator would lead to a substantial reduction in false-positive diagnoses. This could be important in reducing the number of babies who receive unnecessary treatment for infection, which in turn results in decreasing hospital stays. Thus, the committee made a 'consider' recommendation to use either one of the tools to predict newborn babies' risk of sepsis, which is unlikely to be associated with increased NHS resource use.

4.1.5 Other factors the committee took into account

The committee discussed the recommendations from the previous guideline and agreed that the guidance to perform an immediate clinical assessment, review the maternal and neonatal history and carry out a physical examination was important. This will ensure that a clinician has all the information they need to assess the baby's risk of infection and decide whether blood tests and treatment are needed. The committee did not think that this advice had changed since the previous update of the guideline and so this was included as part of the recommendations.

The committee highlighted the changes in obstetric practice since the previous update of the neonatal infection guideline in 2012. The awareness of maternal sepsis has changed, and fear of missing a diagnosis of sepsis has led to more women now being given antibiotics during labour. Currently, use of parenteral antibiotics during, before or after labour for confirmed or suspected bacterial infection (such as septicaemia) is one of the red flag indicators for babies being at high risk of early-onset neonatal infection. The change in perception of maternal sepsis (based on SEPSIS 6) has therefore led to a rise in the number of babies being given potentially unnecessary antibiotic treatment.

The committee also discussed the results of two additional studies that compared the suggested management of the NICE risk factors tables and the Kaiser Permanente neonatal sepsis calculator but did not meet the inclusion criteria for the review (Appendix D3). One (Pettinger 2019) was a systematic review and meta-analysis paper which retrospectively compared the management of the two tools, and the other (Morris 2020), was a cohort study which retrospectively compared the suggested management of the two tools at sites in England and Wales. The study designs did not meet the inclusion criteria for the review, because the sensitivity and specificity of the neonatal sepsis calculator were not assessed, and the Morris study only included babies with culture-confirmed infection. However, it was decided that it was important to consider the results given the direct comparison between the two tools included in the recommendations for this review. The committee felt confident that the Pettinger results reflected issues that had already been considered within the review and did not think that the findings should change any of the recommendations. The Morris paper highlighted instances for a number of babies with culture-confirmed infection where, at 4

hours, antibiotic treatment was recommended by the NICE recommendations but not by the Kaiser neonatal sepsis calculator. The lower sensitivity of the Kaiser neonatal sepsis calculator supported the results of the review, and as this was based specifically in the UK, the committee decided that the findings were therefore relevant to take into consideration when deciding on recommendations. This further supported its decision that the Kaiser Permanente neonatal sepsis calculator could be used, but only where a clinical audit was taking place to help better determine its effectiveness.

The committee also considered equality issues. It noted that risk factors for neonatal infection vary according to ethnicity and the age of the mother. It was also particularly aware of evidence that group B streptococcus (GBS) colonisation was higher in women of Black African family origin, as was the likelihood of having a baby who is preterm (Puthussery et al. 2019). They noted that the likelihood of having a baby who is preterm also increased with maternal age (Fuchs et al 2018). Having a preterm birth and GBS colonisation are included as risk factors in box 1 and so will be used to assess the risk of early-onset infection and determine antibiotic treatment.

4.2 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1-1.3.9 and the research recommendations on clinical prediction models for early-onset infection and the risk of early-onset infection with maternal obesity.

4.3 References – included studies

4.3.1 Clinical prediction models

Carola, David, Vasconcellos, Mansi, Sloane, Amy et al. (2018) Utility of Early-Onset Sepsis Risk Calculator for Neonates Born to Mothers with Chorioamnionitis.. The Journal of pediatrics 195: 48-52e1

Dhudasia MB; Mukhopadhyay S; Puopolo KM (2018) Implementation of the Sepsis Risk Calculator at an Academic Birth Hospital.. Hospital pediatrics 8(5): 243-250

Goel N., Shrestha S., Smith R. et al. (2020) Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population. Archives of disease in childhood. Fetal and neonatal edition 105: 118-122

Hershkovich-Shporen, C., Ujirauli, N., Oren, S. et al. (2019) Not all newborns born to mothers with clinical chorioamnionitis need to be treated. Journal of Maternal-Fetal and Neonatal Medicine

Joshi NS, Gupta A, Allan JM et al. (2019) Management of Chorioamnionitis-Exposed Infants in the Newborn Nursery Using a Clinical Examination-Based Approach.. Hospital pediatrics 9(4): 227-233

Money, N, Newman, J, Demissie, S et al. (2017) Anti-microbial stewardship: antibiotic use in well-appearing term neonates born to mothers with chorioamnionitis.. Journal of perinatology : official journal of the California Perinatal Association 37(12): 1304-1309

Popowski, Thomas, Goffinet, Francois, Maillard, Francoise et al. (2011) Maternal markers for detecting early-onset neonatal infection and chorioamnionitis in cases of premature rupture of membranes at or after 34 weeks of gestation: a two-center prospective study.. BMC pregnancy and childbirth 11: 26

Shakib, Julie, Buchi, Karen, Smith, Elizabeth et al. (2015) Management of newborns born to mothers with chorioamnionitis: is it time for a kinder, gentler approach?.. Academic pediatrics 15(3): 340-4

Sloane A.J., Coleman C., Carola D.L. et al. (2019) Use of a Modified Early-Onset Sepsis Risk Calculator for Neonates Exposed to Chorioamnionitis. Journal of Pediatrics

Strunk T., Buchiboyina A., Sharp M. et al. (2018) Implementation of the Neonatal Sepsis Calculator in an Australian Tertiary Perinatal Centre. Neonatology 113(4): 379-382

4.3.2 Maternal and neonatal risk factors

Dempsey, E, Chen, M-F, Kokottis, T et al. (2005) Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. American journal of perinatology 22(3): 155-9

Dior, Uri P, Kogan, Liron, Eventov-Friedman, Smadar et al. (2016) Very High Intrapartum Fever in Term Pregnancies and Adverse Obstetric and Neonatal Outcomes. Neonatology 109(1): 62-8

Garcia-Munoz Rodrigo, Fermin; Galan Henriquez, Gloria M; Ospina, Cristina Gomez (2014) Morbidity and mortality among very-low-birth-weight infants born to mothers with clinical chorioamnionitis. Pediatrics and neonatology 55(5): 381-6

Garcia-Munoz Rodrigo, Fermin, Galan Henriquez, Gloria, Figueras Aloy, Josep et al. (2014) Outcomes of very-low-birth-weight infants exposed to maternal clinical chorioamnionitis: a multicentre study. Neonatology 106(3): 229-34

Hakansson, S and Kallen, K (2006) Impact and risk factors for early-onset group B streptococcal morbidity: analysis of a national, population-based cohort in Sweden 1997-2001. BJOG : an international journal of obstetrics and gynaecology 113(12): 1452-8

Hakansson, Stellan and Kallen, Karin (2008) High maternal body mass index increases the risk of neonatal early onset group B streptococcal disease. Acta paediatrica (Oslo, Norway : 1992) 97(10): 1386-9

Klinger, Gil, Levy, Itzhak, Sirota, Lea et al. (2009) Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants. American journal of obstetrics and gynecology 201(1): 38e1-6

Mularoni, Alessandra, Madrid, Marisela, Azpeitia, Agueda et al. (2014) The role of coagulase-negative staphylococci in early onset sepsis in a large European cohort of very low birth weight infants. The Pediatric infectious disease journal 33(5): e121-5

Ofman, Gaston; Vasco, Natalia; Cantey, Joseph B (2016) Risk of Early-Onset Sepsis following Preterm, Prolonged Rupture of Membranes with or without Chorioamnionitis. American journal of perinatology 33(4): 339-42

Ronnestad, Arild, Abrahamsen, Tore G, Medbo, Sverre et al. (2005) Septicemia in the first week of life in a Norwegian national cohort of extremely premature infants. Pediatrics 115(3): e262-8

Soraisham, Amuchou S, Singhal, Nalini, McMillan, Douglas D et al. (2009) A multicenter study on the clinical outcome of chorioamnionitis in preterm infants. American journal of obstetrics and gynecology 200(4): 372e1-6

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

Review protocols for review protocols on the accuracy and effectives of clinical prediction models (A.1, Part A – Prognostic accuracy studies and A.2, Part B – Test and treat RCTs), individual maternal risk factors (A.3) and individual neonatal risk factors (A.4) are all included in the appendices below.

A.1 Review protocol for clinical prediction models - part A (prognostic accuracy studies)

ID	Field	Content
0.	PROSPERO registration number	CRD4201915161
1.	Review title	Risk factors for early-onset neonatal infection
2.	Review question	• What is the accuracy of clinical prediction models for early-onset neonatal infection and what is their effectiveness in guiding management in the baby?
3.	Objective	To identify risk prediction models for early-onset neonatal infection that should be used to guide management in the UK: • covers maternal risk factors associated with pre-pregnancy, antenatal, intrapartum and postnatal periods (including previous pregnancy history, antenatal events, gestational age and GBS carriage when known (GBS

		screening is not currently recommended by the UK national screening committee)) and fetal risk factors • includes symptoms and signs in the mother • covers events relating to the baby after birth (postnatal events) and signs of sibling infection up to 72 hours after birth • includes consideration of how soon after birth symptoms, signs or other indicators should raise suspicion of early-onset neonatal infection (for example, 0, 12, 24, 36, 48, or 72 hours; although 0-24 hours probably most likely) 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. • Currently there is one main tool identified by the committee and stakeholders, the neonatal sepsis calculator (Kaiser Permanente). This calculator takes information about both risk factors and clinical signs, and so it effectively uses what could be strictly classed as both diagnostic and prognostic information. According to the current NICE guideline (which was based on an evidence review of individual risk factors and clinical signs), babies should get treatment based on a combined assessment of risk factors and clinical signs; it is then possible to prompt investigations/receive treatment without any clinical signs if the risk is very high. Because of the development of this tool since the original guideline, the aim of the review is to

		determine whether the tool (or other similar tools identified in the course of the review) is good enough (accurate enough) to be used to assess babies instead of current methods where clinicians make a judgment based on individual risk factors and clinical signs that they have identified.
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 be early-onset (within 72 hours of birth) or late-onset (more than 72 hours after birth). Neonatal infection can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. To reduce mortality from early-onset neonatal infection, the current NICE guideline recommends antibiotic prophylaxis during labour and neonatal antibiotic treatment to be based on multiple risk factors, clinical indicators and red flags collectively.
6.	Population	Inclusion: • Unborn or newborn babies under 72 hours • Pregnant women Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections. • Babies with late-onset neonatal infection (onset of infection after 72 hours of age). Studies including babies with early- and late-onset infection will be included if data for early- and late-onset is presented separately. • 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 early-onset neonatal infection. For example: the neonatal early-onset sepsis calculator (Kaiser Permanente) • If sufficient evidence is not found on risk prediction tools for early-onset neonatal infection, a review of individual maternal and fetal risk factors, and individual risk factors in the baby will be carried out.
8.	Comparator/Reference standard/Confounding factors	Reference standard (predictive models): • culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early 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 early-onset neonatal infection (based on study definition of early-onset neonatal infection) • 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 (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 Gabriel Rogers • Mr Fadi Chehadah • Mr Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines 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	Early onset neonatal infection, risk factors

33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ ☐ ☐ ☐ ☐
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.2 Review protocol for clinical prediction models - part B (test and treat RCTs)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Risk factors for early-onset neonatal infection

2.	Review question	What is the accuracy of clinical prediction models for early-onset neonatal infection and what is their effectiveness in guiding management in the baby?
3.	Objective	To identify risk factors for early-onset neonatal infection that should be used to guide management in the UK: • covers maternal risk factors associated with pre-pregnancy, antenatal, intrapartum and postnatal periods (including previous pregnancy history, antenatal events, gestational age and GBS carriage when known (GBS screening is not currently recommended by the UK national screening committee)) and fetal risk factors • includes symptoms and signs in the mother • covers events relating to the baby after birth (postnatal events) and signs of sibling infection up to 72 hours after birth • includes consideration of how soon after birth symptoms, signs or other indicators should raise suspicion of early-onset neonatal infection (for example, 0, 12, 24, 36, 48, or 72 hours; although 0-24 hours probably most likely) • includes which symptoms and signs (individually or in combination) should lead to antibiotic prophylaxis and/or 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 be early-onset (within 72 hours of birth) or late-onset (more than 72 hours after birth). Neonatal infection can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. To reduce mortality from early-onset neonatal infection, the current NICE guideline recommends antibiotic prophylaxis during labour and neonatal antibiotic treatment to be based on multiple risk factors, clinical indicators and red flags collectively.
6.	Population	Inclusion: • Unborn or newborn babies under 72 hours • Pregnant women Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections. • Babies with late-onset neonatal infection (onset of infection after 72 hours of age). Studies including babies with early- and late-onset

		infection will be included if data for early- and late-onset is presented separately. • 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	Any risk tool* for early-onset neonatal infection identified in Part A of the protocol (any validated risk tool using multiple predictors to predict the risk of development or the presence of early-onset neonatal infection) followed by treatment (for example provision of antibiotics or further testing) according to risk stratification by the tool results. *For example: the neonatal early-onset sepsis calculator (Kaiser Permanente) If sufficient evidence is not found on risk prediction tools for early-onset neonatal infection (parts A and B, of which this protocol is part B), a review of individual maternal and fetal risk factors, and individual risk factors in 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 early-onset neonatal infection (based on study definition of early-onset neonatal infection) • 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 within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection • antibiotics for suspected bloodstream infection (within 72 hours of birth or within the study-defined period for early-onset neonatal infection) • Mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth)

		• respiratory distress within 72 hours of birth or within the study-defined period for early-onset neonatal infection • health-related quality of life, measured using a validated tool (during the neonatal period and at the latest time point reported in study) • hospital length of stay • number of babies 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 time point 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 results for term and preterm neonates (subgroup differences $p<0.05$) then results will be stratified by 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 Gabriel Rogers • Mr Fadi Chehadah • Mr Wesley Hubbard
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines 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	Early onset neonatal infection, risk factors
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ ☐ ☐ ☐

		☐
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.3 Review protocol for maternal risk factors

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Maternal and fetal risk factors for early-onset infection
2.	Review question	Which maternal and fetal risk factors for early-onset neonatal infection should be used to guide management?
3.	Objective	To identify risk factors for early-onset neonatal infection/sepsis that should be used to guide management in the UK • includes symptoms and signs in the mother and fetus (including previous pregnancy history) • This review follows on from a review of clinical prediction models for early-onset neonatal infection. Evidence from this review did not support a strong positive recommendation for any risk prediction model for all population groups, therefore a review of individual risk factors is required.

		• This is a prognostic review because it investigates maternal and fetal 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. Early-onset neonatal infection occurs less than 72 hours after birth and can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Unborn or newborn babies under 72 hours • Pregnant women 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	• 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 • Maternal GBS colonisation, bacteriuria, detection (including vaginal or rectal swab) or infection in a previous pregnancy (including where the baby was well) • Suspected or confirmed infection in another baby in the case of a multiple pregnancy • Maternal suspected bacterial infection in the puerperium period • Maternal perineal infections • 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) • Preterm prelabour rupture of membranes • Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth • Gestational age • Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis • Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time

		during labour, or in the 24-hour periods before and after the birth [This does not refer to intrapartum antibiotic prophylaxis] • Intrapartum antibiotic prophylaxis (including the time before birth that it is received)
8.	Reference standard	• culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given within 72 hours of birth where available or within the study-defined period for early 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 this review question 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.
12.	Primary outcomes (critical outcomes)	Outcomes for predictive accuracy studies: • Sensitivity • Specificity • Positive and negative predictive values • 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 babies and preterm babies • 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	01/11/2019		
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 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, 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 Review protocol for neonatal risk factors

ID	Field	Content
0.	PROSPERO registration number	CRD42019162610
1.	Review title	Neonatal risk factors and clinical indicators of early-onset infection
2.	Review question	Which risk factors in the baby (including symptoms and signs) should raise suspicion of early-onset infection?
3.	Objective	To identify risk factors for early-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 early-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 because although the question is an update of one from a previous version of the guideline, the search was carried out in conjunction with the searches for review question 5.1 and 5.2 which are new questions..

5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in newborn babies. Early-onset neonatal infection occurs less than 72 hours after birth and can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths.
6.	Population	Inclusion: • Newborn babies under 72 hours, or study definition for 'early onset' infection 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	**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 • 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)

		• Signs of neonatal encephalopathy **Risk factors (prognostic)** • Gestational age • Colonisation with Group B streptococcus (GBS) or Methicillin-resistant Staphylococcus aureus (MRSA) in the baby • Persistent fetal circulation (persistent pulmonary hypertension)
8.	Comparator/Reference standard/Confounding factors	• culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection • antibiotics for suspected bloodstream infection (in neonate) given within 72 hours of birth where available or within the study-defined period for early onset neonatal infection
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 neonatal units or neonatal intensive care units.
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 • multiple births • admission to neonatal unit		
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	24/06/2018		
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

Literature search strategies for prognostic accuracy models and maternal and neonatal risk factors are all included in the appendices below.

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 28th November 2019. A single search strategy was developed for review questions 1.1 and 1.2. 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).

The search focused on unique risk factors for review questions 1.1 and 1.2 not previously considered for review questions 5.1 and 5.2.

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 exp Fetal Membranes, Premature Rupture/

57 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) adj4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)).tw.

58 (prom or proms or pprom*).tw.

59 Gestational Age/

60 ((gestat* or f?etal* or f?etus*) adj4 (age* or aging* or matur*)).tw.

61 Fever/di, dg [Diagnosis, Diagnostic Imaging]

62 ((intrapartum* or intra-partum* or labo?r* or deliver* or childbirth* or child-birth* or congenit* or conatal*) adj4 (fever* or deliriu* or pyrexia* or hyperthermia*)).tw.

63 Chorioamnionitis/

64 (chorioamnionit* or amnioniti* or funisiti*).tw.

65 (parenteral* adj4 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*)).tw.

66 Antibiotic Prophylaxis/

67 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*) adj4 (prophyla* or premedic* or pre-medic* or prevent*)).tw.

68 Brain Diseases/

69 ((brain* or intracranial* or intra-cranial* or encephalon*) adj4 (diseas* or disorder* or defect* or illness* or inflam* or syndrom*)).tw.

70 encephalopath*.tw.

71 Persistent Fetal Circulation Syndrome/

72 ((persist* or misalign* or mis-align*) adj4 (f?etal* or f?etus* or pulmonar*) adj4 (circulat* or hypertens* or vein*)).tw.

73 (PPHN or PFC or ACD MPV or ACDMPV).tw.

74 or/56-73

75 55 and 74

76 Animals/ not Humans/

77 75 not 76

78 limit 77 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 exp premature fetus membrane rupture/

57 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) adj4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)).tw.

58 (prom or proms or pprom*).tw.

59 gestational age/

60 ((gestat* or f?etal* or f?etus*) adj4 (age* or aging* or matur*)).tw.

61 fever/di [Diagnosis]

62 ((intrapartum* or intra-partum* or labo?r* or deliver* or childbirth* or child-birth* or congenit* or conatal*) adj4 (fever* or deliriu* or pyrexia* or hyperthermia*)).tw.

63 exp chorioamnionitis/

64 (chorioamnionit* or amnioniti* or funisiti*).tw.

65 (parenteral* adj4 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*)).tw.

66 antibiotic prophylaxis/

67 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*) adj4 (prophyla* or premedic* or pre-medic* or prevent*)).tw.

68 brain disease/

69 ((brain* or intracranial* or intra-cranial* or encephalon*) adj4 (diseas* or disorder* or defect* or illness* or inflam* or syndrom*)).tw.

70 encephalopath*.tw.

71 persistent pulmonary hypertension/

72 ((persist* or misalign* or mis-align*) adj4 (f?etal* or f?etus* or pulmonar*) adj4 (circulat* or hypertens* or vein*)).tw.

73 (PPHN or PFC or ACD MPV or ACDMPV).tw.

74 or/56-73

75 55 and 74

76 nonhuman/ not human/

77 75 not 76

78 limit 77 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,kw296

#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 MeSH descriptor: [Fetal Membranes, Premature Rupture] explode all trees

#57 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) near/4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*)):ti,ab,kw

#58 (prom or proms or pprom*):ti,ab,kw

#59 MeSH descriptor: [Gestational Age] this term only

#60 ((gestat* or f?etal* or f?etus*) near/4 (age* or aging* or matur*)):ti,ab,kw

#61 MeSH descriptor: [Fever] this term only and with qualifier(s): [diagnostic imaging - DG, diagnosis - DI]

#62 ((intrapartum* or intra-partum* or labo?r* or deliver* or childbirth* or child-birth* or congenit* or conatal*) near/4 (fever* or deliriu* or pyrexia* or hyperthermia*)):ti,ab,kw

#63 MeSH descriptor: [Chorioamnionitis] this term only

#64 (chorioamnionit* or amnioniti* or funisiti*):ti,ab,kw

#65 ((parenteral*) near/4 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*)):ti,ab,kw

#66 MeSH descriptor: [Antibiotic Prophylaxis] this term only

#67 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*) near/4 (prophyla* or premedic* or pre-medic* or prevent*)):ti,ab,kw

#68 MeSH descriptor: [Brain Diseases] this term only

#69 ((brain* or intracranial* or intra-cranial* or encephalon*) near/4 (diseas* or disorder* or defect* or illness* or inflam* or syndrom*)):ti,ab,kw

#70 (encephalopath*):ti,ab,kw

#71 MeSH descriptor: [Persistent Fetal Circulation Syndrome] this term only

#72 ((persist* or misalign* or mis-align*) near/4 (f?etal* or f?etus* or pulmonar*) near/4 (circulat* or hypertens* or vein*)):ti,ab,kw

#73 (PPHN or PFC or ACD MPV or ACDMPV):ti,ab,kw

#74 {or #56-#73}

#75 #55 and #74

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 MeSH DESCRIPTOR Fetal Membranes, Premature Rupture EXPLODE ALL TREES

57 ((preterm* or pre-term* or premature* or pre-mature* or prelabor* or pre-labor* or pre) NEAR4 (ruptur* or membrane* or disrupt* or erupt* or sever or severed or tear* or breach*))

58 (prom or proms or pprom*)

59 MeSH DESCRIPTOR Gestational Age

60 ((gestat* or f?etal* or f?etus*) NEAR4 (age* or aging* or matur*))

61 MeSH DESCRIPTOR Fever WITH QUALIFIER DI

62 MeSH DESCRIPTOR Fever WITH QUALIFIER DG

63 ((intrapartum* or intra-partum* or labo?r* or deliver* or childbirth* or child-birth* or congenit* or conatal*) NEAR4 (fever* or deliriu* or pyrexia* or hyperthermia*))

64 MeSH DESCRIPTOR Chorioamnionitis

65 (chorioamnionit* or amnioniti* or funisiti*)

66 ((parenteral*) NEAR4 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*))

67 MeSH DESCRIPTOR Antibiotic Prophylaxis

68 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid*) NEAR4 (prophyla* or premedic* or pre-medic* or prevent*))

69 MeSH DESCRIPTOR Brain Diseases

70 ((brain* or intracranial* or intra-cranial* or encephalon*) NEAR4 (diseas* or disorder* or defect* or illness* or inflam* or syndrom*))

71 (encephalopath*)

72 MeSH DESCRIPTOR Persistent Fetal Circulation Syndrome

73 ((persist* or misalign* or mis-align*) NEAR4 (f?etal* or f?etus* or pulmonar*) NEAR4 (circulat* or hypertens* or vein*))

74 (PPHN or PFC or ACD MPV or ACDMPV)

75 #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

76 #55 AND #75

77 * IN DARE

78 #76 AND #77

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* or adenovir*).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

Risk factors included in the search for review questions 5.1 and 5.2

The risk factors searched for as part of review questions 5.1 and 5.2 were considered for this evidence review and results from that search considered as part of the analysis. As a result of this they were removed from this search. This was to ensure there was no duplication of effort and there was a unique set of results for this search.

The following risk factors were combined as 'Not' with the other sections of the search strategy. The Medline risk factor terms are listed below. These were translated across all databases used in the search:

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

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

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

4 ((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.

5 exp Pregnancy, Multiple/

6 ((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.

7 Wound Infection/

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

9 Postpartum Period/

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

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

12 exp Obesity/

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

14 exp Hygiene/

15 exp Sanitation/

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

17 exp Maternal Behavior/

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

19 Illness Behavior/

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

21 Muscle Hypotonia/

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

23 ((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.

24 Feeding Behavior/

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

26 exp Vomiting/

27 (vomit* or emesis*).tw.

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

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

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

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

32 ((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.

33 Bradycardia/ or Tachycardia/

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

35 Respiratory Distress Syndrome, Newborn/

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

37 exp Hypoxia/

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

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

40 exp Cyanosis/

41 exp Oximetry/

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

43 exp Jaundice, Neonatal/

44 (jaundice* or icterus*).tw.

45 exp Apnea/

46 apn?ea*.tw.

47 Seizures/

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

49 exp Cardiopulmonary Resuscitation/

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

51 exp Respiration, Artificial/

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

53 exp Body Temperature/

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

55 (("36*" or "38*") adj2 (C or celsius)).tw.

56 (("96*" or "100*") adj2 (F or fahrenheit)).tw.

57 exp Shock/

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

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

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

61 Sweat/ or Sweating/

62 (sweat* or perspir*).tw.

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

64 (weakness* or fragilit*).tw.

65 Dizziness/

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

67 Thirst/

68 thirst*.tw.

69 Yawning/

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

71 exp Hemorrhage/

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

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

74 exp Thrombocytopenia/

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

76 Blood Coagulation/

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

78 Oliguria/

79 oliguria*.tw.

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

81 Homeostasis/

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

83 exp Hypoglycemia/

84 exp Hyperglycemia/

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

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

87 exp Acidosis/

88 acidos?s*.tw.

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

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

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

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

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

94 (prematur* adj8 risk*).tw.

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

96 ((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.

97 ((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.

98 or/1-97

B.3 Economic 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)

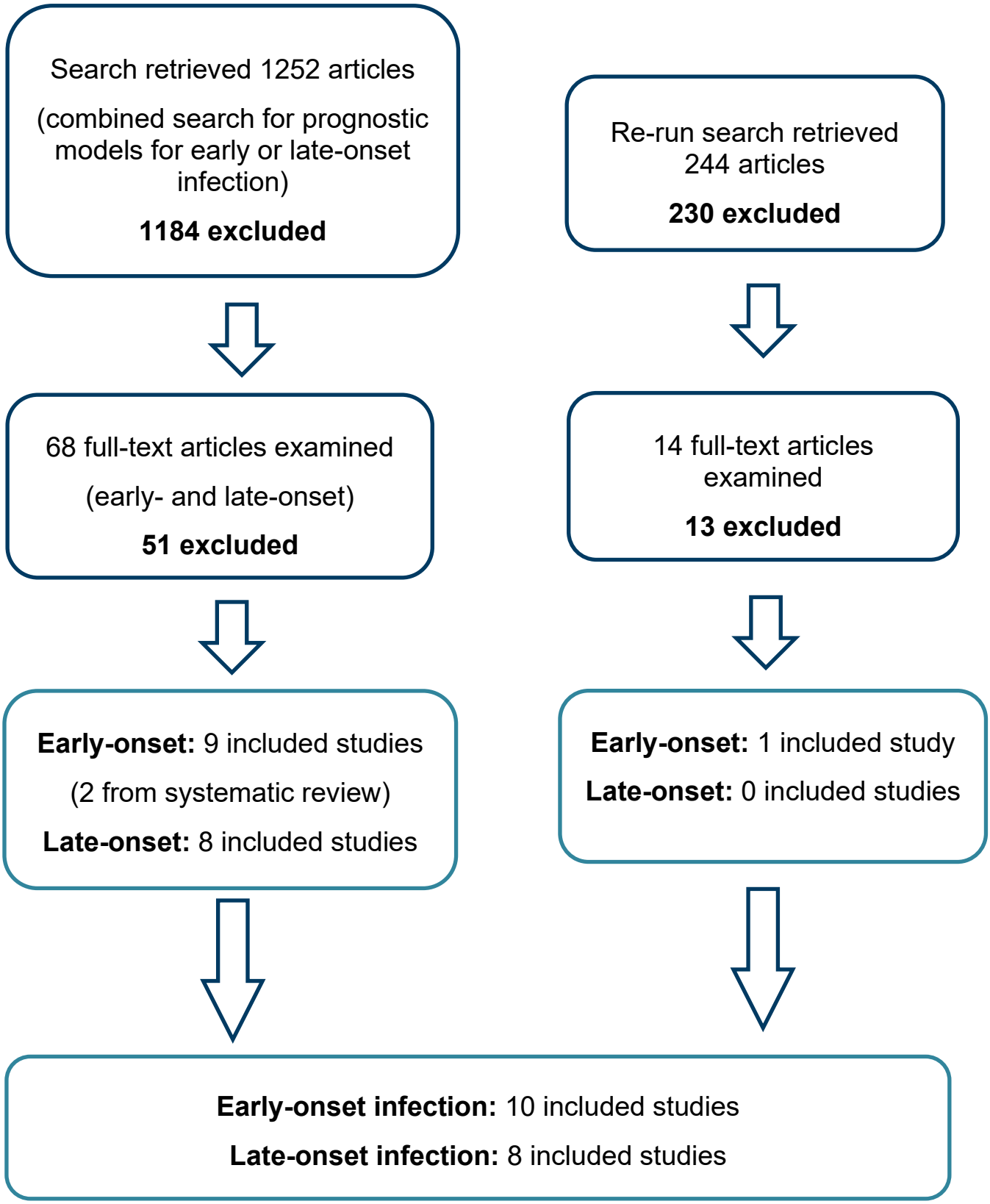
29 25 or 28 (205)

30 3 and 29 (15)

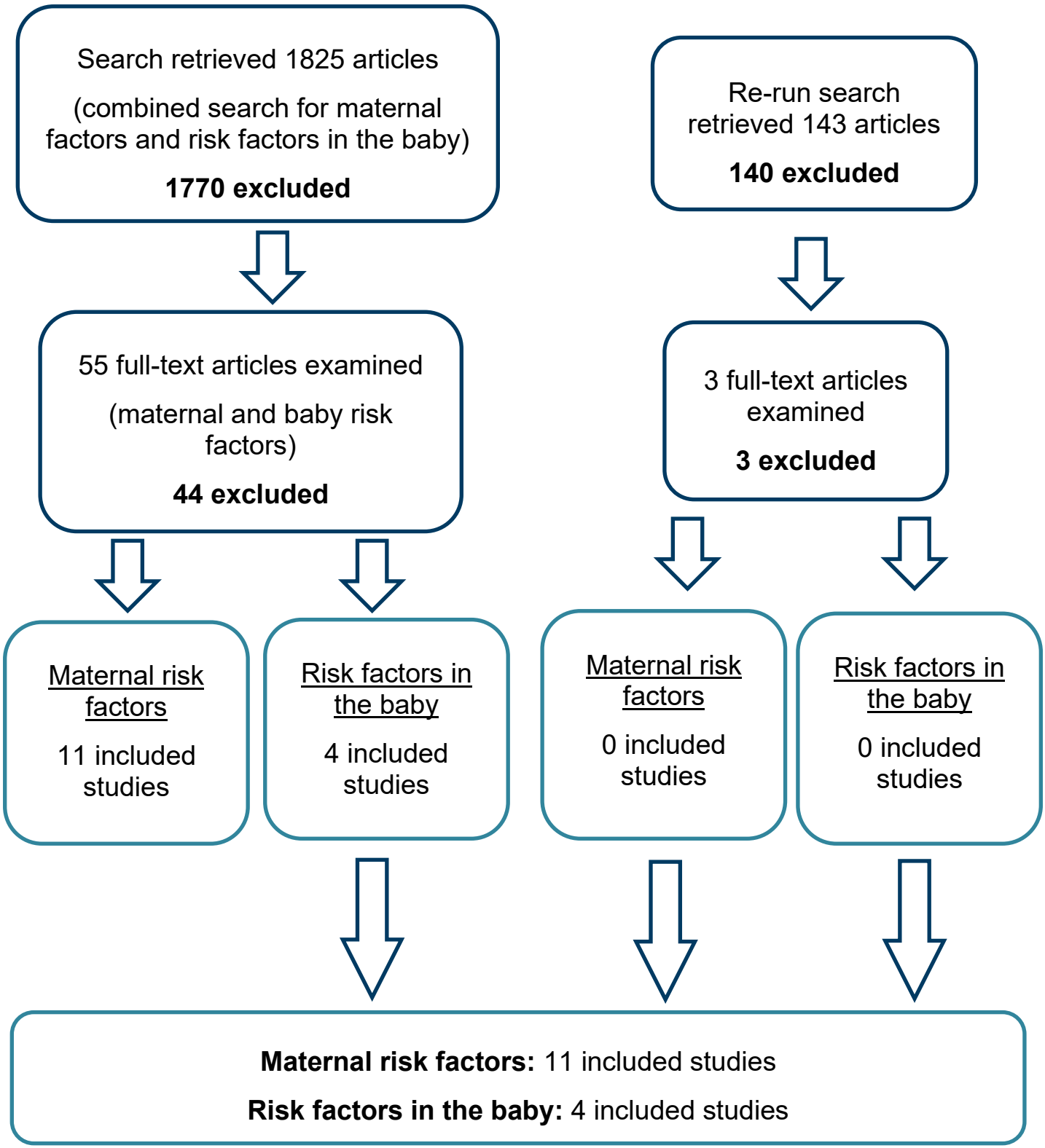
31 limit 30 to yr="2019 -Current" (1)

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

Carola 2018

Bibliographic Reference Carola, David; Vasconcellos, Mansi; Sloane, Amy; McElwee, Dorothy; Edwards, Caroline; Greenspan, Jay; Aghai, Zubair H; Utility of Early-Onset Sepsis Risk Calculator for Neonates Born to Mothers with Chorioamnionitis.; The Journal of pediatrics; 2018; vol. 195; 48-52e1

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Level 3 NICU Study dates November 2006 - March 2017 Duration of follow-up Not reported but investigated early-onset infection Associated studies Sloane 2019
Inclusion criteria	Neonates with gestational age ≥35 weeks Born to mothers with clinical chorioamnionitis diagnosis of chorioamnionitis was made by an obstetrician based on intrapartum fever (temperature ≥38°C) alone or in conjunction with maternal leukocytosis, uterine tenderness, foul-smelling amniotic fluid, and maternal or fetal tachycardia
Exclusion criteria	None reported
Sample characteristics	Sample size 896 Female 51.6% Gestational age - weeks (SD) 39.4 (±1.3) Birth weight - kg (SD) 3.35 (0.43) Group B streptococcus colonisation 24.4% Duration of rupture of membranes - hours (IQR) 13 (8-21)

	Number with positive blood cultures (%) 5 (0.56%)
Prognostic model	Kaiser Permanente neonatal sepsis calculator

Study arms

Diagnostic laboratory evaluation (Complete blood count and C-reactive protein values) (N = 896)

CBC and CRP assessed 6-12 hours after birth. Abnormal CBC: white blood cell <5000/microlitre, an immature:total neutrophil (I:T) ratio ≥0.2, or platelet count <100 000/microlitre. I:T ratio was calculated as described by Manroe et al with an I:T value of ≥0.2 considered elevated. Abnormal CRP level: >1 mg/dL

Clinical signs for predicting early-onset infection (N = 896)

Significant clinical symptoms were considered to be those categorized as “equivocal” or “clinical illness” by the EOS calculator

Kaiser Permanente neonatal sepsis calculator (N = 896)

Background incidence of early-onset infection set at 0.5/1000 live births (CDC national incidence)

Risk of bias

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

(EOS calculator)

2.2 Were predictor assessments made without knowledge of outcome data?

No information

(Unclear if investigators had knowledge of outcome when conducting EOS calculator.)

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

(Unclear if investigators had knowledge of both predictors and outcome)

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 = 5 with event)

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?

Not applicable

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

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

Dhudasia 2018

Bibliographic Reference Dhudasia MB; Mukhopadhyay S; Puopolo KM; Implementation of the Sepsis Risk Calculator at an Academic Birth Hospital.; Hospital pediatrics; 2018; vol. 8 (no. 5)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting teaching hospital within a university health care system with ~5000 annual deliveries, 52 postpartum mother-infant rooms, and a 50-bed, tertiary-care NICU Study dates March 2014 - May 2015 and June 2015 - July 2015 Duration of follow-up 72 hours
Inclusion criteria	Neonates with gestational age ≥36 weeks gestation
Sample characteristics	Sample size 6090 Female 49% Gestational age - weeks (SD) 39.3 (1.3) Birth weight <2500 g 4%
Prognostic model	Kaiser Permanente neonatal sepsis calculator

Study arms

Kaiser Permanente neonatal sepsis calculator (N = 5692)

Baseline incidence 0.5/1000 live births

Standard practice (N = 5692)

based on guidelines provided in the Centers for Disease Control and Prevention (CDC) group B streptococcus (GBS) prevention guidelines16,17 and those recommended by the American Academy of Pediatrics

Risk of bias

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?

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?

Yes

2.3 Are all predictors available at the time the model is intended to be used?

Probably 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 no

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?

Yes

4.2 Were continuous and categorical predictors handled appropriately?

Probably 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

Probably yes

4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of control participants) accounted for appropriately?

Probably 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

Low

Overall Risk of bias and Applicability

Risk of bias

Low

Concerns for applicability

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

Goel 2020

Bibliographic Reference Goel N.; Shrestha S.; Smith R.; Mehta A.; Ketty M.; Muxworthy H.; Abelian A.; Kirupaalar V.; Saeed S.; Jain S.; Asokkumar A.; Natti M.; Barnard I.; Pitchaikani P.K.; Banerjee S. ; Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population; Archives of disease in childhood. Fetal and neonatal edition; 2019; vol. 105

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Wales Study setting 8 maternity hospitals (3 NICUs, 1 subregional NICU, 4 special care units) Study dates February 2018 - April 2018 Duration of follow-up 72 hours
Inclusion criteria	Neonates with gestational age ≥34 weeks
Exclusion criteria	None reported
Sample characteristics	Sample size 3593 Group B streptococcus colonisation In mother: 200 (5.5%) Gestational age <37 weeks 252 (7%) Rupture of membranes >18 hours 573 (16) Maternal temperature ≥38 degrees 194 (5%)
Prognostic model	Kaiser Permanente neonatal sepsis calculator NICE risk factors

Study arms

NICE guidelines (N = 3593) Neonates managed according to NICE guidelines using risk factors (red or non-red flags) to guide initiation of antibiotics

Kaiser Permanente neonatal sepsis calculator (N = 3593)

Used retrospectively. Background incidence for early-onset infection set at 0.5/1000 live births (closest estimated incidence from studies of term and near-term infants in high-income countries including the UK)

Risk of bias

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

2.2 Were predictor assessments made without knowledge of outcome data?

Yes

(Clinicians were blinded)

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?

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

Analysis

4.1 Were there a reasonable number of participants with the outcome?

No

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

Overall risk of bias for analysis domain

Low

Overall Risk of bias and Applicability

Risk of bias

Low

Concerns for applicability

Low

Hershkovich-Shporen, 2019

Bibliographic Reference Hershkovich-Shporen, C.; Ujirauli, N.; Oren, S.; Juster Reicher, A.D.A.; Gadassi, N.; Guri, A.; Flidel-Rimon, O.; Not all newborns born to mothers with clinical chorioamnionitis need to be treated; Journal of Maternal-Fetal and Neonatal Medicine; 2019

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Israel Study setting Kaplan Medical Centre - paediatric emergency department Study dates May 2015 - April 2016 Sources of funding None reported
Inclusion criteria	Gestational age of 35 weeks or more Risk factors for early-onset neonatal sepsis maternal group B Streptococcus (GBS) carrier, maternal fever 38 oC or more, preterm delivery (35–36.6 gestational age), rupture of membrane more than 18 h before delivery, clinical maternal chorioamnionitis, newborns born to mothers that were treated with intra-partum antibiotic prophylaxis Receiving antibiotics in the first 72 hours of life Symptoms of suspected early-onset sepsis Proven sepsis
Exclusion criteria	None reported
Sample characteristics	Sample size 1341 Female 45%

	Mean gestational age (SD) 38 weeks ± 1.7 Mean birth weight (SD) 3184 ± 487 g
Length of follow-up	First 72 hours of life
Prognostic model	Kaiser Permanente neonatal sepsis calculator
Reference factor(s)	Positive blood culture for early-onset neonatal sepsis

Study arms

Standard practice (N = 1341) Symptomatic newborns and newborns to mothers with clinical chorioamnionitis are given antibiotic treatment and complete blood counts and blood cultures are drawn. The infant is treated with empiric antibiotic (ampicillin and gentamycin) therapy for 48 h if cultures are negative. When a pathogen is detected, antibiotic therapy is either continued or, if needed, modified
Kaiser Permanente neonatal sepsis calculator (N = 1341) Kaiser Permanente neonatal sepsis calculator retrospectively applied based on the charts of each of the babies in the standard practice arm. Background incidence of 0.6/1000 (based on incidence in the centre between January 2008 - January 2015)

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?	No information *(Appropriate inclusion criteria. No information about exclusion criteria)*
	Overall risk of bias for selection of participants domain	Unclear *(No information about exclusion criteria)*
	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?	No information *(No definition of proven sepsis)*
	3.3 Were predictors excluded from the outcome definition?	Probably yes
	3.4 Was the outcome defined and determined in a similar way for all participants?	No information *(No definition of proven sepsis)*
	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	Unclear *(No definition of proven sepsis)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.1 Were there a reasonable number of participants with the outcome?	Yes

Section	Question	Answer
	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
	4.7 Were relevant model performance measures evaluated appropriately?	No information *(Limited information about analysis methods)*
	Overall risk of bias for analysis domain	Unclear *(Limited information about analysis methods)*
Overall Risk of bias and Applicability	Risk of bias	Unclear *(Limited information about analysis methods, no information about exclusion criteria, no definition of proven sepsis)*
	Concerns for applicability	Some concerns *Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)*

Joshi 2019

Bibliographic Reference	Joshi NS; Gupta A; Allan JM; Cohen RS; Aby JL; Kim JL; Benitz WE; Frymoyer A; Management of Chorioamnionitis-Exposed Infants in the Newborn Nursery Using a Clinical Examination-Based Approach.; Hospital pediatrics; 2019; vol. 9 (no. 4)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location USA Study setting academic, tertiary care children's hospital that offers obstetric and neonatal services

	Study dates August 2016 - August 2017 Duration of follow-up 72 hours
Inclusion criteria	Born to mothers with clinical chorioamnionitis diagnosed by the obstetric team and is treated with intravenous broad-spectrum antibiotics Neonates with gestational age ≥34 weeks Well-appearing infants
Exclusion criteria	Known congenital anomaly requiring NICU admission
Sample characteristics	Sample size 319 Female 44.5% Birth weight - kg (SD) 3.35 (3.06 - 3.66) Group B streptococcus colonisation Maternal: 18% Rupture of membranes >18 hours 25%
Prognostic model	Kaiser Permanente neonatal sepsis calculator

Study arms

Kaiser Permanente neonatal sepsis calculator (N = 319)

Baseline incidence of 0.6/1000 live births

Standard care (N = 277)

Well-appearing infants remained with their mothers for skin-to-skin care for the first 2 hours after birth and were then admitted to the level II NICU for ongoing clinical monitoring. Laboratory testing and antibiotic treatment were not performed unless clinical signs of illness developed.

Risk of bias

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?

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?

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 no

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?

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?

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?

Probably 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

Low

Overall Risk of bias and Applicability

Risk of bias

Low

Concerns for applicability

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

Money 2017

Bibliographic Reference Money, N; Newman, J; Demissie, S; Roth, P; Blau, J; Anti-microbial stewardship: antibiotic use in well-appearing term neonates born to mothers with chorioamnionitis.; Journal of perinatology : official journal of the California Perinatal Association; 2017; vol. 37 (no. 12); 1304-1309

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting 1 hospital Study dates January 2009 - April 2016 Duration of follow-up Not reported but examined early-onset infection
Inclusion criteria	Born to mothers with clinical chorioamnionitis According to maternal ICD-9 codes Well-appearing infants
Exclusion criteria	Syptomatic patients who required admission to the Neonatal Intensive Care Unit due to equivocal presentation or clinical illness
Sample characteristics	Sample size 362 Female 49.5% Mean age (SD) Maternal: 26.8 (6.0) Gestational age - weeks (SD) 39.5 (1.2) Birth weight - kg (SD) 3.431 (0.438) Group B streptococcus colonisation Maternal: 47 (13%) Duration of rupture of membranes - mean (SD) 14.5 (8.8)
Prognostic model	Kaiser Permanente neonatal sepsis calculator

Study arms

Current practice (N = 362)

Term newborns born to mothers with chorioamnionitis are admitted to an Observation Nursery. Serial vital signs and physical exams are monitored along with continuous pulse oximetry. CDC and AAP recommendations are followed - sepsis evaluations and antibiotic therapy are prescribed for all patients.

Kaiser Permanente neonatal sepsis model (N = 362)

Baseline incidence of early-onset infection set at 0.5/1000 (based on CDC national incidence)

Risk of bias

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?

No

Only well-appearing infants were included (symptomatic patients excluded). Issues with subjective diagnosis of chorioamnionitis

Overall risk of bias for selection of participants domain

High

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

(Unclear if investigators had knowledge of both predictors and outcome.)

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

(EOS calculator.)

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

Analysis

4.1 Were there a reasonable number of participants with the outcome?

No

4.2 Were continuous and categorical predictors handled appropriately?

Yes

4.3 Were all enrolled participants included in the analysis?

No

(Symptomatic patients excluded.)

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?

Not applicable

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

Review was limited to well appearing infants. Potential for subjectivity in diagnosing chorioamnionitis

Concerns for applicability

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

Popowski 2011

Bibliographic Reference Popowski, Thomas; Goffinet, Francois; Maillard, Francoise; Schmitz, Thomas; Leroy, Sandrine; Kayem, Gilles; Maternal markers for detecting early-onset neonatal infection and chorioamnionitis in cases of premature rupture of membranes at or after 34 weeks of gestation: a two-center prospective study.; BMC pregnancy and childbirth; 2011; vol. 11; 26

Study Characteristics

Study design	Prospective cohort study
Study details	Study location France Study setting 2 tertiary university referral centres Study dates January 2004 - February 2006

	Duration of follow-up 72 hours Sources of funding Clinical research grant (CIRC: CRC 03134) and research fellowship grant from French Society of Perinatal Medicine
Inclusion criteria	Women with PROM at or after 34 weeks of gestation Singleton pregnancies
Exclusion criteria	Women in spontaneous labour at admission to the hospital Women who gave birth more than 72 hours after admission
Sample characteristics	Sample size 399 Mean age (SD) Maternal: 31.7 (5.5) Gestational age - weeks (SD) 38.5 (1.6) (at inclusion in the study) Birth weight - kg (SD) 3.24 (4.71)
Prognostic model	Unnamed prediction model

Study arms

C-reactive protein (N = 399)

neonatal CRP ≥10 mg/L

Predictive model (N = 399)

Based on predictive factors: maternal white blood cell count, C-reactive protein concentration, pathogenic genital bacteria. Includes potential confounding factors: gestational age, antibiotic prescription at admission, type of management (expectant or active).

Risk of bias

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?

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?

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?

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

4.1 Were there a reasonable number of participants with the outcome?

No

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?

Probably yes

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

Low

Concerns for applicability

Low

Shakib 2015

Bibliographic Reference	Shakib, Julie; Buchi, Karen; Smith, Elizabeth; Young, Paul C; Management of newborns born to mothers with chorioamnionitis: is it time for a kinder, gentler approach?.; Academic pediatrics; 2015; vol. 15 (no. 3); 340-4

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting University of Utah Hospital Study dates 2006 - mid-2013 Duration of follow-up Not reported but examined early-onset infection
Inclusion criteria	Born to mothers with clinical chorioamnionitis based on a discharge ICD-9 diagnosis code of 762.7, 658.40, 658.41, or 658.43 Neonates with gestational age ≥34 weeks
Exclusion criteria	Admitted to NICU
Sample characteristics	Sample size 698 Group B streptococcus colonisation Mother: 65 (9.3%) (62% unknown) Neonate: 1 (0.22%) Rupture of membranes >18 hours 20% Maternal temperature ≥38 degrees 40% >37.5 degrees
Prognostic model	Kaiser Permanente neonatal sepsis calculator

Study arms

Current practice (N = 698)

University of Utah Hospital current management for neonates who are well-appearing with a gestational age of 34 or more weeks whose mothers had received a diagnosis of chorioamnionitis: A CBC and blood culture are obtained and intravenous ampicillin and gentamicin are initiated. This is discontinued at 48 hours if the blood culture is negative and the infant remains well appearing

Kaiser Permanente neonatal sepsis calculator (N = 698)

No information on background incidence used for early-onset infection

Risk of bias

Selection of participants

1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?

Yes

(Retrospective cohort study.)

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?

No

(N = 1 culture-positive.)

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

(No records were excluded because of missing data.)

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?

Probably yes

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

Moderate

Not all mothers had temperature recorded during labour so used temperature at admission. Highest antepartum temperature is one of the predictors in the neonatal sepsis calculator

Concerns for applicability

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

Sloane 2019

Bibliographic Reference Sloane A.J.; Coleman C.; Carola D.L.; Lafferty M.A.; Edwards C.; Greenspan J.; Aghai Z.H. ; Use of a Modified Early-Onset Sepsis Risk Calculator for Neonates Exposed to Chorioamnionitis; Journal of Pediatrics; 2019

Study Characteristics

Study design	Retrospective cohort study Follow-up from Carola 2018 following revision of neonatal sepsis calculator with a higher baseline incidence of risk of sepsis to 4/1000 live births (0.5/1000 used in Carola 2018)

Study arms

Neonatal sepsis calculator (1) (N = 896)

Baseline incidence of infection set at 0.5/1000 live births (CDC national incidence)

Neonatal sepsis calculator (2) (N = 896)

Baseline incidence of infection set at 4/1000 live births. Based on the EOS incidence of 4.3/1000 live births in the population of infants exposed to chorioamnionitis in the NICU in the study

Risk of bias

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

(EOS calculator)

2.2 Were predictor assessments made without knowledge of outcome data?

No information

(Unclear if assessors had knowledge of outcome.)

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?

No

(N=5 culture-positive.)

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?

Not applicable

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

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

Strunk 2018

Bibliographic Reference Strunk T.; Buchiboyina A.; Sharp M.; Nathan E.; Doherty D.; Patole S. ; Implementation of the Neonatal Sepsis Calculator in an Australian Tertiary Perinatal Centre; Neonatology; 2018; vol. 113 (no. 4); 379-382

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Australia Study setting Perinatal referral centre (King Edward Memorial Hospital for Women, Perth, WA) Study dates Period 1 (pre-calculator): October 2014 - January 2015. Period 2 (post-calculator): July 2016 - December 2016 Duration of follow-up Birth to 1688 hours of life (separated into <24 hours after birth and >24 hours)
Inclusion criteria	Neonates with gestational age ≥35 weeks
Exclusion criteria	None reported
Sample characteristics	Sample size Pre-calculator: 1732; Post-calculator: 2502 Female Pre-calculator: 48.3%; Post-calculator: 48.4% Premature rupture of membranes >24 hours Pre-calculator: 0.6%; Post-calculator: 0.6%
Prognostic model	Kaiser Permanente neonatal sepsis calculator

Study arms

Baseline period (N = 1732)

Neonatal sepsis risk algorithm based on a local adaptation of the American Academy of Pediatrics guidelines

Kaiser Permanente neonatal sepsis calculator (N = 2502)

Neonatal sepsis calculator with background incidence of early-onset infection set at 0.44/1000 live births (based on local 2005-2014 rate). Introduced following 2-month education period.

Risk of bias

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

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

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

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?

Not applicable

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

Some concerns

Study based in USA – differences in GBS screening policy to the UK and possibly differences in incidence rate of infection (background incidence rate is needed for the calculator)

D.2 Maternal and neonatal risk factors

Dempsey, 2005

Bibliographic Reference Dempsey, E; Chen, M-F; Kokottis, T; Vallerand, D; Usher, R; Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis.; American journal of perinatology; 2005; vol. 22 (no. 3); 155-9

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Canada Study setting Royal Victoria Hospital Study dates 1989 - 1999 Duration of follow-up 72 hours Sources of funding None reported
Inclusion criteria	All singleton neonates delivered at <30 weeks gestational age
Exclusion criteria	None reported
Sample characteristics	Sample size 392 Gestational age (weeks) (mean, SD) Non-chorioamnionitis: 27.5 (1.9); Chorioamnionitis: 26.3 (2) Birth weight (g) (mean, SD) Non-chorioamnionitis: 1030 (357); Chorioamnionitis: 920 (284)
Prognostic factors	Chorioamnionitis Histological chorioamnionitis
Reference Factor (s)	Early onset infection

Study arms

Neonates less than 30 weeks' gestational age (N = 392)

Neonates born at <30 weeks' gestation with or without exposure to chorioamnionitis Chorioamnionitis: Histologic chorioamnoinitis defined as the presence of abundant polymorphonuclear leukocytes in the chorion and amnion Early onset infection: A positive blood culture or positive cerebrospinal fluid culture in the

first 72 hours Multivariate analysis used to examine risk factors. Confounding variables adjusted for were: gestational age, antenatal steroid administration, and duration of membrane rupture

Risk of bias

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

(Retrospective analysis but outcomes were based on laboratory results rather than subjective outcomes)

Study Confounding

Study Confounding Summary

Low risk of bias

Statistical Analysis and Reporting

Statistical Analysis and Presentation Summary

Moderate risk of bias

(Limited information about multivariate analysis)

Overall risk of bias and directness

Risk of Bias

Moderate

(Limited information about multivariate analysis)

Directness

Directly applicable

Dior, 2016

Bibliographic Reference Dior, Uri P; Kogan, Liron; Eventov-Friedman, Smadar; Gil, Moran; Bahar, Raz; Ergaz, Zivanit; Porat, Shay; Calderon-Margalit, Ronit; Very High Intrapartum Fever in Term Pregnancies and Adverse Obstetric and Neonatal Outcomes.; Neonatology; 2016; vol. 109 (no. 1); 62-8

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Israel Study setting 2 medical centres in Jerusalem Study dates January 2003 - January 2011 Duration of follow-up 72 hours Sources of funding None reported
Inclusion criteria	Women in labour who had a singleton live birth <50 years old Had a term pregnancy (≥ 37 weeks' gestation) Baby with a birth weight <5000 g Spent >1 hour in the delivery room
Exclusion criteria	Non-emergency cesarean deliveries Labour after a previous cesarean delivery use of prostaglandins during induction of labor Fetal malformations

	Chromosomal abnormalities Unknown fever during labor
Sample characteristics	Sample size 43560 Gestational age (weeks) (%) Low febrile fever - 37-39 weeks: 39%, 40-41 weeks: 54%, >42 weeks: 6%; High febrile fever - 37-39 weeks: 37%, 40-41 weeks: 50%, >42 weeks: 11% Birth weight (%) Low febrile fever - <2500 g: 1%, 2500 - 3499 g: 59%, 3500 - 3999 g: 31%, >4000 g: 7%; High febrile fever - <2500 g: 0%, 2500 - 3499 g: 70%, 3500 - 3999 g: 21%, >4000 g: 8%
Prognostic factors	Intrapartum fever Low fever (38-38.9 degrees); High fever (>39 degrees)
Reference Factor (s)	Early onset infection Blood culture with or without a cerebrospinal fluid culture that was positive for a bacterial species and was obtained from an infant under 72 h of age

Study arms

Babies born at term (N = 43560)

Babies born at term to mothers with a singleton pregnancy. Early onset infection: Blood culture with or without a cerebrospinal fluid culture that was positive for a bacterial species and was obtained from an infant under 72 h of age. Data regarding blood cultures was retrieved from the microbiology laboratory and verified by neonatology specialists Intrapartum fever: Based on maximal temperature measured during labor. Temperature <38 °C: normal fever, Temperature 38.0–38.9 °C: low febrile fever, Temperature ≥ 39 °C: high febrile fever Multivariate analysis used to examine association between intrapartum fever and neonatal infection. Model controlled for gestational age, birth weight (<2,500, 2,500–4,000, and >4,000 g), duration of labor and epidural analgesia

Risk of bias

Summary Study participation

Low risk of bias

Study Attrition Summary

Low risk of bias

Prognostic factor Measurement Summary

Low risk of bias

(Retrospective study based on patient records but prognostic factors were based on test results rather than subjective outcomes)

Outcome Measurement Summary

Low risk of bias

Study Confounding Summary

Low risk of bias

Statistical Analysis and Presentation Summary

Low risk of bias

Risk of Bias

Moderate

Limited information on how factors to be adjusted were selected

Directness

Directly applicable

Garcia-Munoz Rodrigo, 2014a

Bibliographic Reference Garcia-Munoz Rodrigo, Fermin; Galan Henriquez, Gloria M; Ospina, Cristina Gomez; Morbidity and mortality among very-low-birth-weight infants born to mothers with clinical chorioamnionitis.; Pediatrics and neonatology; 2014; vol. 55 (no. 5); 381-6

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Spain Study setting Neonatal Intensive Care Unit Study dates January 2008 - December 2012 Duration of follow-up Until death or discharge (first 72 hours of life for early-onset infection) Sources of funding None reported
Inclusion criteria	Born in maternity unit or admitted to Neonatal Intensive Care Unit in the first 28 days of life

	Birth weight <1500 g or <30 weeks' gestational age
Exclusion criteria	None reported
Sample characteristics	Sample size 451 Female Mothers with chorioamnionitis: 52%, Mothers without chorioamnionitis: 46% Gestational age (weeks) (mean, SD) Mothers with chorioamnionitis: 27.9 (2.3), Mothers without chorioamnionitis: 29.6 (2.7) Birth weight (g) (mean, SD) Mothers with chorioamnionitis: 1029.7 (232.9), Mothers without chorioamnionitis: 1144.0 (253.7)
Prognostic factors	Chorioamnionitis Defined according to adapted Gibbs criteria
Reference Factor (s)	Early onset infection Positive blood culture in the first 72 hours

Study arms

Babies born <30 weeks' gestational age (N = 451)

Babies born at <30 weeks' gestational age to mothers with/without clinical chorioamnionitis Chorioamnionitis: Defined according to adapted Gibbs criteria as maternal fever >38 degrees at least on two occasions separated by 1 hour, plus as least two of the following: uterine tenderness defined as pain referred by the mother on abdomen palpation in the absence of uterine contractions, leucocytosis (>15,000 cells/mm3), maternal tachycardia >100 bpm), fetal tachycardia (>160 bpm), or foul smelling vaginal discharge Early onset infection: bacterial infection documented by a positive blood culture in the first 72 hours of life Multivariate analysis used to examine association between chorioamnionitis and infection. Adjusted for gestational age and body weight

Risk of bias

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

(Definition of chorioamnionitis was provided and appears appropriate.)

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 on the design of the multivariate model were reported, including how factors to be adjusted were selected)

Overall risk of bias and directness

Risk of Bias

Moderate

(Insufficient details on the design of the multivariate model were reported, including how factors to be adjusted were selected.)

Directness

Directly applicable

Garcia-Munoz Rodrigo, 2014b

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)	Early-onset neonatal sepsis bacterial infection documented by a positive blood culture within 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

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

Hakansson, 2006

Bibliographic Reference Hakansson, S; Kallen, K; Impact and risk factors for early-onset group B streptococcal morbidity: analysis of a national, population-based cohort in Sweden 1997-2001.; BJOG : an international journal of obstetrics and gynaecology; 2006; vol. 113 (no. 12); 1452-8

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Sweden Study setting Medical Birth Register and the Hospital Discharge Register kept by the Epidemiological Centre of the Swedish National Board of Health and Welfare Study dates 1997-2001 Duration of follow-up First 27 days of life Sources of funding Va¨sterbotten County Council (S.H.) and by the Wallenberg Foundation (K.K.)
Inclusion criteria	Gestational age >21 weeks
Exclusion criteria	None reported Although stillbirths before 28 weeks' gestation not included because these are not included in the register

Sample characteristics	Sample size 319 (174 with positive blood culture)
Prognostic factors	Gestational age Twin/singleton births
Reference Factor (s)	Early onset infection Isolation of GBS from blood or cerebrospinal fluid

Study arms

Babies with GBS (N = 319)

Babies with early onset neonatal infection. Verified early onset GBS: the isolation of GBS from blood or cerebrospinal fluid Multivariate analysis using multiple logistic regression models. Model adjusted for possible confounders: Year of birth, maternal age, maternal smoking status, parity

Risk of bias

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

(Retrospective analysis but based on test results rather than subjective diagnosis)

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 information about choice of model factors for adjustment)

Directness

Directly applicable

Hakansson, 2008

Bibliographic Reference Hakansson, Stellan; Kallen, Karin; High maternal body mass index increases the risk of neonatal early onset group B streptococcal disease.; Acta paediatrica (Oslo, Norway : 1992); 2008; vol. 97 (no. 10); 1386-9

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Sweden Study setting Medical Birth Register and the Hospital Discharge Register of the Epidemiological Centre of the Swedish National Board of Health and Welfare Study dates 1997 - 2001 Duration of follow-up First 27 days of life (within 6 days of life for early onset infection) Sources of funding The Evy and Gunnar Sandberg Foundation, and The Birgit and Sven Hakan Ohlsson Foundation
Inclusion criteria	Gestational age >22 weeks Vaginal birth or emergency cesarean section
Exclusion criteria	Deliveries that started with a cesarean section

	Included if started with vaginal birth but delivery was with cesarean section
Sample characteristics	Sample size 344,127 mothers Maternal BMI (%) <18.5: 2.6%; 18.5-24.9: 63.9%; 25-29.9: 24.2%; >30: 9.3%
Prognostic factors	Maternal BMI BMI classes categorized according to the definition of the World Health Organisation
Reference Factor (s)	Early onset infection Verified with a positive blood culture

Study arms

Babies born at >22 weeks' gestation (N = 344,127)

Babies born at >22 weeks' gestation to mothers. Early onset infection: verified with a positive blood culture Maternal BMI: categorized according to the definition of the World Health Organisation (underweight <18.5, normal 18.5–24.9, overweight 25–29.9 and obese ≥30). BMI 18.5-24.9 used as reference value for analysis Multiple logistic regression analysis used to examine association between BMI and early onset infection. Model adjusted for possible confounders: year of birth, maternal age, parity, smoking, standard deviation weight scores, small for gestational age, large for gestational age, gestational age, birth weight and gestational diabetes

Risk of bias

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

Partially applicable
BMI categories do not match those used to classify obesity in clinical practice

Klinger, 2009

Bibliographic Reference Klinger, Gil; Levy, Itzhak; Sirota, Lea; Boyko, Valentina; Reichman, Brian; Lerner-Geva, Liat; Israel Neonatal, Network; Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants.; American journal of obstetrics and gynecology; 2009; vol. 201 (no. 1); 38e1-6

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Israel Study setting 28 neonatal departments Study dates 1995 - 2005 Duration of follow-up Unclear. States early-onset infection but does not define time of infection Sources of funding Israel Center for Disease Control and the Israel Ministry of Health

Inclusion criteria	Infants whose data was collected by the Israel Neonatal Network on very low birth weight newborn infants (BW <1500 g)
Exclusion criteria	Babies who died in the delivery room Babies with lethal malformations
Sample characteristics	Sample size 15839 (383 with EOS) Female With early onset infection: 47%; Without early onset infection: 50% Maternal age (mean, SD) With early onset infection: 29.8 years (6.1); Without early onset infection: 29.4 years (5.9) Gestational age at delivery With early onset infection: 27.7 (2.6); Without early onset infection: 29.1 (3.0) Birth weight (mean, SD) With early onset infection: 1005 g (287); Without early onset infection: 1102 g (283)
Prognostic factors	Chorioamnionitis maternal fever (37.8°C orally or 38.0°C rectally) recorded twice in 1 hour, during membrane rupture or within 6 hours after delivery providing no other cause for fever was found Single/multiple birth Gestational age
Reference Factor (s)	Early onset sepsis Positive blood culture within first 72 hours of life

Study arms

Very low birth weight infants (N = 15839)

Included effects of single/multiple births, amnionitis and gestational age on risk of early onset infection (culture confirmed within 72 hours of life). Multivariate analysis used to account for other risk factors (does not state what factors were adjusted for in the model)

Risk of bias

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

(Unclear what factors were adjusted for in multivariate model)

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear what factors were adjusted for in multivariate model)

Directness

Directly applicable

Mularoni, 2014

Bibliographic Reference Mularoni, Alessandra; Madrid, Marisela; Azpeitia, Agueda; Valls i Soler, Adolf; The role of coagulase-negative staphylococci in early onset sepsis in a large European cohort of very low birth weight infants.; The Pediatric infectious disease journal; 2014; vol. 33 (no. 5); e121-5

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Europe (Austria, Czech Republic, Finland, France, Germany, Greece, Italy, Poland, Russia, Spain, Sweden, Switzerland, UK) Study setting European centers participating in EuroNeoNet Study dates January 2006 - December 2009 Duration of follow-up 72 hours Sources of funding Directorate-General for Health and Consumers (DGSANCO) and the Italian Society of Tropical and Infectious Diseases (SIMIT)
Inclusion criteria	Babies weighing 401 - 1500 g Babies with a positive blood culture and clinical signs of sepsis during the first 72 hours of life
Exclusion criteria	Babies that died in the delivery room Units that classified >20% of pathogens as 'other' (nonspecified organism)
Sample characteristics	Sample size 14719
Prognostic factors	Twin/singleton births
Reference Factor (s)	Early onset infection Presence of clinical symptoms and a positive blood culture drawn within 72 hours of birth

Study arms

Very low birth weight neonates (N = 14719)

Very low birth weight infants with early onset neonatal infection. Early onset infection: the presence of clinical symptoms and a positive blood culture drawn within 72 hours of birth Multivariate logistic regression model used to examine association between risk factors and early onset infection. Potential confounders were those whose p value in univariate analysis were <0.1 (birth weight, gestational age, gender, antenatal steroids, single pregnancy, delivery room resuscitation, apgar score at 5 minutes, vaginal delivery)

Risk of bias

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 prognostic factors with significant results in univariate analysis were included in the multivariate model)

Overall risk of bias and directness

Risk of Bias

Moderate

Only prognostic factors with significant results in univariate analysis were included in the multivariate model

Directness

Directly applicable

Ofman, 2016

Bibliographic Reference Ofman, Gaston; Vasco, Natalia; Cantey, Joseph B; Risk of Early-Onset Sepsis following Preterm, Prolonged Rupture of Membranes with or without Chorioamnionitis.; American journal of perinatology; 2016; vol. 33 (no. 4); 339-42

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Parkland Memorial Hospital level IIIC neonatal intensive care unit Study dates September 2005 - September 2014 Duration of follow-up 72 hours Sources of funding None reported
Inclusion criteria	Moderately preterm infants 30-34 weeks' gestational age
Exclusion criteria	Infants with a major congenital anomaly Infants born before 30 weeks
Sample characteristics	Sample size 2192 infants Female No PPROM or chorioamnionitis: 48%; PPROM but no chorioamnionitis: 48%; Chorioamnionitis: 46% Birth weight (median, IQR) No PPROM or chorioamnionitis: 1,960g (1,618–2,250); PPROM but no chorioamnionitis: 2,045g (1,710–2,240); Chorioamnionitis: 1,985g (1,720–2,195) Proven or suspected EOS No PPROM or chorioamnionitis: 5.4%; PPROM but no chorioamnionitis: 5.5%; Chorioamnionitis: 24.6%
Prognostic factors	Chorioamnionitis defined as maternal temperature 38°C during labor, the presence of two or more clinical findings (maternal tachycardia, uterine tenderness, leukocytosis, malodorous amniotic fluid, or fetal tachycardia), and notation of chorioamnionitis by the obstetrician.
Reference Factor (s)	Early onset sepsis Proven or suspected

Study arms

Moderately preterm neonates born to mothers with chorioamnionitis (N = 2192)

Clinical chorioamnionitis: maternal temperature > 38°C during labor, the presence of two or more clinical findings (maternal tachycardia, uterine tenderness, leukocytosis, malodorous amniotic fluid, or fetal

tachycardia), and notation of chorioamnionitis by the obstetrician. Histological chorioamnionitis not recorded Early onset sepsis: Proven (isolation of a pathogen from blood or cerebrospinal fluid culture samples drawn within 72 hours of delivery) or clinically suspected. Babies with clinically suspected infection had: (1) sterile cultures; (2) with at least one clinical sign of infection, including tachypnea, temperature instability, lethargy, or feeding intolerance; and (3) antibiotic therapy for >5 days Multivariate model used for analysis. Factors adjusted for in the model not stated

Risk of bias

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

Moderate risk of bias

(Retrospective study so diagnosis of chorioamnionitis and early onset infection based on medical record)

Outcome Measurement

Outcome Measurement Summary

Moderate risk of bias

(Diagnosis of suspected infection based on clinician's decision rather than objective test results)

Study Confounding

Study Confounding Summary

Low risk of bias

Statistical Analysis and Reporting

Statistical Analysis and Presentation Summary

Moderate risk of bias

(Unclear what factors were adjusted for in multivariate model)

Overall risk of bias and directness

Risk of Bias

High

(Retrospective study so diagnosis of chorioamnionitis based on medical record and diagnosis of suspected infection based on clinician's decision rather than objective test results. Unclear what factors were adjusted for in multivariate model)

Directness

Directly applicable

Ronnestad, 2005

Bibliographic Reference Ronnestad, Arild; Abrahamsen, Tore G; Medbo, Sverre; Reigstad, Hallvard; Lossius, Kristin; Kaaresen, Per I; Engelund, Inger E; Irgens, Lorentz M; Markestad, Trond; Septicemia in the first week of life in a Norwegian national cohort of extremely premature infants.; Pediatrics; 2005; vol. 115 (no. 3); e262-8

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Norway Study setting 21 Norwegian neonatal units Study dates Not reported Duration of follow-up First week of life Sources of funding Research Council of Norway and the Norwegian Foundation for Health and Rehabilitation
Inclusion criteria	Birth weight <1000 g or gestational age 22+0 - 27+6 weeks (extremely premature infants)
Exclusion criteria	None reported
Sample characteristics	Sample size 462 Birth weight (g) (median, IQR)

	Very early onset sepsis: 780 (675-855); Early onset sepsis: 720 (630-841) Gestational age (weeks) (median, IQR) Very early onset sepsis: 25 (25-27); Early onset sepsis: 27 (26-28) Maternal age (years) (median, IQR) Very early onset sepsis: 35 (30-37); Early onset sepsis: 28 (24-35)
Prognostic factors	Chorioamnionitis Gestational age ≤25 vs ≥26 weeks
Reference Factor (s)	Early onset infection The growth of bacteria or fungi in blood cultures in conjunction with clinical signs of systemic infection

Study arms

Extremely premature infants (N = 462)

Extremely premature infants with/without neonatal infection. Neonatal infection - Very early onset: septicemia diagnosed within 24 hours after delivery. Early onset: septicemia diagnosed between 2 and 7 days of age (septicemia = growth of bacteria or fungi in blood cultures in conjunction with clinical signs of systemic infection) Multivariate logistic regression model used to examine association between risk factors and early onset infection. Model adjusted for potential confounders (gestational age)

Risk of bias

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

Moderate risk of bias

(Prognostic factors not clearly defined)

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

(Prognostic factors not clearly defined. Included a model designed to reduce the number of variables included in multivariate analysis)

Directness

Directly applicable

Soraisham, 2009

Bibliographic Reference Soraisham, Amuchou S; Singhal, Nalini; McMillan, Douglas D; Sauve, Reg S; Lee, Shoo K; Canadian Neonatal, Network; A multicenter study on the clinical outcome of chorioamnionitis in preterm infants.; American journal of obstetrics and gynecology; 2009; vol. 200 (no. 4); 372e1-6

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Canada Study setting 24 tertiary neonatal intensive care units Study dates January 2005 - December 2006 Duration of follow-up First 48 hours after birth for early onset infection

	Sources of funding None reported
Inclusion criteria	All singleton infants with birth gestational age <33 weeks No congenital anomalies
Exclusion criteria	None reported
Sample characteristics	Sample size 3094 Female Chorioamnionitis: 51%; No chorioamnionitis: 46% Gestational age (weeks) (mean, SD) Chorioamnionitis: 27.7 (2.7); No chorioamnionitis: 29.1 (2.4) Birth weight (g) (mean, SD) Chorioamnionitis: 1174 (439); No chorioamnionitis: 1347 (460)
Prognostic factors	Chorioamnionitis Inflammation of amnion and chorion
Reference Factor (s)	Early onset infection Positive single- organism cultures from blood or cerebrospinal fluid that were obtained from an infant with signs or risk factors for sepsis during the first 48 hours after birth

Study arms

Singleton babies with gestational age <33 weeks (N = 3094)

Singleton babies with gestational age <33 weeks with or without neonatal infection. Early onset neonatal infection: positive single-organism cultures from blood or cerebrospinal fluid that were obtained from an infant with signs or risk factors for sepsis during the first 48 hours after birth Chorioamnionitis: Inflammation of amnion and chorion. The diagnosis of chorioamnionitis was made by the attending obstetrician, based on the presence of accepted clinical signs which included foul-smelling amniotic fluid, maternal fever during labor, uterine tenderness (without another cause), fetal tachycardia, and maternal leukocytosis Multivariate logistic analysis used to examine association between chorioamnionitis and neonatal infection. Model adjusted for gestational age, birthweight, vaginal delivery, antenatal steroid and maternal hypertension, Apgar score at 5 minutes and illness severity

Risk of bias

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

Moderate risk of bias

(Retrospective study so chorioamnionitis based on clinical judgement which could be subjective)

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

(Retrospective study so chorioamnionitis based on clinical judgement which could be subjective)

Directness

Directly applicable

D.3 Additional studies

Studies that did not meet the inclusion criteria but were considered by the committee

Pettinger, 2019

Bibliographic Reference	Pettinger, K.J.; Mayers, K; McKechnie, L; Phillips, B; Sensitivity of the Kaiser Permanente early-onset sepsis calculator: A systematic review and meta-analysis.; EClinicalMedicine; 2019

Study Characteristics

Study design	Systematic review
Summary	A systematic review of various studies evaluating the accuracy of the neonatal sepsis calculator. Compared the number of babies with early-onset infection who were not picked up by the calculator but would have been identified by the 2012 NICE guidelines.
Outcomes	Proportion of the missed cases of early-onset infection from the neonatal sepsis calculator compared to the NICE guidelines: • Best case scenario (babies where confirmed diagnosis of neonatal infection was unclear are treated as if they were not missed by the calculator) • Worst case scenario (babies where confirmed diagnosis of neonatal infection was unclear are treated as if they were missed by the calculator)
Results Proportion (95% CI)	• Best case: 0.19 (0.11 – 0.29) • Worst case: 0.31 (0.17 – 0.49)
Reason for exclusion from the review	• Insufficient information provided to calculate the sensitivity and specificity of the tools

Morris, 2020

Bibliographic Reference	Morris, R.; Jones, S; Banerjee, S; et al.; 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; Arch Dis Child Fetal Neonatal Ed; 2020

Study Characteristics

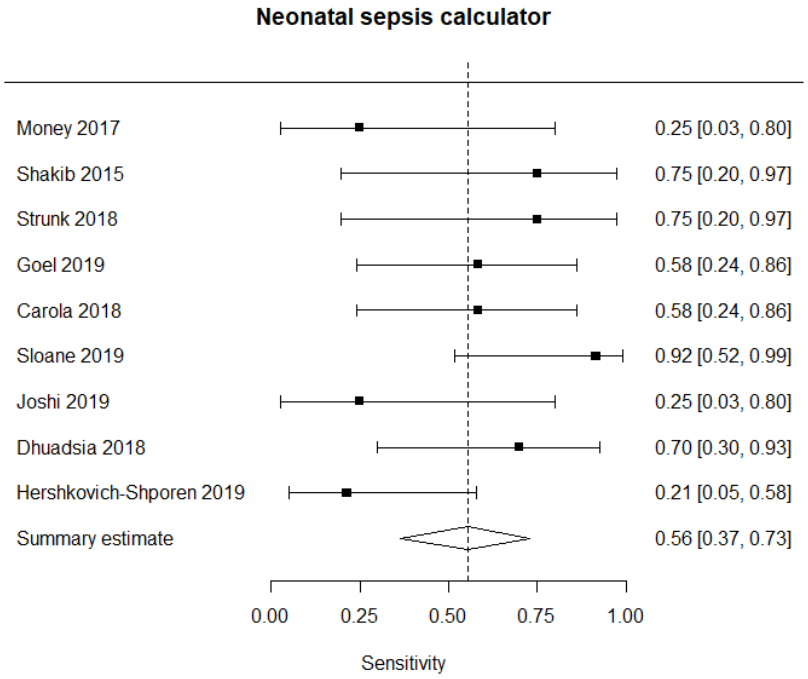
Study design	Retrospective cohort study
Summary	A review of clinical notes from 5 hospital sites in England and Wales between 2008-2017. The neonatal sepsis calculator and 2012 NICE guideline recommendations were retrospectively applied to babies in all sites based on information in clinical notes taken 4 hours after birth.
Outcomes	• Number of babies recommended antibiotic treatment by the NICE guidelines but not by the neonatal sepsis calculator • Number of babies recommended antibiotic treatment by the neonatal sepsis calculator but not by the NICE guidelines • Sensitivity
Results	• Number of babies recommended antibiotic treatment by the NICE guidelines but not by the neonatal sepsis calculator: 12

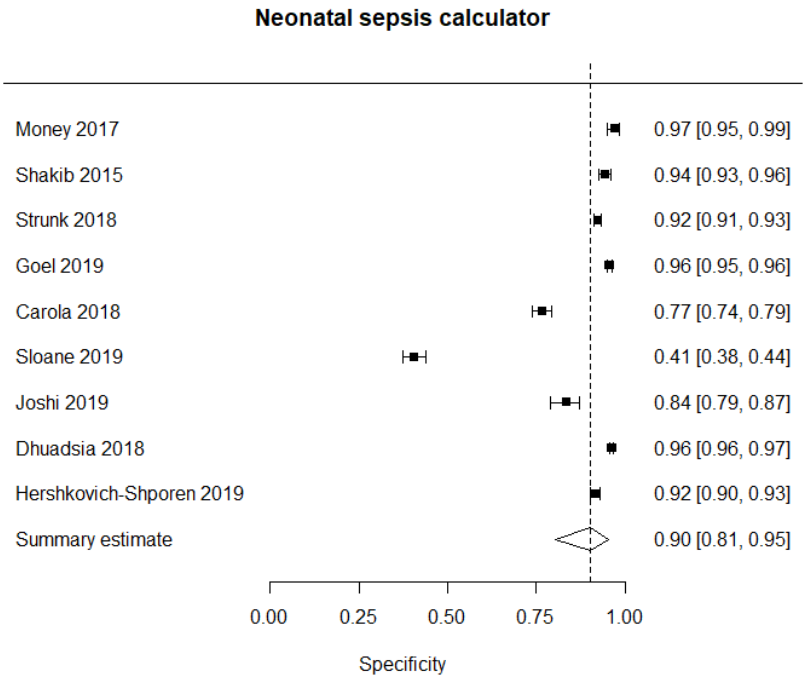
	• Number of babies recommended antibiotic treatment by the neonatal sepsis calculator but not by the NICE guidelines: 0 • Sensitivity: NICE guidelines – 54%; Neonatal sepsis calculator – 37.5%
Reason for exclusion from the review	• Insufficient information provided to calculate the specificity of the tools • Only included babies with culture-confirmed infection

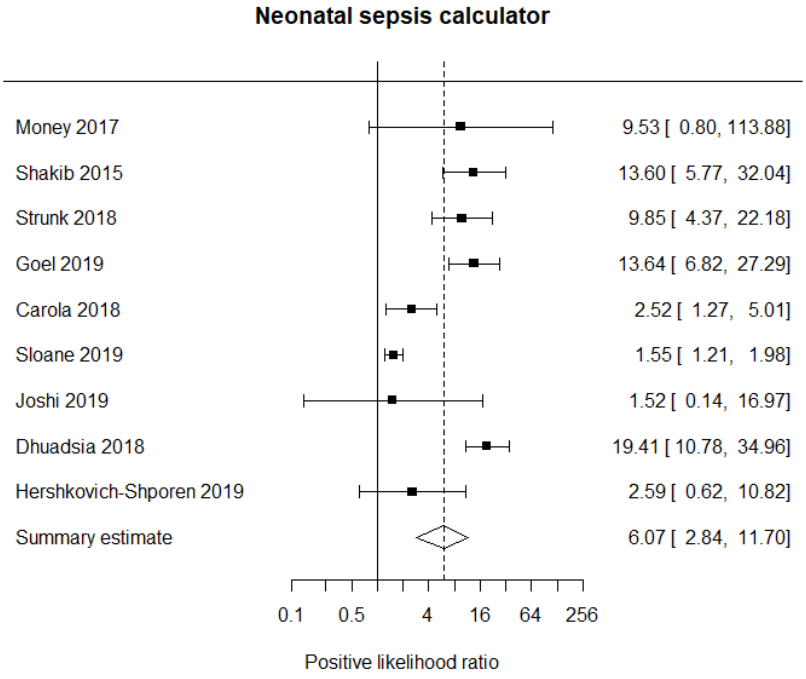
Appendix E – Forest plots

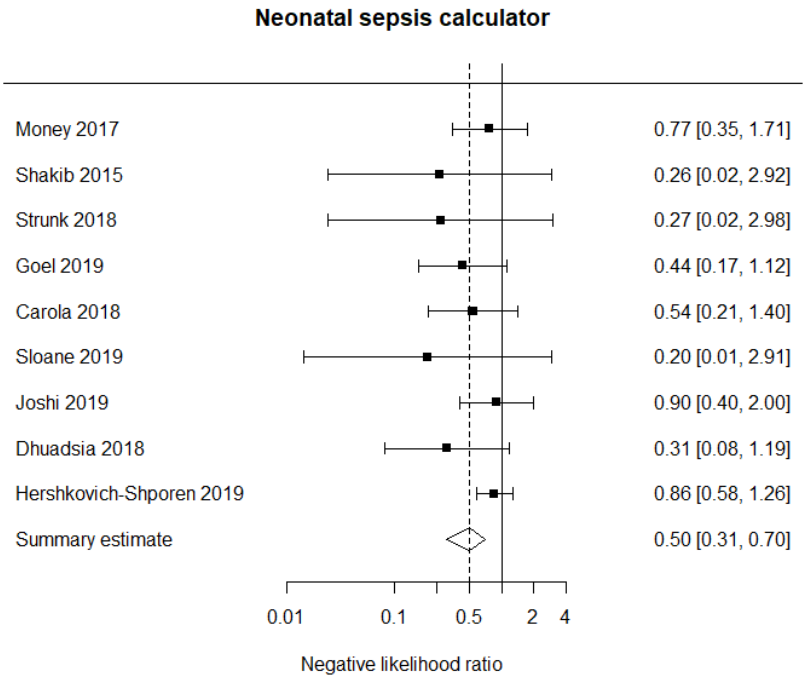
Kaiser Permanente early-onset neonatal sepsis calculator: number of babies recommended antibiotic treatment and blood culture

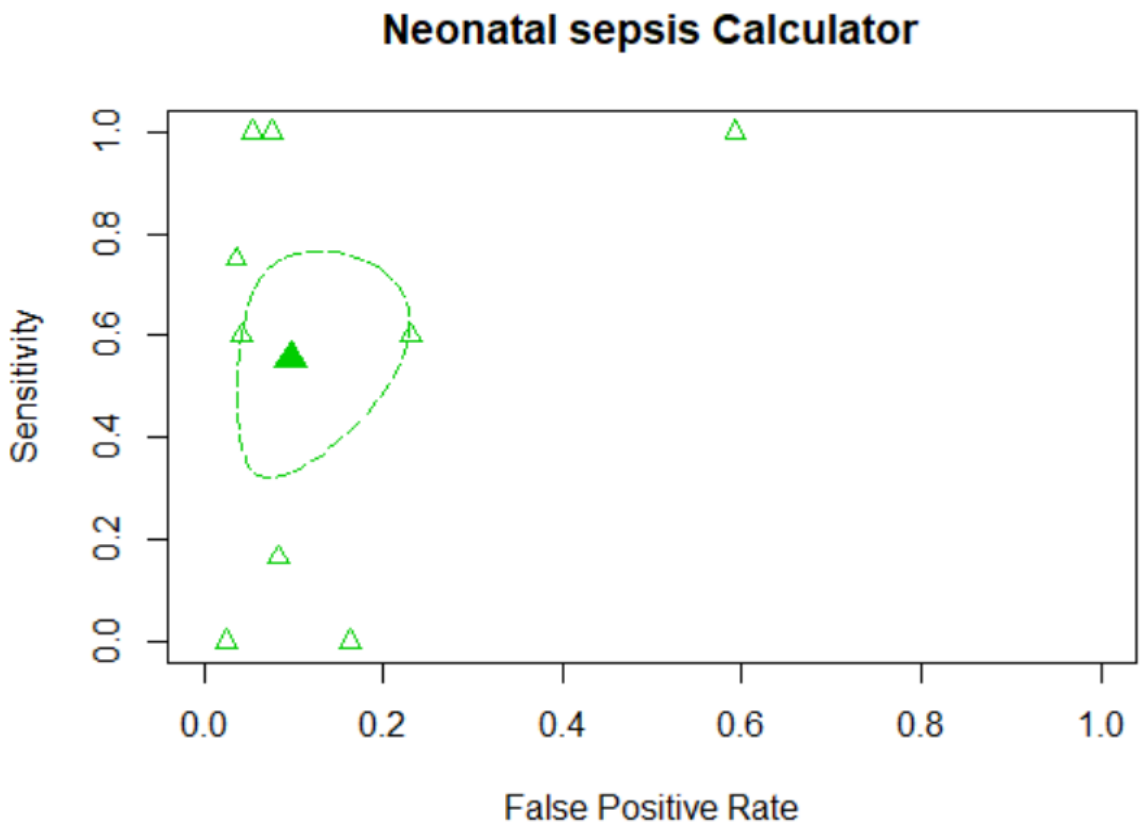
Overall analysis (all studies)



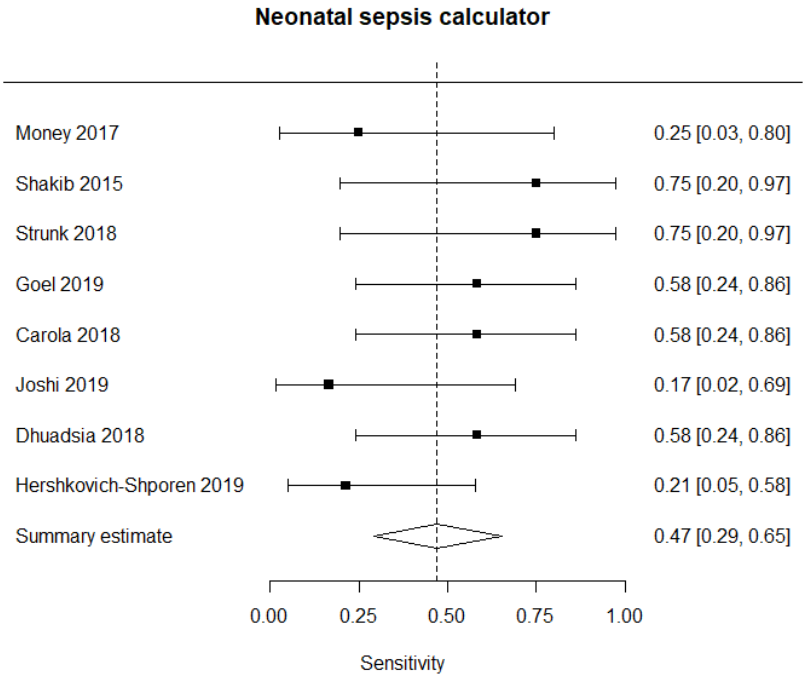

Neonatal sepsis calculator
Money 2017
Shakib 2015
Strunk 2018
Goel 2019
Carola 2018
Sloane 2019
Joshi 2019
Dhuadsia 2018
Hershkovich-Shporen 2019
Summary estimate
0.97 [0.95, 0.99]
0.94 [0.93, 0.96]
0.92 [0.91, 0.93]
0.96 [0.95, 0.96]
0.77 [0.74, 0.79]
0.41 [0.38, 0.44]
0.84 [0.79, 0.87]
0.96 [0.96, 0.97]
0.92 [0.90, 0.93]
0.90 [0.81, 0.95]
0.00
0.25
0.50
0.75
1.00
Specificity

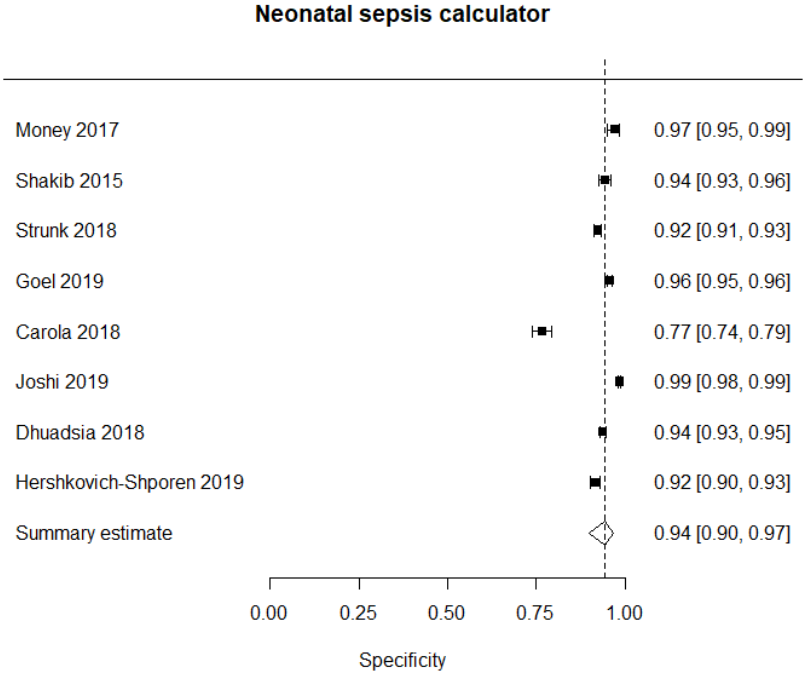

Neonatal sepsis calculator
Money 2017
Shakib 2015
Strunk 2018
Goel 2019
Carola 2018
Sloane 2019
Joshi 2019
Dhuadsia 2018
Hershkovich-Shporen 2019
Summary estimate
9.53 [0.80, 113.88]
13.60 [5.77, 32.04]
9.85 [4.37, 22.18]
13.64 [6.82, 27.29]
2.52 [1.27, 5.01]
1.55 [1.21, 1.98]
1.52 [0.14, 16.97]
19.41 [10.78, 34.96]
2.59 [0.62, 10.82]
6.07 [2.84, 11.70]
0.1
0.5
4
16
64
256
Positive likelihood ratio

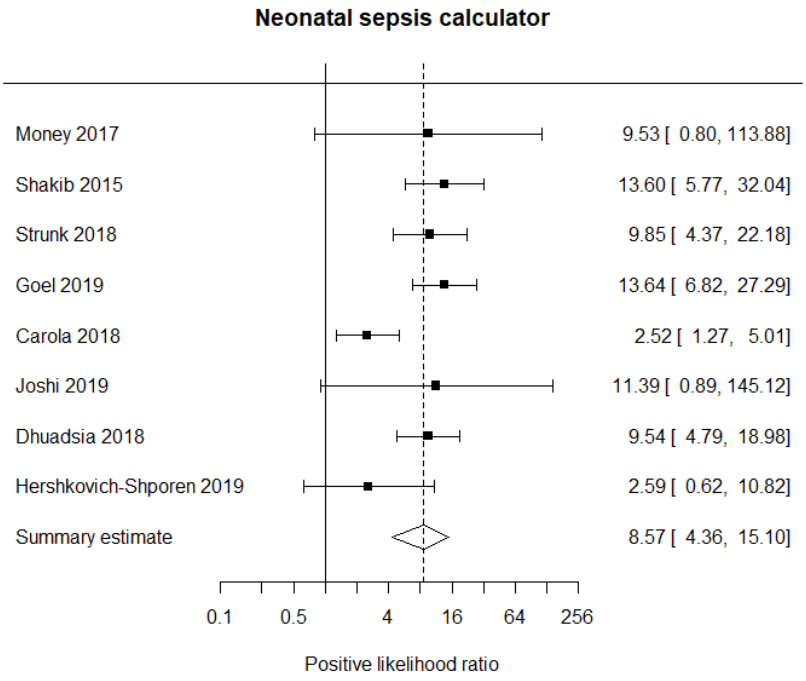

Neonatal sepsis calculator
Money 2017
Shakib 2015
Strunk 2018
Goel 2019
Carola 2018
Sloane 2019
Joshi 2019
Dhuadsia 2018
Hershkovich-Shporen 2019
Summary estimate
0.77 [0.35, 1.71]
0.26 [0.02, 2.92]
0.27 [0.02, 2.98]
0.44 [0.17, 1.12]
0.54 [0.21, 1.40]
0.20 [0.01, 2.91]
0.90 [0.40, 2.00]
0.31 [0.08, 1.19]
0.86 [0.58, 1.26]
0.50 [0.31, 0.70]
0.01
0.1
0.5
2
4
Negative likelihood ratio

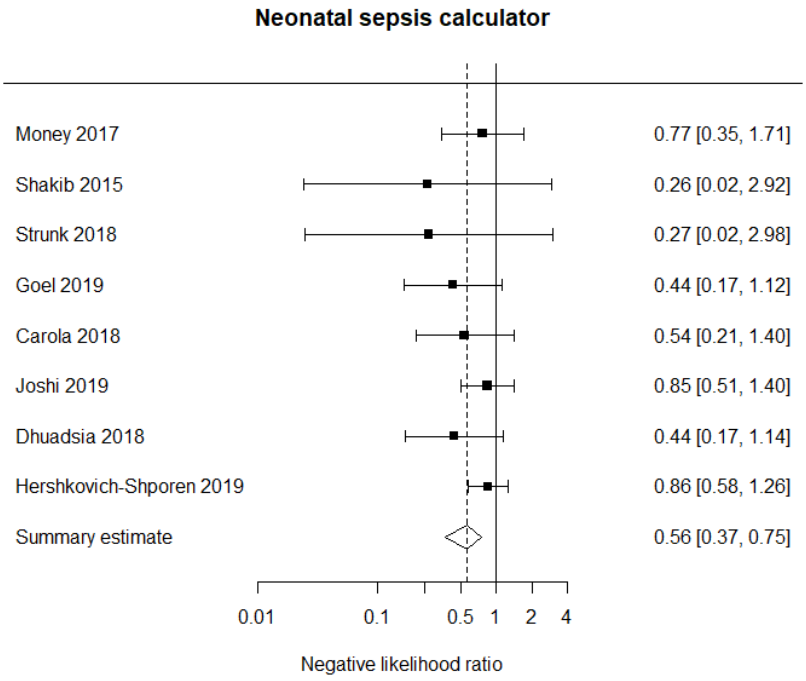

Neonatal sepsis Calculator
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0

Subgroup analysis: lower baseline incidence of sepsis (0.44-0.6/1000 live births)



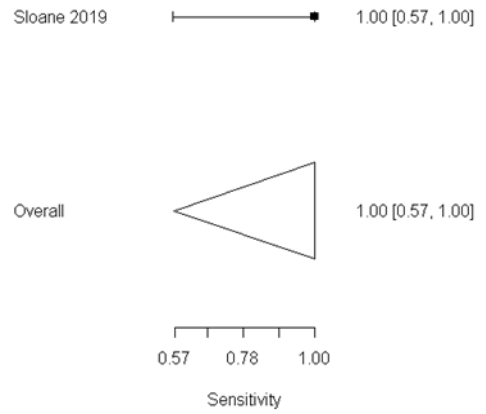


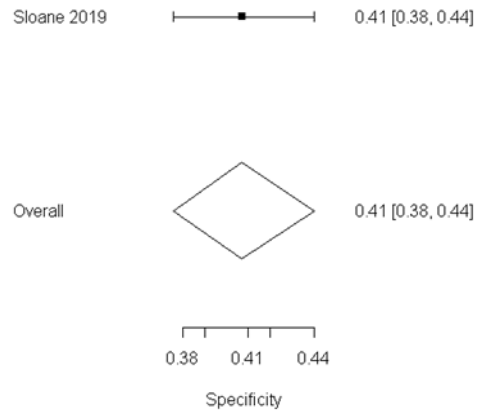


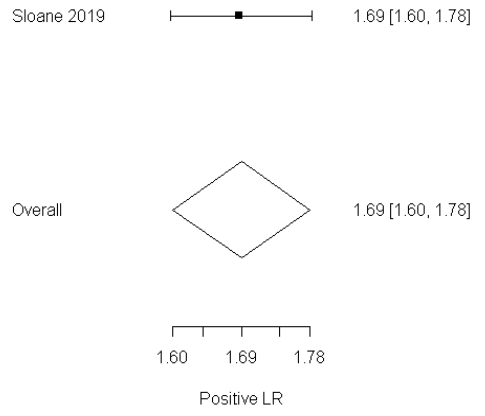


Subgroup analysis: higher baseline incidence of sepsis (4.0/1000 live births)

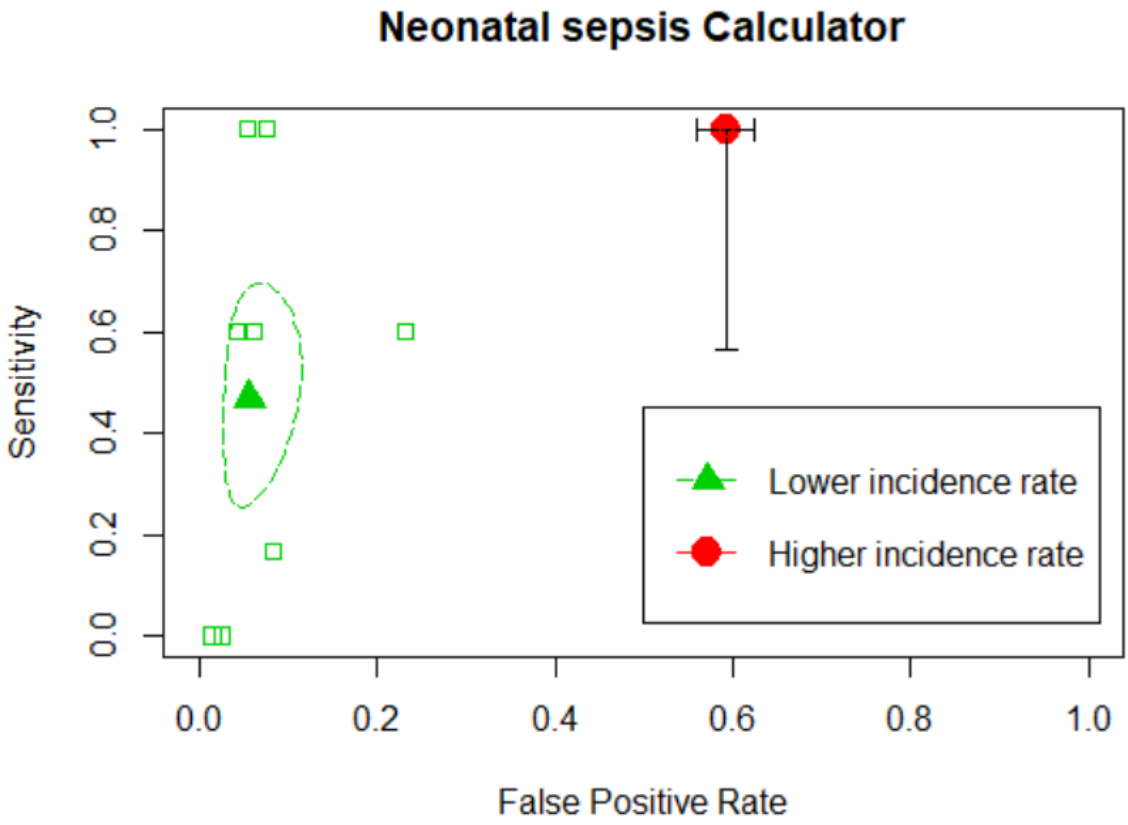
Neonatal sepsis calculator



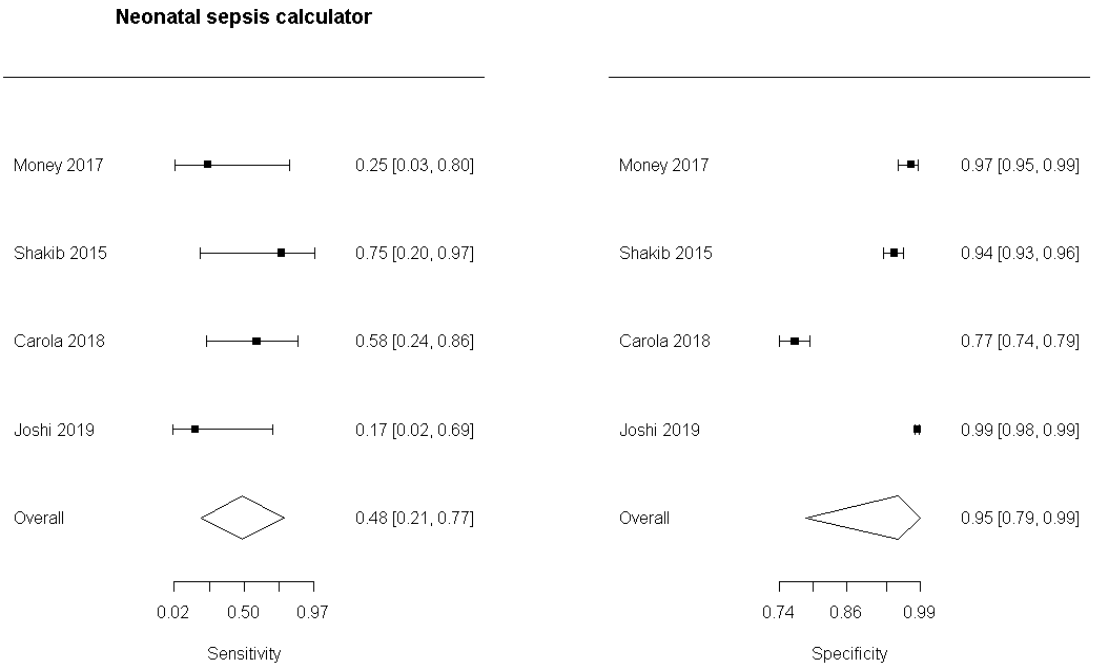


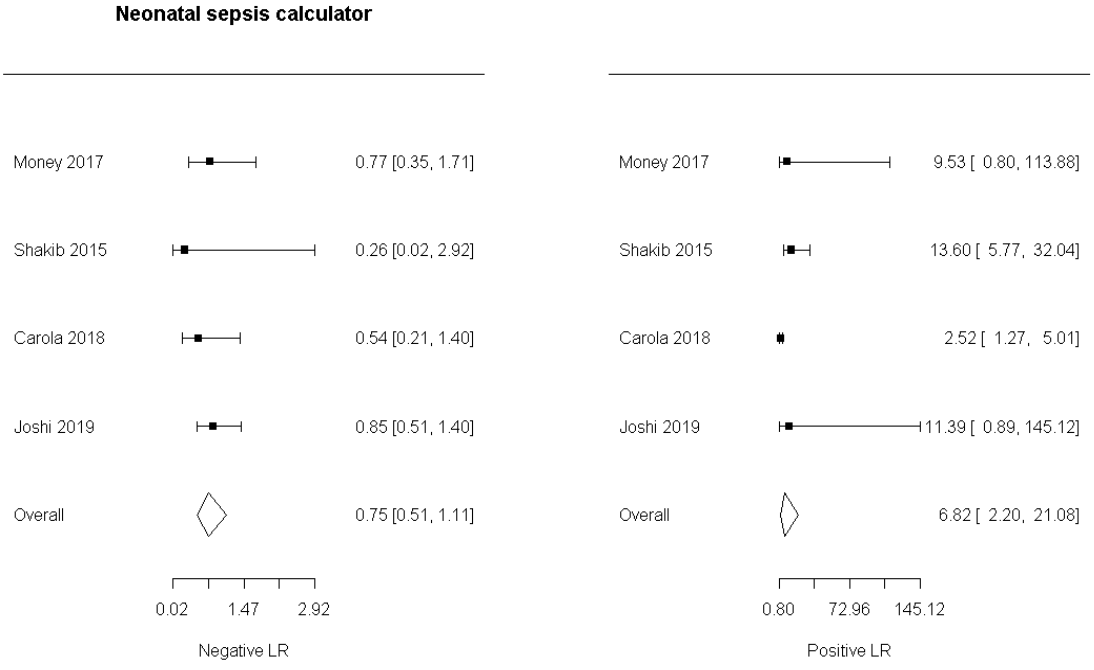


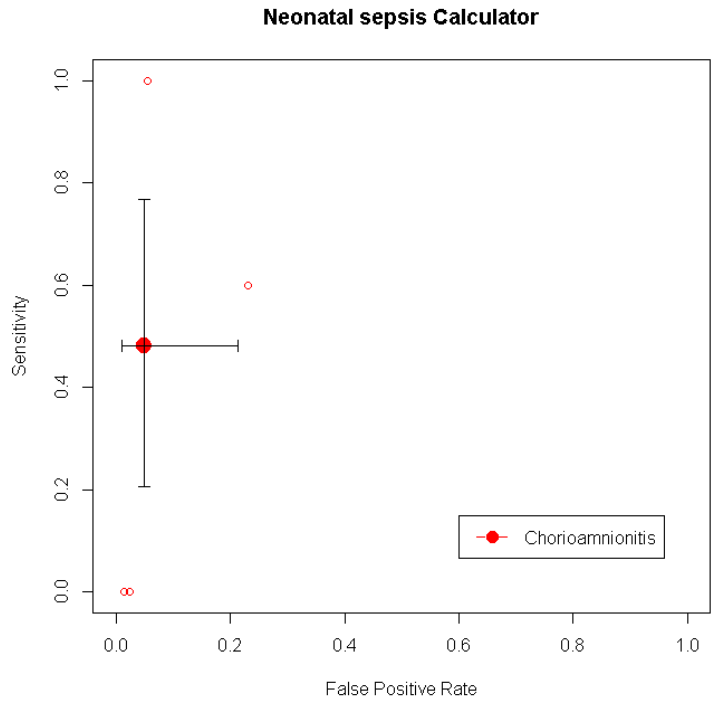
Negative LR not calculable


Neonatal sepsis Calculator
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate
Lower incidence rate
Higher incidence rate

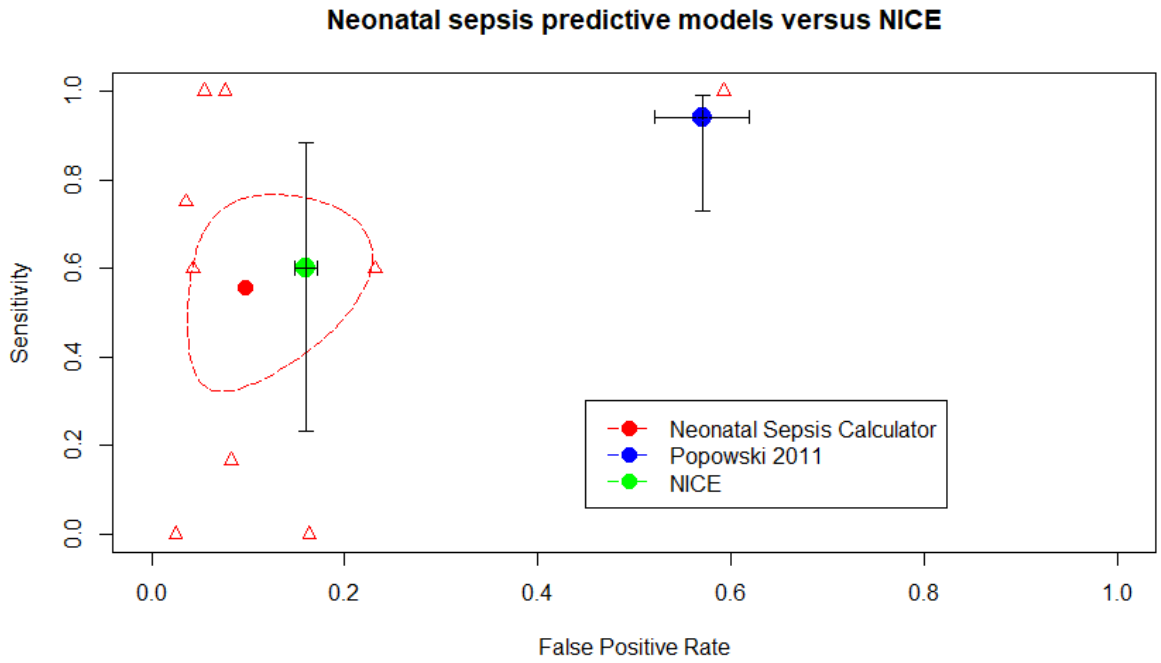
Subgroup analysis: babies born to mothers with chorioamnionitis





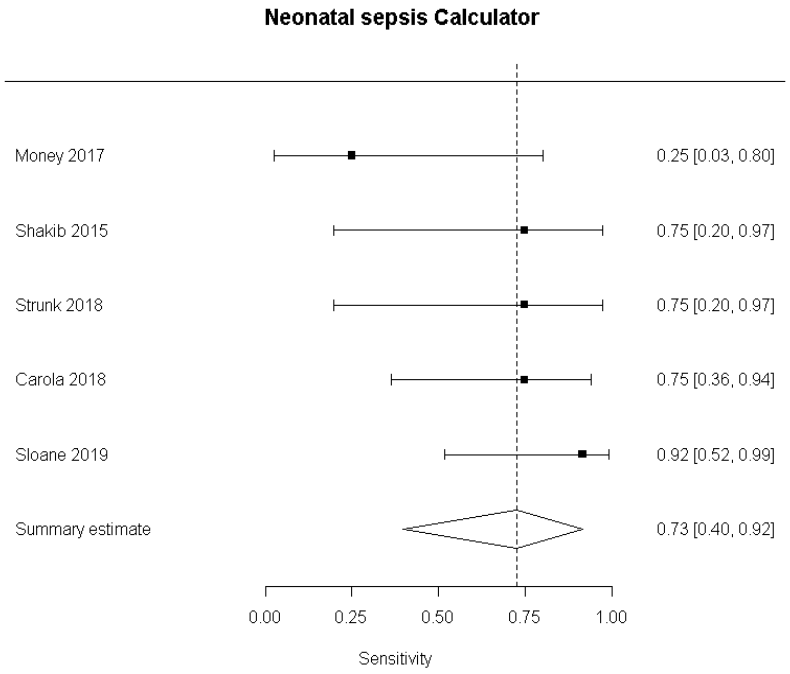


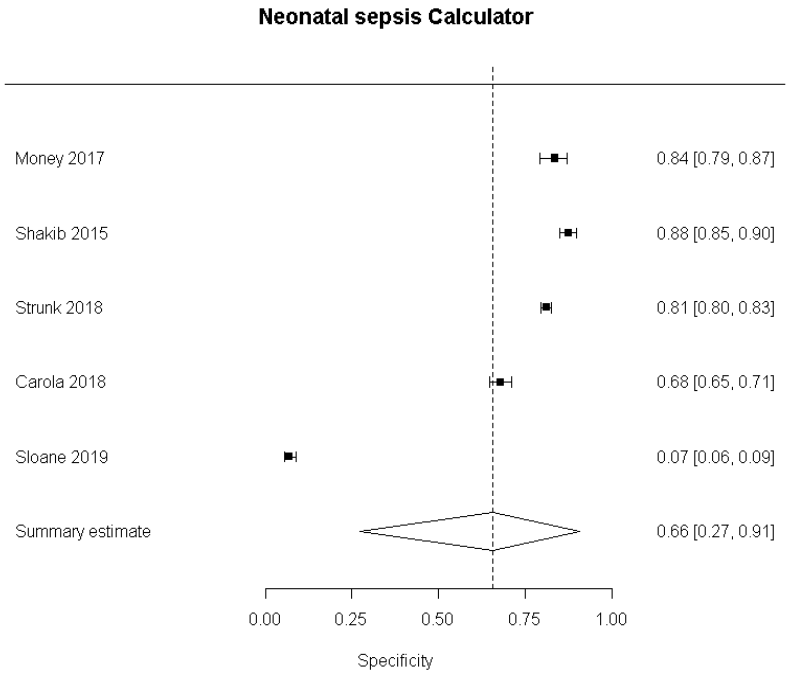
Comparison to standard care

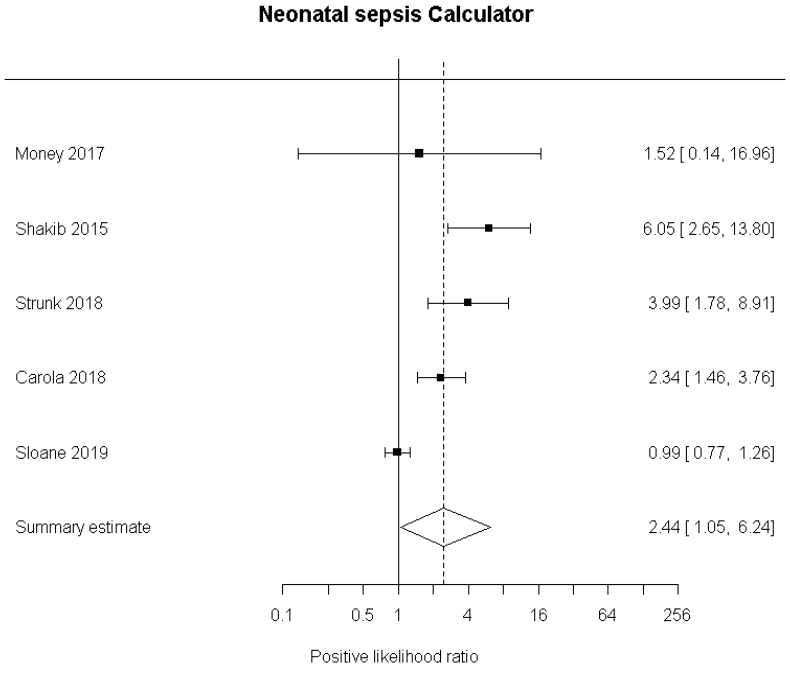


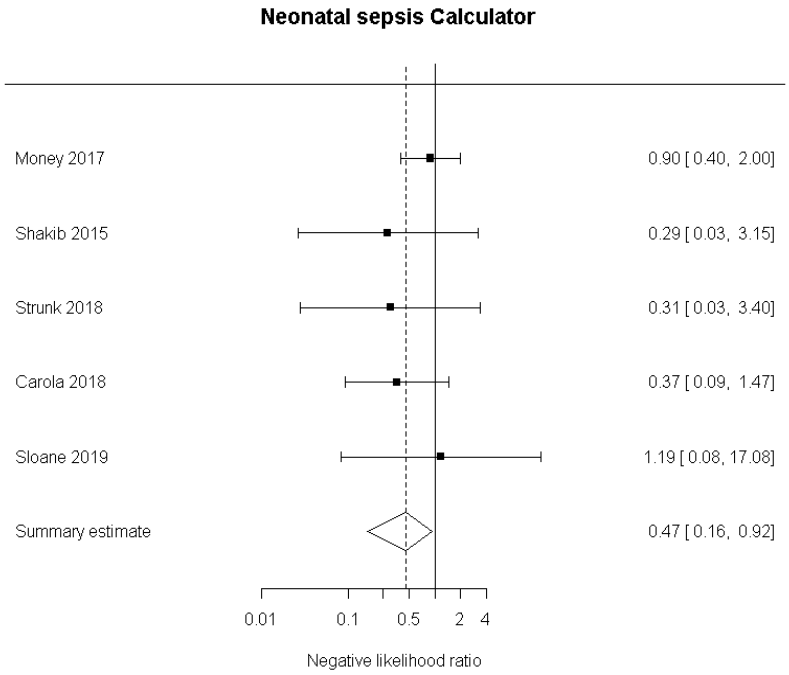
Kaiser Permanente early-onset neonatal sepsis calculator: number of babies recommended either antibiotic treatment and blood culture or blood culture and vital sign monitoring every 4 hours

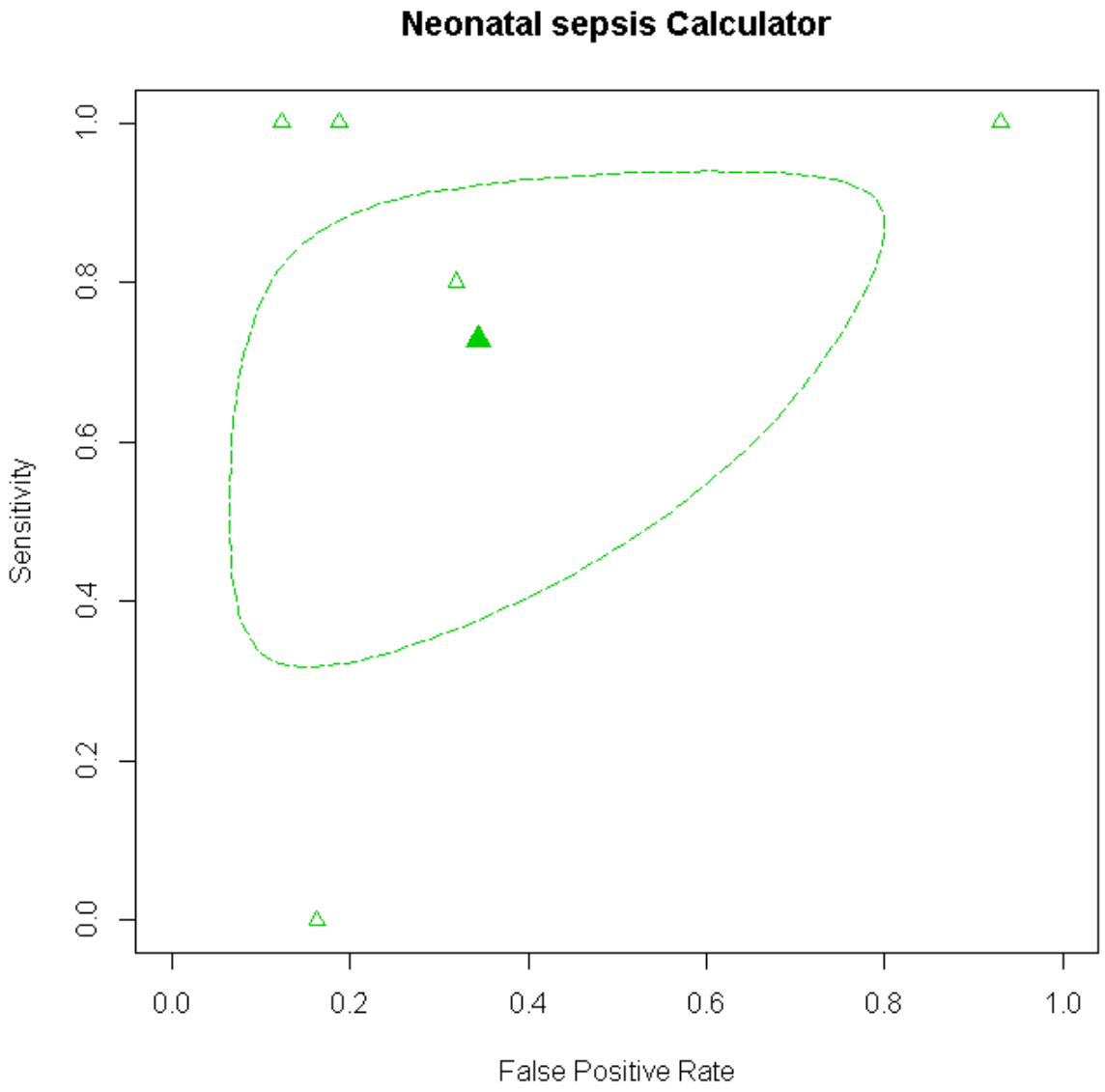
Overall analysis (all studies)



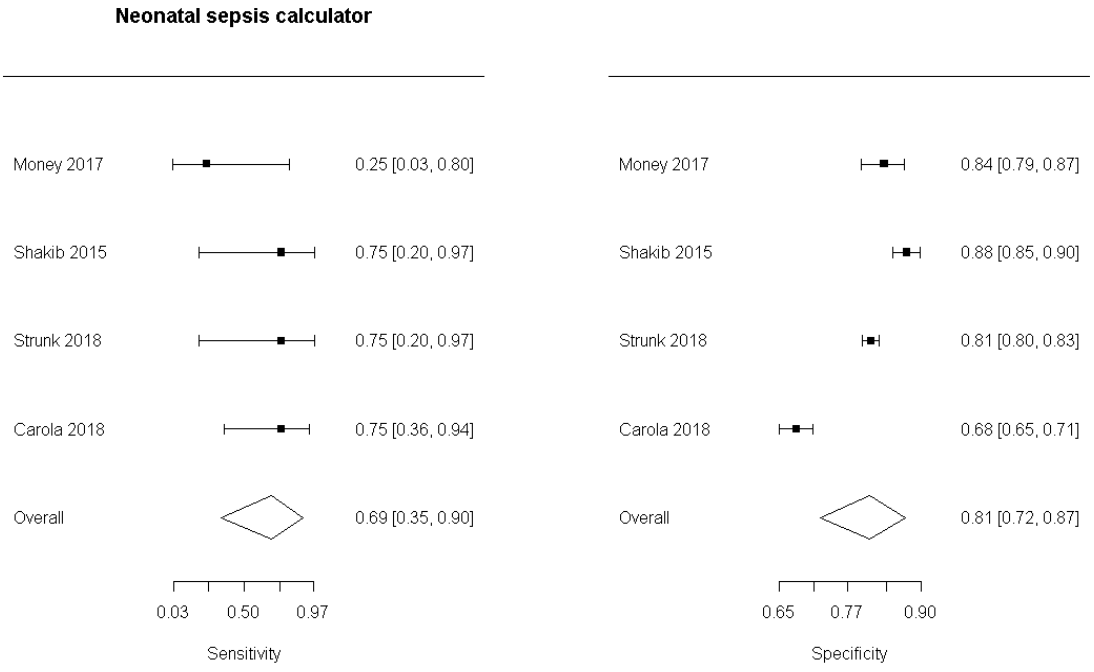

Neonatal sepsis Calculator
Money 2017
Shakib 2015
Strunk 2018
Carola 2018
Sloane 2019
Summary estimate
0.84 [0.79, 0.87]
0.88 [0.85, 0.90]
0.81 [0.80, 0.83]
0.68 [0.65, 0.71]
0.07 [0.06, 0.09]
0.66 [0.27, 0.91]
0.00
0.25
0.50
0.75
1.00
Specificity

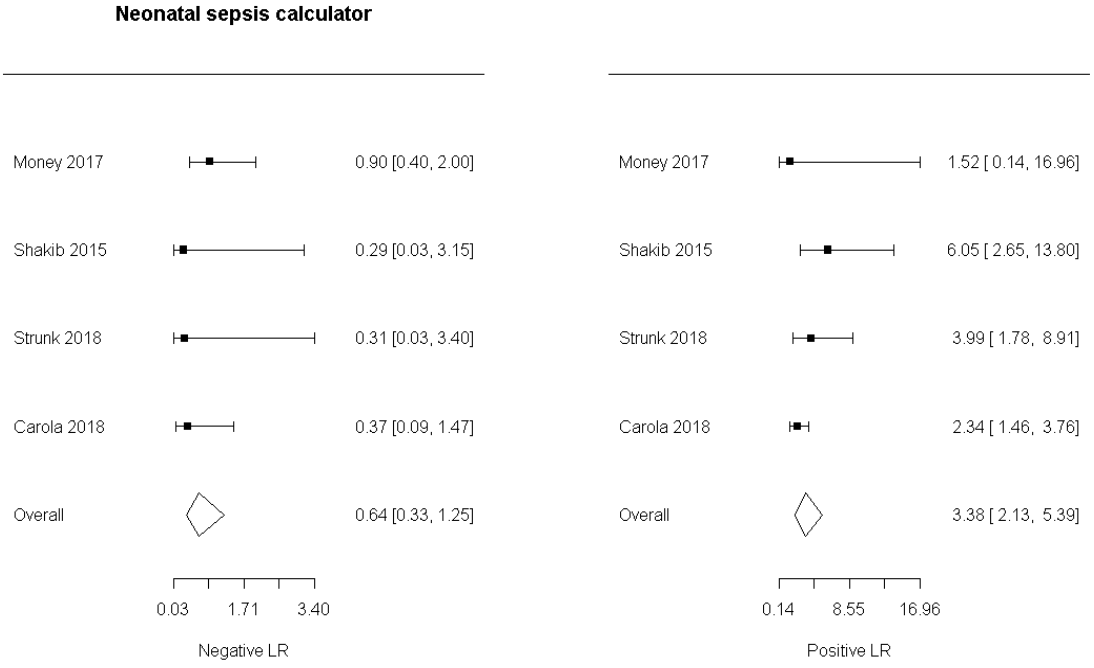

Neonatal sepsis Calculator
Money 2017
Shakib 2015
Strunk 2018
Carola 2018
Sloane 2019
Summary estimate
1.52 [0.14, 16.96]
6.05 [2.65, 13.80]
3.99 [1.78, 8.91]
2.34 [1.46, 3.76]
0.99 [0.77, 1.26]
2.44 [1.05, 6.24]
0.1
0.5
1
4
16
64
256
Positive likelihood ratio


Neonatal sepsis Calculator
Money 2017
0.90 [0.40, 2.00]
Shakib 2015
0.29 [0.03, 3.15]
Strunk 2018
0.31 [0.03, 3.40]
Carola 2018
0.37 [0.09, 1.47]
Sloane 2019
1.19 [0.08, 17.08]
Summary estimate
0.47 [0.16, 0.92]
0.01
0.1
0.5
2
4
Negative likelihood ratio

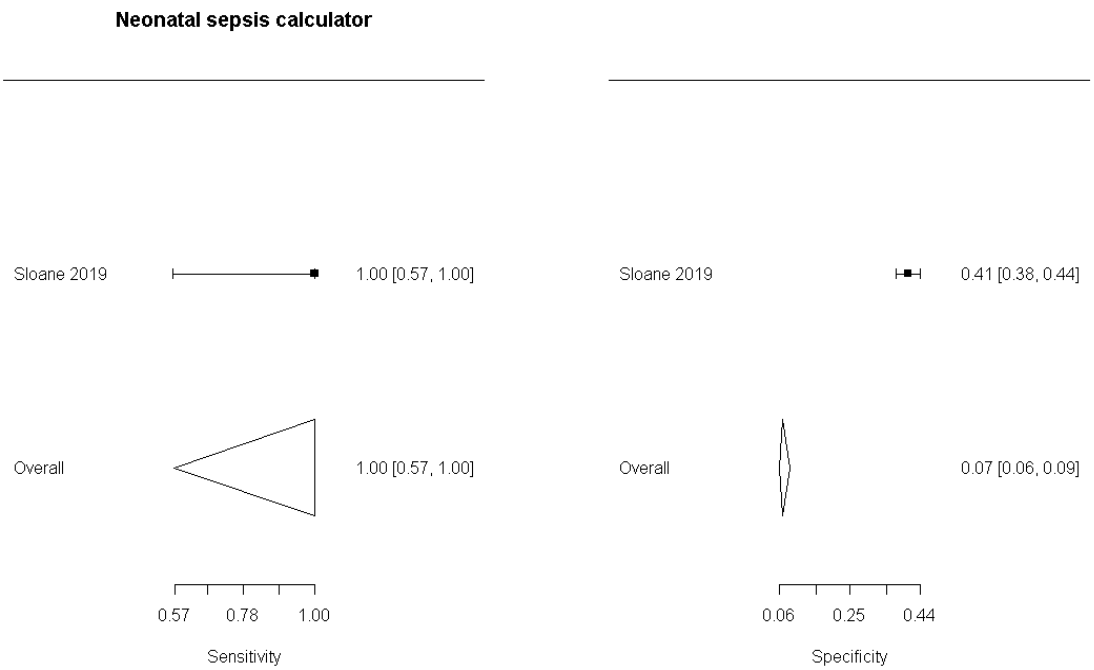

Neonatal sepsis Calculator
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0

Subgroup analysis: lower baseline incidence of sepsis (0.44-0.5/1000 live births)

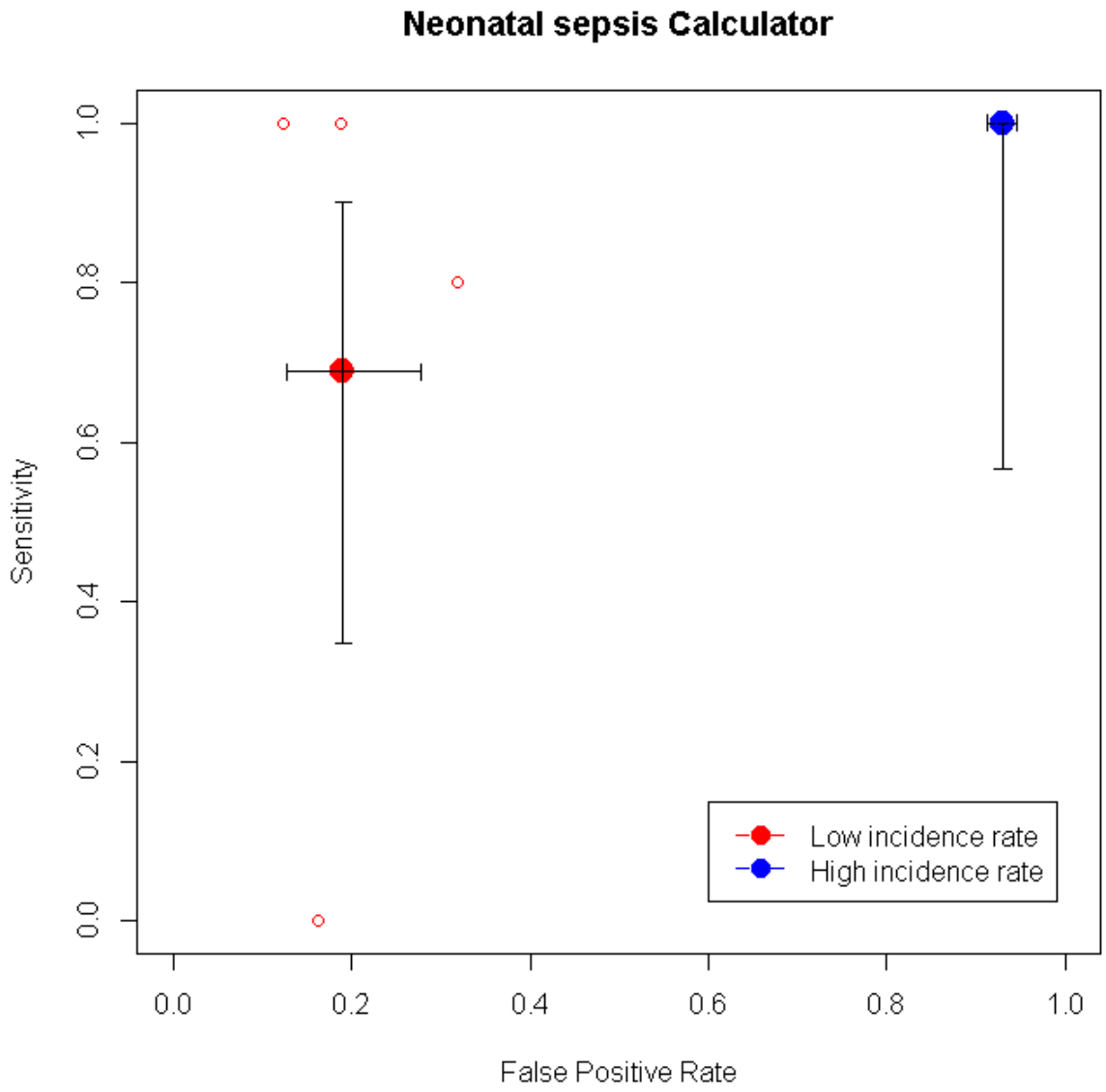




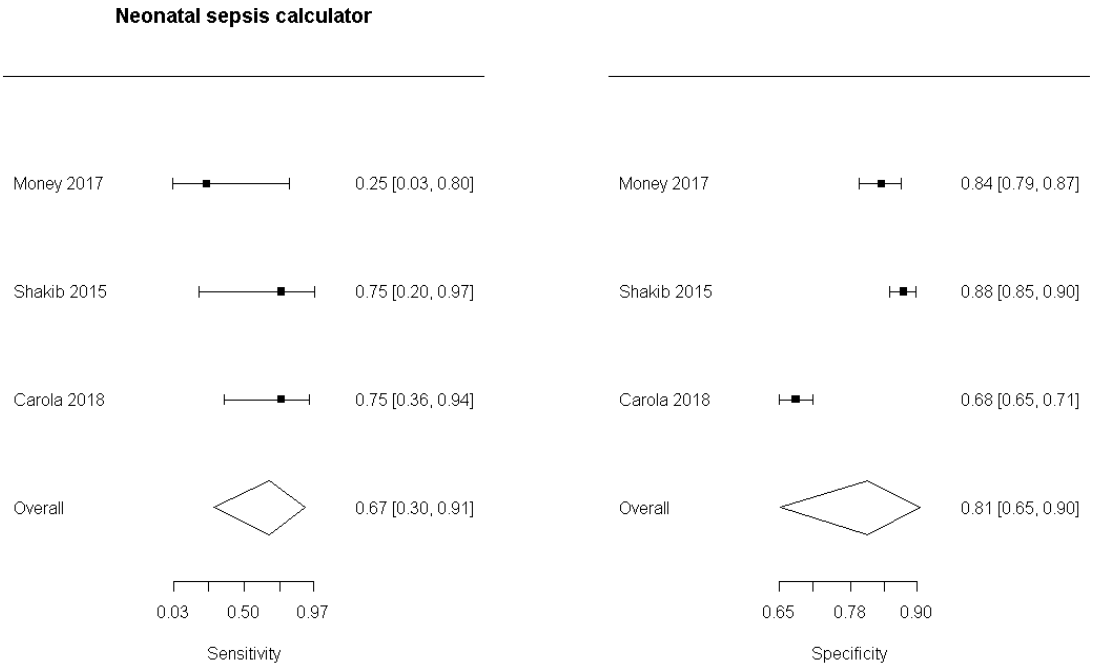
Subgroup analysis: higher baseline incidence of sepsis (4/1000 live births)

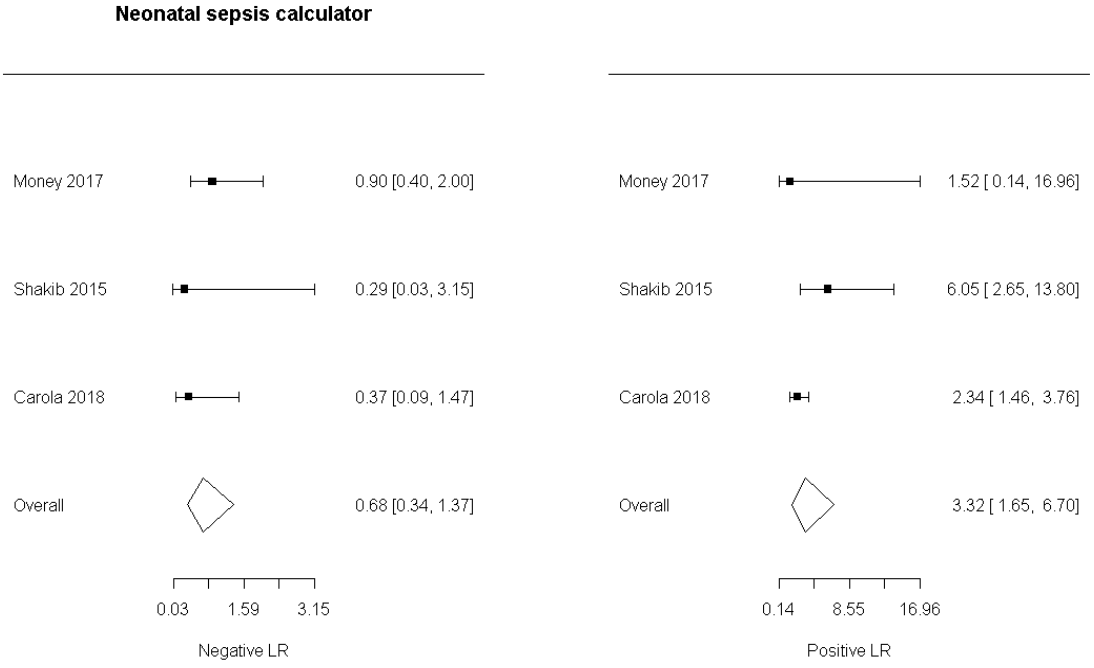


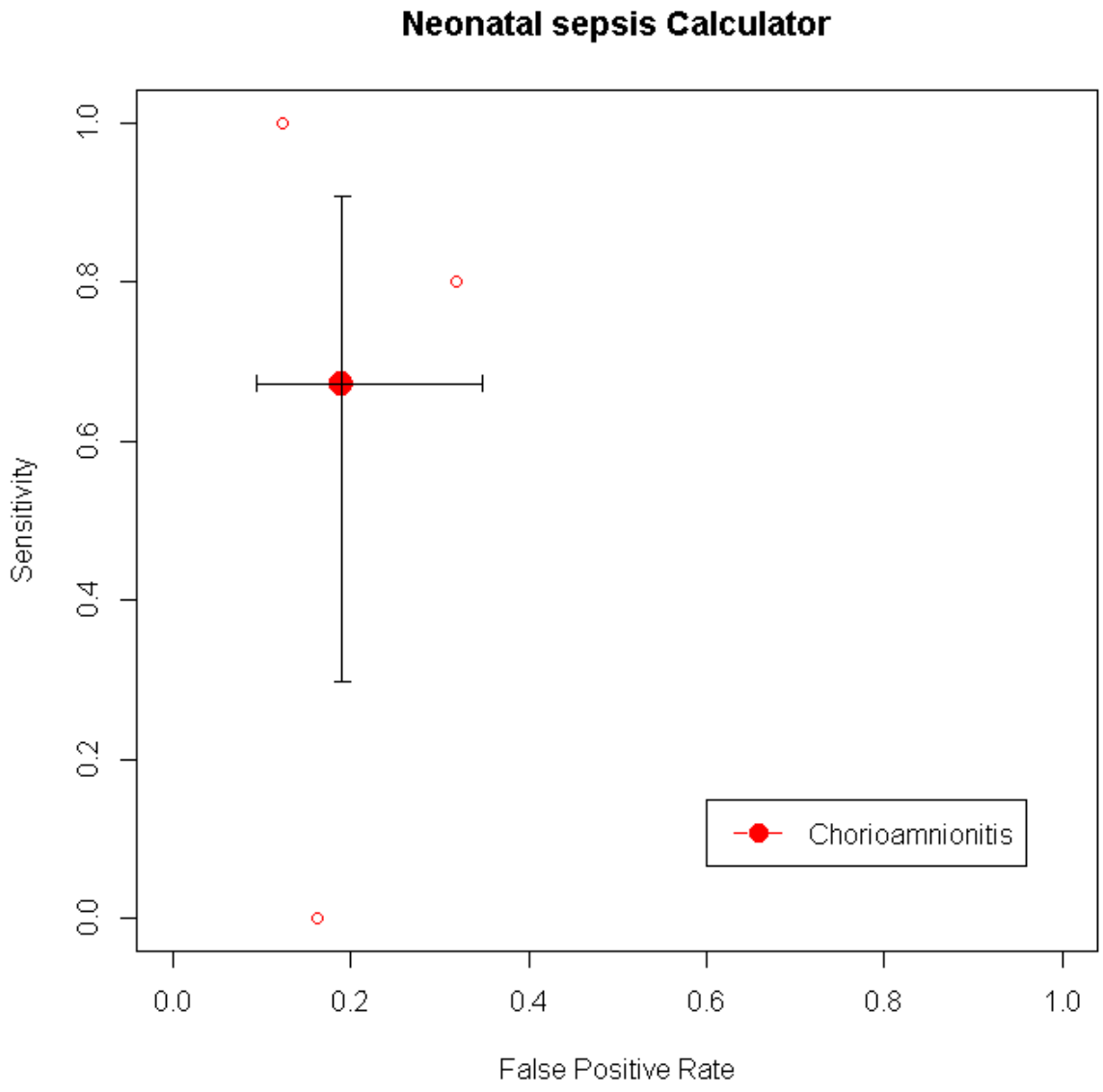
Negative LR not calculable


Neonatal sepsis Calculator
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
Low incidence rate
High incidence rate

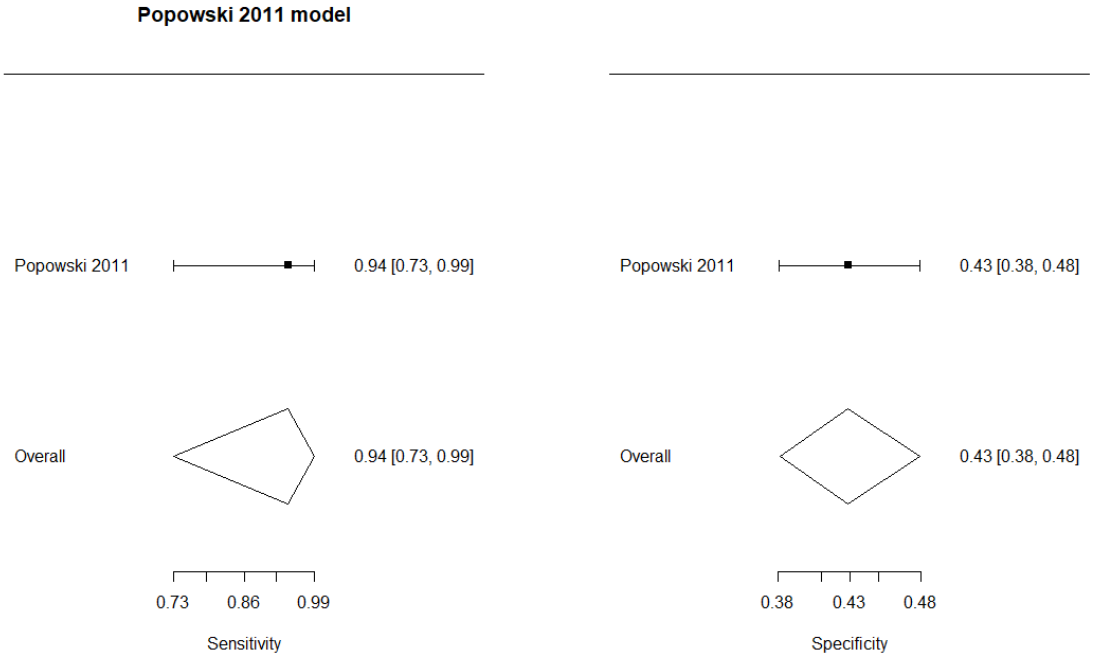
Subgroup analysis: babies born to mothers with chorioamnionitis

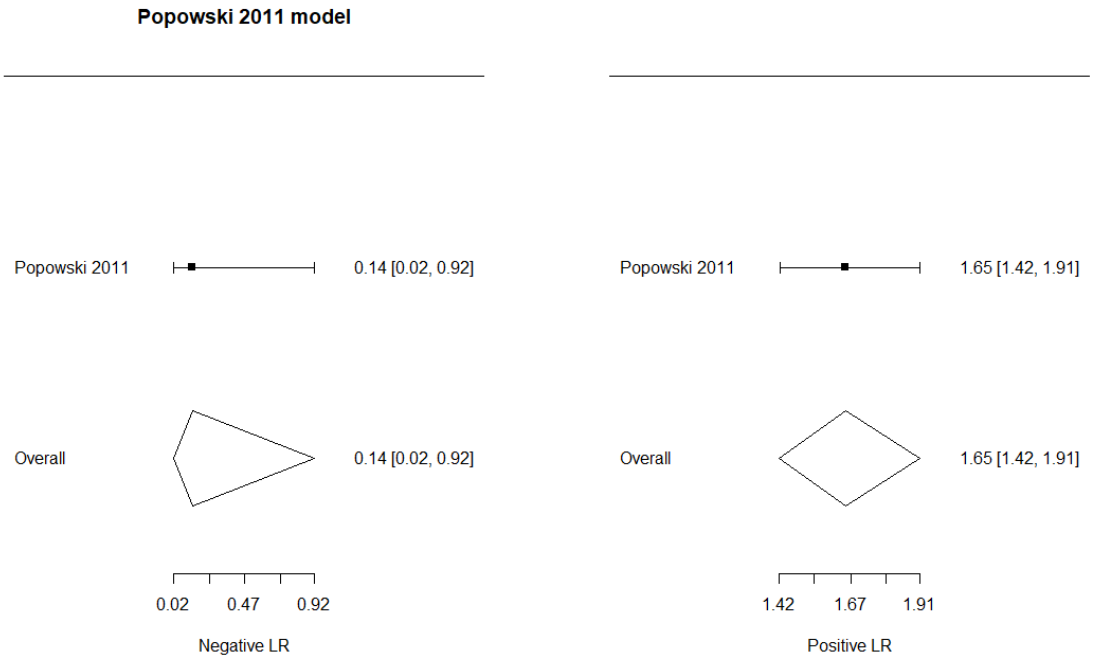


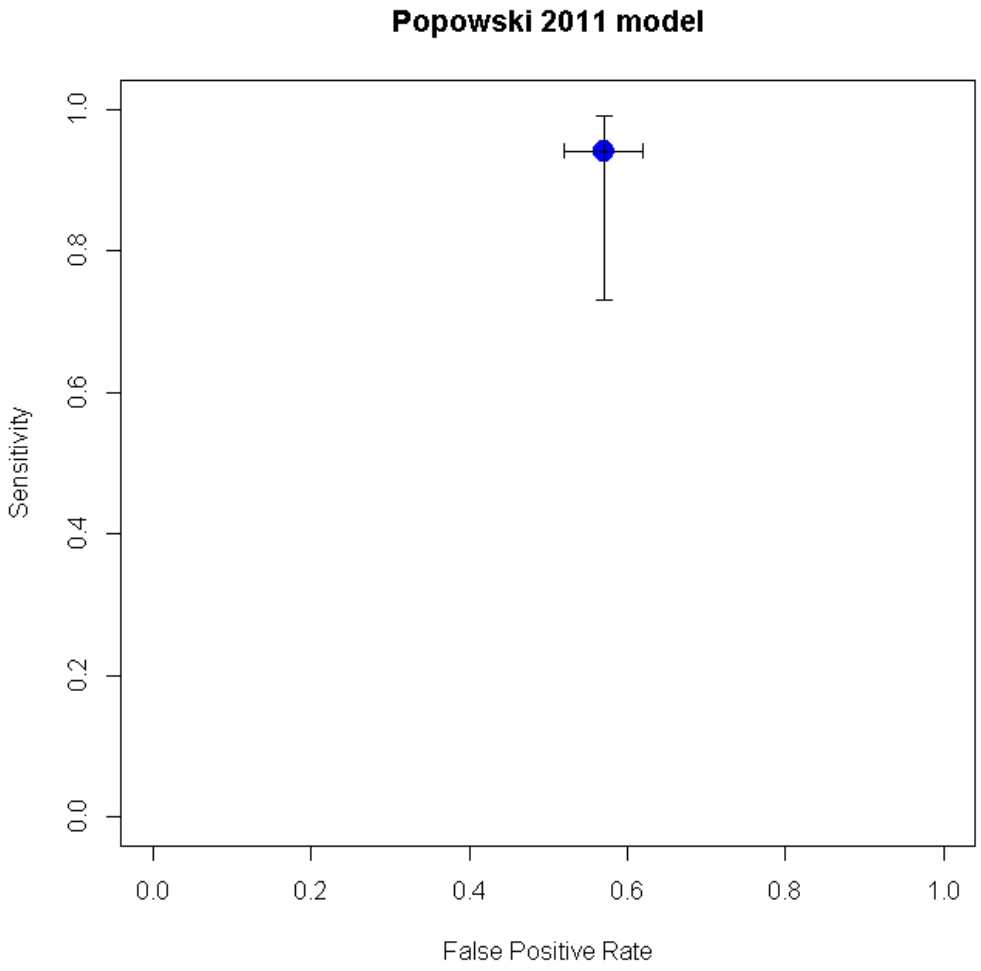



Neonatal sepsis Calculator
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
Chorioamnionitis

Popowski 2011 model – mothers with premature rupture of membranes (based on C-reactive protein and white blood cell count)






Popowski 2011 model
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0

Appendix F – GRADE tables

F.1 Clinical prediction models

Kaiser Permanente early-onset neonatal sepsis calculator: number of babies recommended antibiotic treatment and blood culture

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
Overall analysis (all studies)										
9	Cohort studies (5 prospective, 4 retrospective)	16697	0.56 (0.37, 0.73)	0.90 (0.81, 0.95)	LR+ 6.07 (2.84, 11.70)	Serious[7]	Serious[8]	Very serious[1]	Not serious	Very low
					LR- 0.50 (0.31, 0.70)	Serious[7]	Serious[8]	Not serious	Serious[3]	Very low
Subgroup analysis: lower baseline incidence of sepsis (0.44-0.6/1000 live births)										
8	Cohort studies (5 prospective, 3 retrospective)	16583	0.47 (0.29, 0.65)	0.94 (0.90, 0.97)	LR+ 8.57 (4.36, 15.10)	Serious[7]	Serious[8]	Very serious[1]	Not serious	Very low
					LR- 0.56 (0.37, 0.75)	Serious[7]	Serious[8]	Not serious	Serious[3]	Very low
Subgroup analysis: higher baseline incidence of sepsis (4.0/1000 live births)										
1 (Sloane 2019)	Retrospective cohort study	896	1.00 (0.57, 1.00)	0.41 (0.38, 0.44)	LR+ 1.69 (1.60, 1.78)	Not serious	Serious[8]	N/A[2]	Not serious	Moderate
					LR- *not calculable*[6]	N/A[5]	N/A[5]	N/A[2]	N/A[5]	N/A[5]

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Subgroup analysis: Babies born to mothers with chorioamnionitis										
4	Cohort studies (1 prospective, 3 retrospective)	5552	0.48 (0.21, 0.77)	0.95 (0.79, 0.99)	LR+ 6.82 (2.20, 21.08)	Serious[7]	Serious[8]	Very serious[1]	Not serious	Very low
					LR- 0.75 (0.51, 1.11)	Serious[7]	Serious[8]	Not serious	Very serious[4]	Very low

1. I^2 >66.7%. Quality downgraded 2 levels
2. Single study. Inconsistency not applicable
3. Negative likelihood ratio crossed 1 end of the defined MIDs (0.5 or 1). Quality downgraded 1 level
4. Negative likelihood ratio crossed both ends of the defined MIDs (0.5 and 1). Quality downgraded 2 levels
5. Negative likelihood ratio not calculable and so quality assessment of outcome is not applicable
6. All babies testing positive for infection were identified by the model. Negative likelihood ratio therefore not calculable
7. >33.3% weight of meta-analysis at moderate risk of bias. Quality downgraded 1 level
8. >33.3% weight of meta-analysis from partially applicable studies. Quality downgraded 1 level

Kaiser Permanente early-onset neonatal sepsis calculator: number of babies recommended either antibiotic treatment and blood culture or blood culture and vital sign monitoring every 4 hours

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
Overall analysis (all studies)										
5	Cohort studies (1 prospective, 4 retrospective)	5354	0.73 (0.40, 0.92)	0.66 (0.27, 0.91)	LR+ 2.44 (1.05, 6.24)	Serious[6]	Serious[10]	Very serious[1]	Serious[4]	Very low
					LR- 0.47 (0.16, 0.92)	Serious[6]	Serious[10]	Not serious	Serious[8]	Very low
Subgroup analysis: lower baseline incidence of sepsis (0.44-0.5/1000 live births)										
4	Cohort studies (1 prospective, 3 retrospective)	4458	0.69 (0.35, 0.90)	0.81 (0.72, 0.87)	LR+ 3.38 (2.13, 5.39)	Serious[6]	Serious[10]	Not serious	Not serious	Low
					LR- 0.64 (0.33, 1.25)	Serious[6]	Serious[10]	Not serious	Very serious[5]	Very low
Subgroup analysis: higher baseline incidence of sepsis (4.0/1000 live births)										
1 (Sloane 2019)	Retrospective cohort study	896	1.00 (0.57, 1.00)	0.07 (0.06, 0.09)	LR+ 1.07 (1.06, 1.09)	Not serious	Serious[10]	N/A[3]	Not serious	Moderate
					LR- *not calculable*[7]	N/A[9]	N/A[9]	N/A[3]	N/A[9]	N/A[9]
Subgroup analysis: Babies born to mothers with chorioamnionitis										
3		1956	0.67 (0.30, 0.91)	0.81 (0.65, 0.91)	LR+ 3.32 (1.65, 6.70)	Serious[6]	Serious[10]	Serious[2]	Serious[4]	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
	Retrospective cohort studies				LR- 0.68 (0.34, 1.37)	Serious[6]	Serious[10]	Not serious	Very serious[5]	Very low

1. I^2 >66.7%. Quality downgraded 2 levels
2. I^2 between 33.3% and 66.7%. Quality downgraded 1 level
3. Single study. Inconsistency not applicable
4. Positive likelihood ratio crossed 1 end of the defined MIDs (1 or 2). Quality downgraded 1 level
5. Negative likelihood ratio crossed both ends of the defined MIDs (0.5 and 1). Quality downgraded 2 levels
6. >33.3% weight of meta-analysis at moderate risk of bias. Quality downgraded 1 level
7. All babies testing positive for infection were identified by the model. Negative likelihood ratio therefore not calculable
8. Negative likelihood ratio crossed one end of the defined MIDs (0.5 or 1). Quality downgraded 1 level
9. Negative likelihood ratio not calculable and so quality assessment of outcome is not applicable
10. >33.3% weight of meta-analysis from partially applicable studies. Quality downgraded 1 level

Unnamed model – mothers with premature rupture of membranes (based on C-reactive protein and white blood cell count)

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
Overall analysis										
1 (Popowski 2011)	Prospective cohort study	399	0.94 (0.73, 0.99)	0.43 (0.38, 0.48)	LR+ 1.65 (1.42, 1.91)	Not serious	Not serious	N/A[1]	Not serious	High
					LR- 0.14 (0.02, 0.92)	Not serious	Not serious	N/A[1]	Serious[2]	Moderate

1. Single study. Inconsistency not applicable
2. Negative likelihood ratio crossed 1 end of the defined MIDs (0.5 or 1). Quality downgraded 1 level

c-statistics

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Popowski 2011)	Prospective cohort study	399	0.82 (0.72, 0.92)	Not serious	N/A	Not serious	Serious[1]	Moderate

1. 95% confidence intervals crossed 2 categories of test classification accuracy, ranging from good to outstanding accuracy (0.8 - <0.9 and 0.9 - <1.0). Quality downgraded 1 level

Current NICE guidelines

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
NICE										
1 (Goel 2020)	Cohort study	3588	0.60 (0.23, 0.88)	0.84 (0.83, 0.85)	LR+ 3.8 (1.8, 7.7)	Not serious	Not serious	N/A[1]	Serious[1]	Moderate
					LR- 0.48 (0.16, 1.39)	Not serious	Not serious	N/A[1]	Very serious[2]	Low

1. Positive likelihood ratio crossed one end of the defined MIDs (1 or 2). Quality downgraded 1 level
2. Negative likelihood ratio crossed both ends of the defined MIDs (0.5 and 1). Quality downgraded 2 levels

F.2 Maternal risk factors

Risk factors

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Chorioamnionitis: Histological chorioamnionitis in babies born <30 weeks' gestational age (OR >1 indicates greater risk of infection for babies born to mothers with chorioamnionitis)								
1 (Dempsey 2005)	Retrospective cohort study	392	Adjusted OR 6.9 (2.2, 20.0)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Chorioamnionitis: Clinical chorioamnionitis in very low birth weight babies (OR/RR >1 indicates greater risk of infection for babies born to mothers with chorioamnionitis)								
1 (Garcia-Munoz 2014a)	Prospective cohort study	451	Adjusted RR 6.13 (1.67, 22.58)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
1 (Garcia-Munoz 2014b)	Retrospective cohort study	8330	Adjusted OR 3.10 (2.31-4.17)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Chorioamnionitis: Clinical chorioamnionitis in preterm babies (OR >1 indicates greater risk of infection for babies born to mothers with chorioamnionitis)								
1 (Soraisham 2009)	Retrospective cohort study	3094	Adjusted OR 5.54 (2.87-10.69)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Chorioamnionitis: Clinical chorioamnionitis in moderately preterm babies (OR >1 indicates greater risk of infection for babies born to mothers with chorioamnionitis)								
1 (Ofman 2016)	Retrospective cohort study	2192	Adjusted OR 4.1 (2.83-5.30)	Very serious[4]	Not serious	N/A[1]	Not serious	Low
Chorioamnionitis: Clinical chorioamnionitis in extremely preterm babies (OR >1 indicates greater risk of infection for babies born to mothers with chorioamnionitis)								

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Ronnestad 2005)	Prospective cohort study	451	Adjusted OR 10.5 (3.3-33.4)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Intrapartum fever: Low febrile fever (38.0-38.9◦C) in mothers of babies born at term in a singleton pregnancy (OR >1 indicates greater risk of infection for babies born to mothers with low febrile fever)								
1 (Dior 2016)	Retrospective cohort study	43,560	Adjusted OR 7.44 (3.29, 16.85)	Not serious	Not serious	N/A[1]	Not serious	Moderate
Intrapartum fever: High febrile fever (>39◦C) in mothers of babies born at term in a singleton pregnancy (OR >1 indicates greater risk of infection for babies born to mothers with high febrile fever)								
1 (Dior 2016)	Retrospective cohort study	43,560	Adjusted OR 16.08 (2.15, 120.3)	Not serious	Not serious	N/A[1]	Not serious	Moderate
Maternal obesity: Overweight mothers (BMI 25-29.9) of babies born at >22 weeks' gestational age (OR >1 indicates greater risk of infection for babies born to overweight mothers)								
1 (Hakansson 2008)	Retrospective cohort study	344,127	Adjusted OR 1.3 (0.9, 2.0)	Not serious	Serious[5]	N/A[1]	Serious[2]	Low
Maternal obesity: Obese mothers (BMI 30.0) of babies born at >22 weeks' gestational age (OR >1 indicates greater risk of infection for babies born to obese mothers)								
1 (Hakansson 2008)	Retrospective cohort study	344,127	Adjusted OR 1.8 (1.1, 3.0)	Not serious	Serious[5]	N/A[1]	Not serious	Moderate
Single birth: Very low birth weight babies (OR >1 indicates greater risk of infection for single births)								
1 (Mularoni 2014)	Prospective cohort study	14,719	Adjusted OR 1.4 (1.1, 1.8)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
1 (Klinger 2009)	Prospective cohort study	15,839	Adjusted OR 1.4	Serious[3]	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
			(1.1, 1.8)					
Single birth: Babies born ≥22 weeks' gestational age (OR >1 indicates greater risk of infection for single births)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 1.1 (0.6, 2.0)	Not serious	Not serious	N/A[1]	Serious[2]	Moderate

1. Single study. Inconsistency not applicable
2. Single study where CIs cross the line of no effect. Quality downgraded 1 level
3. Single study at moderate risk of bias. Quality downgraded 1 level
4. Single study at high risk of bias. Quality downgraded 2 levels
5. Single study which is partially applicable. Quality downgraded 1 level

F.3 Neonatal risk factors

Risk factors

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Gestational age: Very early onset infection (up to 2 days). Extremely premature babies (≤25 weeks vs ≥26 weeks) (OR >1 indicates greater risk of infection for extremely premature babies)								
1 (Ronnestad 2005)	Prospective cohort study	462	Adjusted OR 1.1 (0.4, 3.6)	Serious[3]	Not serious	N/A[1]	Serious[2]	Low
Gestational age: Early onset infection (2-7 days days). Extremely premature babies (≤25 weeks vs ≥26 weeks) (OR >1 indicates greater risk of infection for extremely premature babies)								
1 (Ronnestad 2005)	Prospective cohort study	462	Adjusted OR 3.0 (0.6, 14.9)	Serious[3]	Not serious	N/A[1]	Serious[2]	Low

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Gestational age: Very low birthweight babies (comparisons between 1-week increases in gestational age) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Klinger 2009)	Prospective cohort study	15,839	Adjusted OR 0.98 (0.94, 1.03)	Serious[3]	Not serious	N/A[1]	Serious[2]	Low
Gestational age: Babies born ≥22 weeks' gestational age (<28 weeks vs 40 weeks) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 22.1 (8.5, 57.4)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Gestational age: Babies born ≥22 weeks' gestational age (28-31 weeks vs 40 weeks) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 34.1 (18.6, 62.7)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Gestational age: Babies born ≥22 weeks' gestational age (32-34 weeks vs 40 weeks) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 11.2 (6.0, 21.0)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Gestational age: Babies born ≥22 weeks' gestational age (35-36 weeks vs 40 weeks) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 4.7 (2.5, 8.9)	Serious[3]	Not serious	N/A[1]	Not serious	Moderate
Gestational age: Babies born ≥22 weeks' gestational age (37 weeks vs 40 weeks) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 3.5	Serious[3]	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
			(1.8, 6.5)					
Gestational age: Babies born ≥22 weeks' gestational age (≥42 weeks vs 40 weeks) (OR >1 indicates greater risk of infection for babies of lower gestational age)								
1 (Hakansson 2006)	Retrospective cohort study	319	Adjusted OR 1.9 (0.9, 3.7)	Serious[3]	Not serious	N/A[1]	Serious[2]	Low

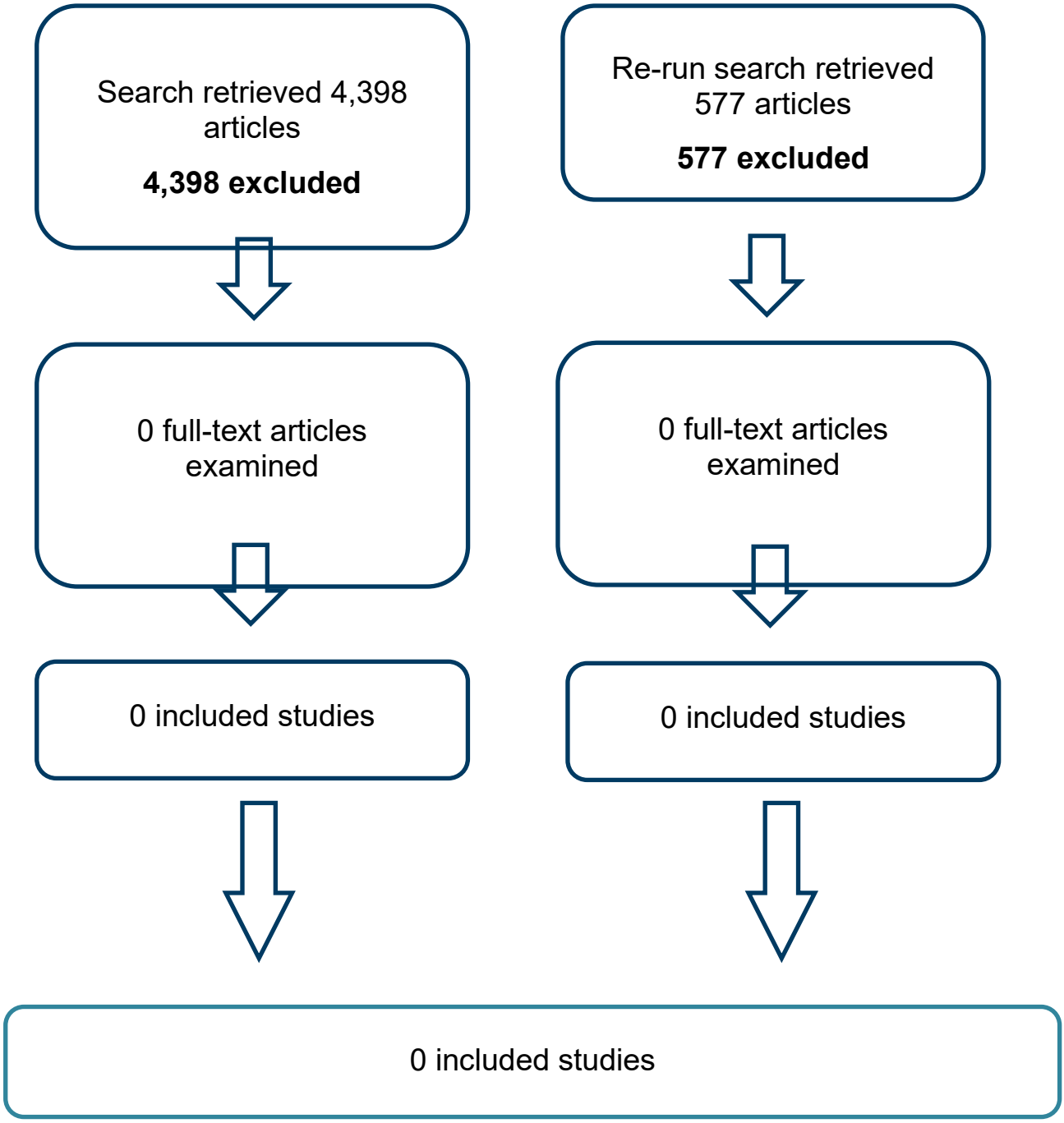
1. Single study. Inconsistency not applicable
2. Single study where CIs cross the line of no effect. Quality downgraded 1 level
3. Single study at moderate risk of bias. Quality downgraded 1 level

Signs and symptoms

No. of studies	Study design	Sample size	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Respiratory distress syndrome: Moderately preterm babies (OR >1 indicates greater risk of infection for babies with respiratory distress syndrome)								
1 (Ofman 2016)	Retrospective cohort study	2192	Adjusted OR 2.05 (1.62-3.14)	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

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 2x2 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 do 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 does 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	**- Outcome to be predicted does 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 do 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 do 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	**- Outcome to be predicted does 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**
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	**- Late-onset neonatal infection**
Chen, Chun-Jen, Lo, Yu-Fang, Huang, Miao-Chiu et al. (2009) A model for predicting risk of serious bacterial infection in	**- Study does not contain the population of interest**

febrile infants younger than 3 months of age.. Journal of the Chinese Medical Association : JCMA 72(10): 521-6	**[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 type 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 type 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 do 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	**- Outcome to be predicted does 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 do 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 emergency medicine : official journal of the Society for Academic Emergency Medicine 12(10): 921-5	**- Study does not contain the population of interest [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, 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	**- Late-onset neonatal infection**
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]**
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	**- Late-onset neonatal infection**
Gur, Ilan, Riskin, Arieh, Markel, Gal et al. (2015) Pilot study of a new mathematical algorithm for early detection of late-onset sepsis in very low-birth-weight infants.. American journal of perinatology 32(4): 321-30	**- Late-onset neonatal infection**
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	**- End point do not match that specified in the protocol**

Newborns Assessed Using the Kaiser Sepsis Calculator. Pediatric and Developmental Pathology	
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 protein concentrations in cord blood.. Clinical chemistry and laboratory medicine 46(8): 1143-8	**- Not possible to calculate a contingency table from the data specified in the protocol**
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**
Lawder, Richard, Whyte, Bruce, Wood, Rachael et al. (2019) Impact of maternal smoking on early childhood health: a retrospective cohort linked dataset analysis of 697 003 children born in Scotland 1997-2009. BMJ open 9(3): e023213	**- Outcome to be predicted does 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**

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	**- Late-onset neonatal infection**
Mahieu LM, De Muynck AO, De Dooy JJ et al. (2000) Prediction of nosocomial sepsis in neonates by means of a computer-weighted bedside scoring system (NOSEP score). Critical care medicine 28(6): 2026-2033	**- Late-onset neonatal infection**
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	**- Late-onset neonatal infection**
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	**- Late-onset neonatal infection**
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-onset neonatal sepsis.. Journal of perinatology : official journal of the California Perinatal Association 27(8): 496-501	**- Set in non-OECD country**
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 do not match that specified in the protocol** ***Frequency of calculator use***
Strunk, Tobias, Campbell, Catherine, Burgner, David et al. (2019) Histological chorioamnionitis and developmental outcomes in very preterm infants. Journal of perinatology : official journal of the California Perinatal Association 39(2): 321-330	**- Outcome to be predicted does not match that specified in the protocol**
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	**- Outcome to be predicted does 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	**- Outcome to be predicted does 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**
van der Ham, David P, van Kuijk, Sander, Opmeer, Brent C et al. (2014) Can neonatal sepsis be predicted in late preterm premature rupture of membranes? Development of a prediction model.. European journal of obstetrics, gynecology, and reproductive biology 176: 90-5	**- Study design does not match protocol**
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**
Villamor-Martinez, E., Lubach, G.A., Rahim, O.M. et al. (2020) Association of histological and clinical chorioamnionitis with neonatal sepsis among preterm infants: A systematic review, meta-analysis, and meta-regression. Frontiers in Immunology 11: e972	**- Systematic review. Reference list checked for possible includes**
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 tool for late onset bacteremia in neonates - a pilot study.. BMC pediatrics 19(1): 253	**- Study design does not match protocol**
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**
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	**- Late-onset neonatal infection**

J.2 Maternal and neonatal risk factors

Clinical studies

Study	Reason for exclusion
Berardi, Alberto, Lugli, Licia, Rossi, Cecilia et al. (2011) Intrapartum antibiotic prophylaxis failure and group-B streptococcus early-onset disease. 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 24(10): 1221-4	- Statistical outcomes do not match those specified in the protocol *[Does not include multivariate model]*
Bobitt, J.R.; Damato, J.D.; Sakakini Jr., J. (1985) Perinatal complications in group B streptococcal carriers: A longitudinal study of prenatal patients. American Journal of Obstetrics and Gynecology 151(6): 711-717	- Reference standard in study does not match that specified in protocol
Cakir, Ufuk; Tayman, Cuneyt; Buyuktiryaki, Mehmet (2019) An Unknown Risk Factor for Sepsis in Very Low Birth Weight Preterms: ABO Blood Groups (BGaPS Study). American journal of perinatology	- Predictive factors do not match the protocol *[Blood type]*
Capanna, Federica, Emonet, Stephane P, Cherkaoui, Abdessalam et al. (2013) Antibiotic resistance patterns among group B Streptococcus isolates: implications for antibiotic prophylaxis for early-onset neonatal sepsis. Swiss medical weekly 143: w13778	- Outcome to be predicted do not match that specified in the protocol
Chan, Grace J, Lee, Anne C C, Baqui, Abdullah H et al. (2013) Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. PLoS medicine 10(8): e1001502	- Systematic review. References checked for possible includes

	[2 studies added for review of full text articles]
Chen, Katherine T, Ringer, Steven, Cohen, Amy P et al. (2002) The role of intrapartum fever in identifying asymptomatic term neonates with early-onset neonatal sepsis. Journal of perinatology : official journal of the California Perinatal Association 22(8): 653-7	- Statistical outcomes do not match those specified in the protocol
Dutta, Sourabh, Reddy, Rajeshwar, Sheikh, Samir et al. (2010) Intrapartum antibiotics and risk factors for early onset sepsis. Archives of disease in childhood. Fetal and neonatal edition 95(2): f99-103	- Based in non-OECD country
Egarter C, Leitich H, Karas H, Wieser F, Husslein P, Kaider A, Schemper M (1996) Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a metaanalysis. American Journal of Obstetrics and Gynecology 174(2): 589-597	- Systematic review. References checked for possible includes
Evers, Annemieke C C, Nijhuis, Lotte, Koster, Maria P H et al. (2012) Intrapartum fever at term: diagnostic markers to individualize the risk of fetal infection: a review. Obstetrical & gynecological survey 67(3): 187-200	- Systematic review. References checked for possible includes
Geethanath, R.M., Ahmed, I., Abu-Harb, M. et al. (2019) Intrapartum antibiotics for prolonged rupture of membranes at term to prevent Group B Streptococcal sepsis. Journal of Obstetrics and Gynaecology 39(5): 619-622	- Study design does not match the protocol
Grimwood, K, Darlow, B A, Gosling, I A et al. (2002) Early-onset neonatal group B streptococcal infections in New Zealand 1998-1999. Journal of paediatrics and child health 38(3): 272-7	- Statistical outcomes do not match those specified in the protocol
Hafed, B M, Bilikova, E, Kovacicova, G et al. (2003) Prognostic factors for 246 neonates with infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 36(9): 1203-5	- Not a peer-reviewed publication *[Article correspondence]*
Hofer, Nora; Muller, Wilhelm; Resch, Bernhard (2012) Neonates presenting with temperature symptoms: role in the diagnosis of early onset sepsis. Pediatrics international : official journal of the Japan Pediatric Society 54(4): 486-90	- Reference standard in study does not match that specified in protocol *[Positive blood, CSF or tracheal aspirate culture]*
Jeong, Heejeong, Han, Su-jin, Yoo, Ha-Na et al. (2015) Comparison of changes in etiologic microorganisms causing early-onset neonatal sepsis between preterm labor and preterm premature rupture of membranes. 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(16): 1923-8	- Outcome to be predicted do not match that specified in the protocol *[Criteria for infection not defined]*

Langley, S. (2000) Group B streptococci and early onset neonatal infection. Nursing times 96(25): 36-37	- Not a peer-reviewed publication
Lawder, Richard, Whyte, Bruce, Wood, Rachael et al. (2019) Impact of maternal smoking on early childhood health: a retrospective cohort linked dataset analysis of 697 003 children born in Scotland 1997-2009. BMJ open 9(3): e023213	- Outcome to be predicted do not match that specified in the protocol
Lorthe, E., Ancel, P.-Y., Torchin, H. et al. (2017) Impact of Latency Duration on the Prognosis of Preterm Infants after Preterm Premature Rupture of Membranes at 24 to 32 Weeks' Gestation: A National Population-Based Cohort Study. Journal of Pediatrics 182: 47	- Predictive factors do not match the protocol *[Factors reported for multivariate analysis do not match the protocol]*
Moore, M.R.; Schrag, S.J.; Schuchat, A. (2003) Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. Lancet Infectious Diseases 3(4): 201-213	- Review article but not a systematic review
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 37(2): 157-161	- Reference standard in study does not match that specified in protocol *[Positive blood, urine or CSF culture]*
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): 20-7	- Outcome to be predicted do not match that specified in the protocol *[Neonatal and infant mortality]*
Ramesh Bhat, Y. and Baby, L.P. (2012) Early onset of neonatal sepsis: Analysis of the risk factors and the bacterial isolates by using the BacT alert system. Journal of Clinical and Diagnostic Research 5(7): 1385-1388	- Statistical outcomes do not match those specified in the protocol
Saccone, Gabriele and Berghella, Vincenzo (2015) Antibiotic prophylaxis for term or near-term premature rupture of membranes: metaanalysis of randomized trials. American journal of obstetrics and gynecology 212(5): 627e1-9	- Systematic review. References checked for possible includes
Salem, Shimrit Yaniv, Sheiner, Eyal, Zmora, Ehud et al. (2006) Risk factors for early neonatal sepsis. Archives of gynecology and obstetrics 274(4): 198-202	- Study design does not match the protocol *[Case-control study]*
Schrag, Stephanie J, Cutland, Clare L, Zell, Elizabeth R et al. (2012) Risk factors for neonatal sepsis and perinatal death	- Predictive factors do not match the protocol

among infants enrolled in the prevention of perinatal sepsis trial, Soweto, South Africa. The Pediatric infectious disease journal 31(8): 821-6	*[Factors reported for multivariate analysis do not match the protocol]*
Strunk, Tobias, Campbell, Catherine, Burgner, David et al. (2019) Histological chorioamnionitis and developmental outcomes in very preterm infants. Journal of perinatology : official journal of the California Perinatal Association 39(2): 321-330	- Outcome to be predicted do not match that specified in the protocol
Tsai, M.-L., Hsu, C.-H., Chang, J.-H. et al. (2004) Group B streptococcal sepsis and meningitis in neonates: An 11-year survey. Clinical Neonatology 11(2): 62-66	- Full text paper not available
Turrentine, M.A., Greisinger, A.J., Brown, K.S. et al. (2013) Duration of intrapartum antibiotics for group B streptococcus on the diagnosis of clinical neonatal sepsis. Infectious Diseases in Obstetrics and Gynecology 2013: 525878	- Reference standard in study does not match that specified in protocol *[Includes suspected infection but does not include treatment with antibiotics in the criteria]*
Veleminsky, Milos and Tosner, Jindrich (2008) Relationship of vaginal microflora to PROM, pPROM and the risk of early-onset neonatal sepsis. Neuro endocrinology letters 29(2): 205-21	- Statistical outcomes do not match those specified in the protocol
Strunk, Tobias, Campbell, Catherine, Burgner, David et al. (2019) Histological chorioamnionitis and developmental outcomes in very preterm infants. Journal of perinatology : official journal of the California Perinatal Association 39(2): 321-330	- Outcome to be predicted do not match that specified in the protocol
Wassen, M M L H, Winkens, B, Dorssers, E M I et al. (2014) Neonatal sepsis is mediated by maternal fever in labour epidural analgesia. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 34(8): 679-83	- Study design does not match the protocol *[Case control study]*
Wojcieszek Aleena M, Stock Owen M, Flenady Vicki (2014) Antibiotics for prelabour rupture of membranes at or near term. Cochrane Database of Systematic Reviews: Reviews issue10	- Systematic review. References checked for possible includes
Wojkowska-Mach, Jadwiga, Borszewska-Kornacka, Maria, Domanska, Joanna et al. (2012) Early-onset infections of very-low-birth-weight infants in Polish neonatal intensive care units. The Pediatric infectious disease journal 31(7): 691-5	- Statistical outcomes do not match those specified in the protocol

Wortham, Jonathan M, Hansen, Nellie I, Schrag, Stephanie J et al. (2016) Chorioamnionitis and Culture-Confirmed, Early-Onset Neonatal Infections. Pediatrics 137(1)	- Statistical outcomes do not match those specified in the protocol
Yoon, B.H., Yang, S.H., Jun, J.K. et al. (1996) Maternal blood C-reactive protein, white blood cell count, and temperature in preterm labor: A comparison with amniotic fluid white blood cell count. Obstetrics and Gynecology 87(2i): 231-237	- Outcome to be predicted do not match that specified in the protocol *[Criteria for neonatal sepsis not defined]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
Dempsey, E, Chen, M-F, Kokottis, T et al. (2005) Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. American journal of perinatology 22(3): 155-9	- Study does not examine early-onset infection *[Examines late-onset infection]*
Dior, Uri P, Kogan, Liron, Eventov-Friedman, Smadar et al. (2016) Very High Intrapartum Fever in Term Pregnancies and Adverse Obstetric and Neonatal Outcomes. Neonatology 109(1): 62-8	- Study does not examine early-onset infection *[Examines late-onset infection]*
Garcia-Munoz Rodrigo, Fermin; Galan Henriquez, Gloria M; Ospina, Cristina Gomez (2014) Morbidity and mortality among very-low-birth-weight infants born to mothers with clinical chorioamnionitis. Pediatrics and neonatology 55(5): 381-6	- Study does not examine early-onset infection *[Examines late-onset infection]*
Garcia-Munoz Rodrigo, Fermin, Galan Henriquez, Gloria, Figueras Aloy, Josep et al. (2014) Outcomes of very-low-birth-weight infants exposed to maternal clinical chorioamnionitis: a multicentre study. Neonatology 106(3): 229-34	- Study does not examine early-onset infection *[Examines late-onset infection]*
Garland, J S, Kanneberg, S, Mayr, K A et al. (2017) Risk of morbidity following catheter removal among neonates with	- Study does not examine early-onset infection

catheter associated bloodstream infection. Journal of neonatal-perinatal medicine 10(3): 291-299	*[Examines late-onset infection]*
Hakansson, S and Kallen, K (2006) Impact and risk factors for early-onset group B streptococcal morbidity: analysis of a national, population-based cohort in Sweden 1997-2001. BJOG : an international journal of obstetrics and gynaecology 113(12): 1452-8	- Study does not examine early-onset infection *[Examines late-onset infection]*
Hakansson, Stellan and Kallen, Karin (2008) High maternal body mass index increases the risk of neonatal early onset group B streptococcal disease. Acta paediatrica (Oslo, Norway : 1992) 97(10): 1386-9	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
Kim, 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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
Mularoni, Alessandra, Madrid, Marisela, Azpeitia, Agueda et al. (2014) The role of coagulase-negative staphylococci in early onset sepsis in a large European cohort of very low birth weight infants. The Pediatric infectious disease journal 33(5): e121-5	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*

Rastogi, Shantanu, Rojas, Mary, Rastogi, Deepa et al. (2015) Neonatal morbidities among full-term infants born to obese mothers. 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(7): 829-35	- Study does not examine early-onset infection *[Examines late-onset infection]*
Ronnestad, Arild, Abrahamsen, Tore G, Medbo, Sverre et al. (2005) Septicemia in the first week of life in a Norwegian national cohort of extremely premature infants. Pediatrics 115(3): e262-8	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
Shah, P, Nathan, E, Doherty, D et al. (2013) Prolonged exposure to antibiotics and its associations in extremely preterm neonates--the Western Australian experience. 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 26(17): 1710-4	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
Soraisham, Amuchou S, Singhal, Nalini, McMillan, Douglas D et al. (2009) A multicenter study on the clinical outcome of chorioamnionitis in preterm infants. American journal of obstetrics and gynecology 200(4): 372e1-6	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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	- Study does not examine early-onset infection *[Examines late-onset infection]*
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): 157-164	- Study does not examine early-onset infection *[Examines late-onset infection]*

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

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

K.1.2 Why this is important

Nine observational studies were identified evaluating the accuracy of clinical prediction models for early-onset neonatal infection. These primarily evaluated the use of the Kaiser Permanente neonatal sepsis calculator. However, most of the evidence has validated the use of this tool in the USA, with only one study examining its use in the UK. In addition, the neonatal sepsis calculator is designed for use with babies at or over 34 weeks' gestational age. There is currently no evidence for the use of clinical prediction models for babies born at a gestational age of less than 34 weeks.

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 early-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 newborn babies most at risk of developing early-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 is currently only one prognostic tool, with limited validation in the UK, to predict which babies are at high risk of early-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 many babies who do not have early-onset neonatal infection being given unnecessary antibiotic treatment. The development of a tool that can predict a babies' risk of early-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 able to make recommendations based on the Kaiser Permanente neonatal sepsis calculator and

	individual risk factors. However, they could not recommend solely using the neonatal sepsis risk calculator, or other prediction tools, until they were validated for use in the UK. 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 early-onset infection. This would help to ensure that babies who need antibiotic treatment receive this as quickly as possible, reducing potential side effects as well as reducing additional treatment costs that result from late diagnosis of neonatal infection. Babies at low risk of infection would also be less likely to receive unnecessary treatment, again reducing additional costs to the NHS.
National priorities	Medium
Current evidence base	This review identified 9 studies reporting data on 2 different prognostic models to predict early-onset neonatal infection. Only one model (Kaiser Permanente neonatal sepsis calculator) has been externally validated. There is currently no evidence for prognostic models designed for use in babies born at less than 34 weeks' gestational age.
Equality considerations	No specific equality concerns are relevant to this research recommendation

K.1.4 Modified PICO table (Part A – prognostic accuracy)

PICO	**Population:** Unborn or newborn babies under 72 hours Pregnant women **Risk tool:** Any validated risk tool using multiple predictors to predict the risk of development or the presence of early-onset neonatal infection **Reference standard:** Culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection **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	9 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:** Unborn or newborn babies under 72 hours 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 within 72 hours of birth • Antibiotics for suspected bloodstream infection within 72 hours of birth • Mortality • Respiratory distress within 72 hours of birth • Health-related quality of life, measured using a validated tool • Hospital length of stay
Current evidence base	No evidence
Study design	Test and treat RCTs
Other comments	Study should be adequately powered

K.2.1 Research recommendation

What is the risk of early-onset neonatal infection with maternal obesity and how does this change with increasing BMI?

K.2.2 Why this is important

One retrospective cohort study (Hakansson 2008) was identified evaluating the association between maternal obesity and early-onset neonatal infection. This defined maternal obesity using the World Health Organisation definition based on BMI (underweight <18.5, normal 18.5–24.9, overweight 25–29.9 and obese ≥30). However, this definition does not reflect the definition that is used in current practice, where mothers with a BMI greater than 35 are now classified as obese. The differences in BMI classifications between this study and clinical practice mean that there is currently no evidence that can be directly applied to clinical practice in the UK. In addition, with only one study currently available it is difficult to assess any associations between BMI and the risk of neonatal infection.

Further research is needed using a robust study design such as prospective cohort studies, to determine the association between maternal obesity and the risk of babies developing early-onset neonatal infection. Research in this area is important to help provide clinicians with a more detailed understanding of the risk factors associated with early-onset infection, thereby helping to identify which babies are most at risk of infection within the first 72 hours of life. Such research is relevant to the NHS due the potential resource impact. Infections are both costly to treat and may result in severe adverse health outcomes. As such, research that helps clinicians identify which babies are most at risk, is likely to result in cost-savings at the population level and also improve health outcomes.

K.2.3 Rationale for research recommendation

Importance to 'patients' or the population	Neonatal infection can have serious consequences if left untreated but there is currently limited information about the risks of maternal obesity on a baby's chance of developing early-onset neonatal infection. An increased understanding of the association between maternal BMI and early-onset infection will help clinicians understand whether a baby is at greater risk of developing infection if they are born to an obese mother. If there is found to be an association between maternal obesity and early-onset neonatal infection, then clinicians will be aware that they may need to monitor the baby more closely for signs of infection. This may lead to quicker decisions about whether a baby needs treatment. A greater understanding the association between maternal obesity and early-onset infection will also ensure help provide more detailed information to mothers about the potential risks of infection.
Relevance to NICE guidance	The committee were unable to make recommendations for risk factors for early-onset infection onset in relation to maternal obesity. However, they felt that not including maternal obesity within the list of risk factors should not result in an increased risk of a baby being missed for treatment for neonatal infection. Future research will help to develop more detailed guidance on the risk factors for early-onset neonatal infection suitable for use in the UK.
Relevance to the NHS	The outcome would help to identify whether maternal obesity is a risk factor for babies to develop early-onset neonatal infection. This information will help to determine whether babies born to mothers who are obese should be considered at higher risk of developing

	infection. This will also help to provide mothers with more detailed information during pregnancy.
National priorities	Medium
Current evidence base	This review identified 1 study reporting data on the association between maternal obesity and early-onset neonatal infection. However, the BMI categories that were used to classify maternal obesity were not relevant to current practice. In UK practice, a mother with a BMI greater than 35 is classified as obese, whereas a BMI of 30 was used to represent maternal obesity in the study. The committee advised that more research is needed to be confident whether maternal obesity is a risk factor for early-onset infection.
Equality considerations	No specific equality concerns are relevant to this research recommendation

K.2.4 Modified PICO table

PICO	**Population:** Unborn or newborn babies under 72 hours Pregnant women **Risk factors:** Maternal obesity (based on BMI definitions used in clinical practice in the UK) **Reference standard:** Culture-proven infection from a sample taken within 72 hours of birth where available or within the study-defined period for early onset neonatal infection **Outcomes:** Association measures, for example: • Odds ratios/hazard ratios • Sensitivity, specificity, positive and negative predictive values
Current evidence base	1 observational study
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