Appendix D –Diagnostic evidence

Aminullah, 2001

Bibliographic Reference	Aminullah A; The role of plasma C-reactive protein in the evaluation of antibiotic treatment in suspected neonatal sepsis; Medical Journal of Indonesia; 2001; vol. 1; 16-21

Study Characteristics

Study type	Cross-sectional study
Study location	Indonesia
Study setting	Neonatal ward and neonatal intensive care unit of the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta
Study dates	April - September 1999
Sources of funding	None reported
Inclusion criteria	Not previously received antibiotic or antiseptic therapy Patients admitted to the neonatal ward with suspected neonatal sepsis Birth weight >1000 g No fatal congenital malformations
Exclusion criteria	None
Sample size	35 (18 with positive blood culture)
Index test(s)	C-reactive protein (CRP)

Reference standard (s)	Blood culture on sample taken
Methodological details	Confirmed infection: 1 or more clinical signs (lethargy, unexplained low Apgar scores, unstable temperature, apneic attacks, unexplained cyanosis, gastrointestinal disturbances, respiratory disorder, hepatomegaly, diarrhea, vomiting, skin lesions and unexplained abnormal hematologiôal parameter) and blood culture. Blood culture: Taken on inclusion into the study CRP: Taken on inclusion into the study and then on day 2 and 4 and at discharge or death of the baby. Cut-off value: 12 mg/dl
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Unclear if a consecutive sample was used)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

(Limited information on exclusion criteria)

Could the selection of patients have introduced bias?

Unclear

(Sampling method unclear and limited information on exclusion criteria)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of reference test results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether index test assessor was aware of reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was aware of reference test results or whether reference test assessor was aware of index test results. Limited information on sampling or exclusion criteria)

Directness

Directly applicable

Anwar ul Haq, 2019

Bibliographic Reference	Anwar ul Haq, H.M.; Anjum, A.A.; Bharo, M.A.; Bhatti, I.A.; Accuracy of C - Reactive protein (CRP) for the diagnosis of neonatal sepsis having blood culture as gold standard; Medical Forum Monthly; 2019; vol. 30 (no. 8); 55-58

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Pakistan Study setting Department of Pediatrics, Bahawal Victoria Hospital, Bahawalpur Study dates December 2018 - May 2019 Sources of funding None reported
Inclusion criteria	Suspicion of sepsis Drowsiness, unwillingness to feed, hypothermia as less than 35oC, fits or having difficulty while breathing, mothers of presenting neonates who were having high grade fever or those who had foul smelling discharge during delivery
Exclusion criteria	None reported
Sample characteristics	Sample size 160 Female 33.1% Mean postnatal age (SD) 5.26 days (3.1) Culture positive sepsis Blood culture confirmed: 48.1% CRP confirmed 51.3%
Index test(s)	C-reactive protein
Reference standard (s)	Blood culture on sample taken
Methodological details	10 ml of blood was drawn from all the study participants and sent to institute's central laboratory for CRP while blood culture were also asked to confirm the presence of neonatal sepsis. CRP was considered as negative with value < 5mg/dl. No information about the timing of blood or CRP samples

Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives. Sensitivity, specificity, positive predictive values, negative predictive values

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Unclear
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear
	Could the selection of patients have introduced bias?	Unclear *(Limited information about selection of participants and no information about exclusion critieria)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	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
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about interpretation of the results but outcome was objective)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear *(No information about the methods used for taking or interpreting the results of the index test)*
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes

Section	Question	Answer
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(No information about the methods for analysing the reference test. But results were objective)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(No information about the methods used for taking or interpreting the results of the reference test)*
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(No information about timing of index and reference tests)*
Overall risk of bias and directness	Risk of Bias	High *(Limited information about the methods used such as selection of participants, exclusion critieria, methods used for taking or interpreting the results of the index and reference tests)*
	Directness	Partially applicable *(Includes results of babies with early- and late-onset infection. Results not reported separately)*

Anwer, 2000

Bibliographic Reference	Anwer, S K; Mustafa, S; Rapid identification of neonatal sepsis.; JPMA. The Journal of the Pakistan Medical Association; 2000; vol. 50 (no. 3); 94-8

Study Characteristics

Study type	Cross-sectional study
Study location	Pakistan
Study setting	Neonatal intensive Care Unit (NICU) of the Abbasi Shaheed Hospital, Karachi
Study dates	March 1994 - October 1994
Sources of funding	None reported
Inclusion criteria	Infants admitted to the neonatal intensive care unit
Exclusion criteria	None
Sample size	50 (21 with positive blood culture)
Average birth weight (variance)	2.32 kg (range 1.3 - 4.12 kg)
Average gestational age (variance)	35.5 weeks (range 31.5 - 39.5 weeks)
Average age at evaluation (variance)	Mean age of onset 4 days (range 12 hours - 20 days)
Index test(s)	C-reactive protein (CRP) White blood cell count

	Neutrophil count Neutrophil count (neutropenia/neutrophilia age adjusted count)and Immature:total neutrophil ratio (>0.2) Platelet count <50,000/mm
Reference standard (s)	Blood culture on sample taken
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Unclear whether it was all neonates admitted to the NICU during the study period)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Unclear whether it was all neonates admitted to the NICU during the study period)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(No information on blinding of the assessor)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(No information on blinding of the assessor)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(No information on blinding of the assessor)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(No information on blinding of the assessor)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(N/A - tests were run from a single blood test)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Unclear

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether it was all neonates admitted to the NICU during the study period and no information on blinding of the assessor for test results)

Directness

Directly applicable

Balasubramanin, 2018

Bibliographic Reference	Balasubramanin, P.; Bandiya, P.; Niranjan, S.H.; Benakappa, N.; Shinde, R.; Role of CSF-CRP as a Diagnostic Marker in Neonatal Meningitis; Journal of Neonatology; 2018; vol. 32 (no. 4); 112-117

Study Characteristics

Study type	Cross-sectional study

Study details	Study location India Study setting Neonatal intensive care unit of Indira Gandhi Institute of Child Health Study dates June 2017 - December 2017 Loss to follow-up 0 Sources of funding None
Inclusion criteria	Age less than 30 days Need for lumbar puncture
Exclusion criteria	Major congenital malformations Traumatic lumbar puncture Presence of another deep-seated focus of infection such as abscess, septic, arthritis, etc. Received antibiotics for >48 hours
Sample characteristics	Sample size 100 (50 with meningitis, 50 without) Female Meningitis group: 38%; non-meningitis group: 18% Culture positive sepsis Meningitis group: CRP 70%, blood culture gram +ve 12% gram -ve 42%; Non-meningitis group: CRP 74%, blood culture gram+ve 18% gram -ve 28% Median postnatal age (IQR) Meningitis group: 20 (10-30); non-meningitis group: 14 Median gestational age (IQR) Meningitis group: 37 weeks (35-39); non-meningitis group: 35 (33-38)

Index test(s)	C-reactive protein
Reference standard (s)	Blood culture on sample taken
Methodological details	Lumbar puncture was done under strict aseptic precautions with the neonate in the lateral position. All the CSF samples reached the laboratory within 10 min of LP. Meningitis was defined as per the unit protocol: in term neonates, the criteria were CSF WBC count >8, glucose <20, and protein >150. In preterm neonates, meningitis was defined as CSF WBC count ≥10, glucose <24, and protein >170, and no meningitis if the CSF WBC count <25, glucose ≥25, and protein <170
Outcomes	Diagnostic test accuracy outcomes: sensitivity, specificity, positive predictive value, negative predictive value, area under the curve

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Yes
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Limited information about interpretation of index test results)*
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Limited information about interpretation of the results relative to the reference standard)*

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(No information about whether the reference test assessor was aware of results of the index test)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(No information about timing between index and reference tests)*
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about timing between index and reference tests or whether assessors were aware of the results of the other test. Limited information about statistical analysis)*

Section	Question	Answer
	Directness	Partially applicable *(Includes babies with early- and late-onset infection. Results not reported separately)*

Beltempo, 2018

Bibliographic Reference Beltempo, Marc; Viel-Theriault, Isabelle; Thibeault, Roseline; Julien, Anne-Sophie; Piedboeuf, Bruno; C-reactive protein for late-onset sepsis diagnosis in very low birth weight infants.; BMC pediatrics; 2018; vol. 18 (no. 1); 16

Study Characteristics

Study type	Cross-sectional study
Study location	Canada
Study setting	Hospital
Study dates	2008 to 2013
Sources of funding	There was no funding
Inclusion criteria	Late-onset infection. No definition by age provided (downgraded once for indirectness) Infants had proven late-onset sepsis if the blood culture or cerebrospinal fluid culture drawn as part of the initial work-up was positive for bacterial pathogens.
Exclusion criteria	Early-onset infection Weight 1500 g or more Episodes of infection/sepsis occurring after the initial episode were excluded from the analysis Excluded after a period of 14 days from the initial episode
Sample size	416 (but 590 separate episodes evaluated)
Average birth weight (variance)	Mean (SD) 1024.8 g (258.1)
Average gestational age (variance)	Mean (SD) 27.9 weeks (2.4)

Average age at evaluation (variance)	Mean (SD) 15.0 (12.8)
Percentage of females	44%
Loss to follow-up	None
Index test(s)	C-reactive protein (CRP)
Reference standard (s)	Blood culture on sample taken CSF culture on sample taken
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

Could the selection of patients have introduced bias?

High

(Retrospective recruitment using a database so certain types of participants could have been missed. Episodes of sepsis were included rather than participants. Therefore, double-counting is an issue.)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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

Could the conduct or interpretation of the index test have introduced bias?

High

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

High

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Unclear

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Unclear

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

High

(Retrospective recruitment using a database so certain types of participants could have been missed. Episodes of sepsis were included rather than participants. Therefore, double-counting is an issue.)

Directness

Partially applicable

(Late-onset is not defined by hours or days)

Berger, 1995

Bibliographic Reference	Berger, C; Uehlinger, J; Ghelfi, D; Blau, N; Fanconi, S; Comparison of C-reactive protein and white blood cell count with differential in neonates at risk for septicaemia.; European journal of pediatrics; 1995; vol. 154 (no. 2); 138-44

Study Characteristics

Study type	Cross-sectional study
Study location	Switzerland
Study setting	Intensive care unit
Study dates	1986 to 1988
Sources of funding	Not mentioned
Inclusion criteria	Late-onset infection: 72 hours onward (corrected age) to 6 weeks Sepsis group had positive blood culture Symptoms and/or signs of neonatal infection
Exclusion criteria	Blood cultures negative for bacteria
Sample size	139 (only 24 were over 72 hours of age)
Average birth weight (variance)	Mean (range) 2486 g (750 to 5100)
Average gestational age (variance)	Mean (range) 35.1 weeks (25 to 42)
Average age at evaluation (variance)	Not provided
Percentage of females	Not provided
Loss to follow-up	None
Index test(s)	C-reactive protein (CRP)

Reference standard (s)	Blood culture on sample taken
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

High

(Only 24 out of 139 participants were over 72 hours of age.)

Index tests: risk of bias

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

(The investigators created an receiver operating characteristic (ROC) curve)

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Knowledge of the result of one test could have influenced the processing of the other.)

Directness

Directly applicable

Blommendahl, 2002

Bibliographic Reference	Blommendahl, Janne; Janas, Martti; Laine, Seppo; Miettinen, Ari; Ashorn, Per; Comparison of procalcitonin with CRP and differential white blood cell count for diagnosis of culture-proven neonatal sepsis.; Scandinavian journal of infectious diseases; 2002; vol. 34 (no. 8); 620-2

Study Characteristics

Study type	Cross-sectional study
Study location	Finland
Study setting	Hospital
Study dates	1997 to 1999
Sources of funding	Not mentioned
Inclusion criteria	Symptoms and/or signs of neonatal infection Only neonates who had a blood sample taken concomitantly for blood culture and the index text Neonatal infection/sepsis Confirmed by positive blood culture
Exclusion criteria	Neonates who had received antibiotic treatment, including maternal antibiotic treatment
Sample size	169
Average birth weight (variance)	Median (IQR) 3090 g (1582 to 3770)
Average gestational age (variance)	Median (IQR) 264 days (218 to 285)

Average age at evaluation (variance)	-
Percentage of females	43%
Loss to follow-up	None
Index test(s)	Procalcitonin (PCT)
Reference standard (s)	Blood culture on sample taken
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

High

(All neonates included)

Index tests: risk of bias

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

Could the conduct or interpretation of the index test have introduced bias?

High

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

High

(Index and reference tests may have been processed with knowledge of each other. No pre-specified cut-off point for the index test)

Directness

Partially applicable

("Neonates" - no definition by age)

Boo, 2008

Bibliographic Reference	Boo, N Y; Nor Azlina, A A; Rohana, J; Usefulness of a semi-quantitative procalcitonin test kit for early diagnosis of neonatal sepsis.; Singapore medical journal; 2008; vol. 49 (no. 3); 204-8

Study Characteristics

Study type	Cross-sectional study
Study location	Kuala Lumpur
Study setting	NICU of Hospital Universiti Kebangsaan Malaysia

Study dates	January 2005 - December 2006
Sources of funding	Faculty of Medicine, Universiti Kebangsaan Malaysia
Inclusion criteria	Infants admitted to the neonatal intensive care unit with signs suggestive of sepsis, or who developed signs of sepsis while in the ward
Exclusion criteria	Infants on antibiotics or developed signs of sepsis within 72 hours of discontinuation of antibiotics
Sample size	87
Average birth weight (variance)	Median (range): Confirmed sepsis: 1060g (690g-3400g) No sepsis: 2100g (535g-4680g)
Average gestational age (variance)	Median (range): Confirmed sepsis: 30 weeks (25-40) No sepsis: 34 weeks (24-41)
Average age at evaluation (variance)	Median age at onset of symptoms (range): Confirmed sepsis: 12.5 days (1-54) No sepsis: 1.0 days (1-103)
Index test(s)	C-reactive protein (CRP) Normal CRP level was defined according to age of infants: day 1 to day 4: < 1.5 mg/ml; more than day 4 of age: < 1.0 mg/ml. CRP level was defined to be raised when it exceeded the normal levels Procalcitonin (PCT) PCT -Q level was considered to be raised when it was z 2 ng/ml.

Reference standard (s)	Blood culture on sample taken
Methodological details	Using blood culture results as the gold standard, the sensitivity, specificity, positive predictive values and negative predictive values of the PCT -Q and CRP for diagnosing sepsis were calculated. The sensitivity of a test was defined as the proportion of infants with sepsis and were correctly identified by the test. The specificity of the test was defined as the proportion of infants without sepsis and were correctly identified by the test. The positive predictive value of a test was defined as the proportion of infants with positive test results and who had sepsis. The negative predictive value of a test and was defined as the proportion of infants with negative test results and who did not have sepsis.
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Unclear if all neonates were included)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Unclear if all neonates were included)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether the assessors were blinded to reference standard results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether the assessors were blinded to reference standard results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether the assessors were blinded to index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear whether the assessors were blinded to index test results)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(All tests from the same blood culture)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear how neonates were selected for inclusion. Unclear whether the assessors were blinded to reference standard/index test results)

Directness

Directly applicable

Boonkasidecha, 2013

Bibliographic Reference	Boonkasidecha, Suppawat; Panburana, Jantana; Chansakulporn, Somboon; Benjasuwantep, Banchaun; Kongsomboon, Kittipong; An optimal cut-off point of serum C-reactive protein in prediction of neonatal sepsis.; Journal of the Medical Association of Thailand = Chotmaihet thangphaet; 2013; vol. 96suppl1; 65-70

Study Characteristics

Study type	Cross-sectional study
Study location	Thailand
Study setting	NICU and nursery ward of Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center, Department of Pediatrics, Srinakharinwirot University
Study dates	Not reported
Sources of funding	None reported

Inclusion criteria	All newborn infants who presented with signs and symptoms of neonatal sepsis Signs and symptoms included thermoregulation instability, lethargy, apnea, respiratory distress, abdominal distension, increasing oxygen requirement or respiratory support, metabolic derangement
Exclusion criteria	Conditions such as postoperative PDA ligation, intracranial hemorrhage and post resuscitation from severe asphyxia Neonates given antibiotics before sepsis work-up
Sample size	53
Average birth weight (variance)	Mean (SD): Normal group: 2200.6g (1043.1) Sepsis group: 2077.3g (859.7)
Average gestational age (variance)	Mean (SD): Normal group: 34 weeks (3.8) Sepsis group: 34 weeks (3.4)
Average age at evaluation (variance)	Average age of onset. Mean (SD): Normal group: 10.5 days (8.1) Sepsis group: 9.15 days (8.2)
Percentage of females	Normal group: 51.9% Sepsis group: 14.9%
Index test(s)	C-reactive protein (CRP) One and a half mL of blood was required for a serum CRP measurement which was performed by using a commercial kit CRP (Latex) US, Roche Diagnostics Corporation, Indianapolis, IN, USA). CRP level was obtained at time of initial sepsis work-up and again at 12-24 hours later
Reference standard (s)	Blood culture on sample taken

Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the assessor of the index tests was blinded to reference test results)

If a threshold was used, was it pre-specified?

No

(But study was aiming to find the optimal cut-off point so a range of values were used)

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the assessor of the index test was blinded to reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the assessor of the reference test was blinded to index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the assessor of the reference test was blinded to index test results)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear if index test assessor was blinded to results of reference test or whether reference test assessor was blinded to results of index test)

Directness

Directly applicable

Huang, 2019

Bibliographic Reference	Huang, H.; Tan, J.; Gong, X.; Li, J.; Wang, L.; Xu, M.; Zhang, X.; Zhang, Y.; Huang, L.; Comparing single vs. Combined cerebrospinal fluid parameters for diagnosing full-term neonatal bacterial meningitis; Frontiers in Neurology; 2019; vol. 10 (no. jan); 12

Study Characteristics

Study type	Cross-sectional study
Study location	Shanghai
Study setting	Four tertiary class A paediatric hospitals
Study dates	January 2000 - December 2017
Sources of funding	None reported
Inclusion criteria	All term neonates who underwent lumbar puncture (LP) in Shanghai
Exclusion criteria	Neonates who experienced traumatic lumbar puncture > 28 days of age

	History of other severe neurological diseases or ventricular drainage
Sample size	1830 (105 bacterial meningitis)
Average birth weight (variance)	Mean (SD): Bacterial meningitis: 3267g (499) Non-bacterial meningitis: 3344g (554)
Average age at evaluation (variance)	Mean (SD): Bacterial meningitis: 13.8 days (7.9) Non-bacterial meningitis: 9.6 (8.9)
Percentage of females	Bacterial meningitis: 49.5% Non-bacterial meningitis: 39.4%
Index test(s)	White blood cell count Cut-off 19.5 (10^6/L)
Reference standard (s)	CSF culture on sample taken Infection diagnosed with positive CSF culture
Methodological details	We compared the diagnostic performance of single and combined parameters by calculating their sensitivity, specificity, AUCs, and positive and negative predictive values with respect to bacterial meningitis in neonates
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Retrospective analysis so unclear)

If a threshold was used, was it pre-specified?

No

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Retrospective analysis so unclear whether index test assessor was aware of results of the reference standard. Test threshold was not pre-specified)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Retrospective analysis so unclear whether reference test assessor was aware of results of the index tests)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Retrospective analysis so unclear whether reference test assessor was aware of results of the index tests)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Test cut-off not pre-specified and study was retrospective so unclear whether test assessors were aware of other index/reference test results)

Directness

Directly applicable

Iskandar, 2019

Bibliographic Reference	Iskandar, A.; Arthamin, M.Z.; Indriana, K.; Anshory, M.; Hur, M.; Di Somma, S.; Comparison between presepsin and procalcitonin in early diagnosis of neonatal sepsis; Journal of Maternal-Fetal and Neonatal Medicine; 2019; vol. 32 (no. 23); 3903-3908

Study Characteristics

Study type	Cross-sectional study
Study location	Indonesia
Study setting	Perinatology Department of Saiful Anwar Hospital, Malang
Study dates	May 2015 - July 2015
Sources of funding	None reported
Inclusion criteria	Age between 0 and 30 days Fulfilling SIRS criteria for neonates. two or more of symptoms including fever or hypothermia (core temperature more than 38 C or less than 36 C), tachycardia, tachypnea and change in blood leucocyte count Abnormality in temperature or leukocytosis
Exclusion criteria	None
Sample size	51 (35 with positive blood cultures)

Average birth weight (variance)	Average birth weight not reported. Number with birth weight: <1500 g: Positive blood culture = 4 (57.1%) Negative blood culture = 3 (42.9%) 1500–2500 g: Positive blood culture = 15 (75.0%) Negative blood culture = 5 (25.0%) >2500 g: Positive blood culture = 16 (66.7) Negative blood culture = 8 (33.3)
Average age at evaluation (variance)	Median (IQR): Positive blood culture: 8.0 days (8) Negative blood culture: 7.5 days (10)
Percentage of females	Positive blood culture = 65.2% Negative blood culture = 34.8%
Index test(s)	Procalcitonin (PCT) PCT levels were measured by enzyme linked immunosorbent assay (ELISA) (Elabscience Biotechnology Corporation, Guangdong, China)
Reference standard (s)	Blood culture on sample taken Neonatal infection diagnosed with positive blood culture. Blood was taken from studied subjects at the same time for culture and biomarker analysis but there was limitation for several subjects, in which the blood samples were taken in slightly different timing, due to blood volume restrictions caused by venous puncture in neonates. Blood cultures were taken from two different places and stored in BD BactecTM Peds PlusTM medium (Becton,Dickinson and Company, Franklin Lakes, NJ). Patient blood was then included into the culture medium and analyzed using VITEK2 system, (BioMerieux Inc., Marcyl' Etoile, France) to determine the micro-organisms presence and antibiotic sensitivity
Methodological details	The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and accuracy were analyzed using 2x2 tables
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Unclear how patients were selected)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Unclear how patients were selected)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

If a threshold was used, was it pre-specified?

No

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test and test threshold was not pre-specified)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Test cut-off was not pre-specified and unclear if the index test assessor was blinded to reference test results or if the reference test assessor was blinded to results of the index test)

Directness

Directly applicable

Jacquot, 2009

Bibliographic Reference	Jacquot, A; Labaune, J-M; Baum, T-P; Putet, G; Picaud, J-C; Rapid quantitative procalcitonin measurement to diagnose nosocomial infections in newborn infants.; Archives of disease in childhood. Fetal and neonatal edition; 2009; vol. 94 (no. 5); f345-8

Study Characteristics

Study type	Cross-sectional study
Study location	France
Study setting	Neonatal ICU
Study dates	2005 to 2006
Sources of funding	Not mentioned
Inclusion criteria	Late-onset infection: 72 hours onwards (corrected age) Diagnosed using Vermont Oxford Network recommendations for CoNS septicaemia (presence of a central catheter, clinical signs of sepsis, two positive blood cultures and intravenous antibacterial therapy for at least 5 days) Symptoms and/or signs of neonatal infection
Exclusion criteria	Neonates who had received antibiotic treatment, including maternal antibiotic treatment Genetic malformation Requiring surgery

	Diagnosed with necrotising enterocolitis
Sample size	73
Average birth weight (variance)	Median (IQR) 995 g (720 to 1350)
Average gestational age (variance)	Median (IQR) 28 weeks (26 to 30)
Average age at evaluation (variance)	Median (IQR) 11 days (8 to 18)
Percentage of females	44%
Loss to follow-up	None
Index test(s)	C-reactive protein (CRP) Procalcitonin (PCT)
Reference standard (s)	Blood culture on sample taken
Methodological details	When late-onset sepsis was suspected, blood samples were obtained within an hour from peripheral veins for a complete blood count, measurement of CRP concentration and two bacterial cultures (1 ml each). PCT concentration was measured together with the CRP and thus did not require additional blood.
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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

Could the conduct or interpretation of the index test have introduced bias?

Low

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Yes

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Low

Directness

Directly applicable

(Normally we would downgrade because there was no upper limit for age given. However, the upper IQR was well within 28 days (it was 18 days).)

Joji, 2018

Bibliographic Reference	Joji, R.; Takpere, A.Y.; Gupta, S.; Evaluation of diagnostic value of C reactive protein in neonatal sepsis; Asian Journal of Microbiology, Biotechnology and Environmental Sciences; 2018; vol. 20 (no. 2); 409-412

Study Characteristics

Study type	Cross-sectional study
Study location	India
Study setting	Shri B Mpatil medical centre
Study dates	Not reported
Sources of funding	None reported
Inclusion criteria	Patients with 2 or more clinical features Respiratory compromise, cardiovascualr compromise, metabolic changes, neurological changes
Exclusion criteria	> 28 days of age Congenital malformations
Sample size	115 (45 with blood culture confirmed sepsis)
Index test(s)	C-reactive protein (CRP)
Reference standard (s)	Blood culture on sample taken
Methodological details	Clinical sepsis definition: Blood culture-confirmed infection Blood samples: Drawn with aseptic precautions prior to antibiotic therapy. Samples were incubated aerobically and observed for 7 days. Reported as sterile if no bacterial growth was seen. Infection diagnosed with positive blood culture CRP: Performed by latex agglutination method. Results were reported as positive or negative (qualitative). Cut-off value: 0.6 mg/dl
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Sampling method unclear)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Sampling method unclear)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of reference test results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether index test assessor was aware of reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Unclear

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was aware of reference test results or whether reference test assessor was aware of index test results)

Directness

Directly applicable

Khair, 2012

Bibliographic Reference	Khair, K B; Rahman, M A; Sultana, T; Roy, C K; Rahman, M Q; Ahmed, A N; Early diagnosis of neonatal septicemia by hematologic scoring system, C-reactive protein and serum haptoglobin.; Mymensingh medical journal : MMJ; 2012; vol. 21 (no. 1); 85-92
Study type	Cross-sectional study
Study location	Bangladesh
Study setting	NICU
Study dates	April 2009 - March 2010
Sources of funding	None reported
Inclusion criteria	Neonates aged 0-28 days with clinically suspected sepsis
Exclusion criteria	Critically ill neonates Neonates with severe jaundice
Sample size	12
Average age at evaluation (variance)	Not reported. 66.7% were less than 7 days of age

Percentage of females	Confirmed sepsis group: 42% Non-sepsis group: Not reported
Index test(s)	C-reactive protein (CRP) 1 ml sample allowed to clot and centrifuged at 1200 rpm for 2 mins. CRP analysed using latex agglutination slide test (cut-off >0.6 mg/dl) White blood cell count White blood cell count, I:T ratio (Peripheral blood smears drawn on clean glass slides and stained by Leishman method. Index tests then performed) Platelet count 1 ml sample anticoagulated with EDTA and using Beckman Coulter HMX automated haematology analyser
Reference standard (s)	Blood culture on sample taken Infection confirmed by positive blood culture. 4 ml of blood samples drawn using peripheral venipuncture within 24 hours of admission
Methodological details	4 ml of blood samples drawn using peripheral venipuncture within 24 hours of admission. Used for complete blood cell count, CRP, haptoglobin and blood culture
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Limited information about patient enrollment)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the assessor of the index test was blinded to reference test results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the assessor of the index test was blinded to reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the assessor of the reference test was blinded to index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the assessor of the reference test was blinded to index test results)

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear if index test assessor was blinded to reference test results or whether reference test assessor was blinded to index tests)

Directness

Directly applicable

Khan, 2019

Bibliographic Reference	Khan, F.; C-reactive Protein as a Screening Biomarker in Neonatal Sepsis; Journal of the College of Physicians and Surgeons--Pakistan : JCPSP; 2019; vol. 29 (no. 10); 951-953

Study Characteristics

Study type	Cross-sectional study
Study location	Pakistan

Study setting	Neonatal unit
Study dates	August 2016 - February 2017
Sources of funding	None reported
Inclusion criteria	Neonates aged 0-28 days with clinically suspected sepsis
Exclusion criteria	Blood cultures that were contaminated Advised antibiotics for any reason 24 hours before admission
Sample size	385 (116 with late-onset infection)
Index test(s)	C-reactive protein (CRP) >5 mg/dl. No information on method of analysis
Reference standard (s)	Blood culture on sample taken
Methodological details	Each neonate was sampled for blood culture and C-reactive protein aseptically. Infection confirmed by positive blood culture. Sensitivity, specificity, negative and positive predictive values were calculated using 2x2 table
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear if the index test assessor was blinded to reference test results or whether the reference test assessor was blinded to results of the index test)

Directness

Directly applicable

Kumar, 2010

Bibliographic Reference	Kumar, R; Musoke, R; Macharia, W M; Revathi, G; Validation of c-reactive protein in the early diagnosis of neonatal sepsis in a tertiary care hospital in Kenya.; East African medical journal; 2010; vol. 87 (no. 6); 255-61

Study Characteristics

Study type	Cross-sectional study
Study location	Kenya
Study setting	KNH Newborn Unit
Study dates	June - September 2005
Sources of funding	None reported
Inclusion criteria	Suspected sepsis based on perinatal risk factors or suspicious clinical findings
Exclusion criteria	History of meconium aspiration, perinatal asphyxia, tissue injury and severe hepatocellular involvement
Sample size	85 (56 culture positive)
Average gestational age (variance)	Median (range): 34 (28-40)

Average age at evaluation (variance)	Median (range): 2 days (1-55)
Index test(s)	C-reactive protein (CRP)
Reference standard (s)	Blood culture on sample taken
Methodological details	Proven sepsis: Blood culture confirmed Blood culture: 1.5 mls of blood was drawn from each infant for complete blood count, culture and CRP assays. CBC and culture were done using standard procedures in haematology and microbiology laboratories. CRP: Samples for CRP were stored at -20°C and analysed as a batch. The test principle was immuno-turbidimetric assay. Measuring range: 0.3-24 mg/dl (0.003-0.24g/l). Cut-off value: 5 mg/l
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of reference test results)

If a threshold was used, was it pre-specified?

No

(Test threshold not specified in methods)

Could the conduct or interpretation of the index test have introduced bias?

High

(Unclear whether index test assessor was aware of reference test results. Test threshold not pre-specified in methods)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Yes

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(From same blood sample)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Low

Directness

Partially applicable

(Includes neonates >3 days of age but median age was 2 days (within timeframe for early-onset infection))

Lopez Sastre, 2006

Bibliographic Reference	Lopez Sastre, Jose B; Perez Solis, David; Roques Serradilla, Vicente; Fernandez Colomer, Belen; Coto Cotallo, Gil D; Krauel Vidal, Xavier; Narbona Lopez, Eduardo; Garcia del Rio, Manuel; Sanchez Luna, Manuel; Belaustegui Cueto, Antonio; Moro Serrano, Manuel; Urbon Artero, Alfonso; Alvaro Iglesias, Emilio; Cotero Lavin, Angel; Martinez Vilalta, Eduardo; Jimenez Cobos, Bartolome; Grupo de Hospitales,

Castrillo; Procalcitonin is not sufficiently reliable to be the sole marker of neonatal sepsis of nosocomial origin.; BMC pediatrics; 2006; vol. 6; 16

Study Characteristics

Study type	Cross-sectional study
Study location	Spain
Study setting	Neonatal services within hospitals
Study dates	January 2000 to January 2001
Sources of funding	Not mentioned
Inclusion criteria	Symptoms and/or signs of neonatal infection Risk factors for late-onset neonatal infection Neonatal infection Aged between 4 and 28 days of life
Exclusion criteria	If pathogens isolated in blood culture were traditional pathogens of vertical transmission And there was a positive maternal vaginal culture with the same pathogen
Sample size	100
Average birth weight (variance)	Median (IQR) 1270 (950 to 1990)
Average gestational age (variance)	Median 29.5 weeks (27 to 34)
Average age at evaluation (variance)	Median (IQR) 13.6 days (10.0 to 24.8)

Percentage of females	43%
Loss to follow-up	None
Index test(s)	Procalcitonin (PCT)
Reference standard (s)	Blood culture on sample taken Infection confirmed with positive blood culture
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

No

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

High

(There is variability with regards to when the symptoms first appeared as to whether the neonate would be included.)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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

(The investigators created a receiver operating characteristic (ROC) curve)

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Not clear as to whether the index and reference test results were analysed independently of each other. There is variability with regards to when the symptoms first appeared as to whether the neonate would be included.)

Directness

Directly applicable

Marconi, 2008

Bibliographic Reference	Marconi, Camila; de Lourdes Rs Cunha, Maria; Lyra, Joao C; Bentlin, Maria R; Batalha, Jackson En; Sugizaki, Maria Fatima; Rugolo, Ligia Mss; Comparison between qualitative and semiquantitative catheter-tip cultures: laboratory diagnosis of catheter-related infection in newborns.; Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology]; 2008; vol. 39 (no. 2); 262-7

Study Characteristics

Study type	Cross-sectional study
Study location	Brazil
Study setting	Neonatal Unit of the University Hospital of the Botucatu Medical School

Study dates	September 2001 - June 2003
Sources of funding	None reported
Inclusion criteria	Catheter tips from patients who had presented one or more blood cultures collected close to the date of catheter removal
Exclusion criteria	Catheters from babies who did not have clinical data and laboratory records available for one week prior to the catheter removal date
Sample size	85 catheters from 63 babies
Index test(s)	Samples from tip of IV long line 1. Semi-quantitative culture (Segments were rolled on the surface of Blood Agar plates and incubated at 37ºC for 72 hours. The plates were examined daily and counted as soon as growth was detected, the result was expressed in CFU). 2. Qualitative method (catheter tips immersed in Brain Heart Infusion (BHI) with subsequent incubation at 37ºC for 72 hours. The broths were examined daily and when cloudy, a subculture was performed in Blood Agar
Reference standard (s)	Blood culture on sample taken collected and cultivated by the Bactec Automated System, according to Koneman et al. guidelines
Methodological details	Catheter tips: The catheters were aseptically removed by the medical staff and the approximately 5 cm distal tips were collected, placed in dry sterile vials and immediately transported to the laboratory for processing. Catheter-related infection: diagnosed according to CDC guidelines by the presence of two or more of the following signs or symptoms: fever (≥ 38ºC), hypothermia (<36ºC), apnea, bradycardia or shock signs, in addition to the presence of one or more positive blood cultures in patients whose catheter semiquantitative culture was positive, if the same microorganism (specie and agent susceptibility) had been isolated from the catheter and the peripheral blood culture without another apparent source of infection focus except the catheter
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Unclear how patients were selected)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Unclear how patients were selected)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear how patients were selected and if the index test assessor was blinded to reference test results or if reference test assessor was blinded to index test results)

Directness

Directly applicable

Martin-Rabadan, 2017

Bibliographic Reference	Martin-Rabadan, P; Perez-Garcia, F; Zamora Flores, E; Nisa, E S; Guembe, M; Bouza, E; Improved method for the detection of catheter colonization and catheter-related bacteremia in newborns.; Diagnostic microbiology and infectious disease; 2017; vol. 87 (no. 4); 311-314

Study Characteristics

Study type	Cross-sectional study
Study location	Spain
Study setting	Neonatal referral unit
Study dates	2011 to 2013
Sources of funding	There was no funding
Inclusion criteria	Symptoms and/or signs of neonatal infection Neonatal infection No ages provided in the methods section

Exclusion criteria	None
Sample size	277 participants However, the study looked at the 372 PICCs
Average birth weight (variance)	Median (IQR) 1485 g (1700)
Average gestational age (variance)	Median (IQR) 30.6 weeks (9.8)
Average age at evaluation (variance)	Median (IQR) 15 days (18)
Percentage of females	57%
Loss to follow-up	None
Index test(s)	Samples from tip of IV long line Peripherally Inserted Central venous Catheters (PICC) lines 1. Roll plate method: PICC tips rolled onto a blood agar plate. 2. Longitudinally spilt method: PICC tips cut open longitudinally with a scalpel (#21 blade) over a sterile petri dish. The fragments were placed on a second blood agar plate and rubbed onto its surface
Reference standard (s)	Blood culture on sample taken Catheter-related infection confirmed by same organism in colonised PICC and blood cultures
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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?

Unclear

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(The study looked at the number of PICC lines rather than the number of participants. Therefore, double-counting is an issue. The index and reference tests might have been analysed together)

Directness

Directly applicable

Mkony, 2014

Bibliographic Reference	Mkony, Martha Franklin; Mizinduko, Mucho Michael; Massawe, Augustine; Matee, Mecky; Management of neonatal sepsis at Muhimbili National Hospital in Dar es Salaam: diagnostic accuracy of C-reactive protein and newborn scale of sepsis and antimicrobial resistance pattern of etiological bacteria.; BMC pediatrics; 2014; vol. 14; 293

Study Characteristics

Study type	Cross-sectional study
Study location	Tanzania
Study setting	Muhimbili National Hospital neonatal unit
Study dates	July 2012 - March 2013
Sources of funding	Belgium Technical Cooperation
Inclusion criteria	Neonates who met the WHO definition for septicaemia Any of: History of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate ≥60 breaths per minute, severe chest indrawing, axillary temperature ≥37.5°C, axillary temperature ≤35.5°C, bulging anterior fontanelle, signs of infection on the skin with pus spots and umbilicus pus spots
Exclusion criteria	Very sick children in decompensate state and requiring resuscitation Neonates with severe congenital malformation such as anencephaly
Sample size	208
Average birth weight (variance)	Average birth weight not reported. Number who were: <1000g: 2 1000 – 1400g: 10 1500 – 2500g: 26 2500g: 170
Average age at evaluation (variance)	Median age (range) 5.6 days (1 – 28)
Percentage of females	48.1%
Index test(s)	C-reactive protein (CRP) Cut-off: >5 mg/l

Reference standard (s)	Blood culture on sample taken Infection confirmed by positive blood culture
Methodological details	Blood culture: Incubated at 37°C for 24 h after which aliquots were sub-cultured on solid agar plates; blood agar (Oxoid, UK) and MacConkey agar (Oxoid, UK) and chocolate agars (Oxoid, UK) for up 96 hours before being regarded as having no growth. Identification was based on microscopic characteristics, colonial characteristics, and Biochemical tests as described by Murray et al. [20], including VITEX (BioMerieux, France) and API 20E (BioMerieux, France). CRP: Blood samples were centrifuged for separation of the serum within 60 minutes of blood collection and analysis was performed using COBRA 400/400 plus system (Roche Diagnostic limited, Switzerland). A value of more than 5 mg/l was considered to be associated with sepsis.
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of reference test results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether index test assessor was aware of reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was aware of reference test results or whether reference test assessor was aware of index test results)

Directness

Directly applicable

Nakamura, 1989

Bibliographic Reference Nakamura, H; Uetani, Y; Nagata, T; Yamasaki, T; Serum C-reactive protein in the early diagnosis of neonatal septicemia and bacterial meningitis.; Acta paediatrica Japonica : Overseas edition; 1989; vol. 31 (no. 5); 567-71

Study Characteristics

Study type	Cross-sectional study
Study location	Japan
Study setting	Neonatal ICU
Study dates	1985 to 1987
Sources of funding	Not mentioned
Inclusion criteria	Symptoms and/or signs of neonatal infection Neonatal infection No start or end age in the methods section
Exclusion criteria	None
Sample size	90
Average birth weight (variance)	Preterm infants: mean (SD) 1743 g (509) Normal-term infants: mean (SD) 3110 g (551)

Average gestational age (variance)	Preterm infants: mean (SD) 32.6 weeks (3.6) Normal-term infants: mean (SD) 39.8 weeks (1.0)
Average age at evaluation (variance)	Preterm infants: mean (SD) 5.8 days (17.0) Normal-term infants: mean (SD) 3.5 days (5.0)
Percentage of females	-
Loss to follow-up	None
Index test(s)	C-reactive protein (CRP)
Reference standard (s)	Blood culture on sample taken CSF culture on sample taken Infection confirmed by positive blood or CSF culture
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

No

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

High

(Participants were selected)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

High

(Participants were selected for the study. The index and reference test results could have been analysed together.)

Directness

Directly applicable

Omar, 2019

Bibliographic Reference	Omar, J.; Isa, S.; Ismail, T.S.T.; Yaacob, N.M.; Soh, N.A.A.C.; Procalcitonin as an early laboratory marker of sepsis in neonates: Variation in diagnostic performance and discrimination value; Malaysian Journal of Medical Sciences; 2019; vol. 26 (no. 4); 61-69

Study Characteristics

Study type	Cross-sectional study
Study location	Malaysia

Study setting	Paediatric Intensive Care Unit of Hospital Universiti Sains Malaysia
Study dates	Not reported
Sources of funding	Short Term Grant, Universiti Sains Malaysia
Inclusion criteria	Neonates with suspected septicaemia due to either preterm ruptured of membrane or prolonged ruptured of membrane, maternal infection, chorioamnionitis, group B streptococcus (GBS) colonisation, or signs of foetal distress during labour. Or with signs and symptoms associated with sepsis such as feeding intolerance, lethargic or tachypnic look, poor perfusion, seizures, respiratory distress, bradycardia, abdominal distention, or vomiting
Exclusion criteria	None
Sample size	60
Average birth weight (variance)	Mean (SD): 2.25 kg (0.92)
Average age at evaluation (variance)	Age of developing sepsis. Mean (SD): 76.8 hours (48.25)
Percentage of females	45%
Index test(s)	Procalcitonin (PCT) Cut-off value >2 ng/ml
Reference standard (s)	Blood culture on sample taken
Methodological details	Sepsis definition: Onset of sepsis <48 hours of life or >48 hours of life (diagnostic results not presented separately) Blood culture: blood samples for the culture test were collected prior to the antibiotic therapies and subsequently incubated in the BACTEC 9240 blood culture system. The presumptive presence of viable microorganisms would be indicated by the positive readings of the BACTEC instrument

	PCT: blood samples from the eligible neonates were collected at presentation, prior to the administration of antibiotic therapy (0 h) and again at 12 h and 24 h post-presentation. A positive sepsis would be indicated by values of more than 2 ng/mL from the use of the electrochemiluminescence technique on Cobas e411
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear if the index test assessor was blinded to reference test results or whether reference test assessor was blinded to results of the index test)

Directness

Directly applicable

Ozdemir, 2020

Bibliographic Reference	Ozdemir, S.A.; Colak, R.; Ergon, E.Y.; Calkavur, S.; Diagnostic Value of Urine sTREM-1 and Urine C-reactive Protein for Infants with Late Onset Neonatal Sepsis; Journal of Pediatric Infectious Diseases; 2020; vol. 15 (no. 2); 72-78

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Turkey Study setting Behcet Uz Children's Hospital Study dates January 2017 - January 2018 Sources of funding None reported
Inclusion criteria	Neonates hospitalised in the NICU and late-onset infection occurred during follow-up

Exclusion criteria	Major congenital malformations Babies born to mothers with clinical chorioamnionitis Perinatal asphyxia Major nephrological problems
Sample characteristics	Sample size 66 Mean gestational age (SD) 33.1 weeks (4.8)
Index test(s)	Urine C-reactive protein
Reference standard (s)	Blood culture on sample taken
Methodological details	For the blood culture, 1-mL blood was obtained for culture bottle. Serum CRP level was analyzed by scattering immunoturbidimetry (Beckman Coulter AU5800); BUN, by kinetic UV test (Beckman Coulter AU5800); SCr, by colorimetrickinetic technique (Beckman Coulter AU5800). All urine samples were collected with urethral catheterization at the time of sepsis diagnosis
Outcomes	Diagnostic test accuracy outcomes: Sensitivity, specificity, positive predictive value, ngative predictive value, positive and negative likelihood ratios, area under the curve

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Yes
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	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
	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(No information about timing of the two tests)*
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(No information about time between reference standard and index test)*
Overall risk of bias and directness	Risk of Bias	Moderate *(No information about time between reference standard and index test)*
	Directness	Directly applicable

Palmer, 2004

Bibliographic Reference	Palmer, Ayo; Carlin, John B; Freihorst, Joachim; Gatchalian, Salvacion; Muhe, Lulu; Mulholland, Kim; Weber, Martin W; WHO Young Infant Study, Group; The use of CRP for diagnosing infections in young infants < 3 months of age in developing countries.; Annals of tropical paediatrics; 2004; vol. 24 (no. 3); 205-12

Study Characteristics

Study type	Cross-sectional study
Study location	Ethiopia, The Gambia, Papua New Guinea and The Philippines
Study setting	Hospitals or outpatient clinics serving large numbers of sick infants
Study dates	Not reported
Sources of funding	None reported
Inclusion criteria	Age <91 days Infants with symptoms of infection
Exclusion criteria	None
Sample size	966 (54 with positive blood culture, 13 positive CSF culture, 15 positive blood and CSF culture)
Average age at evaluation (variance)	Average not reported. Number aged: 0-7 days: 158 8-28 days: 227 29-90 days: 581
Index test(s)	C-reactive protein (CRP) 10 mg/l, 20 mg/l, 40 mg/l

Reference standard (s)	Blood culture on sample taken Infants with signs or symptoms of bacterial infection CSF culture on sample taken Infants with signs of meningitis
Methodological details	Definition of infection: Positive blood or CSF culture Blood and CSF cultures: Blood and CSF cultures were processed using standard bacteriological methods CRP culture: Blood samples were collected by venepuncture, centrifuged and the serum separated. Serum was frozen and stored at –20dC until shipment on dry ice to Hanover, Germany where the CRP determination was performed. Serum CRP levels were measured by laser nephelometry using polystyrol particles covered with a monoclonal mouse anti-CRP antibody (Dade Behring, Marburg, Germany).
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of reference test results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether index test assessor was aware of reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was aware of reference test results or whether reference test assessor was aware of index test results)

Directness

Directly applicable

Philip, 1980

Bibliographic Reference Philip AG; Hewitt JR; Early diagnosis of neonatal sepsis.; Pediatrics; 1980; vol. 65 (no. 5)

Study Characteristics

Study type	Cross-sectional study
Study location	USA
Study setting	Intensive care nursery at the Medical Center Hospital of Vermont
Study dates	October 1975 - June 1979
Sources of funding	None reported
Inclusion criteria	Babies with suspected sepsis or meningitis in the first week after birth
Exclusion criteria	None
Sample size	376
Index test(s)	C-reactive protein (CRP) >0.8 mg/100 ml White blood cell count Cut-off value: <5000 cells/mm^3
Reference standard (s)	Blood culture on sample taken Cut-off value: <5000 cells/mm^3 CSF culture on sample taken
Methodological details	Proven infection definition: Babies whose blood (and sometimes CSF) cultures were positive within 48 hours of test. When a newborn with suspected sepsis or meningitis was identified, evaluation included a gastric aspirate for smear when indicated, a white blood cell count and differential, platelet estimate and blood, urine and cerebrospinal cultures.

	C-reactive protein: Using the latex method White blood cell count: Performed as part of routine laboratory tests
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

(Exclusion criteria not reported)

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether assessor of index tests was blinded to results of reference test)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether assessor of index tests was blinded to results of reference test)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether assessor of reference tests was blinded to results of index tests)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear whether assessor of reference tests was blinded to results of index tests)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was blinded to reference test results or whether reference test assessor was blinded to index test results)

Directness

Directly applicable

Ponnusamy, 2012

Bibliographic Reference	Ponnusamy, Vennila; Venkatesh, Vidheya; Curley, Anna; Musonda, Patrick; Brown, Nicholas; Tremlett, Catherine; Clarke, Paul; Segmental percutaneous central venous line cultures for diagnosis of catheter-related sepsis.; Archives of disease in childhood. Fetal and neonatal edition; 2012; vol. 97 (no. 4); f273-8

Study Characteristics

Study type	Cross-sectional study
Study location	UK
Study setting	Neonatal ICU

Study dates	2009 to 2010
Sources of funding	Not mentioned
Inclusion criteria	Neonates who had a segmental percutaneous central venous line
Exclusion criteria	Lines were excluded if removed within <24 hours in situ
Sample size	143 (However, the analysis was by number of percutaneous central venous lines, which was 189)
Average birth weight (variance)	Median (range) 1045 g (400 to 4500)
Average gestational age (variance)	Median (range) 28.5 weeks (22.7 to 40.5)
Average age at evaluation (variance)	-
Percentage of females	-
Loss to follow-up	None
Index test(s)	Samples from tip of IV long line *The PCVL was cut in the following order to obtain three approximately 1-cm-long formerly subcutaneous segments: (1) tip; (2) proximal, taken 1–2 cm from the point of skin entry; (3) middle. Three segments were collected for all lines removed. For infants with suspected sepsis at line removal, a single peripheral BC was also concurrently obtained and sent for culture and sensitivity. Line segments were cultured by the Maki roll technique and a growth of >15 colony forming units was considered positive*
Reference standard (s)	Blood culture on sample taken Infection confirmed by positive blood culture

Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

No

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

Could the selection of patients have introduced bias?

High

(The methods section said that all central lines were eligible. However, this is not the same thing as the sample of patients being consecutive. The participants could have been selected)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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?

Unclear

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

High

(The index and reference test results could have been analysed together. The study looked at number of central lines, not number of participants. Therefore, there are double-counting issues. Methods don't define the index and reference tests)

Directness

Directly applicable

Puri, 1995

Bibliographic Reference	Puri, J; Revathi, G; Faridi, M M; Talwar, V; Kumar, A; Parkash, B; Role of body surface cultures in prediction of sepsis in a neonatal intensive care unit.; Annals of tropical paediatrics; 1995; vol. 15 (no. 4); 307-11

Study Characteristics

Study type	Cross-sectional study
Study location	India
Study setting	NICU
Study dates	March 1994 - June 1994
Sources of funding	None reported
Inclusion criteria	Premature neonates Born in the hospital and admitted to the NICU Not previously received antibiotic or antiseptic therapy
Exclusion criteria	None

Sample size	35
Average birth weight (variance)	Mean 1365 g
Average gestational age (variance)	Mean 30 weeks
Average age at evaluation (variance)	All samples were taken on 4th day of life (96 hours ±4)
Index test(s)	Surface swab 11 skin samples: scalp, axillae, neckfold, umbilicus, inguinal folds, anal cleft, lumbar area, palms, cubital fossa, soles of feet and popliteal spaces
Reference standard (s)	Blood culture on sample taken
Methodological details	Blood culture: Taken at onset of febrile episode, within 14 days of surface swabs or on development of other clinical signs of septicaemia (lethargy, sluggish reflexes, jaundice, diarrhoea, poor feeding, conjuctivitis). Processed according to conventional techniques. Surface cultures: Taken on 4th day of life (96 hours ±4) (when maximum colonisation occurs). Samples were collected before any soap or antiseptic solution was applied to the umbilicus. Evaluation: Blood and surface culture with the same pathogen: True positive Both cultures sterile or showed non-pathogenic microorganisms: True negative Blood culture sterile but pathogen in skin culture OR Blood and surface cultures revealed different pathogens: False positive Pathogen in blood culture but not skin culture: False negative
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Limited information on how patients were selected)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Limited information about how patients were selected)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

If a threshold was used, was it pre-specified?

Yes

(Definition of infection was stated in methods)

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear if the index test assessor was blinded to results of the reference test)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear if the reference test assessor was blinded to results of the index test)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear how patients were selected and whether the index test assessor was blinded to reference test results or reference test assessor was blinded to index test results)

Directness

Partially applicable

Ramgopal, 2019

Bibliographic Reference Ramgopal, Sriram; Walker, Lorne W; Nowalk, Andrew J; Cruz, Andrea T; Vitale, Melissa A; Immature neutrophils in young febrile infants.; Archives of disease in childhood; 2019; vol. 104 (no. 9); 884-886

Study Characteristics

Study type	Cross-sectional study
Study details	Study location USA Study setting Paediatric emergency department Study dates January 2006 - December 2017 Sources of funding National Institutes of Health

Inclusion criteria	Age less than 60 days With fever (≥38.0°C)
Exclusion criteria	Did not receive blood, urine and CSF cultures Received antibiotics prior to culture Records were missing, local infection was reported, complete blood count was not performed or if they had UTI without bacterial infection
Sample characteristics	Sample size 75
Index test(s)	Immature:total neutrophil ratio White blood cell count
Reference standard (s)	Blood culture on sample taken CSF culture
Methodological details	Infection definiton: growth of a single organism from blood or CSF cultures, excluding known contaminants Complete blood counts were performed through an automated process (Beckman Coulter LH 780, 500 and DXH 500, Beckman Coulter Diagnostics, Pasadena, California, USA). If an immature cell is detected, a manual or image differential is performed to obtain the absolute band count (ABC). For those patients for whom no immature cells are detected, a differential is not performed and the ABC was assigned a count of zero for this study. Immature:total neutrophils were calculated by dividing ABC by the sum of the ABC and absolute neutrophil count.
Outcomes	Diagnostic test accuracy outcomes: Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes

Section	Question	Answer
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Yes
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	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
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index test thresholds not pre-specified)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Section	Question	Answer
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(Time between index and reference tests unclear)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Time between index and reference tests unclear. Index test thresholds not pre-specified)*
	Directness	Directly applicable

Rosenfeld, 2019

Bibliographic Reference	Rosenfeld, Charles R; Shafer, Grant; Scheid, Lisa M; Brown, L Steven; Screening and Serial Neutrophil Counts Do Not Contribute to the Recognition or Diagnosis of Late-Onset Neonatal Sepsis.; The Journal of pediatrics; 2019; vol. 205; 105-111e2

Study Characteristics

Study type	Cross-sectional study
Study location	USA
Study setting	Neonatal ICU

Study dates	2009 to 2013
Sources of funding	Not mentioned
Inclusion criteria	Late-onset infection: 72 hours onwards (corrected age) without stated end-point Symptoms and/or signs of neonatal infection
Exclusion criteria	No central venous catheter
Sample size	140
Average birth weight (variance)	Mean (SD) 1131 g (56)
Average gestational age (variance)	Mean (SD) 28.3 weeks (4)
Average age at evaluation (variance)	Mean (SD) 29.2 days (34)
Percentage of females	58%
Loss to follow-up	None
Index test(s)	Neutrophil count
Reference standard (s)	Blood culture on sample taken Proven if 1-2 blood cultures were positive at ≤4 hours; suspect if both blood cultures were negative by 48 hours or positive after 48 hours
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

No

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

Could the selection of patients have introduced bias?

High

(Retrospective database was used that only had details of neonates who had central venous catheters)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(This study only include neonates with a central venous catheter. Some participants were excluded because they only had 1 blood culture (all should have had 2 or more and be included))

Directness

Directly applicable

Seibert, 1990

Bibliographic Reference	Seibert, K; Yu, V Y; Doery, J C; Embury, D; The value of C-reactive protein measurement in the diagnosis of neonatal infection.; Journal of paediatrics and child health; 1990; vol. 26 (no. 5); 267-70

Study Characteristics

Study type	Cross-sectional study
Study location	Australia
Study setting	Neonatal ICU
Study dates	Not mentioned. Accepted for publication during 1990
Sources of funding	Not mentioned
Inclusion criteria	Late-onset infection: 72 hours onwards (corrected age) without stated end-point Symptoms and/or signs of neonatal infection
Exclusion criteria	None
Sample size	85 neonates. 100 occasions of suspected infection were studied
Average birth weight (variance)	-
Average gestational age (variance)	-
Average age at evaluation (variance)	-

Percentage of females	-
Loss to follow-up	None
Index test(s)	C-reactive protein (CRP)
Reference standard (s)	Blood culture on sample taken Infection confirmed based on overwhelming signs and symptoms of infection and positive blood culture
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

High

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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

Could the conduct or interpretation of the index test have introduced bias?

Unclear

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Participants could have been selected for the study)

Directness

Partially applicable

(No upper age limit provided)

Sharma, 1993

Bibliographic Reference	Sharma A; Kutty CV; Sabharwal U; Rathee S; Mohan H; Evaluation of sepsis screen for diagnosis of neonatal septicemia.; Indian journal of pediatrics; 1993; vol. 60 (no. 4)

Study Characteristics

Study type	Cross-sectional study
Study location	India
Study setting	Not reported
Study dates	Not reported
Sources of funding	None reported
Inclusion criteria	Neonates who were clinically suspected of sepsis with no obvious focus of infection

Exclusion criteria	None
Sample size	50 (10 with confirmed sepsis)
Average birth weight (variance)	Not reported. 70% were low birth weight (<2.5 kg)
Average age at evaluation (variance)	Not reported. 66% greater than 7 days of age
Percentage of females	26%
Index test(s)	C-reactive protein (CRP)
Reference standard (s)	Blood culture on sample taken
Methodological details	Culture positive sepsis: Positive blood culture and clinical signs suggesting septicaemia Blood culture: Investigation at time of admission CRP: Investigation at time of admission. Semiquantitative estimation by Latex agglutination technique (rapitex CRP test). Cut-off value: >6 µgm/ml
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Sampling method unclear)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

(No information about exclusion criteria)

Could the selection of patients have introduced bias?

Unclear

(Patient selection methods and exclusion criteria unclear)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Limited information about methods used)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Limited information about methods used)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Unclear

(Limited information about methods used)

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Limited information about methods used)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Limited information about methods used)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

(All at time of admission)

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Unclear

(Limited information about methods used)

Could the patient flow have introduced bias?

Unclear

(Unclear whether all patients were included in the analysis)

Overall risk of bias and directness

Risk of Bias

High

(Limited information about methods, including sampling methods, exclusion criteria and whether all patients were included in the analysis)

Directness

Directly applicable

Smith, 2008

Bibliographic Reference	Smith, P Brian; Garges, Harmony P; Cotton, C Michael; Walsh, Thomas J; Clark, Reese H; Benjamin, Daniel K Jr; Meningitis in preterm neonates: importance of cerebrospinal fluid parameters.; American journal of perinatology; 2008; vol. 25 (no. 7); 421-6

Study Characteristics

Study type	Cross-sectional study
Study location	USA
Study setting	Neonatal ICU
Study dates	1997 to 2004
Sources of funding	National Institute for Health, National Institute of Child Health and Human Development, Thrasher Research Fund
Inclusion criteria	Participants who had a lumbar puncture

	In a neonatal ICU
Exclusion criteria	>35 weeks gestation CSF reservoirs and ventriculoperitoneal shunts Participants with likely contaminated CSF specimens Participants with viral meningitis diagnosed by viral culture
Sample size	4632
Average birth weight (variance)	-
Average gestational age (variance)	Gestational age, % participants: 22-25 weeks, 18% Gestational age, % participants: 26-29 weeks, 42% Gestational age, % participants: 30-33 weeks, 39%
Average age at evaluation (variance)	-
Percentage of females	44%
Loss to follow-up	None
Index test(s)	White blood cell count
Reference standard (s)	CSF culture on sample taken Or CSF positive Gram stain or positive CSF antigen test concordant with a blood culture
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Unclear

Could the selection of patients have introduced bias?

High

(Retrospective. It is possible for cases to be omitted from databases)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

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?

Unclear

Could the conduct or interpretation of the index test have introduced bias?

High

(It is unlikely that the index and reference tests were analysed separately)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?

High

(It is unlikely that the index and reference tests were analysed separately)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(It is unlikely that the index and reference tests were analysed separately)

Directness

Partially applicable

(The inclusion criteria was not on grounds of clinical signs and symptoms - it was on the basis of whether the participants had a lumbar puncture. We do not know the age range of inclusion.)

Sucilathangam, 2012

Bibliographic Reference	Sucilathangam, G.; Amuthavalli, K.; Velvizhi, G.; Ashihabegum, M.A.; Jeyamurugan, T.; Palaniappan, N.; Early diagnostic markers for neonatal sepsis: Comparing procalcitonin (PCT) and C-reactive protein (CRP); Journal of Clinical and Diagnostic Research; 2012; vol. 6 (no. 4suppl2); 627-631

Study Characteristics

Study type	Cross-sectional study
Study location	India
Study setting	Neonatal intensive care unit (NICU) at Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu
Study dates	April - September 2010
Sources of funding	None reported
Inclusion criteria	Infants admitted to the ward with signs of sepsis, or who developed signs of sepsis while on the ward
Exclusion criteria	Infants who were on antibiotics or those who developed the signs of sepsis within 72 hours of discontinuation of the antibiotics and those who had birth asphyxia, aspiration syndrome or laboratory findings which were suggestive of the inborn errors of metabolism and congenital anomalies
Sample size	50 (14 culture positive)

Average birth weight (variance)	Not reported. Low birth weight: 48%
Average gestational age (variance)	Not reported. Pre-term: 44%
Percentage of females	36%
Index test(s)	C-reactive protein (CRP) Procalcitonin (PCT)
Reference standard (s)	Blood culture on sample taken
Methodological details	Culture confirmed sepsis: Blood culture confirmed infection Blood culture: Blood was obtained from each neonate prior to the commencement of the antibiotics for the sepsis work up, which included haematological parameters like the erythrocyte sedimentation rate, total leukocyte count, the absolute neutrophil count (ANC), the immature neutrophils to total neutrophil count ratio (I/T ratio), platelet count, degenerative changes in the neutrophils, blood culture and antibiotic sensitivity, PCT and C-reactive protein (CRP) estimation CRP: Measured using the A-15 CRP Kit (Bio-system, Costa Brava, Barcelona, Spain). The quantitative measurement of CRP from the serum was done by an immunoturbidimetric method in the laboratory according to the manufacturer's instructions. The reagent was linear up to 150 mg/L. Cut-off value: 6mg/l PCT: Serum PCT level was measured by using a quantitative immuno-luminometry method and the Lumitest kit (BRAHMS Diagnostic, Berlin, Germany). In this assay, a PCT level of ≥0.5 ng/ml was considered as pathological. PCT levels of 0.5-2 ng/ml, 2-10 ng/ml and >10 ng/ml were considered as weakly positive, positive, and strongly positive
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Unclear

(Sampling method unclear)

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Unclear

(Sampling method unclear)

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of reference test results)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether index test assessor was aware of reference test results)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear whether reference test assessor was aware of index test results)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was aware of reference test results or whether reference test assessor was aware of index test results)

Directness

Directly applicable

West, 2012

Bibliographic Reference	West, B.A.; Peterside, O.; Ugwu, R.O.; Eneh, A.U.; Prospective evaluation of the usefulness of C-reactive protein in the diagnosis of neonatal sepsis in a sub-Saharan African region; Antimicrobial Resistance and Infection Control; 2012; vol. 1; 22

Study Characteristics

Study type	Cross-sectional study
Study location	Nigeria
Study setting	Special Care Baby Unit (SCBU) of the University of Port Harcourt Teaching Hospital
Study dates	May 2007 - November 2007
Sources of funding	None reported
Inclusion criteria	All newborns with clinical suspicion or risk factors for sepsis Signs: fever, respiratory distress, poor feeding, jaundice, hypothermia, convulsion, vomiting, irritability, lethargy and abdominal distension. Risk factors: outborn delivery, perinatal asphyxia, preterm delivery, prolonged rupture of membranes, maternal peripartum pyrexia and foul-smelling amniotic fluid
Exclusion criteria	Neonates who received antibiotics before admission Infants of mothers who had intrapartum antibiotics within a week of delivery

Sample size	420 (181 with positive blood culture)
Average birth weight (variance)	Mean (SD): 2.8 kg (0.9)
Average gestational age (variance)	Mean (SD): 36.8 weeks (3.6)
Percentage of females	35%
Index test(s)	C-reactive protein (CRP) Cut-off >6 mg/l
Reference standard (s)	Blood culture on sample taken
Methodological details	Sepsis definition: Positive blood culture Blood culture: 2 ml venous blood collected from a peripheral vein after adequate skin preparation and before the commencement of antibiotics. The blood was aseptically introduced into aerobic and anaerobic culture media. The specimens were processed according to standard methods in the microbiology laboratory [16]. Inoculated blood culture media were considered negative if there was no growth after continuous incubation for up to 7 days CRP: estimated qualitatively using the Lorne CRP latex kit manufactured by the Lorne laboratories Limited (Great Britain), standardized to detect serum CRP levels at or above 6 mg/l. Half a milliliter of venous blood was collected in plain bottles and centrifuged. C-reactive protein was estimated using a drop of undiluted serum placed onto the circle of the agglutination slide with the use of disposable pipettes provided in the kit. One drop of CRP latex reagent was added to the drop of serum and the broad end of the pipette was used to spread the latex reagent over the entire area of the test circle. The agglutination slide was gently tilted backwards and forwards approximately once every two seconds for two minutes. Visible agglutination of latex particles constituted a positive result which indicated a level of CRP>6 mg/l.
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

Risk of bias

Patient selection: risk of bias

Was a consecutive or random sample of patients enrolled?

Yes

Was a case-control design avoided?

Yes

Did the study avoid inappropriate exclusions?

Yes

Could the selection of patients have introduced bias?

Low

Patient selection: applicability

Are there concerns that included patients do not match the review question?

Low

Index tests: risk of bias

Were the index test results interpreted without knowledge of the results of the reference standard?

Unclear

(Unclear whether index test assessor was aware of results of the reference test)

If a threshold was used, was it pre-specified?

Yes

Could the conduct or interpretation of the index test have introduced bias?

Unclear

(Unclear whether index test assessor was aware of results of the reference test)

Index tests: applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low

Reference standard: risk of bias

Is the reference standard likely to correctly classify the target condition?

Yes

Were the reference standard results interpreted without knowledge of the results of the index test?

Unclear

(Unclear whether reference test assessor was aware of results of the index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?

Unclear

(Unclear whether reference test assessor was aware of results of the index test)

Reference standard: applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low

Flow and timing: risk of bias

Was there an appropriate interval between index test(s) and reference standard?

Yes

Did all patients receive a reference standard?

Yes

Did patients receive the same reference standard?

Yes

Were all patients included in the analysis?

Yes

Could the patient flow have introduced bias?

Low

Overall risk of bias and directness

Risk of Bias

Moderate

(Unclear whether index test assessor was aware of reference test results or whether reference test assessor was aware of index test results)

Directness

Directly applicable