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C-reactive protein for diagnosing late-onset infection in newborn infants (Review)

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[Diagnostic Test Accuracy Review]

C-reactive protein for diagnosing late-onset infection in newborn infants

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A B S T R A C T

Background

Late-onset infection is the most common serious complication associated with hospital care for newborn infants. Because confirming the diagnosis by microbiological culture typically takes 24 to 48 hours, the serum level of the inflammatory marker C-reactive protein (CRP) measured as part of the initial investigation is used as an adjunctive rapid test to guide management in infants with suspected late-onset infection.

Objectives

To determine the diagnostic accuracy of serum CRP measurement in detecting late-onset infection in newborn infants.

Search methods

We searched electronic databases (MEDLINE, Embase, and Science Citation Index to September 2017), conference proceedings, previous reviews, and the reference lists of retrieved articles.

Selection criteria

We included cohort and cross-sectional studies evaluating the diagnostic accuracy of serum CRP levels for the detection of late-onset infection (occurring more than 72 hours after birth) in newborn infants.

Data collection and analysis

Two review authors independently assessed eligibility for inclusion, evaluated the methodological quality of included studies, and extracted data to estimate diagnostic accuracy using hierarchical summary receiver operating characteristic (SROC) models. We assessed heterogeneity by examining variability of study estimates and overlap of the 95% confidence interval (CI) in forest plots of sensitivity and specificity.

Main results

The search identified 20 studies (1615 infants). Most were small, single-centre, prospective cohort studies conducted in neonatal units in high- or middle-income countries since the late 1990s. Risk of bias in the included studies was generally low with independent assessment of index and reference tests. Most studies used a prespecified serum CRP threshold level as the definition of a 'positive' index test (typical cut-off level between 5 mg/L and 10 mg/L) and the culture of a pathogenic micro-organism from blood as the reference standard.

At median specificity (0.74), sensitivity was 0.62 (95% CI 0.50 to 0.73). Heterogeneity was evident in the forest plots but it was not possible to conduct subgroup or meta-regression analyses by gestational ages, types of infection, or types of infecting micro-organism. Covariates for whether studies used a predefined threshold or not, and whether studies used a standard threshold of between 5 mg/L and 10 mg/L, were not statistically significant.

Authors' conclusions

The serum CRP level at initial evaluation of an infant with suspected late-onset infection is unlikely to be considered sufficiently accurate to aid early diagnosis or select infants to undergo further investigation or treatment with antimicrobial therapy or other interventions.

PLAIN LANGUAGE SUMMARY

C-reaction protein for diagnosing infection in newborn infants

Review question

We reviewed studies that assessed whether measuring the blood level of C-reactive protein (CRP) helped to make an earlier diagnosis of serious infections in newborn infants.

Background

Newborn infants, especially sick or preterm infants, are at risk of developing severe infections (such as bloodstream infections) during their stay on neonatal units. Infections are often difficult to diagnose early with certainty, and quick tests such as measuring the blood level of a protein that responds to infection (called CRP) are sometimes used to help make an earlier diagnosis. We aimed to assess the evidence for the accuracy of this test.

Study characteristics

We found 20 studies that assessed the accuracy of measuring the blood level of CRP to diagnose infections in newborn infants. These studies were similar enough to justify a combined analysis of their findings.

Key results

The combined analysis indicated that a positive CRP test correctly identified infants with infection about six times out of 10.

Conclusion

Measuring the blood level of CRP is not sufficiently accurate to help early diagnosis of infection in newborn infants.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Question: Should serum CRP levels be used to diagnose late-onset infection in newborn infants?

Study design: prospective or retrospective cohorts and cross-sectional studies. We excluded case reports and studies of case-control design

Sensitivity at median specificity: 0.62 (95% CI 0.50 to 0.73)
Median specificity: 0.74

№ **of studies (infants):** 20 (1615)
№ **of true positives:** 617
№ **of true negatives:** 998

Outcome	Factors that may decrease certainty of evidence					Effect per 1000 infants tested			Test accuracy quality of evidence
	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pretest probability of 20%	Pretest probability of 40%	Pretest probability of 60%	
True positives (infants with late-onset infection)	Not serious	Not serious	Serious	Not serious	None	124 (100 to 146)	248 (200 to 292)	372 (300 to 438)	⊕⊕⊕◯ **Moderate**
False negatives (infants incorrectly classified as not having late-onset infection)						76 (54 to 100)	152 (108 to 200)	228 (162 to 300)	-
True negatives (infants without late-onset infection)	Not serious	Not serious	Serious	Not serious	None	592 (- to -)	444 (- to -)	296 (- to -)	⊕⊕⊕◯ **Moderate**

False positives (infants incorrectly classified as having late-onset infection)	208 (- to -)	156 (- to -)	104 (- to -)	-

CI: confidence interval.

BACKGROUND

Target condition being diagnosed

Late-onset infection in newborn infants

Late-onset infection (occurring more than 72 hours after birth) is the most common serious complication associated with intensive care for newborn infants (McGuire 2004). The incidence of late-onset infection is inversely related to gestational age at birth and has increased as survival rates for preterm infants have improved (van den Hoogen 2010). About 20% of very preterm infants experience an episode of late-onset infection reflecting their level and duration of exposure to invasive procedures and intensive care (Vergnano 2011; Berrington 2012; Oeser 2014). Central line-associated bloodstream infection (CLABSI) is a major subtype of late-onset infection that is associated with the use of central vascular catheters (CVC) to deliver drugs, fluids, or parenteral nutrition for newborn infants (Benjamin 2001; Butler-O'Hara 2012; Shalabi 2015). Other putative risk factors include receipt of broad-spectrum antibiotics and of histamine type 2-receptor antagonists (Shane 2014; Tsai 2014a). However, interunit variation in the incidence of late-onset infection is not fully explained by case-mix and may relate to uptake and use of care or infection control practices (Wong 2012).

Microbiology of late-onset infection

The common causes of late-onset infections in sick or preterm newborn infants are coagulase-negative staphylococci, other Gram-positive cocci (Staphylococcus aureus (S aureus), enterococci), Gram-negative bacilli (mainly enteric bacilli), and fungi (predominantly Candida species) (Stoll 2003; Zaidi 2005; Gordon 2006; Muller-Pebody 2011; Hornik 2012; Shane 2013). Preterm infants, particularly very preterm infants, with late-onset infection have a higher risk of mortality and a range of important morbidities including bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, and need for intensive care and prolonged hospitalisation than comparable infants without infection (Shah 2014). Late-onset infection is associated with higher rates of adverse neurodevelopmental outcomes including visual, hearing, and cognitive impairment, and cerebral palsy (Stoll 2004; Bassler 2009).

Antimicrobial resistance

Delayed treatment of bacterial or fungal late-onset infections may increase the risk of morbidity and mortality in newborn infants. However, because clinical signs of infection in neonates can be non-specific, empirical treatment of all infants with suspected infection will result in the administration of unnecessary courses of antibiotics (Dong 2015). Such widespread use, particularly of broad-spectrum antibiotics, is associated with accelerated selective pressure and the emergence of drug resistance through mechanisms such as extended-spectrum B-lactamase production (de Man 2000; Muller-Pebody 2011; Tsai 2014b).

Index test(s)

Diagnosing late-onset infection in preterm infants

Given the difficulty in establishing an early diagnosis based on clinical features alone, and the high level of associated morbidity and mortality, several 'biomarkers' of infection have been proposed and adopted as tests to determine whether late-onset infection is more or less likely in newborn infants in whom it is suspected (Shane 2013; Gilfillan 2017). The most commonly used and established of these is the serum level of C-reactive protein (CRP). CRP is an acute-phase reactant synthesised by hepatocytes in response to inflammatory cytokines, particularly interleukin (IL)-6, generated by white blood cells reacting to microbial pyrogens such as lipopolysaccharide (Steel 1994). The major physiological role of serum CRP is to bind to microbial polysaccharides and immune complexes and activate the classical complement cascade (Volanakis 2001).

CRP levels can be measured in laboratories within about one hour using a very small volume of serum (20 µL). Serum levels are usually very low (undetectable at the lower limits of sensitivity of standard laboratory analysis, typically 5 mg/L to 10 mg/L), but rise to detectable concentrations following an infectious or inflammatory stimulus over 12 to 24 hours. In infants exposed to infectious inflammatory stimuli, serum CRP levels may rise by more than 100-fold, declining with a half-life of about 18 to 24 hours when the stimulus ceases (Ehl 1999). Many non-infectious inflammatory stimuli including chemical or physical irritation such as extravasation of hypertonic or irritant solutions may also cause serum CRP levels to rise in newborn infants (Hofer 2013).

Clinical pathway

The use of biomarkers in general, and CRP in particular, as adjunctive diagnostic tests in neonatal care settings occurs within three broad clinical contexts.

- *Diagnosing infection*: the serum CRP level is used to determine whether late-onset infection is less or more likely in infants in whom there is a clinical suspicion based on signs such as unstable temperature, respiratory instability (apnoea, desaturation), enteral feed intolerance, or general concern that the infant appears unwell.
- *Screening for infection*: serum CRP levels are monitored at intervals to detect infants in whom an infection may be

developing before being clinically suspected. In clinical practice, this approach is usually targeted to infants considered to be at an elevated risk of acquiring an infection because of specific risk factors such as the presence of a CVC.

• *Monitoring response to treatment*: serial measurement of serum CRP is also used to track the course of late-onset infection and assess the response to antimicrobial treatment, including acting as indicator for stopping antibiotics when a previously elevated serum CRP level has returned to 'normal' (Ehl 1997).

This review addressed the diagnostic accuracy of the serum CRP level **in the first scenario (i.e. diagnosing infection) only**. As detection of an elevated serum CRP level (index test) would be used to trigger application of the reference test in the other scenarios, it is not possible to measure diagnostic accuracy.

Prior test(s)

Serum CRP is typically measured at the initial assessment of an infant with suspected late-onset infection, usually alongside other tests including laboratory culture of a blood sample to culture micro-organisms ('blood culture').

Role of index test(s)

Because the microbiological culture of a potentially pathogenic organism (the reference standard) from a blood sample takes about 24 to 48 hours to complete, the purpose of measuring the serum CRP level is to help make a more immediate assessment of the overall likelihood that an infant is truly infected. In current clinical practice, the main aims are to help decide (Pammi 2015):

• whether the likelihood of infection justifies further invasive tests (such as examination of the cerebrospinal fluid (CSF) to diagnose or exclude meningitis);

• whether it is appropriate to administer antibiotics or other antimicrobial therapy immediately;

• whether other interventions such as removing a CVC that is potentially a nidus for infection are justified.

Alternative test(s)

Several other biomarkers of infection or inflammation have been evaluated in neonatal care settings and different areas of clinical practice. These include haematological indices (peripheral total white blood cell count, neutrophil count, and immature-to-total neutrophil ratio (I/T-ratio); serum procalcitonin; the acute phase protein serum amyloid A; several proinflammatory cytokines such as IL-6, IL-8, and tumour necrosis factor (TNF); and other markers of immune activation (Fowlie 1998; Malik 2003). These alternative biomarkers are generally more expensive to measure than CRP and are not as well established in routine practice (Hedegaard 2015). More recent developments include biomarkers based on detecting microbial DNA ('molecular biomarkers') and computer-

based integration of physiological markers such as heart rate variability to detect infants with a developing infection (Dong 2015).

Rationale

Serum CRP level may be a useful adjunctive diagnostic biomarker for late-onset infection in newborn infants if it has acceptable levels of accuracy. Currently, in the absence of robust evidence to inform guideline or protocol development, clinical practice varies greatly with regard to the role of serum CRP in diagnostic algorithms for late-onset infection (Dong 2015; Pammi 2015). Most studies examining the accuracy of CRP and other biomarkers of late-onset infection have been conducted in single centres and, therefore, are limited by the small sample size. A systematic review to identify, quality-appraise, and synthesise the data in meta-analyses could help clarify the evidence-base to inform policy and practice, and future research.

O B J E C T I V E S

To determine the diagnostic accuracy of serum CRP measurement in detecting late-onset infection in newborn infants.

Secondary objectives

To investigate heterogeneity of test accuracy in the included studies (see: Investigations of heterogeneity).
Possible sources of heterogeneity include between-study variation in the demographic characteristics of study participants (e.g. term versus preterm infants), use of different cut-off values of serum CRP levels used to define a positive test (e.g. 5 mg/L to 10 mg/L versus higher values), and subtypes of late-onset infection (e.g. CLABSI versus non-CLABSI).

M E T H O D S

Criteria for considering studies for this review

Types of studies

Cohort and cross-sectional studies evaluating the diagnostic accuracy of serum CRP for the detection of late-onset infection (more than 72 hours after birth) in newborn infants were eligible for inclusion. Studies using CRP along with another biomarker were eligible provided data on the diagnostic performance of CRP alone could be extracted. We have not included case-control studies as

this design is unlikely to allow valid assessment of diagnostic test accuracy in this clinical context.

For inclusion in meta-analyses, a study of diagnostic accuracy needed to provide sufficient data to construct the '2×2' diagnostic table (true positive, false positive, true negative, and false negative) showing the cross-classification of disease status (microbiologically confirmed infection) and test outcome (serum CRP level). If study reports did not provide data sufficient to construct the diagnostic table, we contacted the corresponding authors to seek the missing data, where appropriate and practicable.

Studies investigating early-onset infection (diagnosed before 72 hours postnatally) were not eligible. Studies investigating both early- and late-onset infection were eligible provided separate data could be extracted for late-onset infection. If not reported, we contacted the corresponding author to request unpublished data on late-onset infection if the article indicated that these data may have been collected.

Participants

Hospitalised newborn infants aged more than 72 hours until the first discharge home after birth were eligible. We excluded studies where the participants were young infants cared for at home or in another community setting who then presented to a primary or secondary healthcare facility with possible infection.

We considered infants across all gestational ages and planned to conduct subgroup analyses by gestational age: term (greater than 37 weeks' gestation), preterm (less than 37 weeks' gestation), and very preterm (less than 32 weeks' gestation).

Index tests

Serum CRP level: we accepted the threshold for the index test as defined by individual studies (expected typically to be in the range 5 mg/L to 10 mg/L).

Target conditions

Microbiologically confirmed late-onset infection (more than 72 hours after birth) including bacteraemia, fungaemia, meningitis, osteomyelitis, septic arthritis, and peritonitis.

We excluded data on the diagnostic accuracy of CRP in infants with 'suspected' or 'probable' infection (also referred to as 'clinical sepsis'), that is, infection suspected because of clinical or laboratory features and findings but not confirmed by microbiological culture of pathogens. If studies reported data on infants with clinical sepsis as well as 'microbiologically confirmed' infection, we extracted the data according to microbiological culture status rather than according to the authors' definition of clinical sepsis. We planned to exclude studies of infants diagnosed with pneumonia based on clinical and radiological features even if supported by microbiological culture of bacteria or fungi from endotracheal aspirates. Although it may be argued that excluding suspected or probable

infection is inconsistent with normal clinical practices, the lack of a widely acceptable and reliable clinical definition makes it less valid to incorporate as an eligibility criterion for this review. We contacted the corresponding author to request unpublished data as necessary, where appropriate and practicable.

Reference standards

Infection diagnosed more than 72 hours after birth, confirmed by culture from a normally sterile site: CSF, blood (from peripheral sites, not from indwelling catheters), bone or joint, peritoneum, pleural space, or findings on autopsy examination consistent with microbial infection (microbiological confirmation or morphological findings consistent with infection). Because 'false-positive' results due to skin contaminants were possible, we excluded cases where infection was attributed to diphtheroids, micrococci, propionibacteria, or a mixed microbial flora (where data were available). We planned to examine specific infections with the following organisms, if data were available: coagulase-negative staphylococci, other bacteria (Gram-negative bacilli, *S aureus,* enterococci), and fungi.

We did not include urinary tract infections because these are uncommon in newborn infants unless associated with bacteraemia and because diagnosis requires urine obtained by sterile urethral catheterisation or suprapubic bladder tap which are sampling methods employed rarely in current practice.

We excluded any studies in which the reference standard incorporated the index test, that is, 'infection' was defined as a positive microbiological culture *and* raised serum CRP level.

Search methods for identification of studies

We used the standard Cochrane Neonatal search strategy adapted for studies of diagnostic test accuracy (Beynon 2013).

Electronic searches

We searched MEDLINE, Embase, and Science Citation Index: see Appendix 1. The initial search was carried out in May 2015 and updated in September 2017.

Searching other resources

We examined the reference lists of all studies identified as potentially relevant.

We searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2017), the European Society for Pediatric Research (1995 to 2017), the UK Royal College of Paediatrics and Child Health (2000 to 2017), and the Perinatal Society of Australia and New Zealand (2000 to 2017). Studies reported only as abstracts were eligible if sufficient information was available from the report or from contact with the authors to fulfil the inclusion criteria.

Data collection and analysis

Two review authors screened all titles and abstracts identified by our search strategy for relevance to the inclusion criteria of this review as detailed in Criteria for considering studies for this review. All references were managed in an EndNote library and then exported to Covidence for study selection.

Selection of studies

We retrieved the full text of all identified articles that were deemed relevant to the review and evaluated them against our inclusion eligibility. Two review authors independently assessed studies for eligibility for inclusion. We resolved disagreements by discussion with a third review author.

Data extraction and management

One review author extracted the following data.

- Author and year of publication.
- Study design including sample size, type of recruitment (prospective or retrospective).
- Study population characteristics and the clinical context in which the test was evaluated.
- Definition of reference standard.
- CRP threshold used.
- Information regarding quality assessment items of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Assessment of methodological quality).
- Data to enable derivation of 2×2 tables of the number of true positives, false positives, false negatives, and true negatives.

One review author extracted data and a second review author checked them. We resolved any discrepancies by discussion and arbitration by a third review author if required.

When contacting corresponding authors to request additional data or information, we took a pragmatic approach to manage resources sensibly. We attempted to contact authors of reports published since 2005 by email only. If there was no contact email address after a reasonable amount of online research, we did not attempt to contact authors by other means such as telephone or post. If our email remained unanswered after one week, we sent one follow-up email. If data could not be obtained after this, a team decision was made to exclude the study. Authors of studies published before 2005 were only contacted if an email address was provided as part of the publication. We reported all excluded studies, with reasons for exclusion given (Characteristics of excluded studies table).

Assessment of methodological quality

We assessed methodological quality of each included study following guidance from the Cochrane Screening and Diagnostic Test Methods Group, which is adapted from the QUADAS-2 tool (Whiting 2011: see Table 1). The four domains assessed for risk of bias were patient selection, index test, reference standard, and flow and timing. Applicability concerns were assessed in the first three domains. In each domain, we answered the signalling questions with 'Yes', 'No', or 'Unclear' and for each domain judged the risk of bias as 'Low', 'High', or 'Unclear' risk.

We excluded studies at high risk of incorporation bias, that is, those studies in which a raised CRP level was part of the diagnostic criteria for infection.

One review author assessed study quality, which a second review author checked. We resolved any disagreements by discussion, with referral to a third review author as necessary.

We summarised overall quality of evidence using GRADE methodology recommended for diagnostic tests (Singh 2012).

Statistical analysis and data synthesis

We constructed 2×2 diagnostic tables for all studies based on dichotomous data from the reference standard (infected or not infected) and index test (the cut-off level for serum CRP for a positive result (suggestive or diagnostic of late-onset infection) as defined by each study). Only the test taken at the same time as the reference standard was used. We created forest plots with 95% confidence intervals (CI) for sensitivity and specificity for each study using Review Manager 5 (Review Manager 2014).

Since reported threshold levels for a positive test differed across studies, we fitted the data in a hierarchical summary receiver operating characteristic (HSROC) model that assumed accuracy and thresholds vary between studies (Rutter 2001). Analyses were conducted in SAS using the NLMIXED procedure (version 9.4, SAS Institute, Cary, NC, USA).

Investigations of heterogeneity

We assessed heterogeneity by examining forest plots of sensitivity and specificity across studies for variability of study estimates and overlap of the 95% CI.

Threshold (cut-off) values

We examined the effect of using different threshold (cut-off) levels of serum CRP to define a positive index test in studies. We expected most studies to use a value between 5 mg/L and 10 mg/L to define a positive test result but that some may have used higher or lower levels. We investigated the effect of studies reporting different thresholds using meta-regression analyses (with a categorical covariate: standard threshold 5 mg/L to 10 mg/L versus any other threshold). We assessed the effect of studies reporting a predefined threshold (categorical covariate: reporting predefined threshold versus not reporting predefined threshold).

Other possible sources of heterogeneity

We planned to examine the effect of population subgroups in meta-regression analyses (including categories as additional co-variates). If there were sufficient data, we hoped to provide summary estimates for each subgroup and assess the statistical significance of differences between these subgroups: gestational age at birth (term, preterm, and very preterm infants), pathogens or putative pathogens (coagulase-negative staphylococci, Gram-negative bacilli, *S aureus,* enterococci, fungi), and subtypes of late-onset infection (CLABSI versus non-CLABSI).

Sensitivity analyses

If sufficient data were available, we planned to explore whether study methodological quality affected the results by removing studies considered at higher risk of bias across key domains (selection, verification).

Post hoc, we removed one study using a very high threshold (considered an outlier) in sensitivity analyses to investigate the impact on estimates.
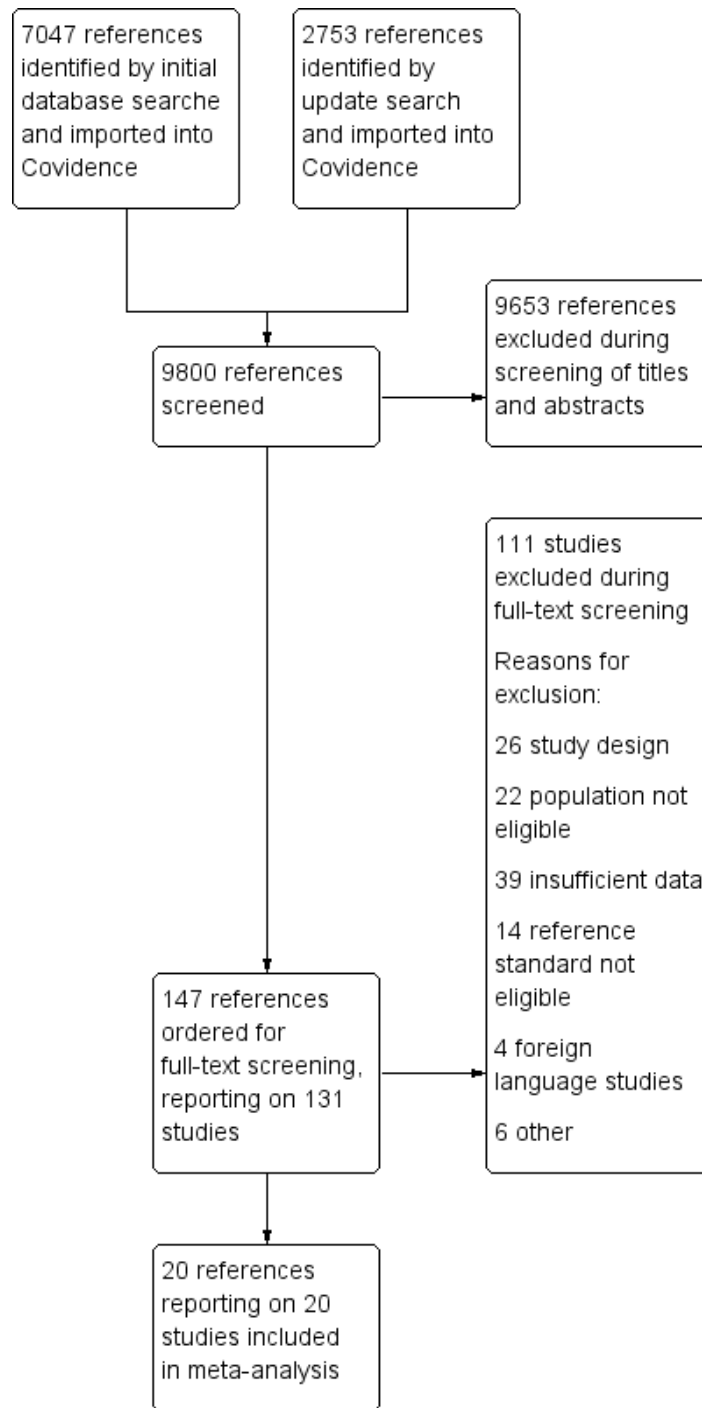
Assessment of reporting bias

We assessed publication bias using funnel plots (the natural logarithm of the diagnostic odds ratio by 1/effective sample size) and Deeks' test in Stata 13 using the midas commands (Deeks 2005).

R E S U L T S

Results of the search

The flow of studies through the review process is illustrated in Figure 1.

Figure 1. Study flow diagram.

We identified 9800 records in our electronic database searches up to September 2017. We excluded 9653 of these on screening the title and abstract. We screened the full text of 147 reports of 131 studies and excluded 111 of these (see Characteristics of excluded studies table).

We included 20 studies reported in 20 papers (total number of studied infants: 1615). Studies were published between 1990 and 2015 with most (15/20) published since 2000. Two studies were cohorts assembled retrospectively (Doellner 1998; Fendler 2008); the remaining 18 studies included prospectively observed cohorts. Most studies (16/20) were carried out in high-income countries in Europe (Bohnhorst 2012; Decembrino 2015; Doellner 1998; Fendler 2008; Jacquot 2009; Kipfmueller 2015; Kordek 2014; Verboon-Maciolek 2006), Asia (Chan 1997; Ng 1997; Choo 2012), North America (Benitz 1998; Pynn 2015), South America (Bustos 2012), or Australasia (Seibert 1990; Sherwin 2008). Four studies were conducted in low- and middle-income countries (Aminullah 2001; Boo 2008; Kumar 2010; Hisamuddin 2015). All but one of the studies were single-centre investigations. Benitz 1998 was a three-centre study.

Sample sizes ranged from 11 to 184 infants. Four studies had a sample size of 25 or fewer (Doellner 1998; Aminullah 2001; Choo 2012; Kipfmueller 2015). Nine studies included between 40 and 100 infants (Verboon-Maciolek 2006; Boo 2008; Fendler 2008; Sherwin 2008; Jacquot 2009; Bustos 2012; Kordek 2014; Decembrino 2015; Hisamuddin 2015). Seven studies had sample sizes of 100 or more infants (Seibert 1990; Chan 1997; Ng 1997; Benitz 1998; Kumar 2010; Bohnhorst 2012; Pynn 2015).

In 16 studies, participants were preterm (or very low birth weight) infants predominantly. Four studies did not report the gestational age range of the included infants but it is likely that most participants were preterm or low birth weight (Aminullah 2001; Kumar 2010; Decembrino 2015; Hisamuddin 2015).

Twelve studies only investigated infants with late-onset infection (Seibert 1990; Ng 1997; Doellner 1998; Aminullah 2001; Verboon-Maciolek 2006; Fendler 2008; Sherwin 2008; Jacquot 2009; Bohnhorst 2012; Kordek 2014; Kipfmueller 2015; Pynn 2015). The remaining studies included infants with early-onset and late-onset infection. We were able to extract data on infants with late-onset infection (or have these data provided by the primary investigators).

Where reported, most studies (9/12) defined late-onset as occurring more than 72 hours after birth, but across studies the definition ranged from 48 hours to six days after birth. We included these studies as this is consistent with the range of definitions that exist in clinical practice and research (Dong 2015).

Fourteen studies used a prespecified threshold of serum CRP level to determine the threshold level (cut-off) for a positive test. These thresholds ranged from 1 mg/L to 12 mg/L with most studies (12/ 14) using a cut-off level between 5 mg/L and 10 mg/L. None of the studies reported sensitivity and specificity at multiple thresholds. Six studies determined the CRP threshold level retrospectively (by modelling the area under the receiver operating curve). These studies determined the following thresholds:

- Fendler 2008: 2.2 mg/L;
- Decembrino 2015: 6 mg/L;
- Benitz 1998: 10 mg/L;
- Verboon-Maciolek 2006: 14 mg/L;
- Sherwin 2008: 18 mg/L;
- Bustos 2012: 111 mg/L.

Methodological quality of included studies

Participant selection

1. Risk of bias

The included studies were at low risk of participant selection bias. While the details of the recruitment process were not always reported, we judged that, on the whole, studies avoided inappropriate exclusions. We specified in our protocol that case-control studies would be excluded from the review as this design would not have been appropriate for the review question.

2. Concerns regarding applicability

Based on the information reported, we judged that the participants and the setting of the included studies were applicable to our review question.

Index test

1. Risk of bias

Overall, the risk that the conduct or interpretation of the index test (serum CRP level) could have introduced bias was low. The serum CRP level was measured in infants presenting with clinical features of late-onset infection before the results of the reference standard were known. Most (14/20) studies prespecified threshold of CRP level consistent with current clinical practice (1 mg/L to 12 mg/L). The other studies determined the optimal threshold post hoc but, with the exception of one outlier (Bustos 2012), this threshold was similar to the range used in studies that prespecified the threshold (2 mg/L to 18 mg/L).

Two studies were at unclear risk that the conduct or interpretation of the index test (serum CRP level) could have introduced bias as

we were unable to determine whether or not the index test results were interpreted without knowledge of the reference standard (Benitz 1998; Boo 2008). In one study, the risk of bias introduced by the conduct of the index test was high because the outcome of the reference standard (blood culture) was known before the interpretation of the CRP level (Fendler 2008).

2. Concerns regarding applicability

Across all studies, the index test, its conduct, and its interpretation were applicable to our review question. While there was expected variation in clinical practice between studies, we did not deem this to be of a magnitude that would cause concerns regarding applicability.

Reference standard

1. Risk of bias

As per our inclusion criteria, all studies used microbiological culture of a potential pathogen from blood or a normally sterile body fluid as the reference standard for late-onset infection. Twelve studies reported some description of the infecting microorganisms (Chan 1997; Ng 1997; Benitz 1998; Aminullah 2001; Verboon-Maciolek 2006; Boo 2008; Fendler 2008; Sherwin 2008; Jacquot 2009; Bohnhorst 2012; Bustos 2012; Pynn 2015). These included coagulase-negative staphylococci (typically representing about 50% of the total cases), *S aureus*, enterococci, *Streptococcus agalacticae*, Gram-negative bacillia, and fungi (typically *Candida* spp.).

Four studies included a clinical and radiological diagnosis of pneumonia within the case definition for the reference standard (Ng 1997; Benitz 1998; Doellner 1998; Sherwin 2008). Two of these studies reported no cases of pneumonia (Ng 1997; Doellner 1998). The other studies reported one (Benitz 1998) and two (Sherwin 2008) cases of pneumonia and it was unclear whether these infants had a concordant positive microbiological culture from blood or a normally sterile body fluid. We did not consider this deviation

from the reference standard definition as a sufficient source of bias to justify excluding the studies. In one study, "urinary sepsis" was eligible for inclusion in case definition, but no episodes of urinary tract infection were reported (Kumar 2010).

We excluded all studies in which the index test (CRP level) was part of the reference standard, that is, those in which a raised CRP level and a positive blood culture was needed for a formal diagnosis of infection. As such, across the included studies, there was a low risk that the reference standard, its conduct, or its interpretation could have introduced bias.

2. Concerns regarding applicability

In all studies, the condition under investigation was infection in newborn infants. Across the included studies, there was some variation with regards to the babies' ages at the time of first clinical suspicion of sepsis and their gestational age. However, through contact with authors, we were able to obtain data for only those babies with late-onset infection, even for those studies that also included younger infants with early-onset infection. We were confident that the target condition investigated in the included studies matched our review question.

Flow and timing

1. Risk of bias

All studies used blood samples taken at the initial investigation of each infant to determine the serum CRP level and for the blood culture. Due to the nature of the reference standard, the blood culture results followed 24 to 48 hours after the index test, depending on laboratory procedure. Across all studies, there was a low risk that the patient flow might have introduced bias.

Overall risk of bias

The methodological quality of the included studies was good and the risk of bias minimal (Figure 2).

Figure 2.   Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

Findings

See Figure 3 for the summary receiver operating curve and Figure 4 for forest plots.

Figure 3.   Summary receiver operating characteristic (SROC) plot of C-reactive protein for neonatal infection. Study estimates of sensitivity and specificity are shown with the SROC curve.
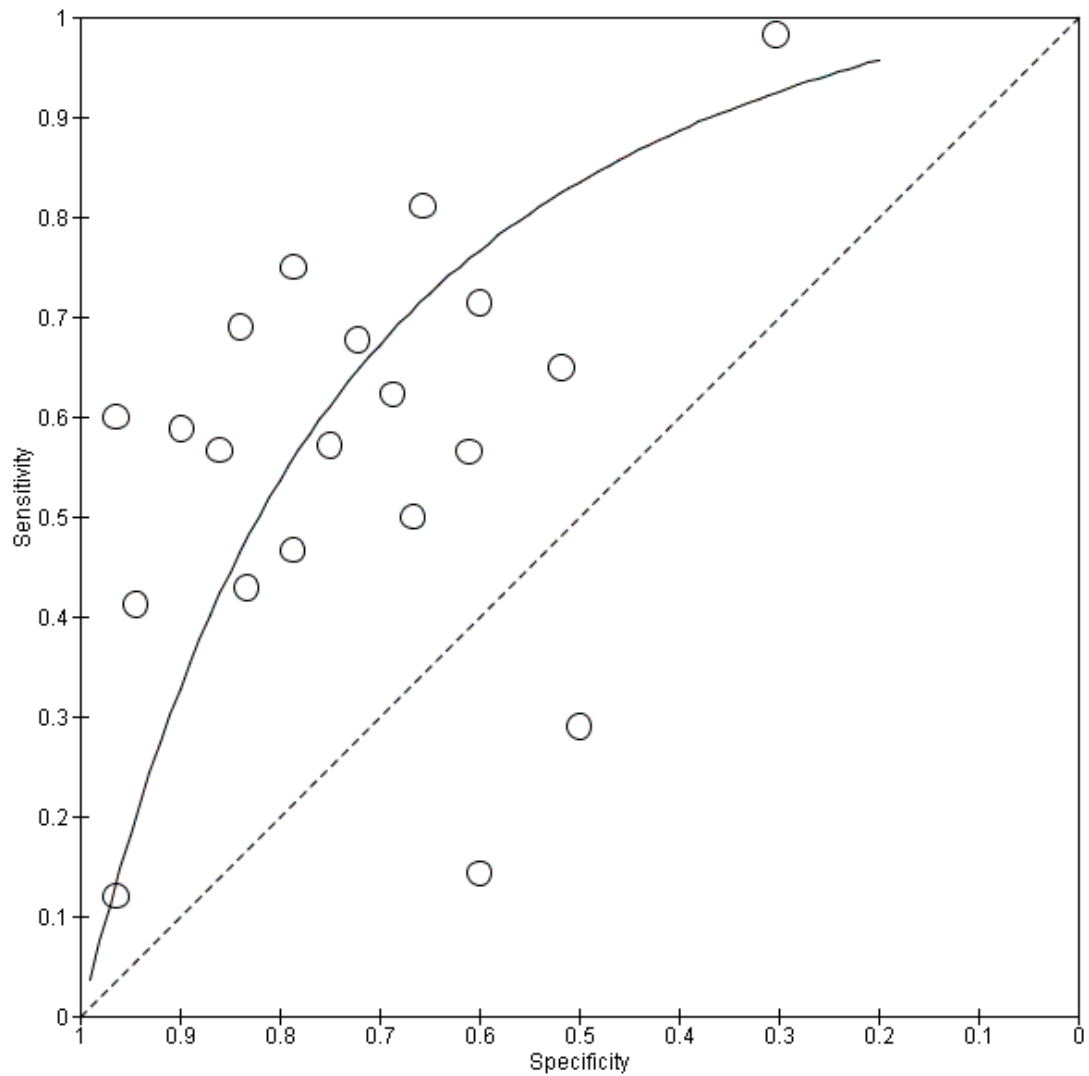
Figure 4.   Forest plot: sensitivity and specificity of C-reactive protein for diagnosing late-onset infection.

Study	TP	FP	FN	TN	predefined threshold	standard threshold (5-10mg/L)	Sensitivity (95% CI)	Specificity (95% CI)
Aminullah 2001	4	1	3	3	yes	no	0.57 [0.18, 0.90]	0.75 [0.19, 0.99]
Benitz 1998	33	41	20	90	no	yes	0.62 [0.48, 0.75]	0.69 [0.60, 0.77]
Bohnhorst 2012	40	18	18	94	yes	yes	0.69 [0.55, 0.80]	0.84 [0.76, 0.90]
Boo 2008	10	7	7	62	yes	no	0.59 [0.33, 0.82]	0.90 [0.80, 0.96]
Bustos 2012	3	1	22	27	no	no	0.12 [0.03, 0.31]	0.96 [0.82, 1.00]
Chan 1997	14	26	16	96	yes	yes	0.47 [0.28, 0.66]	0.79 [0.70, 0.86]
Choo 2012	1	2	6	3	yes	yes	0.14 [0.00, 0.58]	0.60 [0.15, 0.95]
Decembrino 2015	4	11	4	22	no	yes	0.50 [0.16, 0.84]	0.67 [0.48, 0.82]
Doellner 1998	5	6	2	9	yes	yes	0.71 [0.29, 0.96]	0.60 [0.32, 0.84]
Fendler 2008	48	3	16	11	no	no	0.75 [0.63, 0.85]	0.79 [0.49, 0.95]
Hisamuddin 2015	11	9	27	9	yes	yes	0.29 [0.15, 0.46]	0.50 [0.26, 0.74]
Jacquot 2009	17	6	13	37	yes	yes	0.57 [0.37, 0.75]	0.86 [0.72, 0.95]
Kipfmueller 2015	3	3	4	15	yes	yes	0.43 [0.10, 0.82]	0.83 [0.59, 0.96]
Kordek 2014	23	5	11	13	yes	yes	0.68 [0.49, 0.83]	0.72 [0.47, 0.90]
Kumar 2010	55	60	1	26	yes	yes	0.98 [0.90, 1.00]	0.30 [0.21, 0.41]
Ng 1997	27	2	18	54	yes	yes	0.60 [0.44, 0.74]	0.96 [0.88, 1.00]
Pynn 2015	30	35	7	67	yes	yes	0.81 [0.65, 0.92]	0.66 [0.56, 0.75]
Seibert 1990	13	30	10	47	yes	yes	0.57 [0.34, 0.77]	0.61 [0.49, 0.72]
Sherwin 2008	14	1	20	17	no	no	0.41 [0.25, 0.59]	0.94 [0.73, 1.00]
Verboon-Maciolek 2006	24	14	13	15	no	no	0.65 [0.47, 0.80]	0.52 [0.33, 0.71]

We calculated estimates of sensitivity at fixed values of specificity (median, lower and upper quartiles reported in the included studies) on the SROC curve. At median reported specificity (0.74), sensitivity was 0.62 (95% CI 0.50 to 0.73); at the lower quartile reported specificity (0.61), sensitivity was 0.76 (95% CI 0.65 to 0.84); at the upper quartile reported specificity (0.85), sensitivity was 0.44 (95% CI 0.32 to 0.57). GRADE quality of evidence was moderate, downgraded from high for inconsistency (Summary of findings).

We used these data for sensitivity (0.62) and median reported specificity (0.74) to estimate post-test probabilities after a 'positive' or 'negative' CRP test for a range of pretest probabilities in infants being evaluated for possible late-onset infection and receiving a CRP test (Table 2).
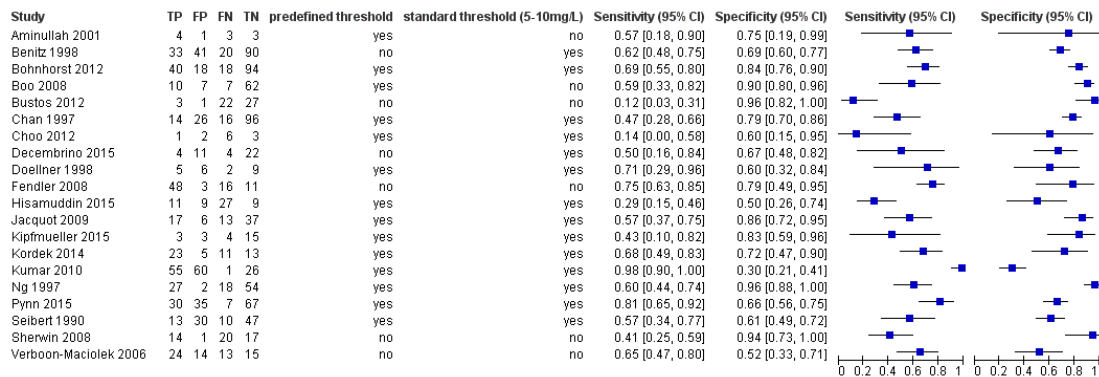
The prevalence of late-onset infection in the included studies ranged from 20% to 82% (median 40%, interquartile range 27% to 61%). We applied the diagnostic test accuracy estimates for sensitivity (0.62) and median specificity (0.74) from our meta-analysis to a hypothetical cohort of 1000 neonates with a prevalence of infection of 20%, 40%, or 60%:

• 20%: on average, 76 cases of infection would be missed and 208 would be wrongly diagnosed with infection;
• 40%: 152 cases of infection would be missed and 156 wrongly diagnosed with infection;
• 60%: 228 cases would be missed and 104 wrongly diagnosed with infection.

Investigation of heterogeneity and sensitivity analyses

It was not possible to conduct any subgroup or meta-regression analyses by gestational age (most participants were preterm infants of a range of gestational ages; some studies included term infants, but subgroup data were not available), subtypes of late-onset infection (most studies did not report CLABSI or other subtypes of late-onset infection), or types of pathogen or putative pathogen

(studies included a range of pathogens, but subgroup data were generally not available).

Threshold values

We examined the effect of using different threshold (cut-off) levels of serum CRP to define a positive index test in studies. All but one of the studies used a serum CRP level threshold between 1 mg/L and 18 mg/L, whether predefined or determined post-hoc (see below), to define a positive test result. Most studies (13/20) used a threshold between 5 mg/L and 10 mg/L.

When covariates on thresholds above or below 5 mg/L to 10 mg/L were added, likelihood ratio tests found no statistically significant difference in goodness of fit for any of these models compared with those without covariates.

Reporting a predefined threshold versus not reporting a predefined threshold

Six studies did not report using a *predefined* threshold. Of these, four studies did not report a standard threshold. There were no statistically significant differences in goodness of fit between any of these models including a covariate for predefined threshold compared with models without covariates.

Sensitivity analyses

One study was an outlier and reported using a cut-off level of 111 mg/L (Bustos 2012). Removing the study had limited impact on effect estimates. At median specificity reported in the included studies (0.72), sensitivity was 0.65 (95% CI 0.53 to 0.75); at the lower quartile for specificity (0.60) sensitivity was 0.76 (95% CI 0.65 to 0.84); at the upper quartile for specificity (0.84) sensitivity was 0.48 (95% CI 0.36 to 0.60).

Publication bias

We assessed publication bias using a funnel plot and Deeks test (Deeks 2005). Visual assessment of the funnel plot did not identify important asymmetry and was not statistically significant (Figure 5).

Figure 5. Deeks' Funnel Plot Asymmetry Test.
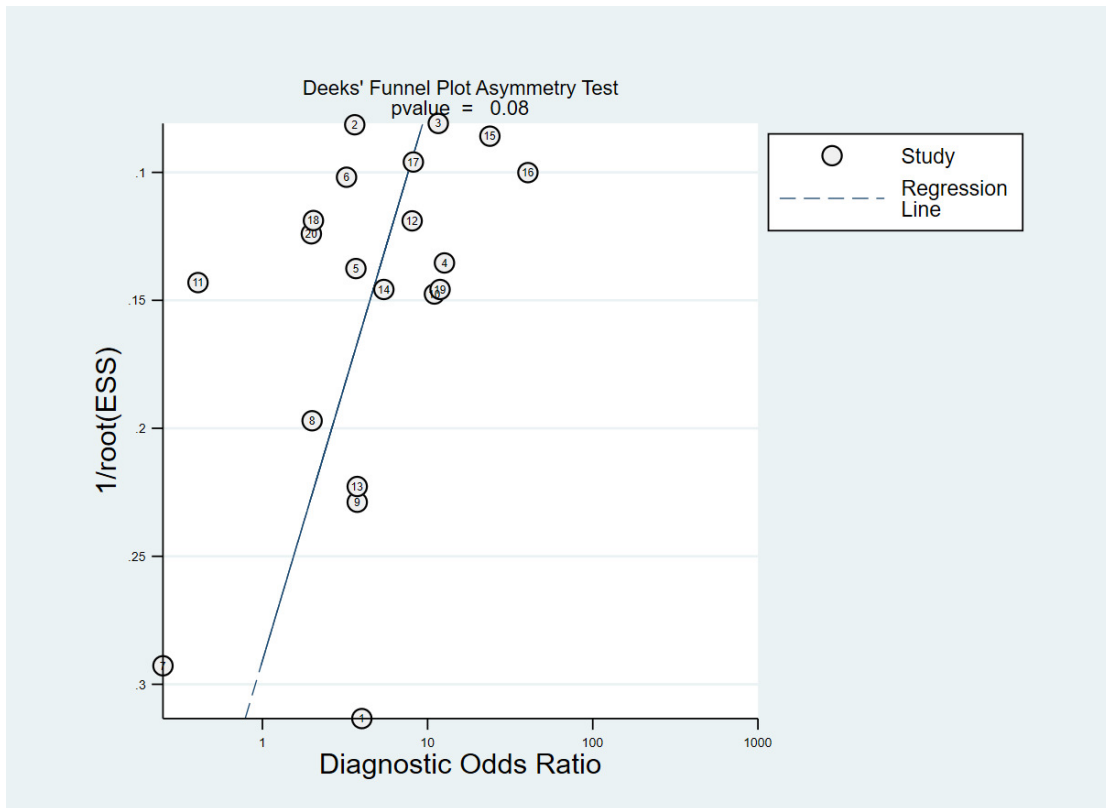
DISCUSSION

Summary of main results

We identified 20 cohort studies reporting the test accuracy of serum CRP for diagnosing late-onset infection in newborn infants. We calculated sensitivity (0.62, 95% CI 0.50 to 0.71) at the median specificity reported in our included studies (0.74). The analyses demonstrated inconsistency, that is, heterogeneity in the estimates of sensitivity and specificity. However, because of limited data availability, we were unable to explore whether the source of this variation was due to between-study differences in the population of infants (preterm versus term infants), the subtypes of infection (such as CLABSI), or the infecting micro-organisms.

Applying these data to a hypothetical cohort of 1000 newborn infants being evaluated for possible late-onset infection, we estimated that, if the prevalence of true infection was 40% (the median prevalence in the included studies), then, on average, 152 cases of infection would be missed (false negative) and 156 non-infected infants would be wrongly diagnosed (false positive). Therefore, serum CRP levels are unlikely to be considered sufficiently accurate as a triage test to select infants for further tests or inter-

ventions. These findings are similar to those in a systematic review and meta-analysis of the accuracy of elevated serum CRP levels for diagnosing serious infection in children (aged one month to 18 years) with febrile illness (Van den Bruel 2011).

Strengths and weaknesses of the review

Index test

The serum CRP threshold level for a 'positive' test used in the included studies was typically between 5 mg/L and 10 mg/L, consistent with current use in clinical practice. In most studies, the threshold was defined a priori, and the estimates of test performance based on this predefined cut-off for a positive test. Six studies did not predefine a threshold for positivity. The investigators performed post hoc analyses to determine the optimal cut-off for test performance, that is, the level of serum CRP that maximised the area under the receiver operator curve. Five of these studies calculated levels between 2.2 mg/L and 18 mg/L (with two studies finding optimal cut-offs between 5 mg/L and 10 mg/L). One study was an outlier with an optimal cut-off of 111 mg/L (confirmed with primary investigator). Neither the published study nor any unpublished data we received from the authors explained this unexpectedly high cut-off. However, in a sensitivity analysis without this study, there was not a substantial impact on estimates of sensitivity at median, upper, or lower quartiles of specificity reported in the included studies.

Reference standard

Our reference standard was microbiologically confirmed late-onset infection (more than 72 hours after birth) including bacteraemia, fungaemia, meningitis, osteomyelitis, septic arthritis, and peritonitis. The definition of late-onset infection used in the included studies varied. Some studies additionally included urinary tract infection or radiologically confirmed pneumonia within their case definition. These studies typically had none or very few participants with these diagnoses in the absence of bacteraemia, and we made a consensus decision to include their data rather than to exclude the full study.

Similarly, we accepted the primary study authors' definition of *late-onset* infection with regards to the infant's age when evaluated. Definitions ranged from 48 hours to six days after birth. While this is a deviation from our proposed definition of more than 72 hours after birth, we made a pragmatic consensus decision to include studies in order to reflect the available evidence as well as variation in the precise definition of 'late-onset' that exists in clinical practice (Haque 2005).

While variations in case-definition may have contributed to differences in the rates of confirmed infection in studied cohorts, it is likely that between-study differences in thresholds for investigating suspected infection are also important factors. We were unable to explore this possibility as we had insufficient data to determine how eligibility for inclusion criteria were applied in practice. Studies of diagnostic test accuracy in this context typically accept that variation in clinical decisions exists. However, though potentially contributing to heterogeneity in estimates of test performance, this pragmatic approach may make study findings more generally applicable.

There are concerns about how fully the reference standard defines all of those infants who truly have bloodstream infection. Microbiological cultures may not detect cases of bacteraemia or fungaemia if an insufficient volume of the infant's blood is incubated ('false negative'). Conversely, microbiological cultures may also generate 'false positive' results if blood sampling techniques allow entry of contaminating micro-organisms (typically coagulase-negative staphylococci from the infant's skin) (Oeser 2013). Insufficient data were available to undertake a subgroup analysis of infection with coagulase-negative staphylococci versus other bacteria to explore whether test accuracy was affected by the likelihood of identified micro-organisms representing true bloodstream infections. However, any such analysis may be confounded by between-species differences in the capacity of micro-organisms to trigger inflammatory cascades and generation of CRP.

Since these potential sources of verification bias may affect estimates of test performance, some studies required additional evidence of infection (usually clinical signs such as episodes of apnoea or temperature instability) for infants to meet the reference standard. However, some studies used a reference standard that incorporated the index test, that is, the serum CRP level was part of the definition of 'infection' in addition to microbiological culture of a pathogen from blood or a normally sterile body fluid. We excluded these studies because of their risk of bias; index test accuracy would be overestimated if the reference standard could only be met by infants with an elevated serum CRP level.

Search strategy

We undertook a comprehensive literature search for studies using a strategy designed by an information specialist. We did not use 'study type' filters as these increase the risk of relevant studies being missed due to inconsistent indexing in electronic databases (Wilczynski 2007). As with systematic reviews of interventional studies, publication bias may exist if studies which did not indicate good test performance were not submitted or accepted for publication (Leeflang 2014). Visual assessment of the funnel plot identified no important asymmetry and was not statistically significant (P = 0.1) and may indicate heterogeneity rather than publication bias.

We contacted study authors to obtain missing or unpublished data. While several authors provided additional information, many did not and this resulted in the exclusion of studies that might have been eligible for inclusion. We excluded 39 studies due to insufficient data. Similarly, we excluded four studies published in languages other than English as we did not have the resources to ob-

tain a reliable translation.

We employed review methods to reduce the risk of reviewer error and bias, including independent and duplicate study selection as well as checking of data extraction and risk of bias assessments. We assessed the risk of bias of included studies using the QUADAS-2 tool. Overall, studies were at low risk of bias but some use of the 'unclear' category was unavoidable due to missing detail in study reports. We excluded case-control studies as this design is unlikely to allow valid assessment of diagnostic test accuracy in this clinical context. As described above, we excluded studies at high risk of incorporation bias (serum CRP level part of the reference standard) as these studies overestimate test performance. The only 'high' risk of bias was identified in a retrospective study in which the result of the reference standard was known before the index test was performed (although the laboratory test result was not likely to have been affected by this knowledge).

Heterogeneity

Heterogeneity is a well-recognised feature in reviews of diagnostic test accuracy (Reitsma 2005). We observed between-study variation in the estimates of sensitivity and specificity in the forest plot (Figure 3). We have not determined the degree to which this heterogeneity exceeded that expected due to chance (Naaktgeboren 2016). Our study selection, data extraction, and assessment of study quality was limited by missing details on procedures and infant characteristics, such as gestational age, blood sampling techniques, and methods used to determine the serum CRP level. Because of these data limitations, we were unable to explore sources of heterogeneity by subgroup analyses by gestational age (term versus preterm infants), type of infection (CLABSI versus other infections), type of infecting organism (coagulase-negative staphylococci versus other pathogens), or type of laboratory technique used to measure serum CRP levels (high-sensitivity CRP versus standard methods).

Setting

Most included studies assessed the accuracy of elevated serum CRP levels for diagnosing late-onset infection in preterm infants in neonatal units in high- or middle-income countries. While these data are likely to be applicable to preterm infants cared for in modern neonatal units in high- and (some) middle-income countries, the review findings are less likely to be generalised to resource-limited settings in low- or middle-income countries where late-onset infection in newborn infants differs with regard to epidemiology, microbiology, pathogenesis, treatment options, and outcomes (Vergnano 2005; Zea-Vera 2015).

Applicability of findings to the review question

The review findings are specific to the accuracy of the serum CRP level in determining whether infection is less or more likely in infants in whom there is a clinical suspicion based on signs for other findings. The review does not address whether serial monitoring of the serum CRP level may be useful in screening well neonates for infection before it is suspected clinically, or in assessing the response to treatment, including helping to decide whether to stop antibiotics (Ehl 1997).

The timely diagnosis of late-onset infection based on clinical features and signs in newborn infants, particularly very preterm infants, remains challenging (Verstraete 2015). This analysis suggests that the serum CRP level as an adjunctive triage test for late-onset infection is not sufficiently accurate to determine which infants should receive treatment with antimicrobial agents or further tests. Applying the likelihood ratios derived from the meta-analyses to a hypothetical cohort of infants with suspected late-onset infection indicates that the test would generate a substantial number of both false-negative and false-positive results across a range of plausible prevalences (see Table 2 for post-test probabilities across range of pretest probabilities). For example, if the estimated pretest probability of infection for a given infant was 40% (the median for the included studies), then adding in the serum CRP level to the assessment would generate a post-test probability of 26% for a negative test (does not 'rule out' infection) and a post-test probability of 61% for a positive test (does not 'rule in' infection).

This suboptimal diagnostic performance of serum CRP is consistent with estimates of its accuracy in other contexts including for diagnosing serious infection in children (aged one month to 18 years) with febrile illness (Van den Bruel 2011). The possible explanations for this lack of diagnostic accuracy include the potential for false-positive results if CRP levels are elevated by triggers such as inflammation due to extravasation, cholestasis, or gastrointestinal pathology (Hofer 2013). Conversely, serum CRP levels may not rise, or rise only slowly, in some infected infants, particularly very preterm infants with coagulase-negative staphylococcal bacteraemia (false-negative results) (Lai 2015; Gilfillan 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The serum C-reactive protein (CRP) level at initial evaluation of an infant with suspected late-onset infection does not aid early diagnosis and is not likely to be considered a sufficiently accurate test to select infants who would undergo further investigation or be treated with antimicrobial therapy or other interventions.

Implications for research

Given the poor performance of serum CRP in this context, research efforts might focus on other serum biomarkers, such as

procalcitonin, that are elevated more quickly in response to infection or inflammation (Gilfillan 2017). Newer methods using molecular markers to identify pathogenic micro-organisms (such as real-time polymerase chain reaction or microarray techniques) are worthy of further research. These new techniques can provide results more quickly than standard microbiological culture (six to eight hours versus 24 to 36 hours), and evidence of their diagnostic accuracy is accumulating (Pammi 2017).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aminullah 2001

Study characteristics	
Patient sampling	Prospective investigation of newborn infants (birth weight > 1 kg) with suspected late-onset (> 72 hours) infection
Patient characteristics and setting	Newborn infants with birth weight > 1 kg (gestational age range not reported) in 1 neonatal unit in Indonesia
Index tests	Serum CRP level > 12 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Serum CRP measured at initial evaluation, reference standard determined over 24-48 hours subsequently
Comparative	
Notes	1999
Methodological quality			

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Aminullah 2001   *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Benitz 1998

Study characteristics	
Patient sampling	Prospective evaluation of all infants with suspected infection
Patient characteristics and setting	Newborn infants (mean gestational age at birth 32 weeks), 3 NICU in USA
Index tests	Serum CRP level > 10 mg/L
Target condition and reference standard(s)	Suspected or confirmed (microbiological culture of blood, CSF, or joint aspiration) late-onset infection ("without consideration of CRP levels")
Flow and timing	Serum CRP measured at initial evaluation, reference standard determined over 24-48 hours subsequently

Benitz 1998   *(Continued)*

Comparative	
Notes	The study included 'pneumonia' within the reference standard definition, but the investigators reported only 1 case of pneumonia in the entire study cohort

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Benitz 1998   *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Bohnhorst 2012

Study characteristics	
Patient sampling	Prospective evaluation of all neonates (term and preterm) with suspected infection after day 4
Patient characteristics and setting	Newborn infants (mean gestational age at birth 28 weeks), 1 NICU in Germany
Index tests	Serum CRP level > 10 mg/L (defined a priori)
Target condition and reference standard(s)	Unclear if index test (serum CRP level) informed decisions to perform more tests (e.g. CSF sampling and culture) or diagnosis of 'suspected' infection if blood was negative
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	Uncertain whether knowledge of initial serum CRP level affected care and investigation pathway

Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

Bohnhorst 2012   *(Continued)*

		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boo 2008

Study characteristics	
Patient sampling	Prospective evaluation of newborn infants with suspected infection; not stated if consecutive or randomly sampled cohort

Boo 2008   *(Continued)*

Patient characteristics and setting	Newborn infants (median gestation at birth 32 weeks) with suspected infection after day 2, NICU in Malaysia (1/18 infants evaluated on day 1 after birth)
Index tests	Serum CRP level > 1 mg/L (defined a priori)*
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	*The unit for measuring serum CRP level was 'mg/mL' in the report but this was confirmed by the investigators to be a typographical error and should have been mg/L

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			

Boo 2008   *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Bustos 2012

Study characteristics

Patient sampling	Prospective evaluation of newborn infants with suspected infection; not stated if consecutive or randomly sampled cohort
Patient characteristics and setting	Neonates with clinically suspected late-onset sepsis (gestational age 23-35 weeks) in 1 NICU in Chile
Index tests	Serum CRP level > 111 mg/L (calculated post hoc)
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	

Methodological quality

Bustos 2012 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Bustos 2012   *(Continued)*

Were all patients included in the analysis?	Yes		
		Low	

Chan 1997

Study characteristics

Patient sampling	Prospective sample of VLBW infants; unclear whether randomly selected
Patient characteristics and setting	VLBW infants (mean gestation at birth 28 weeks) with suspected infection after day 3, 1 NICU in Singapore
Index tests	Serum CRP > 10 mg/L (defined a priori)
Target condition and reference standard(s)	Infection confirmed by blood, CSF, or joint aspiration microbiological culture
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference stan-	Yes		

Chan 1997   *(Continued)*

dard?			
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Choo 2012

Study characteristics	
Patient sampling	Prospective cohort of neonates (unclear whether consecutive or random sample)
Patient characteristics and setting	Newborn infants (> 29 weeks' gestation at birth) in 1 NICU in Korea
Index tests	Serum CRP > 10 mg/L (defined a priori)
Target condition and reference standard(s)	Blood culture-confirmed infection

Choo 2012   *(Continued)*

Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	We thank the investigators for providing data for infants with suspected late-onset infection

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low

Choo 2012   *(Continued)*

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Decembrino 2015

Study characteristics	
Patient sampling	Prospective cohort of infants (consecutive enrolment)
Patient characteristics and setting	Infants in 1 NICU in Italy (gestational age or age at study entry not reported)
Index tests	Serum CRP level > 6 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	We thank Dr Decembrino for providing unpublished data.

Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Decembrino 2015   *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Doellner 1998

Study characteristics	
Patient sampling	Retrospective cohort study of newborn infants with suspected late-onset (> 48 hours) infection during first week after birth
Patient characteristics and setting	Newborn infants (mean gestation 38 weeks) admitted to 1 NICU in Norway
Index tests	Serum CRP level > 10 mg/L
Target condition and reference standard(s)	Neonatal infection confirmed by positive blood culture (some infants may have had an *additional* diagnosis of pneumonia*)
Flow and timing	Blood samples for CRP and blood culture were taken at the same time, blood culture result available over 24-48 hours
Comparative	
Notes	The study authors provided additional information for construction of 2×2 tables for infants with late-onset (> 48 hours) infection (*The authors were unable to clarify how many infants who met the reference standard had pneumonia.)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Doellner 1998   (*Continued*)

		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Fendler 2008

Study characteristics	
Patient sampling	Retrospective analysis of preterm neonates treated for suspected late-onset infection
Patient characteristics and setting	Preterm infants (median gestational age 29 weeks) with suspected late-onset infection who had all investigations (biomarkers and blood culture) assessed at the same time in 1 NICU in Poland
Index tests	Serum CRP level. Threshold of 2.2 mg/L determined retrospectively with Youden method on an ROC curve
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	

Fendler 2008 *(Continued)*

Notes	Data from 5 eligible infants not available for analysis. Further data provided by primary investigators.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	No		
If a threshold was used, was it pre-specified?	No		
		High	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Fendler 2008   (*Continued*)

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Hisamuddin 2015

Study characteristics			
Patient sampling	Prospective study of consecutive infants with suspected sepsis*		
Patient characteristics and setting	Infants (birth weight > 1500 g, gestational age > 32 weeks) with suspected sepsis in 1 NICU in Pakistan		
Index tests	Serum CRP level > 5 mg/L		
Target condition and reference standard(s)	Blood culture-confirmed infection		
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours		
Comparative			
Notes	* This study included both infants with early-onset sepsis (0-5 days after birth) and infants with late-onset sepsis (≥ 6 days after birth). The authors provided unpublished data on infants aged > 6 days We thank Dr Hisam for providing unpublished data.		

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Hisamuddin 2015   *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Jacquot 2009

Study characteristics	
Patient sampling	Prospective study of all newborn infants with clinical suspicion of late-onset infection
Patient characteristics and setting	Neonates (median gestation 28 weeks) evaluated for suspected infection, 1 NICU in France
Index tests	Serum CRP level > 10 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection*
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	*29/30 infants had blood culture confirmed infection, and 1 infant was classified as infection based on clinical features but without microbiological confirmation

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low

Jacquot 2009 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kipfmueller 2015

Study characteristics	
Patient sampling	Prospective study of VLBW infants with suspected late-onset infection
Patient characteristics and setting	VLBW infants (mean gestational age 28 weeks) in 1 NICU in Germany
Index tests	Serum CRP level > 10 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	Non-infected group consisted of infants with clinical suspicion of infection without a positive blood culture. 1 indicator of 'clinical suspicion' was detection of a serum CRP level > 10 mg/L

Kipfmueller 2015   *(Continued)*

Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Kipfmueller 2015 *(Continued)*

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kordek 2014

Study characteristics

Patient sampling	Prospective study of all newborn infants with clinical suspicion of late-onset infection
Patient characteristics and setting	Newborn infants (median gestational age 30 weeks) in 1 NICU in Poland
Index tests	Serum CRP level > 5 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test All tests			

Kordek 2014   (*Continued*)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kumar 2010

Study characteristics	
Patient sampling	Prospective investigation of newborn infants evaluated for possible late-onset infection
Patient characteristics and setting	Newborn infants (gestational age range not described) in 1 NICU in Kenya
Index tests	Serum CRP level > 5 mg/L

Target condition and reference standard(s)	Blood or CSF culture-confirmed infection (plus urine culture*)
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	*Urinary sepsis was eligible for inclusion in case definition, but no episodes of urine infection were reported

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge	Yes		

Kumar 2010 *(Continued)*

of the results of the index tests?			
		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Ng 1997

Study characteristics	
Patient sampling	Prospective study of all VLBW infants evaluated for possible late-onset infection
Patient characteristics and setting	VLBW infants (mean gestational age 30 weeks) in 1 NICU in Hong Kong
Index tests	Serum CRP level > 10 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection*
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	*Radiologically diagnosed pneumonia was eligible for inclusion in case definition, but no episodes of pneumonia were reported

Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Ng 1997 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

DOMAIN 2: Index Test All tests

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

DOMAIN 3: Reference Standard

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**

DOMAIN 4: Flow and Timing

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Pynn 2015

Study characteristics	
Patient sampling	Prospective observational study of neonates with suspected late-onset infection
Patient characteristics and setting	Newborn infants (median gestation 28 weeks) in 1 NICU in USA
Index tests	Serum CRP level > 10 mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection*
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	*Definition of coagulase-negative staphylococcal bacteraemia required 2 positive blood cultures

Methodological quality			
Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	Low
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	Low
DOMAIN 3: Reference Standard			

Pynn 2015 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Seibert 1990

Study characteristics	
Patient sampling	Prospective study of very preterm infants evaluated for suspected late-onset (> 72 hours) infection
Patient characteristics and setting	Very preterm newborn infants (23-31 weeks' gestation) in 1 NICU in Australia
Index tests	Serum CRP level > 10mg/L
Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	
Methodological quality	

Seibert 1990   *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
		Unclear	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Seibert 1990 *(Continued)*

Were all patients included in the analysis?	Yes		
		Low	

Sherwin 2008

Study characteristics

Patient sampling	Prospective cohort study of neonates with suspected late-onset infection
Patient characteristics and setting	Neonates (23-42 weeks' gestation) in 1 NICU in New Zealand
Index tests	Serum CRP level > 18 mg/L* determined retrospectively with reference to ROC curve
Target condition and reference standard(s)	Blood culture-confirmed infection**
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	*Presumed typographical error in table describing sensitivity and specificity; threshold reported in pg/mL, rather than mg/L **2/117 participating infants were diagnosed with pneumonia; unclear from the published data whether these infants had suspected late- or early-onset sepsis and whether or not they had a positive blood culture

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			

Sherwin 2008   *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Verboon-Maciolek 2006

Study characteristics	
Patient sampling	Prospective cohort study of infants with suspected late-onset infection
Patient characteristics and setting	Preterm neonates (median gestation 29 weeks) in 1 NICU in the Netherlands
Index tests	Serum CRP level > 14 mg/L determined retrospectively with reference to ROC curve

Verboon-Maciolek 2006   *(Continued)*

Target condition and reference standard(s)	Blood culture-confirmed infection
Flow and timing	Index test and reference standard samples were drawn simultaneously, blood culture result available over 24-48 hours
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Verboon-Maciolek 2006   *(Continued)*

		Low	Low
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

CRP: C-reactive protein; CSF: cerebrospinal fluid; NICU: neonatal intensive care unit; ROC: receiver operating characteristic; VLBW: very low birth weight.

Characteristics of excluded studies   *[ordered by study ID]*

Study	Reason for exclusion
Aboud 2010	Study design not eligible. Case-control study
Adhikari 1986	Insufficient data. Participants' ages unclear, unable to decide if late-onset or early-onset sepsis was investigated. Decided not to try and contact the authors due to age of study
Adib 2012	Insufficient data. Data for infants with late-onset sepsis (> 72 hours) were not reported separately. These data were requested from the authors but not provided
Adly 2014	Insufficient data. Published data was not sufficient to assess eligibility for inclusion. Additional data were requested from the authors but not provided
Ahmed 2005	Study design not eligible. Case-control study
Ahmed 2013	Insufficient data. Abstract only. Could not locate authors for full data
Ainbender 1982	Insufficient data. Decided not to contact the authors due to age of study
Al-Zwaini 2009	Insufficient data
Alexejew 1990	Study design not eligible. Review article

Aliefendioglu 2014	Study design not eligible. Case-control study
Alt 1982	Study design not eligible. Case-control study
Amato 1984	Reference standard incorporated the index test.
Ammo 2008	Insufficient data. Abstract only. We were unable to locate the full text or contact the authors to request further data
Ananina 1963	Insufficient data. Decided not to contact the authors due to age of study
Ang 1990	Insufficient data. Data not extractable. Could not locate authors for clarification
Anwer 2000	Population not eligible. Unclear from paper if late-onset or early-onset sepsis was investigated. We decided not to try and contact the authors due to age of study
Apostolou 2002	Insufficient data. We decided not to contact the authors due to age of study
Arani 2013	Population not eligible. Early-onset sepsis
Arati 2014	Insufficient data to populate 2×2 table. No email address available for corresponding author
Arayici 2014	Study design not eligible. Case-control study
Arnon 2004	Population not eligible. Comparison of CRP levels in babies who died of sepsis and those who survived
Arnon 2005	Study design not eligible. Case-control study
Arnon 2007	Population not eligible. Early-onset sepsis
Athhan 2002	Insufficient data. We decided not to contact the authors due to age of study
Athiraman 2011	Insufficient data for. Could not locate authors for additional information
Ayazi 2014	Insufficient data. Published data did not allow extraction of information on infants with late-onset sepsis only. This information was requested from the authors but not provided
Aydin 2012	Study design not eligible. Case-control study
Aydin 2013	Study design not eligible. Case-control study
Baptista-Gonzales 1989	Population not eligible. Early-onset sepsis
Baruti-Gafurri 2010	Study design not eligible. Case-control study
Batfalsky 2012	Study design not eligible. Case-control study

Beceiro Mosquera 2009	Population not eligible. Early-onset sepsis
Berger 1995	Insufficient data. Could not locate authors for additional information
Berrington 2014	Other. CRP not investigated
Bhandari 2008	Other. No mention of CRP in the paper
Bhargava 2011	Study design not eligible. Case-control study
Bhargava 2013	Study design not eligible. Case-control study
Blanco 1996	Insufficient data. We decided not to contact the authors due to age of study
Blommendahl 2002	Insufficient data. We decided not to contact the authors due to age of study
Boonkasidecha 2013	Insufficient data. Data from both early-onset sepsis and late-onset sepsis included in the study. We contacted authors for late-onset sepsis-only data but received no reply
Boskabadi 2010	Study design not eligible. Case-control study
Bressan 2010	Population not eligible. Participants were admitted from the community
Buck 1994	Insufficient data. We decided not to contact the authors due to age of study
Bustos Betanzo 2007	Study design not eligible. Case-control study
Catal 2014	Study design not eligible. Case-control study
Ceccon 2006	Foreign language study. The abstract published in English contained insufficient information to assess eligibility. We contacted the authors but received no reply
Cekmez 2011	Study design not eligible. Case-control study
Celik 2010	Reference standard incorporated the index test
Celik 2012	Reference standard incorporated the index test
Cesur 2009	Study design not eligible. Case-control study
Cetinkaya 2009	The reference standard incorporated the index test
Chen 2009	Population not eligible. Participants were admitted to hospital from the community
Davis 2015	Reference standard not eligible. This study used the NEO-KISS classification (German surveillance system for nosocomial infections in VLBW infants) as the reference standard. However, as blood culture results are part of the NEO-KISS classification, we contacted the authors to request diagnostic data for CRP using

	blood culture results as the reference standard. We received no reply
Dhanalakshmi 2015	Published data insufficient to assess eligibility for inclusion. Additional data requested from the authors but not provided
Dorado Moles 2007	Other. Case-control study of infants with suspected infection compared with infants with other neonatal conditions not due to infection (respiratory distress, encephalopathy)
Duhan 2016	Insufficient data to assess eligibility and to construct 2×2 table (investigators contacted October 2017)
Edgar 1994	Insufficient data. Data for infants with late-onset sepsis (> 72 hours) were not reported separately. These data were requested from the authors but not provided. We thank Dr Edgar for responding to our emails and trying to find the requested data
Edgar 2010	Insufficient data. Data for infants with late-onset sepsis (> 72 hours) were not reported separately. These data were requested from the authors but not provided. We thank Dr Edgar for responding to our emails and trying to find the requested data
El Shimi 2017	Reference standard incorporated the index test
El-Sonbaty 2016	Insufficient data to assess eligibility and to construct 2×2 table (investigators contacted October 2017)
Enguix 2001	Study design not eligible. Case-control study
Escobar 2015	Population not eligible. Early-onset sepsis
Fattah 2017	Case-control study
Franz 1999	Reference standard incorporated the index test
Ganesan 2016	Insufficient data to assess eligibility and to construct 2×2 table (investigators contacted October 2017)
Garland 2003	Insufficient data. We decided not to contact the authors due to age of study
Goldfinch 2015	Insufficient data. Abstract only, full text not found
Gorbe 2007	Foreign language study. The abstract did not contain sufficient information for inclusion. We were unable to reach the authors to request further data
Gura 2003	Foreign language study. Insufficient data contained in abstract. Decided not to contact the authors due to age of study
Hegadi 2015	Insufficient data to populate 2×2 table. No email address available for corresponding author
Khair 2012	Population not eligible. Early-onset and late-onset sepsis combined. Late-onset sepsis-only data requested from authors but not provided

(Continued)

Khassawneh 2007	Insufficient data. Published data did not allow extraction of information on infants with late-onset sepsis only. This information was requested from the authors but not provided
Kite 1988	Population not eligible. Combination of early-onset and late-onset sepsis. Unable to extract appropriate data after feedback from authors. We thank Dr Kite for his time and effort in replying to our email and trying to provide the requested data
Kocabas 2007	Case-control study. No data on infants who had a negative sepsis evaluation
Krauel 1987	Population not eligible. Not exclusively late-onset sepsis and mixed population. Decided not to contact the authors due to age of study
Krediet 1992	Insufficient data. This study included infants with pneumonia but without a positive blood culture in the 'sepsis' group. We contacted the authors to request data on infants with positive blood culture only but received no reply
Kuster 1998	Other. Sensitivity and specificity calculations were based on CRP measurements taken before the onset on sepsis. We decided not to try to contact the authors due to age of study
Laborada 2003	Population not eligible. Combination of early-onset and late-onset sepsis. Decided not to try and contact authors due to age of study
Lai 2015	Insufficient data. Study did not collect diagnostic data for CRP
Liu 2016	Insufficient data to assess eligibility and to construct 2×2 table (investigators contacted October 2017)
Lu 2016	The reference standard incorporated the index test
Magudumana 2000	Insufficient data. Unable to extract appropriate data. Decided not to try and contact authors due to age of study
Manucha 2002	All participants < 4 days old ('early-onset' infection)
Matesanz 1980	Insufficient data. No usable data. Decided not to try and contact the authors due to age of study
Mehr 2001	Insufficient data. No usable data. Decided not to try and contact the authors due to age of study
Mustafa 2005	Population not eligible. Combination of early-onset and late-onset sepsis. Could not locate author to request late-onset sepsis only data
Nakamura 1989	Population not eligible. Combination of early-onset and late-onset sepsis. Could not locate author to request late-onset sepsis only data
Noto 2012	Insufficient data. Abstract only. Authors' contact details not provided
Nuntnarumit 2002	Reference standard not eligible. The reference standard used in this paper included both positive and negative blood culture. We were unable to locate the authors to request positive blood culture only data

Okulu 2015	Reference standard incorporated index test
Omran 2018	Case-control study. Insufficient data to assess eligibility and to construct 2×2 table (investigators contacted October 2017)
Park 2014	The reference standard incorporated the index test
Perez Solis 2006	Study design not eligible. Case-control study
Pourcyrous 1989	Insufficient data. Abstract only. Decided not to try and contact the authors due to age of study. Could not locate full text
Prasad 2015	Insufficient data. Authors contacted but did not provide additional data
Qin 2017	Included only infants with early-onset sepsis (< 72 hours)
Russell 1992	The reference standard incorporated the index test
Sakha 2008	Population not eligible. Combination of late-onset and early-onset sepsis. Could not locate author to request late-onset sepsis only data
Sarafidis 2017	Study did not use a threshold of CRP to distinguish between infants with 'high' or 'low' CRP
Sharma 1993	Population not eligible. Unclear how many participants had late-onset sepsis. Decided not to contact authors due to age of study
Stein 2015	Population not eligible. Participants were admitted to hospital from the community
Topuz 2012	Foreign language paper. The abstract published in English did not contain sufficient data to assess eligibility. We contacted the authors to request further information but received no reply
Turner 2006	Population not eligible. Combination of confirmed sepsis and clinical sepsis (without a positive blood culture). Authors were contacted and informed us that the requested data were no longer available
Tyagi 2016	Insufficient data to assess eligibility and to construct 2×2 table (investigators contacted October 2017)
Ussat 2015	The reference standard incorporated the index test
Vazzalwar 2005	Case-control study
Wu 2013	The reference standard incorporated the index test
Yao 2016	Case-control study
Ye 2017	Case-control study
Zarkesh 2015	Population not eligible. Infants were admitted to hospital from the community

(Continued)

Zhao 2015	Comparison of CRP levels before and after antibiotic treatment

CRP: C-reactive protein; VLBW: very low birth weight.

Characteristics of studies awaiting classification *[ordered by study ID]*

Ohlin 2010

Study characteristics	
Patient sampling	Prospective cohort
Patient characteristics and setting	Newborn infants with suspected infection (mostly infants with early-onset infection, but some with late-onset)
Index tests	Serum C-reactive protein level > 10 mg/L
Target condition and reference standard(s)	Microbiologically confirmed infection
Flow and timing	
Comparative	
Notes	Awaiting data for infants with late-onset infection

D A T A

Presented below are all the data for all of the tests entered into the review.
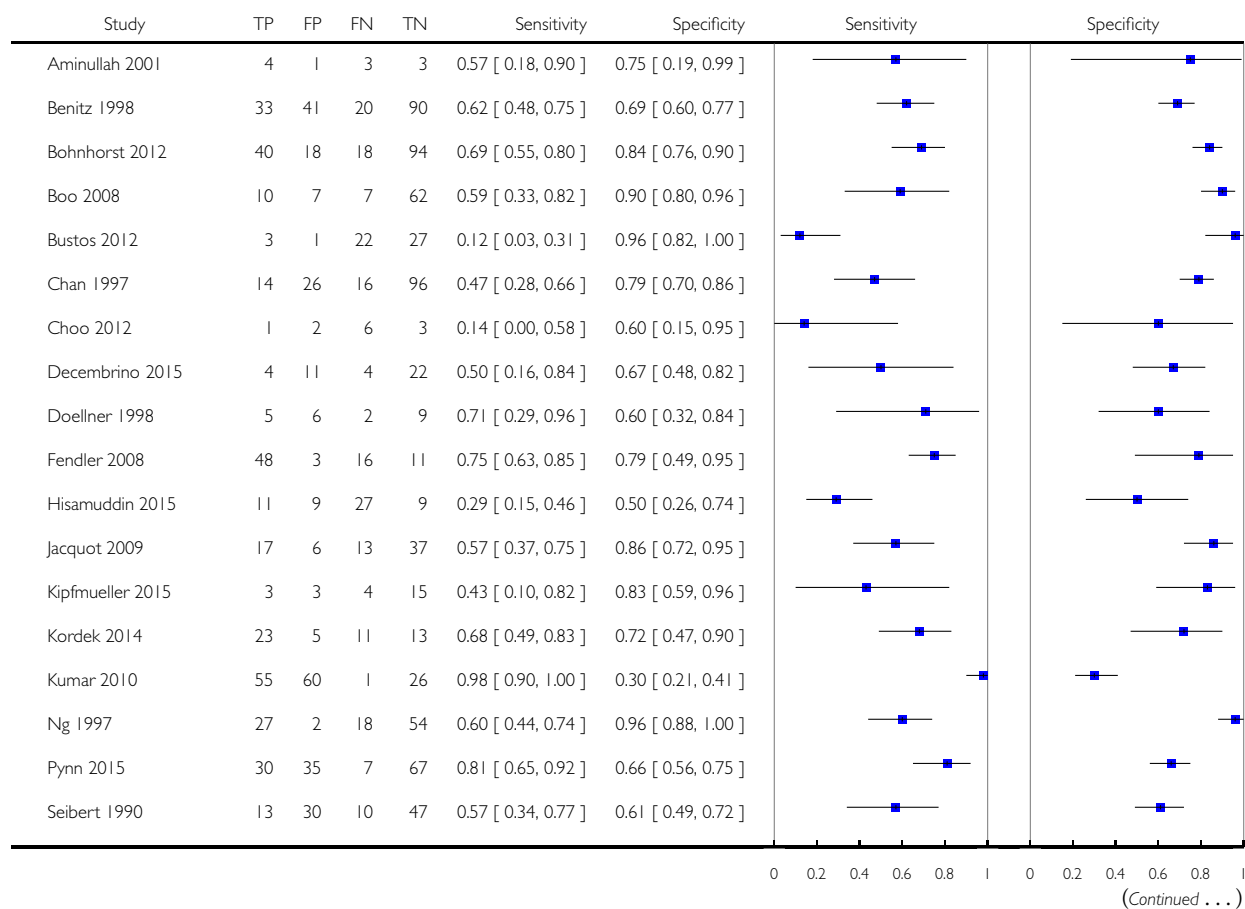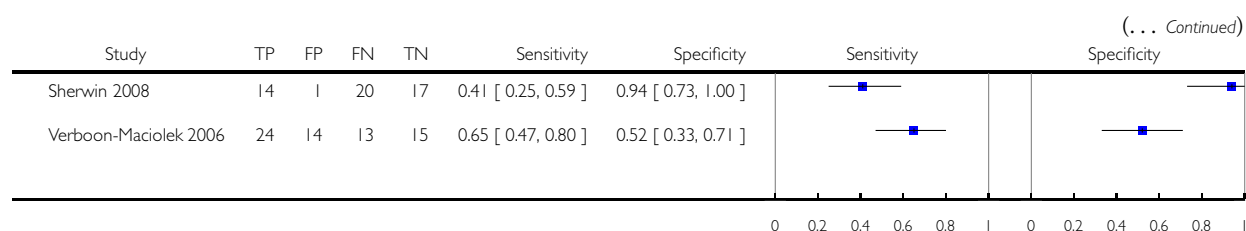
Tests.   Data tables by test

Test	No. of studies	No. of participants
1 CRP	20	1615

Test 1.   CRP.

Review: C-reactive protein for diagnosing late-onset infection in newborn infants

Test: 1 CRP

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Aminullah 2001	4	1	3	3	0.57 [0.18, 0.90]	0.75 [0.19, 0.99]		
Benitz 1998	33	41	20	90	0.62 [0.48, 0.75]	0.69 [0.60, 0.77]		
Bohnhorst 2012	40	18	18	94	0.69 [0.55, 0.80]	0.84 [0.76, 0.90]		
Boo 2008	10	7	7	62	0.59 [0.33, 0.82]	0.90 [0.80, 0.96]		
Bustos 2012	3	1	22	27	0.12 [0.03, 0.31]	0.96 [0.82, 1.00]		
Chan 1997	14	26	16	96	0.47 [0.28, 0.66]	0.79 [0.70, 0.86]		
Choo 2012	1	2	6	3	0.14 [0.00, 0.58]	0.60 [0.15, 0.95]		
Decembrino 2015	4	11	4	22	0.50 [0.16, 0.84]	0.67 [0.48, 0.82]		
Doellner 1998	5	6	2	9	0.71 [0.29, 0.96]	0.60 [0.32, 0.84]		
Fendler 2008	48	3	16	11	0.75 [0.63, 0.85]	0.79 [0.49, 0.95]		
Hisamuddin 2015	11	9	27	9	0.29 [0.15, 0.46]	0.50 [0.26, 0.74]		
Jacquot 2009	17	6	13	37	0.57 [0.37, 0.75]	0.86 [0.72, 0.95]		
Kipfmueller 2015	3	3	4	15	0.43 [0.10, 0.82]	0.83 [0.59, 0.96]		
Kordek 2014	23	5	11	13	0.68 [0.49, 0.83]	0.72 [0.47, 0.90]		
Kumar 2010	55	60	1	26	0.98 [0.90, 1.00]	0.30 [0.21, 0.41]		
Ng 1997	27	2	18	54	0.60 [0.44, 0.74]	0.96 [0.88, 1.00]		
Pynn 2015	30	35	7	67	0.81 [0.65, 0.92]	0.66 [0.56, 0.75]		
Seibert 1990	13	30	10	47	0.57 [0.34, 0.77]	0.61 [0.49, 0.72]		

```
              0  0.2  0.4  0.6  0.8  1      0  0.2  0.4  0.6  0.8  1
```

(*Continued* . . .)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Sherwin 2008	14	1	20	17	0.41 [0.25, 0.59]	0.94 [0.73, 1.00]		
Verboon-Maciolek 2006	24	14	13	15	0.65 [0.47, 0.80]	0.52 [0.33, 0.71]		

0 0.2 0.4 0.6 0.8 1   0 0.2 0.4 0.6 0.8 1

ADDITIONAL TABLES

Table 1. Risk of bias and applicability items and criteria for their assessment (QUADAS-2)

Item	Criteria for their assessment
Domain 1: participant selection	
Describe methods of participant selection (prior testing, presentation, intended use of index test and setting)	
A. Risk of bias	
Was a consecutive or random sample of participants enrolled?	'Yes' if described enrolling a consecutive or random sample of newborns prior to discharge from hospital 'No' if criteria for 'yes' not achieved 'Unclear' if the study did not describe the method of enrolment
Did the study avoid inappropriate exclusions?	'Yes' if exclusions were detailed and review authors reached consensus on the appropriateness of any exclusion 'No' if inappropriate exclusions were reported 'Unclear' if insufficient information was provided
Could the selection of participants have introduced bias?	A judgement of low, high, or unclear risk of bias was made based on a balanced assessment of the responses to the above signalling questions
B. Concerns about applicability	
Is there concern that the included participants did not match the review question?	A judgement of low, high, or unclear concern about applicability will be made based on how closely the sample matches a population of newborn infants with suspected infection
Domain 2: index test	
Describe the index test and how it was conducted and interpreted	
A. Risk of bias	

Were the index test results interpreted without knowledge of the results of the reference standard?	'Yes' if the serum CRP level was measured before the microbial culture result was available 'No' if reference standard results were available to those who ordered or interpreted the serum CRP level 'Unclear' if insufficient information was provided.
If a threshold was used, was it prespecified?	'Yes' if a threshold was prespecified. 'No' if authors selected a cut-off value based on the analysis of data collected 'Unclear' if insufficient information was provided.
Could the conduct or interpretation of the index test have introduced bias?	A judgement of low, high, or unclear risk of bias will be made based on a balanced assessment of the responses to the above signalling questions

B. Concerns about applicability

Was there concern that the index test, its conduct, or interpretation differ from the review question?	A judgement of low, high, or unclear concern about applicability will be made based on a balanced assessment of the information detailed under 'index test' description

Domain 3: reference standard

Describe the reference standard(s) and how they were conducted and interpreted

A. Risk of bias

Was the reference standard likely to correctly classify the target condition?	'Yes' if an appropriate reference standard (as defined in the protocol) was used 'No' if an inappropriate reference standard (not defined in the protocol) was used 'Unclear' if the reference standard used was not clearly specified
Were the reference standard results interpreted without knowledge of the results of the index test?	'Yes' if the person undertaking the reference test did not know the results of the microbial culture 'No' if the CRP level results were interpreted with prior knowledge of the index test result 'Unclear' if insufficient information provided.
Could the reference standard, its conduct, or its interpretation have introduced bias?	A judgement of low, high, or unclear risk of bias was made based on a balanced assessment of the responses to the above signalling questions

B. Concerns about applicability

Was there concern that the target condition as defined by the reference standard did not match the question?	A judgement of low, high, or unclear concern about applicability was made based on setting, population, risks, prevalence???

Table 1.   Risk of bias and applicability items and criteria for their assessment (QUADAS-2)   *(Continued)*

Domain 4: flow and timing	
Describe any participants who did not receive the index test or reference standard or who were excluded from the 2×2 table (refer to flow diagram) and describe the time interval and any interventions between index test and reference standard(s)	
A. Risk of bias	
Did all infants receive a reference standard?	'Yes' if the study specifically stated that all infants received blood culture, lumbar puncture, or other biopsy to identify infection (including autopsy examination) 'No' if the study only assessed suspected or probable infection (not confirmed microbiologically) 'Unclear' if insufficient information was provided.
Were all infants included in the analysis?	'Yes' if the study had no withdrawals or the withdrawals were clearly described 'No' if the number of participants contributing to the 2×2 table did not match the number of participants recruited and no reasons for exclusions were described 'Unclear' if information was not enough to establish the flow of participants
Could the patient flow have introduced bias?	A judgement of low, high, or unclear risk of bias was made based on a balanced assessment of the responses to the above signalling questions

Table 2.   Post-test probabilities for late-onset infection for a sample of population prevalences

Pretest probability	Post-test probability after a positive result	Post-test probability after a negative result
0.2	0.37	0.11
0.3	0.51	0.18
0.4	0.61	0.26
0.5	0.70	0.34
0.6	0.78	0.44

APPENDICES

Appendix 1. Search strategy

MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Via Ovid
1 exp Infant, Newborn/ (507086)
2 Premature Birth/ (7396)
3 (neonat$ or neo nat$).ti,ab. (204089)
4 (newborn$ or new born$ or newly born$).ti,ab. (135419)
5 (preterm or preterms or pre term or pre terms).ti,ab. (50291)
6 (preemie$ or premie or premies).ti,ab. (121)
7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (12210)
8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (26659)
9 (lbw or vlbw or elbw).ti,ab. (5938)
10 infan$.ti,ab. (345004)
11 (baby or babies).ti,ab. (54493)
12 "Intensive Care Units, Neonatal"/ (10315)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (854743)
14 C-Reactive Protein/ (32529)
15 c-reactive protein.ti,ab. (44280)
16 CRP.ti,ab. (30090)
17 Interleukin-6/ (48141)
18 IL-6.ti,ab. (71459)
19 interleukin-6.ti,ab. (35713)
20 acute phase reactant$.ti,ab. (3064)
21 Biological Markers/ (172550)
22 biomarker$.ti,ab. (113562)
23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (371276)
24 exp Sepsis/ (95928)
25 sepsis.ti,ab. (68288)
26 infection$.ti,ab. (1022808)
27 exp Bacterial Infections/ (745229)
28 (bacteraemia or bacteremia).ti,ab. (22257)
29 (fungaemia or fungemia).ti,ab. (1664)
30 exp Candidiasis/ (27375)
31 candidiasis.ti,ab. (12078)
32 exp Meningitis/ (48258)
33 meningitis.ti,ab. (42079)
34 Pneumonia, Bacterial/ (8792)
35 Urinary Tract Infections/ (32771)
36 Catheter-related Infections/ (2533)
37 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (1653493)
38 13 and 23 and 37 (3447)
39 exp animals/ not humans.sh. (4037496)
40 38 not 39 (3184)
Embase via Ovid
1 exp Infant/ (898706)
2 Prematurity/ (76784)
3 (neonat$ or neo nat$).ti,ab. (253737)
4 (newborn$ or new born$ or newly born$).ti,ab. (162735)
5 (preterm or preterms or pre term or pre terms).ti,ab. (66105)
6 (preemie$ or premie or premies).ti,ab. (165)

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (15808)
8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (31872)
9 (lbw or vlbw or elbw).ti,ab. (7572)
10 infan$.ti,ab. (406724)
11 (baby or babies).ti,ab. (71539)
12 newborn intensive care/ (22338)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1220384)
14 C Reactive Protein/ (98704)
15 c-reactive protein.ti,ab. (59724)
16 CRP.ti,ab. (53596)
17 Interleukin 6/ (140947)
18 IL-6.ti,ab. (98082)
19 interleukin-6.ti,ab. (41784)
20 acute phase reactant$.ti,ab. (4241)
21 Biological Marker/ (150561)
22 biomarker$.ti,ab. (170601)
23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (472866)
24 exp Sepsis/ (181816)
25 newborn sepsis/ (4927)
26 sepsis.ti,ab. (96170)
27 infection$.ti,ab. (1249750)
28 exp Bacteremia/ (35078)
29 exp Fungemia/ (4805)
30 (bacteraemia or bacteremia).ti,ab. (27114)
31 (fungaemia or fungemia).ti,ab. (2019)
32 exp Candidiasis/ (40057)
33 candidiasis.ti,ab. (15095)
34 exp Meningitis/ (75363)
35 meningitis.ti,ab. (49821)
36 Pneumococcal meningitis/ (908)
37 Urinary Tract Infection/ (75050)
38 Catheter infection/ (11655)
39 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 (1501019)
40 13 and 23 and 39 (5912)
41 animal/ (1656079)
42 human/ (15731222)
43 41 not (41 and 42) (1247837)
44 40 not 43 (5877)
Science Citation Index via Web of Science

# 4	**1,256**	#3 AND #2 AND #1 *Indexes= SCI-EXPANDED Times-pan=1900-2015*		

# 3	194,557	**TOPIC:** (sepsis) *OR* **TOPIC:** ("bacterial infection*") *OR* **TOPIC:** (bacteremia or bacteraemia) *OR* **TOPIC:** (fungaemia or fungemia) *OR* **TOPIC:**(candidiasis) *OR* **TOPIC:** (meningitis) *OR* **TOPIC:** ("pneumococcal meningitis") *OR* **TOPIC:** ("urinary tract infection*") *OR* **TOPIC:** ("catheter infection*") *Indexes=SCI-EXPANDED Timespan=1900-2015*			
# 2	241,196	**TOPIC:** ("c reactive protein") *OR* **TOPIC:** ("Interleukin 6") *OR* **TOPIC:** ("acute phase reactants") *OR* **TOPIC:** ("biological markers") *OR* **TOPIC:** (biomarker*) *Indexes=SCI-EXPANDED Timespan=1900-2015*			
# 1	616,040	**TOPIC:** ((neonat* or neo nat* or newborn* or new born* or newly born*)) *OR* **TOPIC:** ((preterm or preterms or pre term or pre terms or preemie* or premie* or premies)) *OR* **TOPIC:** ("premature birth" or "premature delivery") *OR* **TOPIC:** (low birthweight* or "low birth weight*") *OR* **TOPIC:** (lbw or vlbw or elbw) *OR* **TOPIC:** (infant or infants or infancy or baby or babies) *OR* **TOPIC:** ("neonatal intensive care") *Indexes=SCI-EXPANDED Timespan=1900-2015*			

(Continued)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- On the advice of a referee, we used a hierarchical summary receiver operating characteristic model rather than the proposed bivariate random-effects approach because included studies did not use a common cut-off.

- We included studies in which infants with urinary tract infection or radiologically confirmed pneumonia fulfilled the case definition for late-onset infection. These studies typically had none or very few participants with these diagnoses in the absence of bacteraemia.

- We accepted the primary study authors' definition of *late-onset* infection with regards to the infant's age when evaluated (range from 48 hours to six days after birth).