National Institute for Health and Care Excellence

Draft

Neonatal infection: antibiotics for prevention and treatment

[G] Evidence review for investigations before starting treatment for late-onset neonatal infection

NICE guideline <number>

Evidence reviews underpinning recommendations 1.7.1-1.7.8 in the NICE guideline

December 2020

Draft for Consultation

These evidence reviews were developed by NICE Guideline Updates Team

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Investigations for late-onset neonatal infection

1.1 Review question

What investigations should be performed before starting treatment in babies with symptoms of late-onset neonatal infection?

1.1.1 Introduction

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

Accurately determining which babies have late-onset neonatal infection is important to help establish who should receive antibiotic treatment. There are a number of tests that can potentially be used to evaluate whether a baby has late-onset neonatal infection. It is therefore important to determine which tests are the most accurate and cost-effective for use in clinical practice. The aim of this review is to evaluate these tests and determine which are the most effective for the diagnosis of late-onset neonatal infection.

1.1.2 Summary of the protocol

Table 1 PICO table

Population	• Term babies up to 28 days of age and preterm babies up to 28 days corrected gestational age
Diagnostic test	• C-reactive protein (CRP) and other acute phase reactants • procalcitonin (PCT) • interleukins • cytokines • white blood cell count (including neutrophil count, which can be high or low, and the ratio of immature to total neutrophils, left shift, band granulocyte) • platelet count • cerebrospinal fluid (CSF) examination • urine microscopy or culture, including mode of collection (for example, catheter, suprapubic aspiration) • rapid tests (for example, polymerase chain reaction (PCR) (excluding CSF PCR) • surface swabs (skin, nose, ear, umbilical, rectal, axilla and groin, eye, throat) • Samples from tip of IV long line • chest X-ray
Reference standard	• For tests based on CSF parameters (CSF examination): CSF culture or CSF-PCR test on sample taken from 72 hours after birth to 28 days (corrected age)

	• For all other tests (excluding CSF examination): blood culture on sample taken from 72 hours after birth to 28 days (corrected age)
Outcomes	Diagnostic/predictive accuracy measures: • Positive and negative likelihood ratios • Sensitivity (detection rate) • Specificity • Positive and negative predictive values

1.1.3 Methods and process

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

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

Diagnostic accuracy studies were considered in addition to systematic reviews. The review protocol specified that, where possible, subgroup analyses would be conducted for gestational age of the baby (preterm vs term), as well as comparing babies already in hospital with those admitted to the hospital from home. No data were found for either of the subgroups. However, some studies had examined the same diagnostic test but used different thresholds as the cut-off to indicate infection. For any tests where a wide range of cut-off values were used (C-reactive protein and procalcitonin), the data were separated in subgroups based on the threshold used. Studies which investigated C-reactive protein were separated into three groups based on threshold values – either <10 mg/l, 10 mg/l or >10 mg/l. Studies which investigated procalcitonin were separated into two groups – those which used a cut-off ≤10 ng/ml and a single study which used a cut-off value of 1000 ng/ml. This approach was presented to the committee who agreed that the subgroups used were appropriate.

Where data was only reported for some of the outcomes, data for the other outcomes (sensitivity, specificity, likelihood ratios) were calculated based on the information provided in the studies. This meant that comparisons could be made between the diagnostic accuracy of each test.

For imprecision, clinical decision thresholds based on the likelihood ratio were set for each measure, above or below which a test would be recommended or considered of no clinical use. As the committee did not have any preference for clinical decision thresholds, the pre-specified threshold values stated in the methods chapter (2 for LR+ and 0.5 for LR-) were used with the line of no effect as the second clinical decision line in both cases.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A search was carried out to identify studies for this evidence review. This returned a total of 4,569 results. The protocol resulted in a higher number of potentially included studies, but the committee highlighted how some of the tests for late-onset neonatal infection are not currently used by the NHS and others, such as those that require a high volume of blood, are not practical for use with neonates. Consequently, only the

tests which are currently available for neonates in the NHS were included in the analysis. The tests which were excluded from the review following discussion with the committee were: Acute phase reactants (other than C-reactive protein and procalcitonin), white blood cell left shift and band granulocytes, neutrophil to lymphocyte ratio, neutrophil CD64 expression, neutrophil and monocyte CD64 indexes, urinary neutrophil gelatinase-associated lipocalin, 16s rRNA polymerase chain reaction, multiplex polymerase chain reaction and resistin. All other tests that matched the protocol were eligible for inclusion. Using this additional exclusion criteria 106 studies were identified as potential includes. Full text articles were ordered and reviewed against the inclusion criteria, of which 32 cross-sectional studies met the inclusion criteria for the review.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 453 results of which 12 were identified as possible included studies. After full text review, 4 met the inclusion criteria. In total there were therefore 36 cross-sectional studies which met the inclusion criteria for this review.

See appendix B for full literature search strategies and appendix C for a study selection flowchart.

1.1.4.2 Excluded studies

See appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the diagnostic evidence

Table 2 Summary of included clinical studies

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
Aminullah 2001 (n=35)	• Cross-sectional • Follow-up time not reported	Indonesia *Neonatal ward and neonatal intensive care unit*	• 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	• C-reactive protein (CRP) *Cut-off 12 mg/dl*	• Blood culture
Anwar ul Haq 2019 (n=160)	• Cross-sectional • Follow-up time not reported	Pakistan *Department of Pediatrics*	• Suspicion of sepsis	• C-reactive protein	• Blood culture
Anwer 2000 (n=50)	• Cross-sectional • Follow-up time not reported	Pakistan *Neonatal Intensive Care Unit*	• Infants admitted to the neonatal intensive care unit	• White blood cell count	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
				<5000/>20000 cells/mm^3 • Neutrophil count *Neutropenia/neutrophilia age adjusted count* • Immature: total neutrophil ratio *>0.2* • Platelet count *<50,000/mm*	
Balasubramanin 2018 (n=100)	• Cross-sectional • Follow-up time not reported	India *Neonatal Intensive Care Unit*	• Age less than 30 days • Need for lumbar puncture	• C-reactive protein	• Blood culture
Beltempo 2018 (n=416)	• Cross-sectional • Follow-up time not reported	Canada *Hospital*	• Late-onset infection	• C-reactive protein (CRP) *>10 mg/l*	• Blood culture • CSF culture
Berger 1995 (n=24)	• Cross-sectional • Follow-up time not reported	Switzerland *Intensive care unit*	• Late-onset infection *72 hours (corrected age) – 6 weeks*	• C-reactive protein (CRP) *>20 mg/l* • Immature: total neutrophils *>0.65* • Neutrophil count *>5000 /mm^3*	• Blood culture
Blommendahl 2002 (n=169)	• Cross-sectional • Follow-up time not reported	Finland *Hospital*	• Symptoms and/or signs of neonatal infection • Only neonates who had a blood sample taken concomitantly for blood culture and the index text	• C-reactive protein (CRP) *1 mg/l* • Procalcitonin (PCT) *1 µg/ml*	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
			• Neonatal infection/sepsis		
Boo 2008 (n=87)	• Cross-sectional • Follow-up time not reported	Kuala Lumpar *Neonatal Intensive Care Unit*	• Infants admitted to the neonatal intensive care unit with signs suggestive of sepsis, or who developed signs of sepsis while in the ward	• C-reactive protein (CRP) *Age-adjusted cut-off values (>1 mg/ml from 4 days of age onwards)* • Procalcitonin (PCT) *>2 ng/ml*	• Blood culture
Boonkasidecha 2013 (n=53)	• Cross-sectional • Follow-up time not reported	Thailand *Neonatal Intensive Care Unit and nursery ward*	• All newborn infants who presented with signs and symptoms of neonatal sepsis	• C-reactive protein (CRP) *>1.90 mg/l (at time of blood culture)* *>1.25 mg/l (12-24 hours after blood culture)*	• Blood culture
Huang 2019 (n=1830)	• Cross-sectional • Follow-up time not reported	Shanghai *4 tertiary class A paediatric hospitals*	• All term neonates who underwent lumbar puncture (LP) in Shanghai	• White blood cell count *Cut-off 19.5 (10^6/L)*	• CSF culture
Iskandar 2019 (n=51)	• Cross-sectional • Follow-up time not reported	Indonesia *Perinatology Department*	• Age between 0 and 30 days • Fulfilling SIRS criteria for neonates	• Procalcitonin (PCT) *161.33 pg/ml*	• Blood culture
Jacquot 2009 (n=73)	• Cross-sectional • Follow-up time not reported	France *Neonatal Intensive Care Unit*	• Late-onset infection: 72 hours onwards (corrected age) • Symptoms and/or signs of neonatal infection	• C-reactive protein (CRP) *>10 mg/l* • Procalcitonin (PCT) *0.6 ng/ml*	• Blood culture
Joji 2018 (n=115)	• Cross-sectional	India *Medical centre*	• Patients with 2 or more clinical	• C-reactive protein (CRP)	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
	• Follow-up time not reported		features of infection	*Cut-off value: 0.6 mg/dl*	
Khair 2012	• Cross-sectional • Follow-up time not reported	Bangladesh *Neonatal Intensive Care Unit*	• Neonates aged 0-28 days with clinically suspected sepsis	• C-reactive protein (CRP) *Cut-off >0.6 mg/dl* • White blood cell count *<5000/>25000/mm³ at birth* *>30000 12-24 hours* *>21000 day 2 onwards* • I:T ratio *>0.2* • Platelet count *100,000 cells/mm3*	• Blood culture
Khan 2019	• Cross-sectional • Follow-up time not reported	Pakistan *Neonatal Unit*	• Neonates aged 0-28 days with clinically suspected sepsis	• C-reactive protein (CRP) *>5 mg/dl*	• Blood culture
Kumar 2010	• Cross-sectional • Follow-up time not reported	Kenya *Newborn unit*	• Suspected sepsis based on perinatal risk factors or suspicious clinical findings	• C-reactive protein (CRP) *Cut-off: 5 mg/l*	• Blood culture
Lopez Sastre 2006 (n=100)	• Cross-sectional • Follow-up time not reported	Spain *Neonatal services within hospitals*	• Symptoms and/or signs of neonatal infection • Risk factors for late-onset neonatal infection • Aged between 4 and 28 days of life	• Procalcitonin (PCT) *0.59 ng/ml*	• Blood culture
Makhoul 2005 (n=360)	• Cross-sectional • Follow-up time not reported	Israel *Neonatal Intensive Care Unit*	• Late-onset infection *72 hours onwards (corrected age)*	• Rapid test *PCR amplification (Detection threshold*	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
			• Symptoms and/or signs of neonatal infection	*10 CFU/ml)*	
Makhoul 2006 (n=111)	• Cross-sectional • Follow-up time not reported	Israel *Neonatal Intensive Care Unit*	• Late-onset infection *72 hours onwards (corrected age)* • Symptoms and/or signs of neonatal infection	• Rapid test *Staphylococcus - specific polymerase chain reaction (PCR) (Detection threshold 10 CFU/ml)*	• Blood culture
Marconi 2008 (n=63)	• Cross-sectional • Follow-up time not reported	Brazil *Neonatal Unit*	• Catheter tips from patients who had presented one or more blood cultures collected close to the date of catheter removal	• Samples from tip of IV long line *1. Semi-quantitative culture (Culture of tip yielded ≥15 colony forming units of the same colony type)* *2. Quantitative method (Culture medium clouding)*	• Blood culture
Martin-Rabdn 2017 (n=277)	• Cross-sectional • Follow-up time not reported	Spain *Neonatal referral unit*	• Symptoms and/or signs of neonatal infection	• Samples from tip of IV long line *Culture of tip yielded ≥15 colony forming units of the same colony type* *1. Longitudinal*	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
				ly split metho d 2. *Roll plate metho d*	
Mkony 2014 (n=208)	• Cross-sectional • Follow-up time not reported	Tanzania *Neonatal Unit*	• Neonates who met the WHO definition for septicaemia	• C-reactive protein (CRP) *Cut-off: >5 mg/l*	• Blood culture
Nakamura 1989 (n=90)	• Cross-sectional • Follow-up time not reported	Japan *Neonatal Intensive Care Unit*	• Symptoms and/or signs of neonatal infection	• C-reactive protein (CRP) *>1 mg/dl*	• Blood culture • CSF culture
Omar 2019 (n=60)	• Cross-sectional • Follow-up time not reported	Malaysia *Paediatric Intensive Care Unit*	• Neonates with suspected septicaemia	• Procalcitonin (PCT) *Cut-off value >2 ng/ml*	• Blood culture
Ozdemir 2020 (n=66)	• Cross-sectional • Follow-up time not reported	Turkey *Children's hospital*	• Neonates hospitalised in the NICU and late-onset infection occurred during follow-up	• Urine C-reactive protein	• Blood culture
Palmer 2004 (n=966)	• Cross-sectional • Follow-up time not reported	Ethiopia, The Gambia, Papua New Guinea, The Philippines *Hospitals or outpatient clinics*	• Age <91 days • Infants with symptoms of infection	• C-reactive protein (CRP) *10 mg/l, 20 mg/l, 40 mg/l*	• Blood culture • CSF culture
Philip 1980 (n=376)	• Cross-sectional • Follow-up time not reported	USA *Intensive care nursery*	• Babies with suspected sepsis or meningitis in the first week after birth	• C-reactive protein (CRP) *>0.8 mg/100 ml* • White blood cell count *Cut-off value: <5000 cells/mm^3*	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
Ponnusamy 2012 (n=143)	• Cross-sectional • Follow-up time not reported	UK *Neonatal Intensive Care Unit*	• Neonates who had a segmental percutaneous central venous line	• Samples from tip of IV long line *Blood culture and line segment culture-positive with same organism*	• Blood culture
Puri 1995 (n=35)	• Cross-sectional • Follow-up time not reported	India *Neonatal Intensive Care Unit*	• Premature neonates • Born in the hospital and admitted to the NICU • Not previously received antibiotic or antiseptic therapy	• Surface swab *11 skin samples: scalp, axillae, neckfold, umbilicus, inguinal folds, anal cleft, lumbar area, palms, cubital fossa, soles of feet and popliteal spaces*	• Blood culture
Ramgopal 2019 (n=75)	• Cross-sectional • Follow-up time not reported	USA *Paediatric emergency department*	• Age less than 60 days • With fever (≥38.0°C)	• Immature: total neutrophil ratio • White blood cell count	• Blood culture • CSF culture
Rosenfeld 2019 (n=140)	• Cross-sectional • Follow-up time not reported	USA *Neonatal Intensive Care Unit*	• Late-onset infection: 72 hours onwards (corrected age) • Symptoms and/or signs of neonatal infection	• Neutrophil count *≥5400 and ≤1800* • Ratio of I:T neutrophils *>0.12*	• Blood culture
Seibert 1990 (n=85)	• Cross-sectional • Follow-up time not reported	Australia *Neonatal Intensive Care Unit*	• Late-onset infection: 72 hours onwards (corrected age) without stated end-point	• C-reactive protein (CRP) *>10 mg/l*	• Blood culture

Study	Study type and follow-up time	Study location and setting	Population	Index tests	Reference tests
			• Symptoms and/or signs of neonatal infection		
Sharma 1993 (n=50)	• Cross-sectional • Follow-up time not reported	India *Setting not reported*	• Neonates who were clinically suspected of sepsis with no obvious focus of infection	• C-reactive protein (CRP) *Cut-off value: >6 µgm/ml*	• Blood culture
Smith 2008 (n=4632)	• Cross-sectional • Follow-up time not reported	USA *Neonatal Intensive Care Unit*	• Patients who had a lumbar puncture in a neonatal ICU	• CSF White blood cell count *>10 cells/mm^3*	• CSF culture
Sucilathangam 2012 (n=50)	• Cross-sectional • Follow-up time not reported	India *Neonatal Intensive Care Unit*	• Infants admitted to the ward with signs of sepsis, or who developed signs of sepsis while on the ward	• C-reactive protein (CRP) *Cut-off value: 6mg/l* • Procalcitonin (PCT) *Cut-off value: ≥0.5 ng/ml*	• Blood culture
West 2012 (n=420)	• Cross-sectional • Follow-up time not reported	Nigeria *Special care baby unit*	• All newborns with clinical suspicion or risk factors for sepsis	• C-reactive protein (CRP) *Cut-off >6 mg/l*	• Blood culture

See appendix D for full evidence tables.

1.1.6 Summary of the diagnostic evidence

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95% CI)	Effect size* (95%CI)	Quality
C-reactive protein (≤10 mg/l): Sample at time of blood culture					
14	2083	0.80 (0.68, 0.88)	0.71 (0.63, 0.78)	LR+ 2.77 (2.33, 3.29)	Very low
				LR- 0.29 (0.19, 0.41)	Low
C-reactive protein (10 mg/l): Sample at time of blood culture					
5	928	0.62 (0.50, 0.73)	0.73 (0.59, 0.83)	LR+ 2.33 (1.55, 3.49)	Very low
				LR- 0.53 (0.38, 0.69)	Very low
C-reactive protein (>10 mg/l): Sample at time of blood culture					

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95% CI)	Effect size* (95%CI)	Quality
3	325	0.77 (0.56, 0.90)	0.69 (0.38, 0.89)	LR+ 2.93 (0.95, 7.75)	Very low
				LR- 0.40 (0.12, 1.08)	Very low
C-reactive protein (≤10 mg/l): Sample taken 12-24 hours after blood culture					
2	257	0.88 (0.59, 0.97)	0.91 (0.38, 0.99)	LR+ not calculable	Low
				LR- 0.23 (0.03, 0.99)	Very low
C-reactive protein (10 mg/l): Sample taken 24 hours after blood culture					
1	416	0.84 (0.76, 0.90)	0.70 (0.65, 0.75)	LR+ 2.82 (2.32, 3.39)	Moderate
				LR- 0.23 (0.14, 0.34)	Moderate
C-reactive protein (10 mg/l): Sample taken 48 hours after blood culture					
1	416	0.73 (0.66, 0.80)	0.79 (0.74, 0.84)	LR+ 3.52 (2.72, 4.52)	Moderate
				LR- 0.34 (0.26, 0.44)	Moderate
C-reactive protein (from urine sample – 9.4 ng/ml): Sample taken when infection was diagnosed					
1	66	0.52 (0.35, 0.68)	0.80 (0.64, 0.90)	LR+ 2.58 (1.22, 5.44)	Low
				LR- 0.62 (0.39, 0.88)	Moderate
Procalcitonin (lower threshold) (≤10 ng/ml)					
7	535	0.76 (0.67, 0.84)	0.65 (0.57, 0.72)	LR+ 2.21 (1.64, 2.91)	Low
				LR- 0.37 (0.24, 0.54)	Very low
Procalcitonin (higher threshold) (1000 ng/ml)					
1	169	0.77 (0.50, 0.92)	0.62 (0.54, 0.70)	LR+ 2.02 (1.40, 2.91)	Very low
				LR- 0.37 (0.14, 1.01)	Very low
Neutrophil count (>5000 / ≤1800 ≥5400 / age-adjusted count)					
3	329	0.60 (0.48, 0.70)	0.62 (0.51, 0.72)	LR+ 1.61 (1.05, 2.37)	Very low
				LR- 0.66 (0.44, 0.95)	Very low
Neutrophils (I:T ratio) (>0.12 / >0.2 / >0.65)					
6	961	0.70 (0.39, 0.89)	0.55 (0.26, 0.81)	LR+ 1.62 (1.03, 2.81)	Very low
				LR- 0.58	Very low

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95% CI)	Effect size* (95%CI)	Quality
				(0.28, 0.96)	
White blood cell count (from blood culture) (<5000 cells/mm^3 / <5000 >20000 cells/mm^3)					
3	526	0.46 (0.32, 0.60)	0.87 (0.66, 0.96)	LR+ 4.37 (1.10, 12.70)	Very low
				LR- 0.64 (0.43, 0.95)	Very low
White blood cell count (from CSF sample) (>19.5 cells/mm^3 / >20 cells/mm^3)					
2	6462	0.94 (0.31, 1.00)	0.93 (0.52, 0.99)	LR+ Not calculable	Very low
				LR- 0.21 (0.00, 1.33)	Very low
Platelet count (100 cells/mm^3 / 150 cells/mm^3)					
2	150	0.53 (0.34, 0.71)	0.63 (0.19, 0.92)	LR+ 2.13 (0.48, 8.15)	Very low
				LR- 0.98 (0.34, 3.00)	Very low
Surface swabs (anal cleft)					
1	31	0.07 (0.02, 0.26)	0.46 (0.22, 0.71)	LR+ 0.13 (0.03, 0.67)	Low
				LR- 2.03 (1.08, 3.79)	Low
Surface swabs (axilla)					
1	31	0.45 (0.26, 0.66)	0.46 (0.22, 0.71)	LR+ 0.84 (0.41, 1.68)	Very low
				LR- 1.19 (0.58, 2.47)	Very low
Surface swabs (cubital fossa)					
1	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Low
				LR- 3.35 (1.38, 8.10)	Low
Surface swabs (ear)					
1	31	0.55 (0.34, 0.74)	0.79 (0.51, 0.93)	LR+ 2.63 (0.82, 8.46)	Very low
				LR- 0.57 (0.33, 0.99)	Low
Surface swabs (external genitalia)					
1	31	0.02 (0.00, 0.19)	0.62 (0.35, 0.84)	LR+ 0.06 (0.00, 1.08)	Low
				LR- 1.56 (1.00, 2.43)	Very low
Surface swabs (gastric aspirate)					

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95% CI)	Effect size* (95%CI)	Quality
1	31	0.45 (0.26, 0.66)	0.71 (0.43, 0.89)	LR+ 1.55 (0.57, 4.21)	Very low
				LR- 0.77 (0.45, 1.32)	Very low
Surface swabs (inguinal fold)					
1	31	0.02 (0.00, 0.19)	0.38 (0.16, 0.65)	LR+ 0.04 (0.00, 0.61)	Low
				LR- 2.60 (1.25, 5.42)	Low
Surface swabs (lumbar area)					
1	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Low
				LR- 3.35 (1.38, 8.10)	Low
Surface swabs (nasal swab)					
1	31	0.50 (0.30, 0.70)	0.71 (0.43, 0.89)	LR+ 1.71 (0.64, 4.57)	Very low
				LR- 0.71 (0.40, 1.24)	Very low
Surface swabs (neckfold)					
1	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Low
				LR- 3.35 (1.38, 8.10)	Low
Surface swabs (palms)					
1	31	0.12 (0.04, 0.32)	0.29 (0.11, 0.57)	LR+ 0.17 (0.05, 0.57)	Low
				LR- 3.02 (1.23, 7.40)	Low
Surface swabs (pharynx)					
1	31	0.45 (0.26, 0.66)	0.54 (0.29, 0.78)	LR+ 0.99 (0.45, 2.14)	Very low
				LR- 1.01 (0.53, 1.94)	Low
Surface swabs (popliteal space)					
1	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Low
				LR- 3.35 (1.38, 8.10)	Low
Surface swabs (scalp: occipital)					
1	31	0.07 (0.02, 0.26)	0.38 (0.16, 0.65)	LR+ 0.11 (0.02, 0.57)	Low
				LR- 2.48	Low

No. studies	Sample size	Sensitivity (95%CI)	Specificity (95% CI)	Effect size* (95%CI)	Quality
				(1.18, 5.19)	
Surface swabs (soles)					
1	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Low
				LR- 3.35 (1.38, 8.10)	Low
Surface swabs (umbilicus)					
1	31	0.60 (0.39, 0.77)	0.79 (0.51, 0.93)	LR+ 2.86 (0.90, 9.10)	Very low
				LR- 0.51 (0.28, 93)	Low
Tip of the IV long line (longitudinal split method) (Culture of tip yielded ≥15 colony forming units of the same colony type)					
1	277	0.97 (0.91, 0.99)	0.88 (0.84, 0.92)	LR+ 8.41 (6.06, 11.67)	Moderate
				LR- 0.04 (0.01, 0.11)	Moderate
Tip of the IV long line (qualitative method) (Culture of tip yielded ≥15 colony forming units of the same colony type)					
1	85	0.99 (0.89, 1.00)	0.60 (0.45, 0.73)	LR+ 2.48 (1.72, 3.60)	Low
				LR- not calculable	Moderate
Tip of the IV long line (roll plate method) (Culture of tip yielded ≥15 colony forming units of the same colony type)					
3	387	0.73 (0.50, 0.88)	0.80 (0.53, 0.93)	LR+ 3.96 (1.68, 8.99)	Very low
				LR- 0.36 (0.18, 0.60)	Very low

* LR+: Positive likelihood ratio, LR-: Negative likelihood ratio

See appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

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

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

1.1.7.2 Excluded studies

See appendix J for excluded studies.

1.1.8 Economic model

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

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1 The outcomes that matter most

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

If a test does not accurately identify babies with infection and those without infection, then there are a number of potential harms. False positive results will result in babies being given antibiotics unnecessarily, exposing them to the risk of side effects. As antibiotics can only be given in hospital, this can lead to separation of the mother and baby, potentially causing anxiety and distress to the family. False positive results will also incur the costs associated with a hospital stay and can contribute to the development of antibiotic resistance. However, a false negative result is the biggest concern for parents and clinicians as there can be serious consequences if neonatal infection is left untreated. The most serious consequence is death of the baby, but delayed treatment can also have long-term health consequences, such as neuro-disability, which can have both emotional and financial impacts on the family as well as downstream treatment costs for the healthcare system. False negatives for babies with meningitis may result in a shorter treatment duration than necessary which can have long-term consequences for the baby, such as issues with neurodevelopment. A false negative may also affect communication with parents, who may be given a different prognosis than would be expected for meningitis. Consequently, the committee prioritised negative likelihood ratios over positive likelihood ratios – the committee believed that it was important that negative test results were accurate, and that neonatal infection was not incorrectly ruled out.

1.1.9.2 The quality of the evidence

Thirty-four studies were included in the review, and the majority of the evidence evaluated either CRP or procalcitonin. The evidence was very low to moderate quality, with most outcome measures rated as either low or very low quality. Most studies were directly applicable to the research question, although 3 were downgraded due to a lack of information about the age of the babies included in the study. Another study evaluating surface swabs was downgraded for differences in the population and clinical practice between the study setting (India) and the UK. Outcomes from this study were low to very low quality, with considerable imprecision. Many of the likelihood ratios suggested that a positive test from a surface swab could

indicate either an increase or a decrease in the probability of a baby having an infection. These conflicting results were also seen for negative likelihood ratios. This supported a recommendation from the 2012 version of this guideline for early-onset infection, that skin swab microscopy or culture should not be performed as part of the investigations for infection. The committee therefore decided to apply this recommendation to both early- and late- onset neonatal infection.

One of the key issues raised by the committee was the use of blood cultures as the reference standard in most of the studies. Positive blood cultures are considered the gold standard test for diagnosing neonatal infection, but it is widely acknowledged that this is not a perfect method. Babies can have a negative blood culture despite having neonatal infection. Blood samples are difficult to obtain in neonates and may be contaminated and accurate results depend on proper technique in taking and incubating the sample. This could affect the results of a study, as a baby with neonatal infection but a negative blood culture will appear as a false positive result if a diagnostic test correctly identifies them as having an infection. However, as blood cultures reflect current practice and are still considered the most accurate test for diagnosing late-onset infection, the committee did not think the studies should be downgraded for risk of bias.

The committee noted that a very wide range of cut-off values were used for the diagnostic tests within the analysis, in particular for CRP levels. The most commonly used threshold for CRP in the UK is 10 mg/l, and so the committee thought that these data were the most applicable to decision making. Much of the evidence for CRP was based on the test being performed at the same time as the blood culture when a baby was first identified as being at risk of infection. The committee explained that CRP is often low at the start of an infection and takes approximately one day before there is a detectable response. The result of a single CRP test is therefore not considered a useful marker in practice. Instead, clinicians usually take one sample at the time of the initial blood culture to obtain a baseline reading, and then repeat the test 18-24 hours later to see if there has been a change in CRP concentration. If there is little change in CRP concentration during this period, then clinicians can rule out infection and antibiotic treatment can be stopped. Only three studies performed more than one CRP test, with the results indicating that, at a cut-off value of 10 mg/l, the test was more sensitive 24 hours after the first blood sample. Likelihood ratios indicated that when a CRP test took place at the time of the initial blood culture, a positive result would indicate a moderate increase in the probability of a baby having infection, and a negative result would increase a slight decrease in the probability of infection. When a CRP test took place 24 or 48 hours later, a positive result would still indicate a moderate increase, but a negative result would indicate a moderate decrease in infection risk, thereby giving a clinician more confidence in the result. However, these studies evaluated absolute CRP values in relation to a pre-specified threshold rather than looking for a change in CRP over time. Consequently, the committee could not recommend how much CRP should increase before a clinician can be confident that a baby has late-onset neonatal infection.

Three studies examined the diagnostic accuracy of culturing the tip of the IV long line for identifying IV catheter-related infections. There were some questions over how well the methods of these studies would relate to clinical practice, as it would be unlikely that a clinician would remove an IV line to test the IV tip while the baby was still unwell. There were also concerns over how appropriate the tests were to evaluate infection. Three techniques were evaluated, and the committee highlighted that the Maki roll plate method is the most common in clinical practice. However, this evaluates the presence of extra-luminal rather than intra-luminal bacteria and is therefore likely to miss many of the organisms associated with neonatal infection. In contrast the longitudinal split and qualitative methods would identify intra-luminal

bacteria. However, these are not used commonly in UK practice as the methods may introduce contamination into the IV tips, thereby potentially giving false positive results and resulting in babies being given antibiotic treatment unnecessarily. The committee agreed that while these methods may be useful once antibiotic treatment has been started to identify whether the correct antibiotic is being used, they are less useful for diagnosing infection and making decisions on whether antibiotic treatment should be started.

Other tests included in the review (neutrophil count, IT ratio and white blood cell count) had low diagnostic accuracy, with lower sensitivity than CRP and likelihood ratios that suggested that a negative result would only indicate a slight decrease in the probability of infection. The committee therefore decided these would not be an effective method of ruling out neonatal infection and could instead result in many babies receiving unnecessary treatment. The results for platelet counts showed a similar degree of imprecision to surface swabs, with likelihood ratios indicating that neither a positive or negative test result could guarantee whether a baby had an increased or decreased probability of infection. The committee agreed that these results could not be used to inform the recommendations.

1.1.9.3 Benefits and harms

A test that can accurately identify whether a baby has late-onset neonatal infection can help to ensure that only babies with an infection will be given antibiotics. This also reduces the adverse effects associated with unnecessary treatment for both the baby and the baby's family, as well as reducing the costs associated with treatment. Although blood cultures are currently the gold standard technique, it can take more than 30 hours for blood culture results to be available and as a result, many babies are treated for suspicion of infection rather than confirmed infection until the results of the blood culture are returned. A test that could identify which babies had infection more quickly and accurately than a blood test would therefore help to reduce the number of babies who are treated with antibiotics until culture results are available.

No tests showed sufficient diagnostic accuracy to recommend them as an alternative to blood culture, but a combination of evidence and clinical experience from the committee was used to suggest that CRP is a useful test alongside blood cultures. Although the baseline value is unlikely to change the number of babies receiving treatment, the additional information provided by the results of the second CRP test can identify babies who do not have infection, thereby reducing the number of babies who continue antibiotic treatment unnecessarily. For this reason, the committee were keen to highlight the importance of performing two CRP tests, one when starting treatment to provide a baseline value for the baby, and another 18-24 hours later to identify any rise in CRP levels that are typical of a response to infection. The committee also considered whether the likelihood of a baby having an infection might be taken more seriously if there were positive results from a number of tests rather than just blood cultures and CRP tests. However, there was low quality evidence for the other tests in the review, and the committee decided that they did not show sufficient diagnostic accuracy for this to be considered. Given the poor diagnostic accuracy, the committee decided against making a research recommendation for further evidence on these tests.

The committee considered the recommendations from the 2012 version of this guideline on diagnosing early-onset neonatal infection. It discussed how the bacteria that cause infections differ between early-onset infection and late-onset infection. However, it agreed that the tests used to identify early-onset infection would still be appropriate, even if the organisms responsible for the infection differed. As such, it made similar recommendations to those for the early-onset infection section of the

guideline. This included performing a blood culture before the first dose of antibiotics so that a blood sample was available for analysis as quickly as possible, and so that a baseline value was available for the baby before treatment began.

A test that can accurately diagnose meningitis is also important to ensure that all babies with meningitis receive the correct treatment. Lumbar puncture is the gold standard test for identifying babies with meningitis. Although there was no evidence in this review for the safety of lumbar punctures, the committee discussed how, in it's clinical experience, the benefits of identifying babies with meningitis outweighs the risks of the procedure, which it considered to be low. The use of lumbar punctures was already recommended in the 2012 version of this guideline for babies with suspected early-onset infection, and the committee therefore included this in the recommendations. Given the importance of diagnosing meningitis, the committee made a strong recommendation in favour of lumbar puncture if there is a strong suspicion of sepsis or meningitis, but stated that this should only take place if it is safe to do so.

1.1.9.4 Cost effectiveness and resource use

The committee agreed that, as its recommendations are consistent with current practice, there would be no major resource impact associated with their adoption. The committee was mindful that, as well as having potentially catastrophic consequences for the neonate, any infection that is missed can generate very substantial costs for the health and care system. Therefore, even if there is an increase in CRP tests and lumbar puncture, this is likely to be offset by savings associated with accurately diagnosed and managed cases. Correct identification of all those without infection (true negatives) will avoid over-prescribing of antibiotics. This reduces the adverse effects and costs associated with unnecessary treatment for both the baby and the baby's family.

1.1.9.5 Other factors the committee took into account

The committee discussed how basing the recommendations on those used for diagnosing early-onset infection was useful as these were designed to meet the criteria stated in the Public Health England 'Start Smart – Then Focus' guidance which outlines procedures for antimicrobial stewardship in secondary care. This should help to ensure that babies who develop neonatal infection get the antibiotic treatment they require without increasing the risk of over-prescribing and the development of antimicrobial resistance.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1-1.7.8.

1.1.11 References – included studies

1.1.11.1 Effectiveness

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Appendices

Appendix A – Review protocols

Review protocol for what investigations should be performed before starting treatment in babies with symptoms of late-onset neonatal infection?

ID	Field	Content
0.	PROSPERO registration number	CRD42020157804
1.	Review title	Investigations before starting treatment for late-onset neonatal infection in babies
2.	Review question	What investigations should be performed before starting treatment in babies with symptoms of late-onset neonatal infection?
3.	Objective	To determine the diagnostic test accuracy and cost effectiveness of tests used for detection of late-onset neonatal infection in neonates with symptoms and signs or risk factors that indicate the need to start antibiotic treatment This question also includes consideration of the intervals between presentation and testing, testing and treatment, and the timing of decisions to continue or stop treatment
4.	Searches	The following databases will be searched:

		• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language • Human studies • Conference abstracts • No date limit will be included Other searches: None The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. It may be early-onset (within 72 hours of birth) or late-onset

		(more than 72 hours after birth). Neonatal infection can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. Late-onset neonatal infection is present in 7 of every 1000 newborn babies and responsible for 61 of every 1000 neonatal admissions. Coagulase-negative staphylococci, Enterobacteriaceae and *Staphylococcus aureus* are the most common organisms identified.
6.	Population	Inclusion: • Term babies up to 28 days of age and preterm babies up to 28 days corrected gestational age with symptoms or signs of, or risk factors for, late-onset neonatal infection presenting after 72 hours of birth or from study-defined period for development of late-onset neonatal infection Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with suspected or confirmed localised infections. • Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a

		history of surgery which was not the cause of the infection will not be excluded. • Babies with suspected or confirmed meningitis who are not receiving care in neonatal units (covered by the NICE guideline on bacterial meningitis and meningococcal septicaemia)
7.	Test	• C-reactive protein (CRP) and other acute phase reactants • procalcitonin (PCT) • interleukins • cytokines • white blood cell count (including neutrophil count, which can be high or low, and the ratio of immature to total neutrophils, left shift, band granulocyte) • platelet count • cerebrospinal fluid (CSF) examination • urine microscopy or culture, including mode of collection (for example, catheter, suprapubic aspiration) • rapid tests (for example, polymerase chain reaction (PCR) (excluding CSF PCR) • surface swabs (skin, nose, ear, umbilical, rectal, axilla and groin, eye, throat)

		• Samples from tip of IV long line • chest X-ray
8.	Reference standard	• For tests based on CSF parameters (CSF examination): CSF culture or CSF-PCR test on sample taken from 72 hours after birth to 28 days (corrected age) • For all other tests (excluding CSF examination): blood culture on sample taken from 72 hours after birth to 28 days (corrected age)
9.	Types of study to be included	Cross sectional diagnostic test accuracy studies Systematic reviews of the diagnostic test accuracy studies
10.	Other exclusion criteria	Non-English language studies Case-control studies will be excluded
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question.
12.	Primary outcomes (critical outcomes)	Diagnostic/predictive accuracy measures including: • sensitivity (detection rate) • specificity

		• positive and negative predictive values • positive and negative likelihood ratios
13.	Secondary outcomes (important outcomes)	Not applicable.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies into a standardised form for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.

		A stopping rule will be used to terminate screening if the following criteria are met: - At least 50% of the database has been screened - 500 records have been screened with no further included studies Reference lists of systematic reviews will also be checked for potential includes
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the QUADAS-2 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of diagnostic test accuracy data will be conducted for all diagnostic tests that are reported by more than one study, with reference to the Cochrane Handbook for systematic reviews of diagnostic test accuracy. Random-effects models will be fitted for all analyses. A bivariate model will be fitted when 5 or more studies are available to be meta-analysed. A univariate model will be fitted when there are fewer than 5 studies available. • Bivariate meta-analyses will be performed in R using the 'mada' package • Univariate meta-analysis will be performed in excel.

		Modified GRADE will be used to assess certainty in the evidence base. In cases where heterogeneity make meta-analysis inappropriate, data for each study will be presented as separate lines in the GRADE profile.
17.	Analysis of sub-groups	**Stratifications:** • term vs preterm babies • babies who have been admitted to hospital from home
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	01/01/2018

22.	Anticipated completion date	12/08/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Piloting of the study selection process	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Data extraction	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐

		Risk of bias (quality) assessment	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Data analysis	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Late onset neonatal infection, diagnostic test accuracy
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	The guideline with supporting evidence reviews will be published on the NICE website.

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Appendix B – Literature search strategies

Clinical search literature search strategy

The search was conducted on 30th October 2019. The following databases were searched: Medline, Medline In Process, Medline E-pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews, (via the Wiley platform), and the DARE database (via the CRD platform).

Population and investigations terms

The search terms used to identify the population and investigations are reproduced below for all databases. The population and investigations terms were combined as 'And' to identify papers that discussed both.

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

1 exp Infant, Newborn/

2 Term Birth/

3 Infant Care/

4 Perinatal Care/

5 Intensive Care Units, Neonatal/

6 Intensive Care, Neonatal/

7 Infant Health/

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

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

10 or/1-9

11 exp Bacterial Infections/

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

13 exp Sepsis/

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

15 (septic* adj4 shock*).tw.

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

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

1 18 or/11-17
2 19 exp Streptococcus/
3 20 exp Staphylococcus/
4 21 (streptococc* or staphylococc*).tw.
5 22 (GBS or MRSA or NRCS-A or MSSA).tw.
6 23 (met?icillin-resistant adj3 aureus).tw.
7 24 exp Escherichia coli/
8 25 ((Escheric* or E) adj2 coli).tw.
9 26 exp Listeria/
10 27 listeria*.tw.
11 28 exp Klebsiella/
12 29 klebsiella*.tw.
13 30 exp Pseudomonas/
14 31 (pseudomonas or chryseomonas or flavimonas).tw.
15 32 Enterobacteriaceae/
16 33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.
17 34 ((enteric or coliform) adj2 bac*).tw.
18 35 exp Neisseria/
19 36 neisseria*.tw.
20 37 exp Haemophilus influenzae/
21 38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or
22 pfeiffer* or meningitidis)).tw.
23 39 exp Serratia/
24 40 serratia*.tw.
25 41 exp Cronobacter/
26 42 (cronobact* or sakazaki* or malonatic*).tw.
27 43 exp Acinetobacter/
28 44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.
29 45 exp Fusobacterium/
30 46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

1 47 exp Enterococcus/

2 48 enterococc*.tw.

3 49 or/19-48

4 50 18 or 49

5 51 10 and 50

6 52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

7 53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or
8 babies* or offspring) adj4 infect*).tw.

9 54 52 or 53

10 55 51 or 54

11 56 ((inflam* or excit*) adj4 (marker* or flag* or indicat*)).tw.

12 57 C-Reactive Protein/

13 58 (C adj2 react* adj4 protein*).tw.

14 59 (Creact* adj4 protein*).tw.

15 60 CRP.tw.

16 61 Acute-Phase Reaction/

17 62 Acute-Phase Proteins/

18 63 (acute* adj2 phas* adj4 (react* or respons* or state* or protein*)).tw.

19 64 APR.tw.

20 65 Serum Amyloid A Protein/

21 66 (serum* adj4 amyloid* adj4 A).tw.

22 67 SAA.tw.

23 68 Orosomucoid/

24 69 (orosomucoid* or seromucoid*).tw.

25 70 (serum* adj4 (fibronectin* or sialomuin*)).tw.

26 71 alpha-2-Antiplasmin/

27 72 ((acid* or alpha*) adj4 (antiplasmin* or anti-plasmin* or glycoprotein*)).tw.

28 73 (alpha* adj4 plasmin* adj4 inhibitor*).tw.

29 74 AGP.tw.

30 75 Hepcidins/

1 76 hepcidin*.tw.

2 77 Blood Sedimentation/

3 78 ((blood* or erythrocyte*) adj4 sediment*).tw.

4 79 Haptoglobins/

5 80 haptoglobin*.tw.

6 81 (h?emoglobin* adj4 bind* adj4 protein*).tw.

7 82 Procalcitonin/

8 83 Calcitonin/

9 84 (procalcitonin* or calcitonin*).tw.

10 85 PCT.tw.

11 86 exp Interleukins/

12 87 Interleukin 1 Receptor Antagonist Protein/

13 88 (interleukin* or IL-6 or IL6 or IL-1 or IL1).tw.

14 89 Cytokines/

15 90 exp Receptors, Cytokine/

16 91 cytokine*.tw.

17 92 exp Leukocyte Count/

18 93 ((leukocyte* or leucocyte* or lymphocyte* or WBC*) adj4 (count* or number* or
19 polymorphonuclear* or total* or calculat* or amount* or estimat* or quant* or sum*)).tw.

20 94 (white* adj2 (blood* or cell*) adj4 (count* or number* or polymorphonuclear* or total* or
21 calculat* or amount* or estimat* or quant* or sum*)).tw.

22 95 exp Colony-Stimulating Factors/

23 96 ((colony* or colonies*) adj4 stimulat* adj4 (factor* or activit* or determin* or influenc* or
24 agen*)).tw.

25 97 Granulocytes/

26 98 Neutrophils/

27 99 (granulocyte* or neutrophil* or neutrocyt*).tw.

28 100 ((LE or band or granuloid*) adj4 cell*).tw.

29 101 (G-CSF or GM-CSF or "CSF-2" or TC-GM-CSF or CSF-GM or rhGM-CSF).tw.

30 102 Platelet Count/

31 103 ((platelet* or thrombocyt*) adj4 (count* or number* or total* or calculat* or amount* or
32 estimat* or quant* or sum*)).tw.

1 104 Cerebrospinal Fluid/an, di, dg [Analysis, Diagnosis, Diagnostic Imaging]

2 105 ((cerebrospinal* or cerebr*-spinal* or cephalorhachidian* or cranial* or spinal* or
3 brain*-ventricl* or neurolymph* or neuro-lymph*) adj4 (fluid* or liquid* or solut*) adj4 (exam*
4 or test* or analys* or inspect* or explor* or scan* or investigat*)).tw.

5 106 (CSF* adj4 (exam* or test* or analys* or inspect* or explor* or scan* or
6 investigat*)).tw.

7 107 Spinal Puncture/

8 108 ((spinal* or spine* or lumbar*) adj4 (puncture* or tap*)).tw.

9 109 Latex Fixation Tests/

10 110 (latex* adj4 (test* or kit* or method* or fixat* or agglutinat* or antigen* or assay* or
11 serotyp* or react*)).tw.

12 111 (streptex* or pastorex* or wellcogen*).tw.

13 112 (LPA or LAT or LFT).tw.

14 113 Reagent Strips/

15 114 ((urin* or reagent* or immunochromographic* or immuno-chromographic* or Nephur*
16 or test*) adj4 (strip* or dipstick* or dip-stick* or tap* or paper*)).tw.

17 115 StripAssay*.tw.

18 116 exp Polymerase Chain Reaction/

19 117 (polymerase* adj4 chain* adj4 react*).tw.

20 118 PCR.tw.

21 119 Urinalysis/

22 120 Urine/mi [Microbiology]

23 121 urinalys*.tw.

24 122 (urin* adj4 (cultur* or mcroscop* or test* or analys* or exam* or investigat*)).tw.

25 123 UA.tw.

26 124 exp Catheters/

27 125 Catheterization/

28 126 exp Urinary Catheterization/

29 127 (catheter* or cannula*).tw.

30 128 ((suprapubic* or supra-pubic* or bladder* or detrusor*) adj4 (aspirat* or punctur*)).tw.

31 129 (SPA or SBA).tw.

32 130 (iQ200* or (iChem* adj4 workstation*)).tw.

1 131 Flow Cytometry/

2 132 (flow* adj4 (cytometr* or microfluoromet* or cytofluorometr* or lateral*)).tw.

3 133 (LFB or LFA).tw.

4 134 Sysmex*.tw.

5 135 (Xpert adj4 (MTB or RIF)).tw.

6 136 ((rapid* or quick* or accelerat* or fast* or speed* or swift*) adj4 (test* or kit* or
7 method* or detect* or discover* or identif* or recogni* or assay* or agglutinat* or
8 immunoassay* or immunochromatographic*)).tw.

9 137 (RDT or RADT or DIMA).tw.

10 138 exp Fluorescent Antibody Technique/

11 139 ((fluorescen* or immunofluorescen* or immuno-fluorescen*) adj4 (techni* or antibod*
12 or anti-bod* or trac* or cell* or hybridi?ation* or test* or method* or identif* or detect*)).tw.

13 140 FISH.tw.

14 141 Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization/

15 142 (matrix* adj10 spectrom*).tw.

16 143 (MALDI* or MALD-MS* or TOF-MS* or LDI-MS*).tw.

17 144 FilmArray*.tw.

18 145 "Staining and Labeling"/

19 146 (gram* adj4 (stain* or label*)).tw.

20 147 Limulus Test/

21 148 (limulus* adj4 (lysate* or test* or assay* or exam* or analys* or investigat* or method*
22 or detect* or endotoxin* or toxin* or coagul* or serum*)).tw.

23 149 LAL.tw.

24 150 swab*.tw.

25 151 ((surface* or exterior* or outer* or superficial*) adj4 (culture* or wipe* or mop or
26 smear*)).tw.

27 152 ((skin* or dermis* or epidermis* or nose* or nasal* or paranasal* or ear or ears or
28 umbilic* or rectal* or rectum* or axilla* or underarm* or under-arm* or armpit* or arm-pit* or
29 groin* or genital* or eye* or ocular* or oculus* or throat* or pharyn* or laryn* or neck*) adj4
30 (culture* or wipe* or mop or smear*)).tw.

31 153 Infusions, Intravenous/

32 154 ((IV or I-V or intravenous*) adj4 (line* or infusion* or sampl* or fragment* or specimen*
33 or indicat* or segment* or drip* or admin* or dos* or inject* or deliver* or transfus* or tip*)).tw.

34 155 exp Radiography, Thoracic/

1 156 X-Rays/

2 157 ((chest* or thorax* or thorac* or bronch* or lung*) adj4 (x-ray* or xray* or radio* or
3 roentgen* or imag*)).tw.

4 158 or/56-157

5 159 55 and 158

6 160 Animals/ not Humans/

7 161 159 not 160

8 162 limit 161 to english language

9

10 Embase

11 1 newborn/

12 2 term birth/

13 3 infant care/

14 4 perinatal care/

15 5 neonatal intensive care unit/

16 6 newborn intensive care/

17 7 child health/

18 8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

19 9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or
20 babies* or offspring)).tw.

21 10 or/1-9

22 11 exp bacterial infection/

23 12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening*
24 or pneumon* or nosocomial*)).tw.

25 13 exp sepsis/

26 14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

27 15 (septic* adj4 shock*).tw.

28 16 (bacter?emia* or bacill?emia*).tw.

29 17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

30 18 or/11-17

31 19 exp Streptococcus/

1 20 exp Staphylococcus/
2 21 (streptococc* or staphylococc*).tw.
3 22 (GBS or MRSA or NRCS-A or MSSA).tw.
4 23 (met?icillin-resistant adj3 aureus).tw.
5 24 exp Escherichia coli/
6 25 ((Escheric* or E) adj2 coli).tw.
7 26 exp Listeria/
8 27 listeria*.tw.
9 28 exp Klebsiella/
10 29 klebsiella*.tw.
11 30 exp Pseudomonas/
12 31 (pseudomonas or chryseomonas or flavimonas).tw.
13 32 Enterobacteriaceae/
14 33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.
15 34 ((enteric or coliform) adj2 bac*).tw.
16 35 exp Neisseria/
17 36 neisseria*.tw.
18 37 exp Haemophilus influenzae/
19 38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or
20 pfeiffer* or meningitidis)).tw.
21 39 exp Serratia/
22 40 serratia*.tw.
23 41 exp cronobacter/
24 42 (cronobact* or sakazaki* or malonatic*).tw.
25 43 exp Acinetobacter/
26 44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.
27 45 exp Fusobacterium/
28 46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.
29 47 exp Enterococcus/
30 48 enterococc*.tw.

1 49 or/19-48

2 50 18 or 49

3 51 10 and 50

4 52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

5 53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or
6 babies* or offspring) adj4 infect*).tw.

7 54 52 or 53

8 55 51 or 54

9 56 ((inflam* or excit*) adj4 (marker* or flag* or indicat*)).tw.

10 57 C reactive protein/

11 58 (C adj2 react* adj4 protein*).tw.

12 59 (Creact* adj4 protein*).tw.

13 60 CRP.tw.

14 61 acute phase response/

15 62 acute phase protein/

16 63 (acute* adj2 phas* adj4 (react* or respons* or state* or protein*)).tw.

17 64 APR.tw.

18 65 serum amyloid A/

19 66 (serum* adj4 amyloid* adj4 A).tw.

20 67 SAA.tw.

21 68 orosomucoid/

22 69 (orosomucoid* or seromucoid*).tw.

23 70 (serum* adj4 (fibronectin* or sialomuin*)).tw.

24 71 alpha 2 antiplasmin/

25 72 ((acid* or alpha*) adj4 (antiplasmin* or anti-plasmin* or glycoprotein*)).tw. (

26 73 (alpha* adj4 plasmin* adj4 inhibitor*).tw.

27 74 AGP.tw. (

28 75 hepcidin/

29 76 hepcidin*.tw.

30 77 erythrocyte sedimentation rate/

1 78 ((blood* or erythrocyte*) adj4 sediment*).tw.

2 79 haptoglobin/

3 80 haptoglobin*.tw.

4 81 (h?emoglobin* adj4 bind* adj4 protein*).tw.

5 82 procalcitonin/

6 83 calcitonin/

7 84 (procalcitonin* or calcitonin*).tw.

8 85 PCT.tw.

9 86 interleukin 1/ or interleukin 1 derivative/ or interleukin derivative/

10 87 interleukin 1 receptor blocking agent/

11 88 interleukin 6/

12 89 (interleukin* or IL-6 or IL6 or IL-1 or IL1).tw.

13 90 cytokine/

14 91 exp cytokine receptor/ (

15 92 cytokine*.tw.

16 93 exp leukocyte count/

17 94 ((leukocyte* or leucocyte* or lymphocyte* or WBC*) adj4 (count* or number* or
18 polymorphonuclear* or total* or calculat* or amount* or estimat* or quant* or sum*)).tw.

19 95 (white* adj2 (blood* or cell*) adj4 (count* or number* or polymorphonuclear* or total* or
20 calculat* or amount* or estimat* or quant* or sum*)).tw.

21 96 colony stimulating factor/

22 97 ((colony* or colonies*) adj4 stimulat* adj4 (factor* or activit* or determin* or influenc* or
23 agen*)).tw.

24 98 granulocyte/

25 99 neutrophil/

26 100 (granulocyte* or neutrophil* or neutrocyt*).tw.

27 101 ((LE or band or granuloid*) adj4 cell*).tw.

28 102 (G-CSF or GM-CSF or "CSF-2" or TC-GM-CSF or CSF-GM or rhGM-CSF).tw.

29 103 platelet count/

30 104 ((platelet* or thrombocyt*) adj4 (count* or number* or total* or calculat* or amount* or
31 estimat* or quant* or sum*)).tw.

32 105 cerebrospinal fluid analysis/ or cerebrospinal fluid examination/

106 ((cerebrospinal* or cerebr*-spinal* or cephalorhachidian* or cranial* or spinal* or brain*-ventricl* or neurolymph* or neuro-lymph*) adj4 (fluid* or liquid* or solut*) adj4 (exam* or test* or analys* or inspect* or explor* or scan* or investigat*)).tw.

107 (CSF* adj4 (exam* or test* or analys* or inspect* or explor* or scan* or investigat*)).tw. (

108 lumbar puncture/

109 ((spinal* or spine* or lumbar*) adj4 (puncture* or tap*)).tw.

110 latex agglutination test/

111 (latex* adj4 (test* or kit* or method* or fixat* or agglutinat* or antigen* or assay* or serotyp* or react*)).tw.

112 (streptex* or pastorex* or wellcogen*).tw.

113 (LPA or LAT or LFT).tw.

114 test strip/

115 ((urin* or reagent* or immunochromographic* or immuno-chromographic* or Nephur* or test*) adj4 (strip* or dipstick* or dip-stick* or tap* or paper*)).tw.

116 StripAssay*.tw.

117 exp polymerase chain reaction/

118 (polymerase* adj4 chain* adj4 react*).tw.

119 PCR.tw.

120 exp urinalysis/

121 urinalys*.tw.

122 (urin* adj4 (cultur* or mcroscop* or test* or analys* or exam* or investigat*)).tw.

123 UA.tw.

124 exp catheter/

125 catheterization/

126 exp bladder catheterization/

127 (catheter* or cannula*).tw.

128 ((suprapubic* or supra-pubic* or bladder* or detrusor*) adj4 (aspirat* or punctur*)).tw.

129 (SPA or SBA).tw.

130 (iQ200* or (iChem* adj4 workstation*)).tw.

131 flow cytometry/

132 (flow* adj4 (cytometr* or microfluoromet* or cytofluorometr* or lateral*)).tw.

1 133 (LFB or LFA).tw.

2 134 Sysmex*.tw.

3 135 (Xpert adj4 (MTB or RIF)).tw.

4 136 ((rapid* or quick* or accelerat* or fast* or speed* or swift*) adj4 (test* or kit* or
5 method* or detect* or discover* or identif* or recogni* or assay* or agglutinat* or
6 immunoassay* or immunochromatographic*)).tw.

7 137 (RDT or RADT or DIMA).tw.

8 138 exp fluorescent antibody technique/

9 139 ((fluorescen* or immunofluorescen* or immuno-fluorescen*) adj4 (techni* or antibod*
10 or anti-bod* or trac* or cell* or hybridi?ation* or test* or method* or identif* or detect*)).tw.

11 140 FISH.tw.

12 141 exp matrix-assisted laser desorption-ionization mass spectrometry/

13 142 (matrix* adj10 spectrom*).tw.

14 143 (MALDI* or MALD-MS* or TOF-MS* or LDI-MS*).tw.

15 144 FilmArray*.tw.

16 145 gram staining/

17 146 (gram* adj4 (stain* or label*)).tw.

18 147 limulus lysate test/

19 148 (limulus* adj4 (lysate* or test* or assay* or exam* or analys* or investigat* or method*
20 or detect* or endotoxin* or toxin* or coagul* or serum*)).tw.

21 149 LAL.tw.

22 150 swab*.tw.

23 151 ((surface* or exterior* or outer* or superficial*) adj4 (culture* or wipe* or mop or
24 smear*)).tw.

25 152 ((skin* or dermis* or epidermis* or nose* or nasal* or paranasal* or ear or ears or
26 umbilic* or rectal* or rectum* or axilla* or underarm* or under-arm* or armpit* or arm-pit* or
27 groin* or genital* or eye* or ocular* or oculus* or throat* or pharyn* or laryn* or neck*) adj4
28 (culture* or wipe* or mop or smear*)).tw.

29 153 intravenous drug administration/

30 154 ((IV or I-V or intravenous*) adj4 (line* or infusion* or sampl* or fragment* or specimen*
31 or indicat* or segment* or drip* or admin* or dos* or inject* or deliver* or transfus* or tip*)).tw.

32 155 exp thorax radiography/

33 156 X ray/

157 ((chest* or thorax* or thorac* or bronch* or lung*) adj4 (x-ray* or xray* or radio* or roentgen* or imag*)).tw.

158 or/56-157

159 55 and 158

160 nonhuman/ not human/

161 159 not 160

162 limit 161 to english language

163 limit 162 to (conference abstract or conference paper or "conference review")

164 162 not 163

CDSR

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

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

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

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

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

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

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

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

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

#10 {or #1-#9}

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

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

#13 MeSH descriptor: [Sepsis] explode all trees

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

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

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

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

#18 {or #11-#17}

#19 MeSH descriptor: [Streptococcus] explode all trees

#20 MeSH descriptor: [Staphylococcus] explode all trees

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

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

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

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

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

#26 MeSH descriptor: [Listeria] explode all trees

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

#28 MeSH descriptor: [Klebsiella] explode all trees

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

#30 MeSH descriptor: [Pseudomonas] explode all trees

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

#32 MeSH descriptor: [Enterobacteriaceae] explode all trees

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

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

#35 MeSH descriptor: [Neisseria] explode all trees

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

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

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

#39 MeSH descriptor: [Serratia] explode all trees

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

#41 MeSH descriptor: [Cronobacter] explode all trees

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

#43 MeSH descriptor: [Acinetobacter] explode all trees

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

#45 MeSH descriptor: [Fusobacterium] explode all trees

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

#47 MeSH descriptor: [Enterococcus] explode all trees

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

#49 {or #19-#48}

#50 #18 or #49

#51 #10 and #50

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

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

#54 #52 or #53

#55 #51 or #54

#56 ((inflam* or excit*) near/4 (marker* or flag* or indicat*)):ti,ab,kw

#57 MeSH descriptor: [C-Reactive Protein] this term only

#58 (("C") near/2 (react*) near/4 (protein*)):ti,ab,kw

#59 ((Creact*) near/4 (protein*)):ti,ab,kw

#60 (CRP):ti,ab,kw

#61 MeSH descriptor: [Acute-Phase Reaction] this term only

#62 MeSH descriptor: [Acute-Phase Proteins] this term only

#63 ((acute*) near/2 (phas*) near/4 (react* or respons* or state* or protein*)):ti,ab,kw

#64 (APR):ti,ab,kw

#65 MeSH descriptor: [Serum Amyloid A Protein] this term only

#66 ((serum* near/4 amyloid* near/4 "A")):ti,ab,kw

#67 (SAA):ti,ab,kw

#68 MeSH descriptor: [Orosomucoid] this term only

#69 (orosomucoid* or seromucoid*):ti,ab,kw

#70 ((serum*) near/4 (fibronectin* or sialomuin*)):ti,ab,kw

#71 MeSH descriptor: [alpha-2-Antiplasmin] this term only

#72 ((acid* or alpha*) near/4 (antiplasmin* or anti-plasmin* or glycoprotein*)):ti,ab,kw

#73 ((alpha* near/4 plasmin* near/4 inhibitor*)):ti,ab,kw

#74 (AGP):ti,ab,kw

#75 MeSH descriptor: [Hepcidins] this term only

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

#77 MeSH descriptor: [Blood Sedimentation] this term only

#78 ((blood* or erythrocyte*) near/4 (sediment*)):ti,ab,kw

#79 MeSH descriptor: [Haptoglobins] this term only

#80 (haptoglobin*):ti,ab,kw

#81 ((h?emoglobin* near/4 bind* near/4 protein*)):ti,ab,kw

#82 MeSH descriptor: [Procalcitonin] this term only

#83 MeSH descriptor: [Calcitonin] this term only

#84 (procalcitonin* or calcitonin*):ti,ab,kw

#85 (PCT):ti,ab,kw

#86 MeSH descriptor: [Interleukins] explode all trees

#87 MeSH descriptor: [Interleukin 1 Receptor Antagonist Protein] this term only

#88 (interleukin* or IL-6 or IL6 or IL-1 or IL1):ti,ab,kw

#89 MeSH descriptor: [Cytokines] this term only

#90 MeSH descriptor: [Receptors, Cytokine] explode all trees

#91 (cytokine*):ti,ab,kw

#92 MeSH descriptor: [Leukocyte Count] explode all trees

#93 ((leukocyte* or leucocyte* or lymphocyte* or WBC*) near/4 (count* or number* or polymorphonuclear* or total* or calculat* or amount* or estimat* or quant* or sum*)):ti,ab,kw

#94 ((white*) near/2 (blood* or cell*) near/4 (count* or number* or polymorphonuclear* or total* or calculat* or amount* or estimat* or quant* or sum*)):ti,ab,kw

#95 MeSH descriptor: [Colony-Stimulating Factors] explode all trees

#96 ((colony* or colonies*) near/4 (stimulat*) near/4 (factor* or activit* or determin* or influenc* or agen*)):ti,ab,kw

#97 MeSH descriptor: [Granulocytes] this term only

#98 MeSH descriptor: [Neutrophils] this term only

#99 (granulocyte* or neutrophil* or neutrocyt*):ti,ab,kw

#100 ((LE or band or granuloid*) near/4 (cell*)):ti,ab,kw

#101 (G-CSF or GM-CSF or "CSF-2" or TC-GM-CSF or CSF-GM or rhGM-CSF):ti,ab,kw

#102 MeSH descriptor: [Platelet Count] this term only

#103 ((platelet* or thrombocyt*) near/4 (count* or number* or total* or calculat* or amount* or estimat* or quant* or sum*)):ti,ab,kw

#104 MeSH descriptor: [Cerebrospinal Fluid] this term only

#105 ((cerebrospinal* or "cerebr*-spinal*" or cephalorhachidian* or cranial* or spinal* or "brain*-ventricl*" or neurolymph* or "neuro-lymph*") near/4 (fluid* or liquid* or solut*) near/4 (exam* or test* or analys* or inspect* or explor* or scan* or investigat*)):ti,ab,kw

#106 ((CSF*) near/4 (exam* or test* or analys* or inspect* or explor* or scan* or investigat*)):ti,ab,kw

#107 MeSH descriptor: [Spinal Puncture] this term only

#108 ((spinal* or spine* or lumbar*) near/4 (puncture* or tap*)):ti,ab,kw

#109 MeSH descriptor: [Latex Fixation Tests] this term only

#110 ((latex*) near/4 (test* or kit* or method* or fixat* or agglutinat* or antigen* or assay* or serotyp* or react*)):ti,ab,kw

#111 (streptex* or pastorex* or wellcogen*):ti,ab,kw

#112 (LPA or LAT or LFT):ti,ab,kw

#113 MeSH descriptor: [Reagent Strips] this term only

#114 ((urin* or reagent* or immunochromographic* or immuno-chromographic* or Nephur* or test*) near/4 (strip* or dipstick* or dip-stick* or tap* or paper*)):ti,ab,kw

#115 (StripAssay*):ti,ab,kw

#116 MeSH descriptor: [Polymerase Chain Reaction] explode all trees

#117 ((polymerase*) near/4 (chain*) near/4 (react*)):ti,ab,kw

#118 (PCR):ti,ab,kw

#119 MeSH descriptor: [Urinalysis] this term only

#120 MeSH descriptor: [Urine] this term only and with qualifier(s): [microbiology - MI]

#121 (urinalys*):ti,ab,kw

#122 ((urin*) near/4 (cultur* or mcroscop* or test* or analys* or exam* or investigat*)):ti,ab,kw

#123 (UA):ti,ab,kw

#124 MeSH descriptor: [Catheters] explode all trees

#125 MeSH descriptor: [Catheterization] this term only

#126 MeSH descriptor: [Urinary Catheterization] explode all trees

#127 (catheter* or cannula*):ti,ab,kw

#128 ((suprapubic* or supra-pubic* or bladder* or detrusor*) near/4 (aspirat* or punctur*)):ti,ab,kw

#129 (SPA or SBA):ti,ab,kw

#130 ((iQ200*) or (iChem* near/4 workstation*)):ti,ab,kw

#131 MeSH descriptor: [Flow Cytometry] this term only

#132 ((flow*) near/4 (cytometr* or microfluoromet* or cytofluorometr* or lateral*)):ti,ab,kw

#133 (LFB or LFA):ti,ab,kw

#134 (Sysmex*):ti,ab,kw

#135 ((Xpert) near/4 (MTB or RIF)):ti,ab,kw

#136 ((rapid* or quick* or accelerat* or fast* or speed* or swift*) near/4 (test* or kit* or method* or detect* or discover* or identif* or recogni* or assay* or agglutinat* or immunoassay* or immunochromatographic*)):ti,ab,kw

#137 (RDT or RADT or DIMA):ti,ab,kw

#138 MeSH descriptor: [Fluorescent Antibody Technique] this term only

#139 ((fluorescen* or immunofluorescen* or immuno-fluorescen*) near/4 (techni* or antibod* or anti-bod* or trac* or cell* or hybridi?ation* or test* or method* or identif* or detect*)):ti,ab,kw

#140 (FISH):ti,ab,kw

#141 MeSH descriptor: [Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization] this term only

#142 ((matrix* near/10 spectrom*)):ti,ab,kw

#143 (MALDI* or MALD-MS* or TOF-MS* or LDI-MS*):ti,ab,kw

#144 (FilmArray*):ti,ab,kw

#145 MeSH descriptor: [Staining and Labeling] this term only

#146 ((gram*) near/4 (stain* or label*)):ti,ab,kw

#147 MeSH descriptor: [Limulus Test] this term only

#148 ((limulus*) near/4 (lysate* or test* or assay* or exam* or analys* or investigat* or method* or detect* or endotoxin* or toxin* or coagul* or serum*)):ti,ab,kw

#149 (LAL):ti,ab,kw

#150 (swab*):ti,ab,kw

#151 ((surface* or exterior* or outer* or superficial*) near/4 (culture* or wipe* or mop or smear*)):ti,ab,kw

#152 ((skin* or dermis* or epidermis* or nose* or nasal* or paranasal* or ear or ears or umbilic* or rectal* or rectum* or axilla* or underarm* or under-arm* or armpit* or arm-pit* or groin* or genital* or eye* or ocular* or oculus* or throat* or pharyn* or laryn* or neck*) near/4 (culture* or wipe* or mop or smear*)):ti,ab,kw

#153 MeSH descriptor: [Infusions, Intravenous] this term only

#154 ((IV or I-V or intravenous*) near/4 (line* or infusion* or sampl* or fragment* or specimen* or indicat* or segment* or drip* or admin* or dos* or inject* or deliver* or transfus* or tip*)):ti,ab,kw

#155 MeSH descriptor: [Radiography, Thoracic] explode all trees

#156 MeSH descriptor: [X-Rays] this term only

#157 ((chest* or thorax* or thorac* or bronch* or lung*) near/4 (x-ray* or xray* or radio* or roentgen* or imag*)):ti,ab,kw

#158 {or #56-#157}

#159 #55 and #158

DARE

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES

2 MeSH DESCRIPTOR Term Birth

3 MeSH DESCRIPTOR Infant Care

4 MeSH DESCRIPTOR Perinatal Care

5 MeSH DESCRIPTOR Intensive Care Units, Neonatal

6 MeSH DESCRIPTOR Intensive Care, Neonatal

7 MeSH DESCRIPTOR Infant Health

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

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

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

11 MeSH DESCRIPTOR Bacterial Infections EXPLODE ALL TREES

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

13 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES

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

15 (septic* NEAR4 shock*)

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

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

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

19 MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES

20 MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES

21 (streptococc* or staphylococc*)

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

23 (met?icillin-resistant NEAR3 aureus)

24 MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES

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

26 MeSH DESCRIPTOR Listeria EXPLODE ALL TREES

27 (listeria*)

28 MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREES

29 (klebsiella*)

30 MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES

31 (pseudomonas or chryseomonas or flavimonas)

32 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES

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

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

35 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES

36 (neisseria*)

37 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES

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

39 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES

40 (serratia*)

41 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES

42 (cronobact* or sakazaki* or malonatic*)

43 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES

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

45 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES

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

47 MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES

48 (enterococc*)

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

50 (#18 OR #49)

51 (#10 AND #50)

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

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

54	(#52 OR #53)
55	(#51 OR #54)
56	((inflam* or excit*) NEAR4 (marker* or flag* or indicat*))
57	MeSH DESCRIPTOR C-Reactive Protein
58	((C) NEAR2 (react*) NEAR4 (protein*))
59	(Creact* NEAR4 protein*)
60	(CRP)
61	MeSH DESCRIPTOR Acute-Phase Reaction
62	MeSH DESCRIPTOR Acute-Phase Proteins
63	((acute*) NEAR2 (phas*) NEAR4 (react* or respons* or state* or protein*))
64	(APR)
65	MeSH DESCRIPTOR Serum Amyloid A Protein
66	((serum*) NEAR4 (amyloid*) NEAR4 (A))
67	(SAA)
68	MeSH DESCRIPTOR Orosomucoid

1		
2	69	(orosomucoid* or seromucoid*)
3		
4	70	((serum*) NEAR4 (fibronectin* or sialomuin*))
5		
6	71	MeSH DESCRIPTOR alpha-2-Antiplasmin
7		
8	72	((acid* or alpha*) NEAR4 (antiplasmin* or anti-plasmin* or glycoprotein*))
9		
10	73	((alpha*) NEAR4 (plasmin*) NEAR4 (inhibitor*))
11		
12	74	(AGP)
13		
14	75	MeSH DESCRIPTOR Hepcidins
15		
16	76	(hepcidin*)
17		
18	77	MeSH DESCRIPTOR Blood Sedimentation
19		
20	78	((blood* or erythrocyte*) NEAR4 (sediment*))
21		
22	79	MeSH DESCRIPTOR Haptoglobins
23		
24	80	(haptoglobin*)
25		
26	81	((h?emoglobin*) NEAR4 (bind*) NEAR4 (protein*))
27		
28	82	MeSH DESCRIPTOR Calcitonin
29		
30	83	(procalcitonin* or calcitonin*)

84 (PCT)

85 MeSH DESCRIPTOR Interleukins EXPLODE ALL TREES

86 MeSH DESCRIPTOR Interleukin 1 Receptor Antagonist Protein

87 (interleukin* or IL-6 or IL6 or IL-1 or IL1)

88 MeSH DESCRIPTOR Cytokines

89 MeSH DESCRIPTOR Receptors, Cytokine EXPLODE ALL TREES

90 (cytokine*)

91 MeSH DESCRIPTOR Leukocyte Count EXPLODE ALL TREES

92 ((leukocyte* or leucocyte* or lymphocyte* or WBC*) NEAR4 (count* or number* or polymorphonuclear* or total* or calculat* or amount* or estimat* or quant* or sum*))

93 ((white*) NEAR2 (blood* or cell*) NEAR4 (count* or number* or polymorphonuclear* or total* or calculat* or amount* or estimat* or quant* or sum*))

94 MeSH DESCRIPTOR Colony-Stimulating Factors EXPLODE ALL TREES

95 ((colony* or colonies*) NEAR4 (stimulat*) NEAR4 (factor* or activit* or determin* or influenc* or agen*))

96 MeSH DESCRIPTOR Granulocytes

97 MeSH DESCRIPTOR Neutrophils

98 (granulocyte* or neutrophil* or neutrocyt*)

99 ((LE or band or granuloid*) NEAR4 (cell*))

100 (G-CSF or GM-CSF or "CSF-2" or TC-GM-CSF or CSF-GM or rhGM-CSF)

101 MeSH DESCRIPTOR Platelet Count

102 ((platelet* or thrombocyt*) NEAR4 (count* or number* or total* or calculat* or amount* or estimat* or quant* or sum*))

103 MeSH DESCRIPTOR Cerebrospinal Fluid

104 ((cerebrospinal* or cerebr*-spinal* or cephalorhachidian* or cranial* or spinal* or brain*-ventricl* or neurolymph* or neuro-lymph*) NEAR4 (fluid* or liquid* or solut*) NEAR4 (exam* or test* or analys* or inspect* or explor* or scan* or investigat*))

105 ((CSF*) NEAR4 (exam* or test* or analys* or inspect* or explor* or scan* or investigat*))

106 MeSH DESCRIPTOR Spinal Puncture

107 ((spinal* or spine* or lumbar*) NEAR4 (puncture* or tap*))

108 MeSH DESCRIPTOR Latex Fixation Tests

109 ((latex*) NEAR4 (test* or kit* or method* or fixat* or agglutinat* or antigen* or assay* or serotyp* or react*))

110 (streptex* or pastorex* or wellcogen*)

111 (LPA or LAT or LFT)

112 MeSH DESCRIPTOR Reagent Strips

113 ((urin* or reagent* or immunochromographic* or immuno-chromographic* or Nephur* or test*) NEAR4 (strip* or dipstick* or dip-stick* or tap* or paper*))

114 (StripAssay*)

115 MeSH DESCRIPTOR Polymerase Chain Reaction EXPLODE ALL TREES

116 (PCR)

117 ((polymerase*) NEAR4 (chain*) NEAR4 (react*))

118 MeSH DESCRIPTOR Urinalysis

119 MeSH DESCRIPTOR Urine WITH QUALIFIER MI

120 (urinalys*)

121 ((urin*) NEAR4 (cultur* or mcroscop* or test* or analys* or exam* or investigat*))

122 (UA)

123 MeSH DESCRIPTOR Catheters EXPLODE ALL TREES

124 MeSH DESCRIPTOR Catheterization

125 MeSH DESCRIPTOR Urinary Catheterization EXPLODE ALL TREES

126 (catheter* or cannula*)

127 ((suprapubic* or supra-pubic* or bladder* or detrusor*) NEAR4 (aspirat* or punctur*))

128 (SPA or SBA)

129 ((iQ200*) or (iChem* NEAR4 workstation*))

130 MeSH DESCRIPTOR Flow Cytometry

131 ((flow*) NEAR4 (cytometr* or microfluoromet* or cytofluorometr* or lateral*))

132 (LFB or LFA)

133 (Sysmex*)

134 ((Xpert) NEAR4 (MTB or RIF))

135 ((rapid* or quick* or accelerat* or fast* or speed* or swift*) NEAR4 (test* or kit* or method* or detect* or discover* or identif* or recogni* or assay* or agglutinat* or immunoassay* or immunochromatographic*))

136 (RDT or RADT or DIMA)

137 MeSH DESCRIPTOR Fluorescent Antibody Technique EXPLODE ALL TREES

138 ((fluorescen* or immunofluorescen* or immuno-fluorescen*) NEAR4 (techni* or antibod* or anti-bod* or trac* or cell* or hybridi?ation* or test* or method* or identif* or detect*))

139 (FISH)

140 MeSH DESCRIPTOR Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization

141 ((matrix* NEAR10 spectrom*))

142 (MALDI* or MALD-MS* or TOF-MS* or LDI-MS*)

143 (FilmArray*)

144 MeSH DESCRIPTOR Staining and Labeling

145 ((gram*) NEAR4 (stain* or label*))

146 MeSH DESCRIPTOR Limulus Test

147 ((limulus*) NEAR4 (lysate* or test* or assay* or exam* or analys* or investigat* or method* or detect* or endotoxin* or toxin* or coagul* or serum*))

148 (LAL)

149 (swab*)

150 ((surface* or exterior* or outer* or superficial*) NEAR4 (culture* or wipe* or mop or smear*))

151 ((skin* or dermis* or epidermis* or nose* or nasal* or paranasal* or ear or ears or umbilic* or rectal* or rectum* or axilla* or underarm* or under-arm* or armpit* or arm-pit* or groin* or genital* or eye* or ocular* or oculus* or throat* or pharyn* or laryn* or neck*) NEAR4 (culture* or wipe* or mop or smear*))

152 MeSH DESCRIPTOR Infusions, Intravenous

153 ((IV or I-V or intravenous*) NEAR4 (line* or infusion* or sampl* or fragment* or specimen* or indicat* or segment* or drip* or admin* or dos* or inject* or deliver* or transfus* or tip*))

154 MeSH DESCRIPTOR Radiography, Thoracic EXPLODE ALL TREES

155 MeSH DESCRIPTOR X-Rays

156 ((chest* or thorax* or thorac* or bronch* or lung*) NEAR4 (x-ray* or xray* or radio* or roentgen* or imag*))

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

158 #55 AND #157

159 * IN DARE

160 #158 AND #159

Systematic Review Search Filter

The following systematic review filter was combined as ‘And’ with the population and investigations terms for the Medline databases and Embase. CDSR and DARE are systematic review databases so did not require the addition of a filter.

The Medline version of the filter is reproduced below. Embase has a validated translation of this that was used in the search.

1 MEDLINE or pubmed).tw.
2 systematic review.tw.
3 systematic review.pt.
4 meta-analysis.pt.
5 intervention$.ti.
6 or/1-5

Virus terms

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

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

1 exp Virus Diseases/
2 exp Viruses/
3 (virus* or viral* or retrovir* or arbovir* or lentivir* or deltaretrovir* or adenovir*).tw.
4 HIV*.tw.
5 (cytomegalovir* or CMV*).tw.
6 herpes*.tw.
7 (papillomavir* or HPV*).tw.
8 ((hepatitis* or hepatitid*) adj2 (A or B or C or D or E)).tw.
9 (parechovir* or echovir*).tw.
10 (yellow* adj2 fever*).tw.
11 rhinovir*.tw.
12 (coronavir* or deltacoronavir*).tw.
13 rotavir*.tw.
14 (enterovir* or coxsackie*).tw.
15 exp Malaria/

16 (malaria* or paludism*).tw.

17 exp Syphilis/

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

19 or/1-18

Health Economics literature search strategy

Sources searched to identify economic evaluations

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

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

Health economics search strategy

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

13 exp Sepsis/ (123123)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (100090)

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

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

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

18 or/11-17 (1097119)

19 exp Streptococcus/ (78627)

20 exp Staphylococcus/ (104852)

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

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

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

24 exp Escherichia coli/ (278943)

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

26 exp Listeria/ (15143)

27 listeria*.tw. (18688)

28 exp Klebsiella/ (19836)

29 klebsiella*.tw. (26962)

30 exp Pseudomonas/ (71592)

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

32 Enterobacteriaceae/ (18945)

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

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

35 exp Neisseria/ (20482)

36 neisseria*.tw. (18785)

37 exp Haemophilus influenzae/ (13731)

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

39 exp Serratia/ (6599)

40 serratia*.tw. (8439)

41 exp Cronobacter/ (655)

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

43 exp Acinetobacter/ (9822)

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

45 exp Fusobacterium/ (3796)

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

47 exp Enterococcus/ (19718)

48 enterococc*.tw. (26150)

49 or/19-48 (765874)

50 18 or 49 (1614537)

51 10 and 50 (65444)

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

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

54 52 or 53 (16770)

55 51 or 54 (74853)

56 Economics/ (27206)

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

58 Economics, Dental/ (1911)

59 exp Economics, Hospital/ (24558)

60 exp Economics, Medical/ (14206)

61 Economics, Nursing/ (3999)

62 Economics, Pharmaceutical/ (2941)

63 Budgets/ (11315)

64 exp Models, Economic/ (15053)

65 Markov Chains/ (14321)

66 Monte Carlo Method/ (28322)

67 Decision Trees/ (11133)

68 econom$.tw. (238765)

69 cba.tw. (9764)

70 cea.tw. (20532)

71 cua.tw. (999)

72 markov$.tw. (17997)

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

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

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

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

77 budget$.tw. (23716)

78 expenditure$.tw. (49355)

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

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

81 or/56-80 (926379)

82 "Quality of Life"/ (194718)

83 quality of life.tw. (229884)

84 "Value of Life"/ (5706)

85 Quality-Adjusted Life Years/ (12284)

86 quality adjusted life.tw. (10842)

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

88 disability adjusted life.tw. (2741)

89 daly$.tw. (2486)

90 Health Status Indicators/ (23409)

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

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

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

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

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (381)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (9001)

97 (qol or hql or hqol or hrqol).tw. (44126)

98 (hye or hyes).tw. (60)

99 health$ year$ equivalent$.tw. (38)

100 utilit$.tw. (171457)

101 (hui or hui1 or hui2 or hui3).tw. (1304)

102 disutili$.tw. (396)

103 rosser.tw. (94)

104 quality of wellbeing.tw. (14)

105 quality of well-being.tw. (381)

106 qwb.tw. (190)

107 willingness to pay.tw. (4500)

108 standard gamble$.tw. (783)

109 time trade off.tw. (1037)

110 time tradeoff.tw. (238)

111 tto.tw. (899)

112 or/82-111 (493012)

113 81 or 112 (1350947)

114 55 and 113 (3480)

115 limit 114 to ed=20190716-20200724 (226)

116 animals/ not humans/ (4686781)

117 115 not 116 (213)

118 limit 117 to english language (208)

1

Database: MiP (Ovid)

1 exp Infant, Newborn/ (0)

2 Term Birth/ (0)

3 Infant Care/ (0)

4 Perinatal Care/ (0)

5 Intensive Care Units, Neonatal/ (0)

6 Intensive Care, Neonatal/ (0)

7 Infant Health/ (0)

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

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

10 or/1-9 (34405)

11 exp Bacterial Infections/ (0)

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

13 exp Sepsis/ (0)

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

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

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

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

18 or/11-17 (35377)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

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

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

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

24 exp Escherichia coli/ (0)

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

26 exp Listeria/ (0)

27 listeria*.tw. (2351)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (4101)

30 exp Pseudomonas/ (0)

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

32 Enterobacteriaceae/ (0)

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

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

35 exp Neisseria/ (0)

36 neisseria*.tw. (1256)

37 exp Haemophilus influenzae/ (0)

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

39 exp Serratia/ (0)

40 serratia*.tw. (829)

41 exp Cronobacter/ (0)

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

43 exp Acinetobacter/ (0)

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

45 exp Fusobacterium/ (0)

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

47 exp Enterococcus/ (0)

48 enterococc*.tw. (3589)

49 or/19-48 (59520)

50 18 or 49 (83682)

51 10 and 50 (2543)

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

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

54 52 or 53 (1309)

55 51 or 54 (3367)

56 Economics/ (0)

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

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (1)

66 Monte Carlo Method/ (2)

67 Decision Trees/ (0)

68 econom$.tw. (47080)

69 cba.tw. (456)

70 cea.tw. (2004)

71 cua.tw. (198)

72 markov$.tw. (5795)

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

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

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

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

77 budget$.tw. (5074)

78 expenditure$.tw. (6509)

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

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

81 or/56-80 (172313)

82 "Quality of Life"/ (0)

83 quality of life.tw. (40043)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (1728)

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

88 disability adjusted life.tw. (523)

89 daly$.tw. (479)

90 Health Status Indicators/ (0)

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

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

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

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

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

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

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

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

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

100 utilit$.tw. (32031)

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

102 disutili$.tw. (60)

103 rosser.tw. (4)

104 quality of wellbeing.tw. (9)

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

106 qwb.tw. (13)

107 willingness to pay.tw. (957)

108 standard gamble$.tw. (62)
109 time trade off.tw. (119)
110 time tradeoff.tw. (11)
111 tto.tw. (145)
112 or/82-111 (74419)
113 81 or 112 (236895)
114 55 and 113 (231)
115 limit 114 to dt=20190716-20200724 (89)
116 animals/ not humans/ (1)
117 115 not 116 (89)
118 limit 117 to english language (89)

1

Database: Medline E-pubs (Ovid)
1 exp Infant, Newborn/ (0)
2 Term Birth/ (0)
3 Infant Care/ (0)
4 Perinatal Care/ (0)
5 Intensive Care Units, Neonatal/ (0)
6 Intensive Care, Neonatal/ (0)
7 Infant Health/ (0)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (6371)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (1421)
10 or/1-9 (6871)
11 exp Bacterial Infections/ (0)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (2219)
13 exp Sepsis/ (0)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (1706)

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

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

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

18 or/11-17 (4700)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

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

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

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

24 exp Escherichia coli/ (0)

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

26 exp Listeria/ (0)

27 listeria*.tw. (198)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (476)

30 exp Pseudomonas/ (0)

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

32 Enterobacteriaceae/ (0)

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

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

35 exp Neisseria/ (0)

36 neisseria*.tw. (177)

37 exp Haemophilus influenzae/ (0)

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

39 exp Serratia/ (0)

40 serratia*.tw. (72)

41 exp Cronobacter/ (0)

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

43 exp Acinetobacter/ (0)

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

45 exp Fusobacterium/ (0)

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

47 exp Enterococcus/ (0)

48 enterococc*.tw. (403)

49 or/19-48 (6238)

50 18 or 49 (9619)

51 10 and 50 (455)

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

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

54 52 or 53 (268)

55 51 or 54 (651)

56 Economics/ (0)

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

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (0)

66 Monte Carlo Method/ (0)

67 Decision Trees/ (0)

68 econom$.tw. (6645)

69 cba.tw. (61)

70 cea.tw. (331)

71 cua.tw. (17)

72 markov$.tw. (718)

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

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

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

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

77 budget$.tw. (555)

78 expenditure$.tw. (1143)

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

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

81 or/56-80 (21922)

82 "Quality of Life"/ (0)

83 quality of life.tw. (7520)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (388)

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

88 disability adjusted life.tw. (101)

89 daly$.tw. (88)

90 Health Status Indicators/ (0)

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

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

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

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

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

1

2

3

Database: Embase (Ovid)
1 newborn/ (526097)
2 term birth/ (3569)
3 infant care/ (1049)

4 perinatal care/ (14198)

5 neonatal intensive care unit/ (10192)

6 newborn intensive care/ (26405)

7 child health/ (27137)

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

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

10 or/1-9 (841089)

11 exp bacterial infection/ (838120)

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

13 exp sepsis/ (263922)

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

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

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

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

18 or/11-17 (1201558)

19 exp Streptococcus/ (128274)

20 exp Staphylococcus/ (209430)

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

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

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

24 exp Escherichia coli/ (361361)

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

26 exp Listeria/ (24096)

27 listeria*.tw. (22102)

28 exp Klebsiella/ (59561)

29 klebsiella*.tw. (42289)

30 exp Pseudomonas/ (144052)

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

32 Enterobacteriaceae/ (23812)

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

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

35 exp Neisseria/ (32218)

36 neisseria*.tw. (22936)

37 exp Haemophilus influenzae/ (29007)

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

39 exp Serratia/ (14280)

40 serratia*.tw. (10397)

41 exp cronobacter/ (817)

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

43 exp Acinetobacter/ (27955)

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

45 exp Fusobacterium/ (7678)

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

47 exp Enterococcus/ (49841)

48 enterococc*.tw. (37571)

49 or/19-48 (967441)

50 18 or 49 (1894492)

51 10 and 50 (70672)

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

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

54 52 or 53 (22885)

55 51 or 54 (83775)

56 exp Health Economics/ (845404)

57 exp "Health Care Cost"/ (290992)

58 exp Pharmacoeconomics/ (202216)

59 Monte Carlo Method/ (40279)

60 Decision Tree/ (13001)

61 econom$.tw. (368838)

62 cba.tw. (12788)

63 cea.tw. (34786)

64 cua.tw. (1498)

65 markov$.tw. (30389)

66 (monte adj carlo).tw. (48341)

67 (decision adj3 (tree$ or analys$)).tw. (23602)

68 (cost or costs or costing$ or costly or costed).tw. (772396)

69 (price$ or pricing$).tw. (57398)

70 budget$.tw. (38616)

71 expenditure$.tw. (74588)

72 (value adj3 (money or monetary)).tw. (3455)

73 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8625)

74 or/56-73 (1760062)

75 "Quality of Life"/ (469927)

76 Quality Adjusted Life Year/ (26663)

77 Quality of Life Index/ (2774)

78 Short Form 36/ (29036)

79 Health Status/ (127411)

80 quality of life.tw. (439622)

81 quality adjusted life.tw. (19747)

82 (qaly$ or qald$ or qale$ or qtime$).tw. (20178)

83 disability adjusted life.tw. (4103)

84 daly$.tw. (4016)

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

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

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

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

89 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (455)

90 (euroqol or euro qol or eq5d or eq 5d).tw. (20619)

91 (qol or hql or hqol or hrqol).tw. (97056)

92 (hye or hyes).tw. (135)

93 health$ year$ equivalent$.tw. (41)

94 utilit$.tw. (289831)

95 (hui or hui1 or hui2 or hui3).tw. (2300)

96 disutili$.tw. (924)

97 rosser.tw. (124)

98 quality of wellbeing.tw. (42)

99 quality of well-being.tw. (486)

100 qwb.tw. (253)

101 willingness to pay.tw. (8837)

102 standard gamble$.tw. (1104)

103 time trade off.tw. (1708)

104 time tradeoff.tw. (291)

105 tto.tw. (1683)

106 or/75-105 (989974)

107 74 or 106 (2593254)

108 55 and 107 (5731)

109 limit 108 to dc=20190716-20200724 (558)

110 nonhuman/ not human/ (4649157)

111 109 not 110 (522)

112 limit 111 to english language (510)

113 limit 112 to (conference abstract or conference paper or "conference review") (113)

114 112 not 113 (397)

1

Database: Econlit (Ovid)

1 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (732)

2 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (45)

3 1 or 2 (767)

4 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (49)

5 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (17)

6 (septic* adj4 shock*).tw. (1)

7 (bacter?emia* or bacill?emia*).tw. (3)

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

9 (streptococc* or staphylococc*).tw. (18)

10 (GBS or MRSA or NRCS-A or MSSA).tw. (40)

11 (met?icillin-resistant adj3 aureus).tw. (8)

12 (((Escheric* or E) adj2 coli) or ecoli*).tw. (47)

13 listeria*.tw. (6)

14 klebsiella*.tw. (0)

15 (pseudomonas or chryseomonas or flavimonas).tw. (6)

16 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (1)

17 ((enteric or coliform) adj2 bac*).tw. (0)

18 neisseria*.tw. (1)

19 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (14)

20 serratia*.tw. (0)

21 (cronobact* or sakazaki* or malonatic*).tw. (1)

22 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2)

23 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (0)

24 enterococc*.tw. (5)

25 or/4-24 (194)

26 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (11)

27 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1)

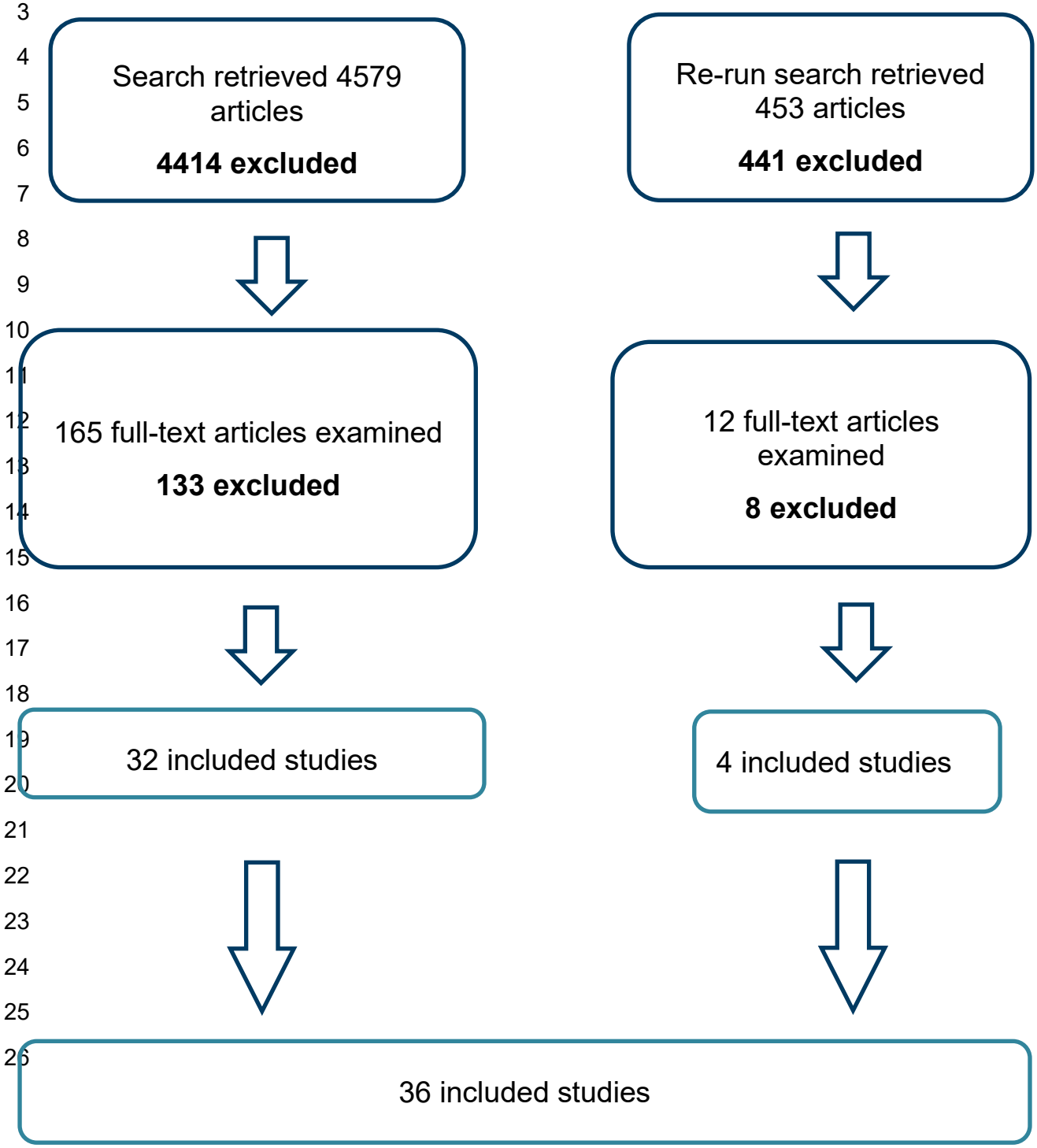
28 26 or 27 (12)

29 25 or 28 (205)

30 3 and 29 (15)

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

Appendix C –Diagnostic evidence study selection



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

1 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

1

2

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

3 **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

1 **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)*

1

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

1 **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

1 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

1

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

2 **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

1 **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)*

1
2

1

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

2 **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

1 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)

1

2

3

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

4 **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

1 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

1

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

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

1 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)

1

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

2 **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

1 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

1

2

3

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

4 **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

1 **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

1

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

2 **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

1

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

2 **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

1 **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

1 **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).)

1

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

1 **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

2 **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

1

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

1 **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

1

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

2 **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

1 **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

1

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

2 **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

1 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))

1

2

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

1 **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

1 **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

1

Makhoul, 2005

2

Bibliographic Reference	Makhoul, Imad R; Smolkin, Tatiana; Sujov, Polo; Kassis, Imad; Tamir, Ada; Shalginov, Raia; Sprecher, Hannah; PCR-based diagnosis of neonatal staphylococcal bacteremias.; Journal of clinical microbiology; 2005; vol. 43 (no. 9); 4823-5

3 **Study Characteristics**

Study type	Cross-sectional study
Study location	Israel
Study setting	Neonatal ICU
Study dates	Not mentioned. The study was received for publication in 2005

Sources of funding	Not mentioned
Inclusion criteria	Late-onset infection: 72 hours onwards (corrected age) without stated end-point (downgraded once for indirectness) Symptoms and/or signs of neonatal infection
Sample size	360
Average birth weight (variance)	Mean (SD) 1962 g (874)
Average gestational age (variance)	Mean (SD) 33.5 weeks (4.4)
Average age at evaluation (variance)	Mean (SD) 15.4 days (17.3)
Percentage of females	-
Loss to follow-up	None
Index test(s)	Rapid test PCR amplification
Reference standard (s)	Blood culture on sample taken
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

1

2

3 **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?	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

Section	Question	Answer
	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 *(It is not clear whether the index and reference test results were analysed together. Episodes of sepsis were analysed rather than participants experiencing sepsis. Therefore, double-counting could be an issue)*
	Directness	Directly applicable

Makhoul, 2006

Bibliographic Reference	Makhoul, Imad R; Yacoub, Afeefi; Smolkin, Tatiana; Sujov, Polo; Kassis, Imad; Sprecher, Hannah; Values of C-reactive protein, procalcitonin, and Staphylococcus-specific PCR in neonatal late-onset sepsis.; Acta paediatrica (Oslo, Norway : 1992); 2006; vol. 95 (no. 10); 1218-23

1 **Study Characteristics**

Study type	Cross-sectional study
Study location	Israel
Study setting	Neonatal ICU
Study dates	Not mentioned. Study was received for publication in 2005
Sources of funding	A. & E. Blum Medical Research Fund
Inclusion criteria	Late-onset infection: 72 hours onwards (corrected age) without stated end-point (downgraded once for indirectness) Symptoms and/or signs of neonatal infection
Exclusion criteria	None
Sample size	111
Average birth weight (variance)	Mean (SD) 1064 g (255)
Average gestational age (variance)	Mean (SD) 28.5 weeks (2.5)
Average age at evaluation (variance)	-

Percentage of females	-
Loss to follow-up	None
Index test(s)	C-reactive protein (CRP) Procalcitonin (PCT) Rapid test Staphylococcus -specific polymerase chain reaction (PCR)
Reference standard (s)	Blood culture on sample taken
Outcomes	Diagnostic test accuracy outcomes: true positives, false negatives, false positives and true negatives

1

2 **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
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear

Section	Question	Answer
	If a threshold was used, was it pre-specified?	No
	Could the conduct or interpretation of the index test have introduced bias?	Unclear
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 could have been analysed together. There was no threshold for CRP or PCT in the methods section)*
	Directness	Directly applicable

1

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

2 **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

1 **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

1

2

3

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

4 **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

1 **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

1

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

2 **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

1 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

1

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

2 **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

1 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

1

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

2 **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

1 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

1

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

2 **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

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3 **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

1 **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

1 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)

1 **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

1 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

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3

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

4 **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

1 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

1

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

2 **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

1 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

1

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

2 **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

1 **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

1

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

2 **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

1 ## 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

1

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

1 **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

1 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)

1

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)

2 **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

1 **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

1 **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.)

1

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

2 **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

1

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

2 **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

1 **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)

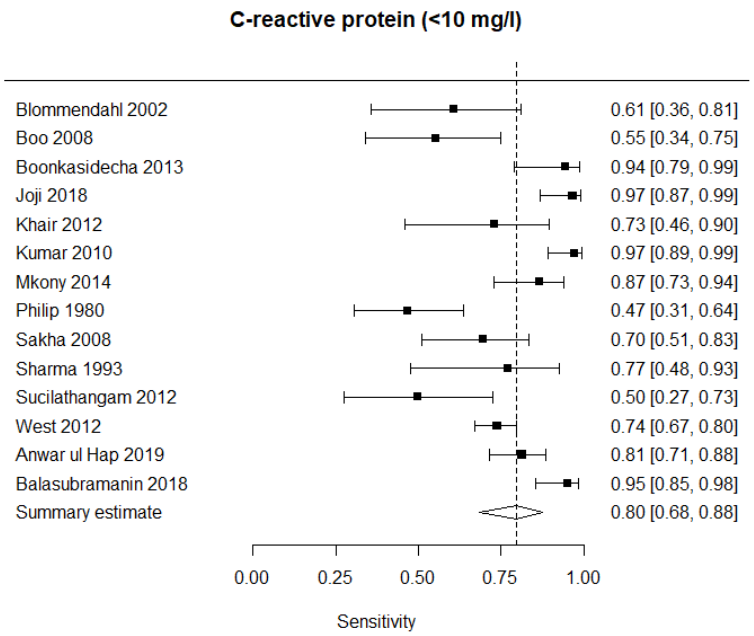
Directness

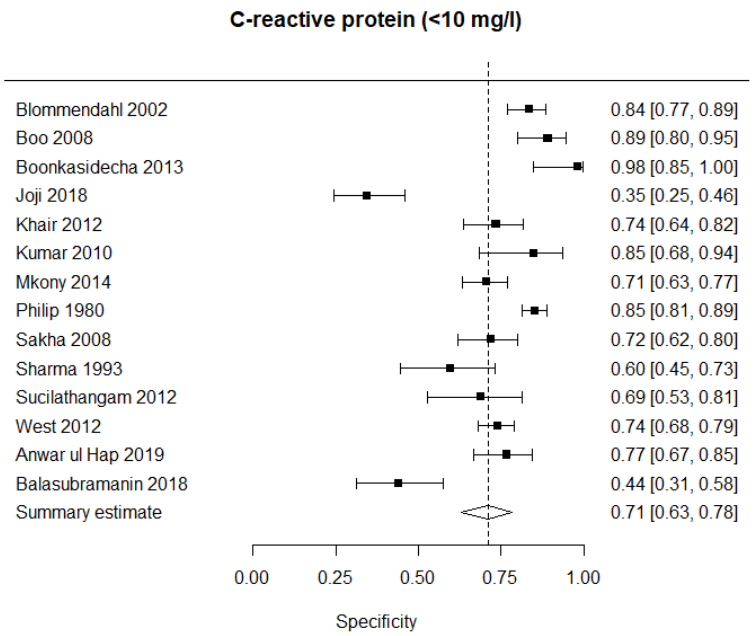
Directly applicable

Appendix E – Forest plots and ROC curves

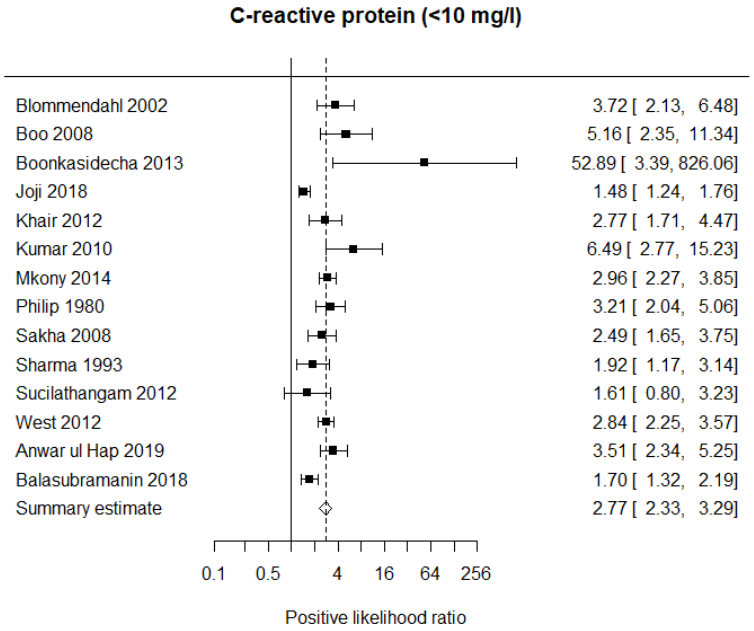
C-reactive protein (<10 mg/l) at time of blood culture

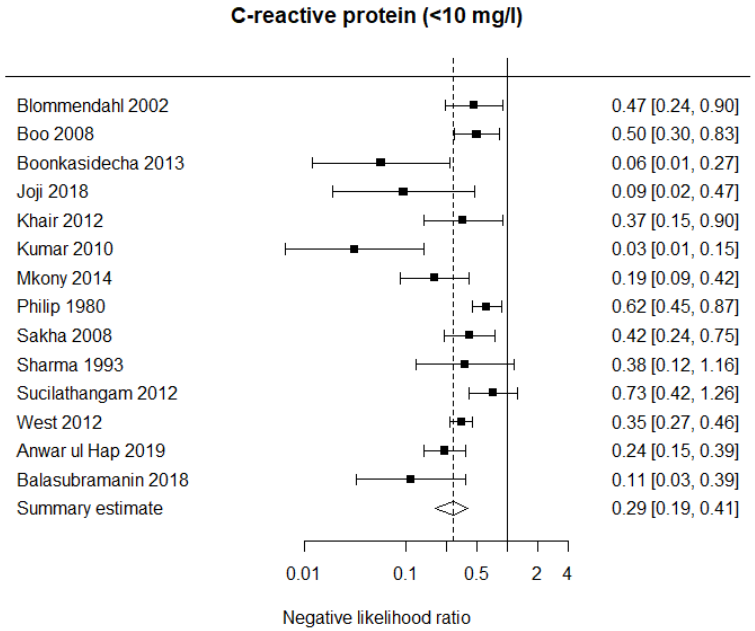
Sensitivity and specificity





1 Likelihood ratios





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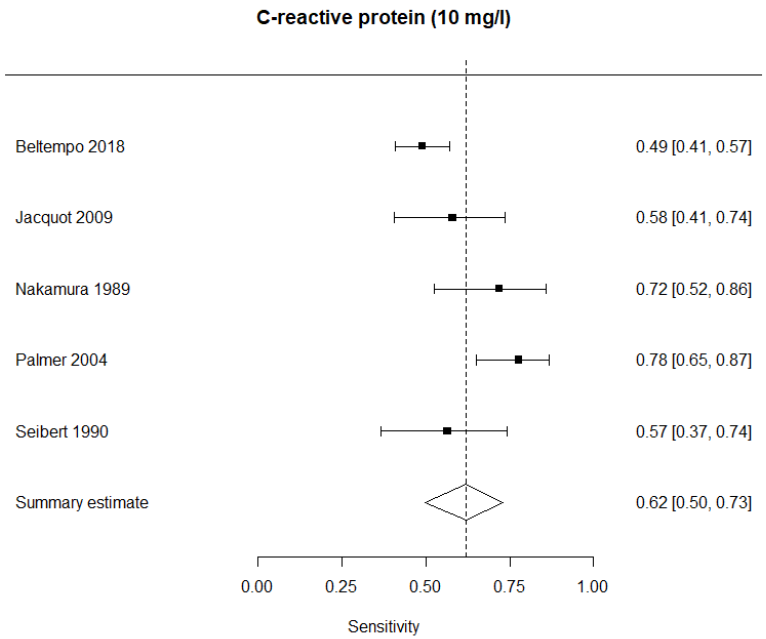
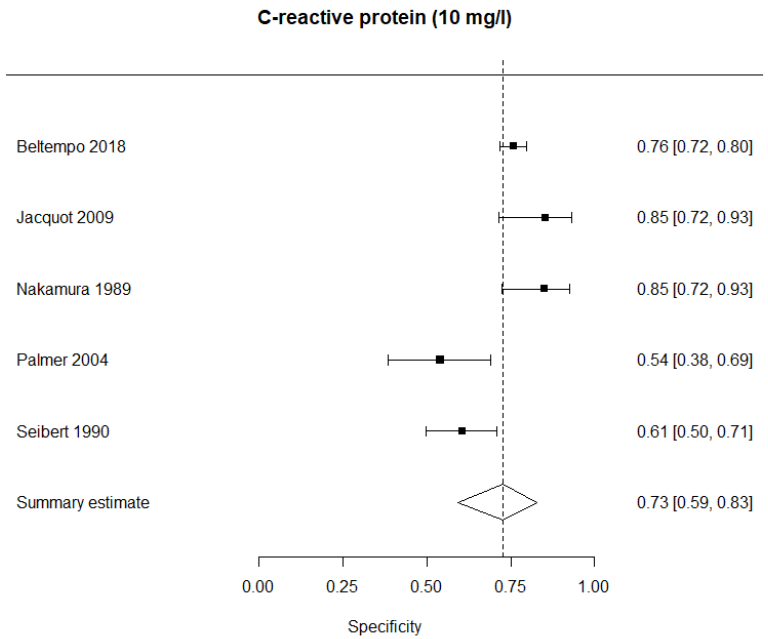
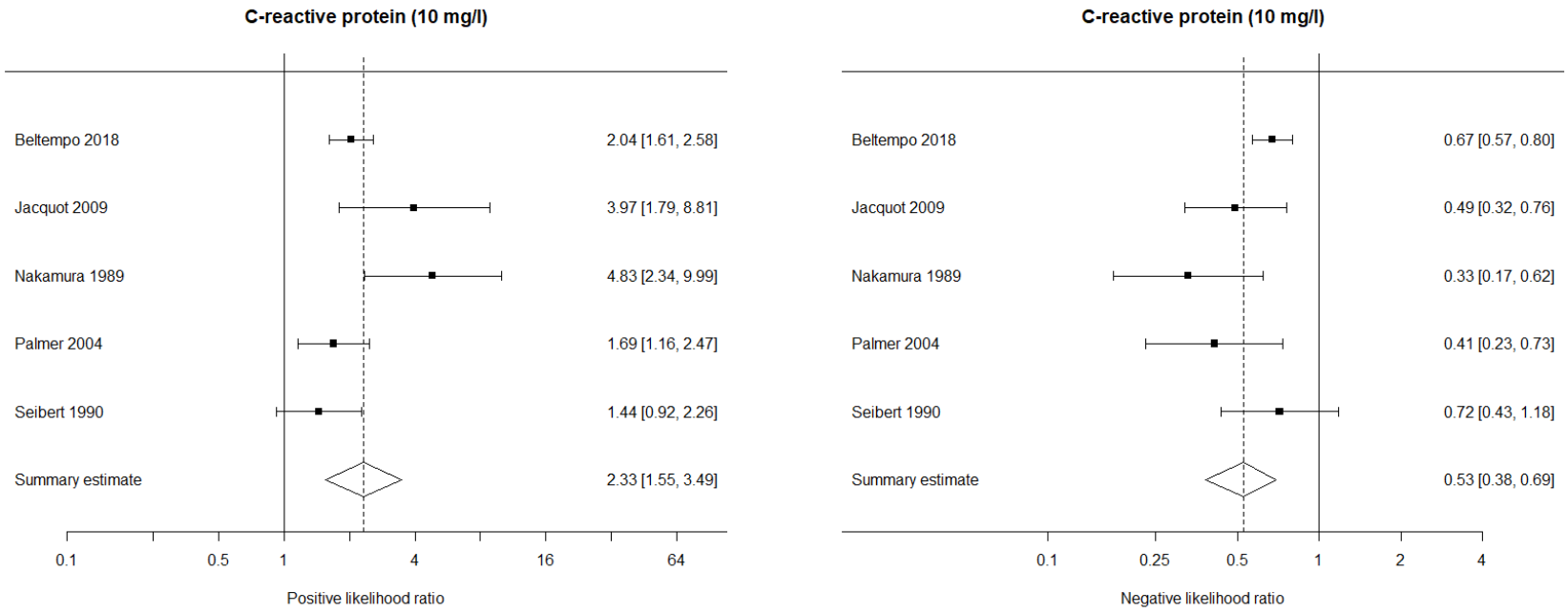
C-reactive protein (10 mg/l) at time of blood culture

Sensitivity and specificity





1 Likelihood ratios



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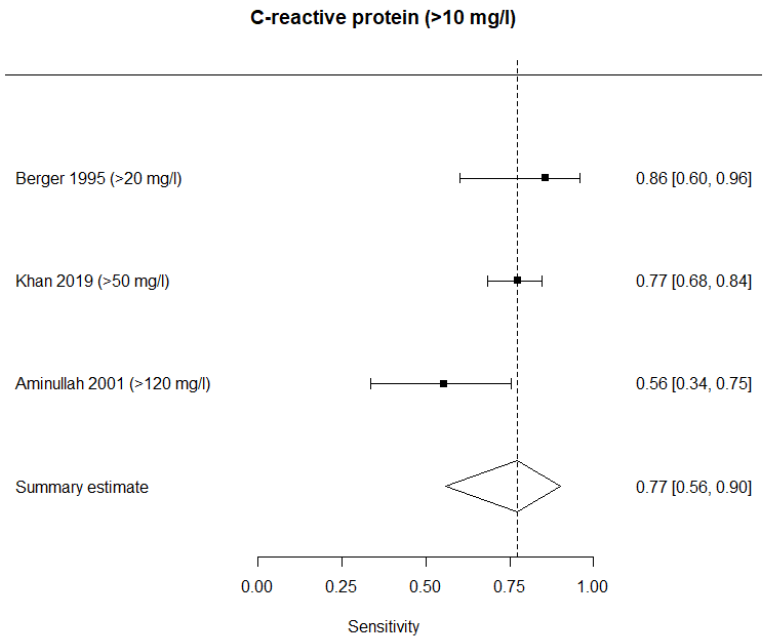
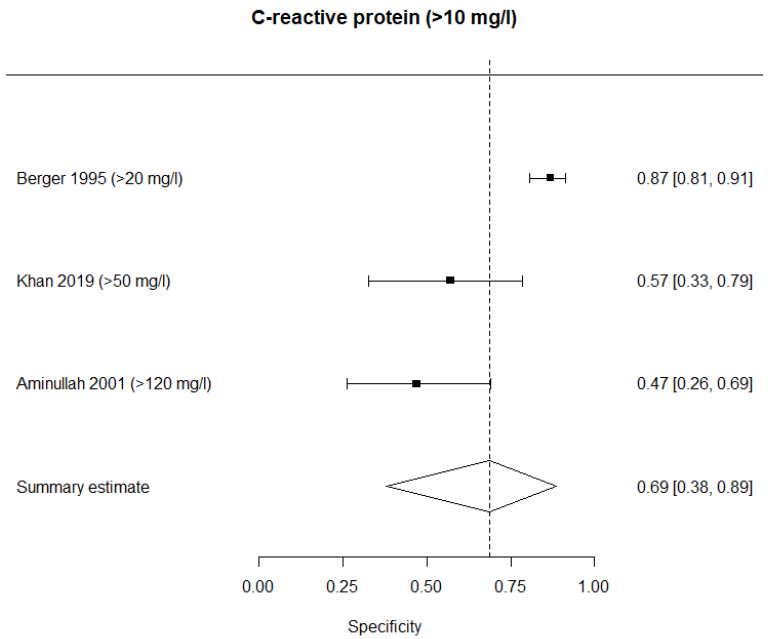
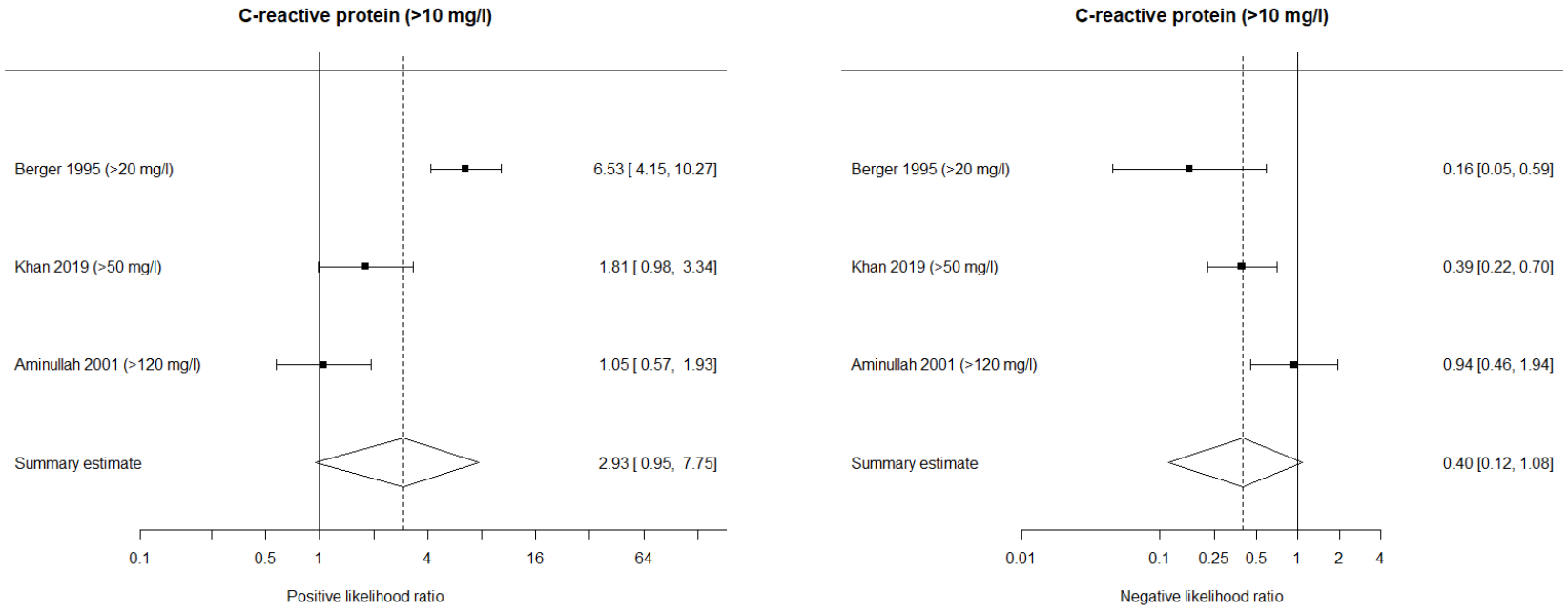
C-reactive protein (>10 mg/l) at time of blood culture

Sensitivity and specificity





1 Likelihood ratios



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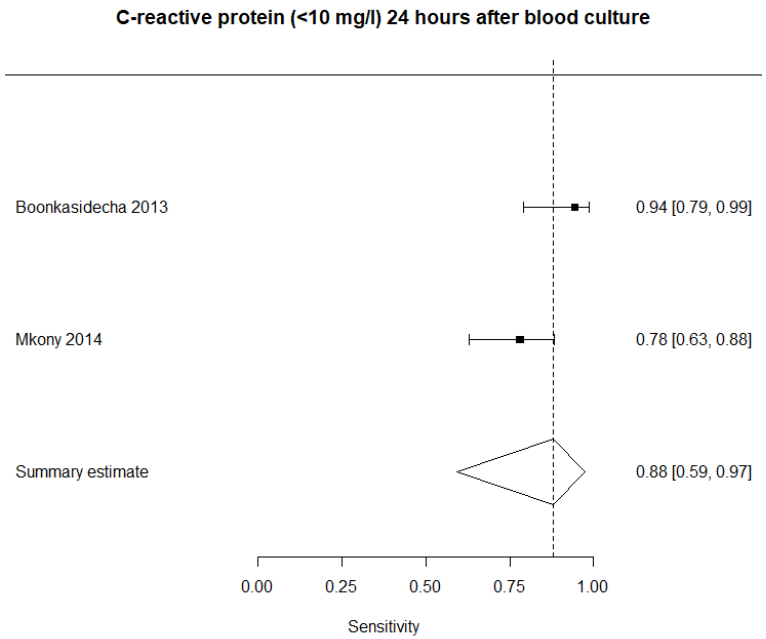
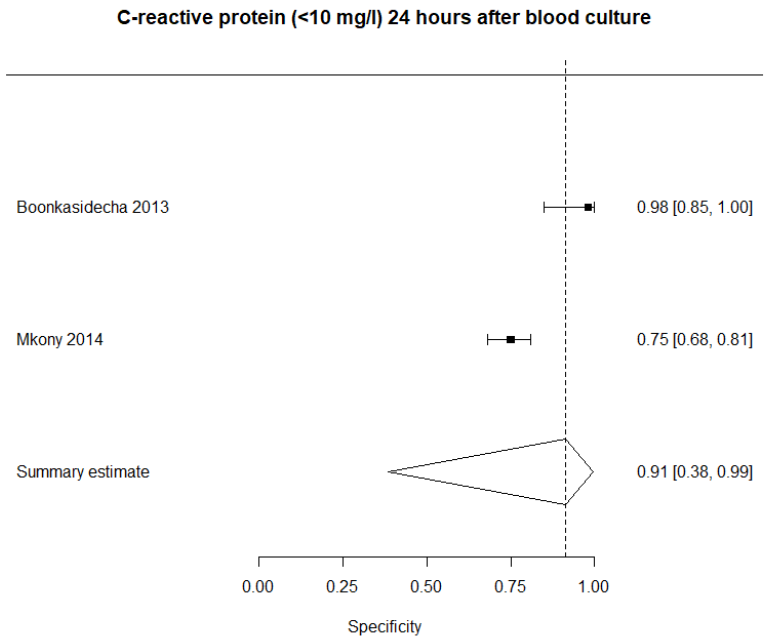
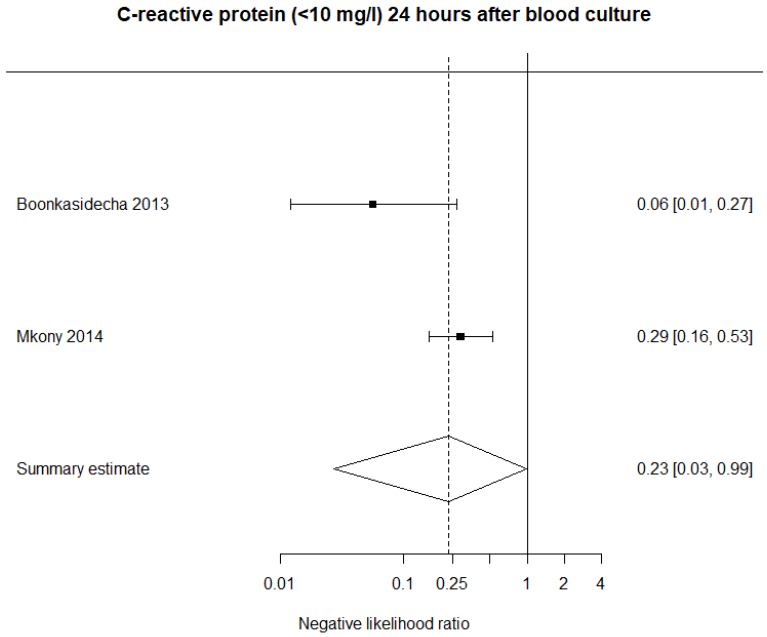
C-reactive protein (<10 mg/l) 12-24 hours after blood culture

Sensitivity and specificity





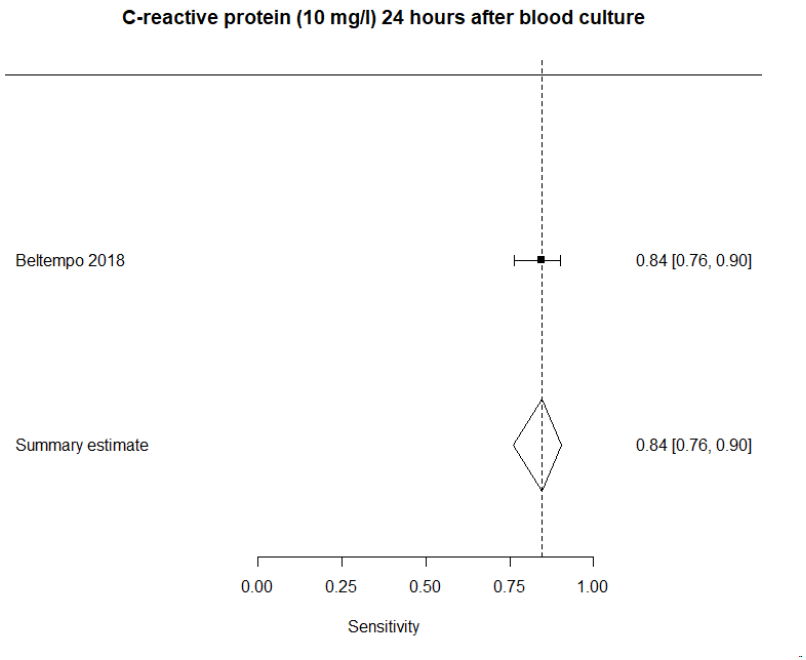
Likelihood ratios

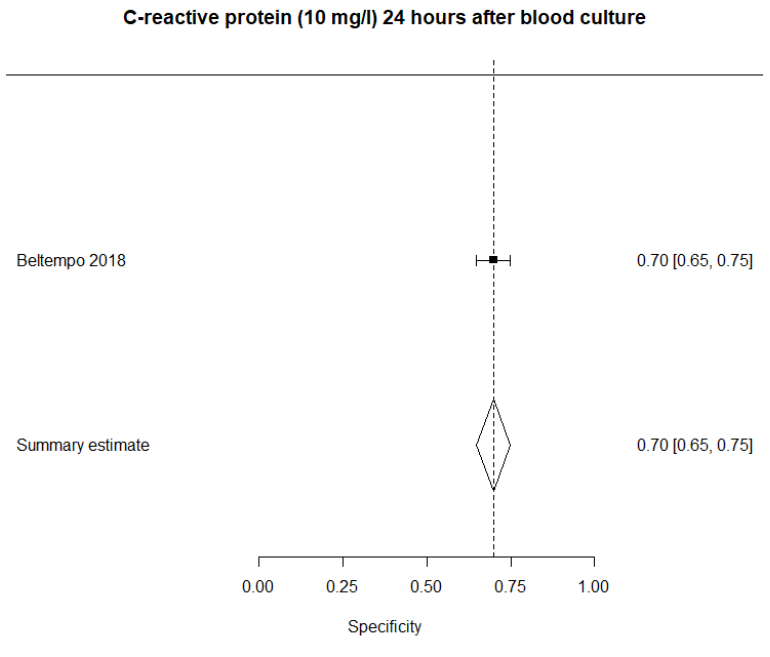


LR+ not calculable

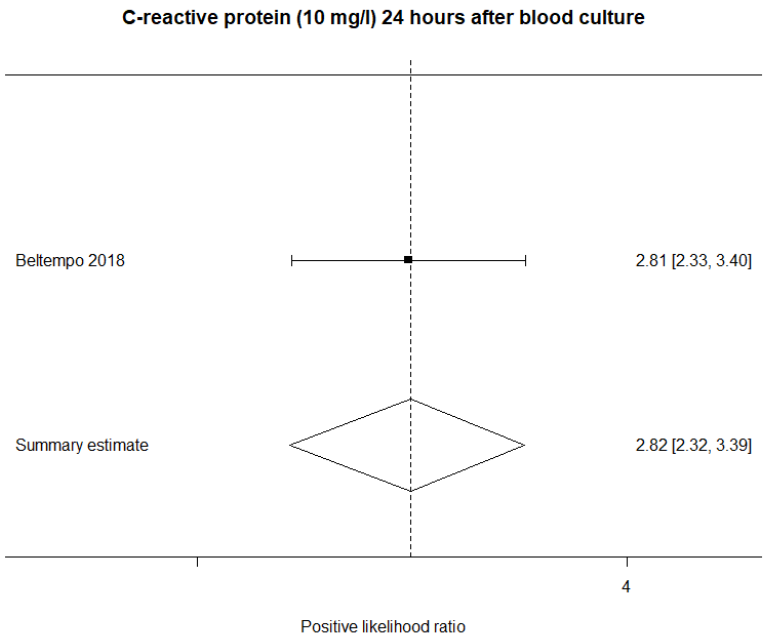
C-reactive protein (10 mg/l) 24 hours after blood culture

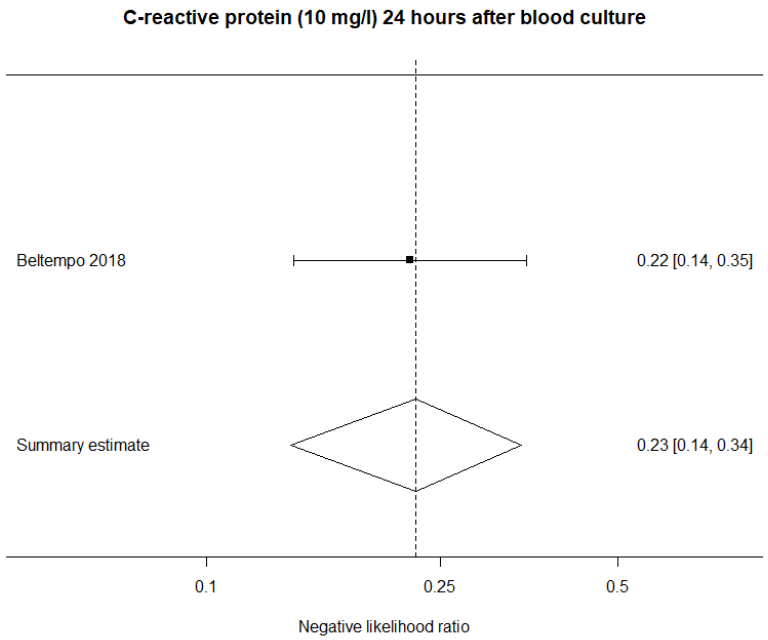
Sensitivity and specificity





1 Likelihood ratios





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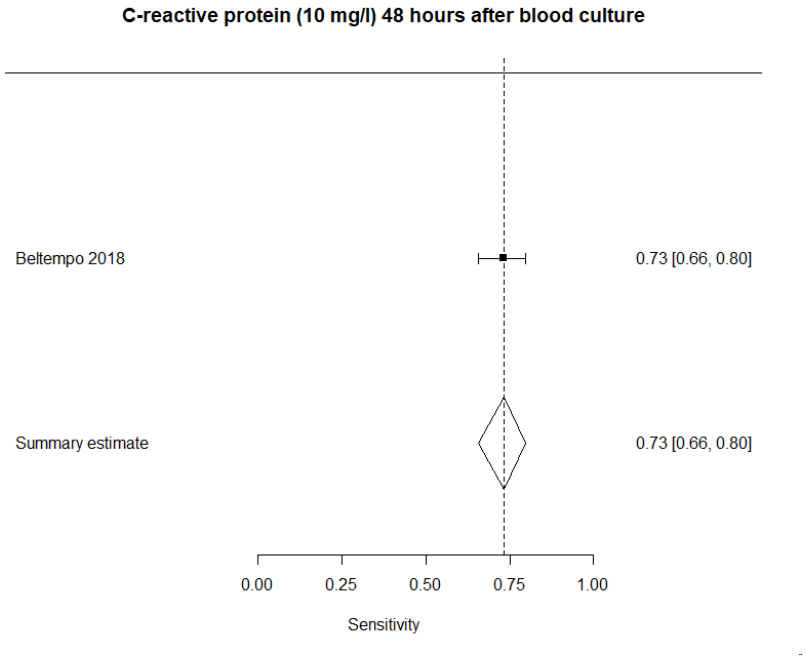
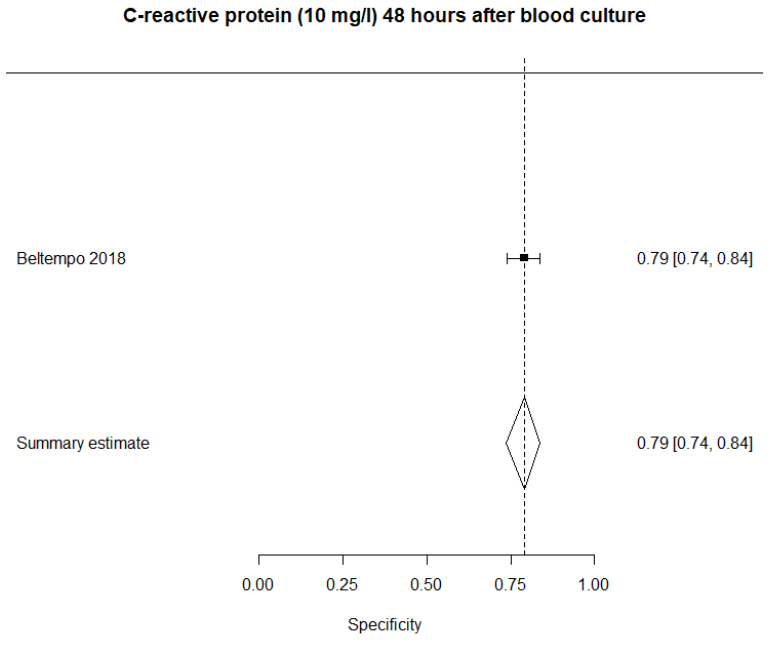
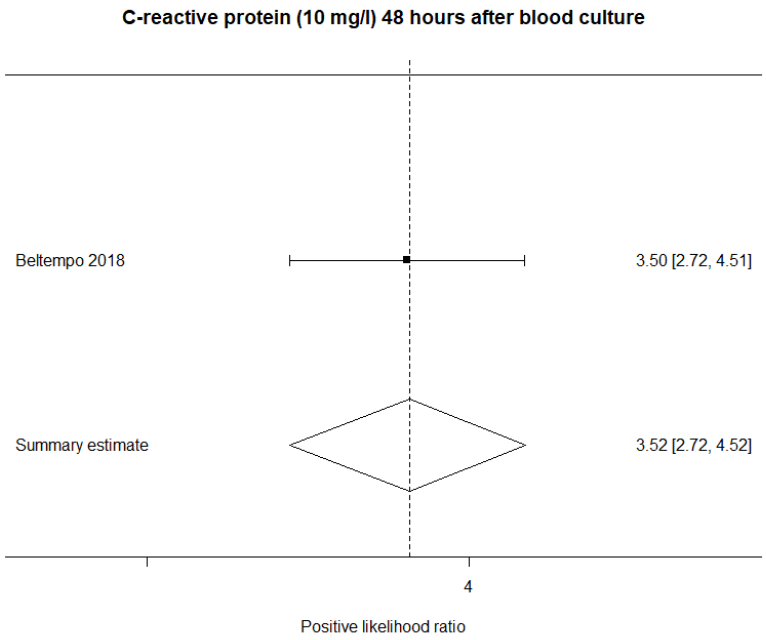
C-reactive protein (10 mg/l) 48 hours after blood culture

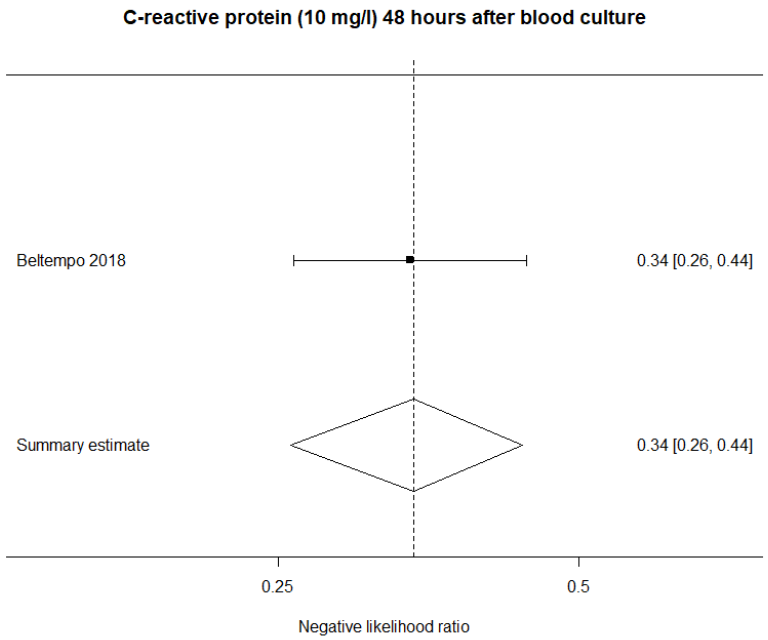
Sensitivity and specificity





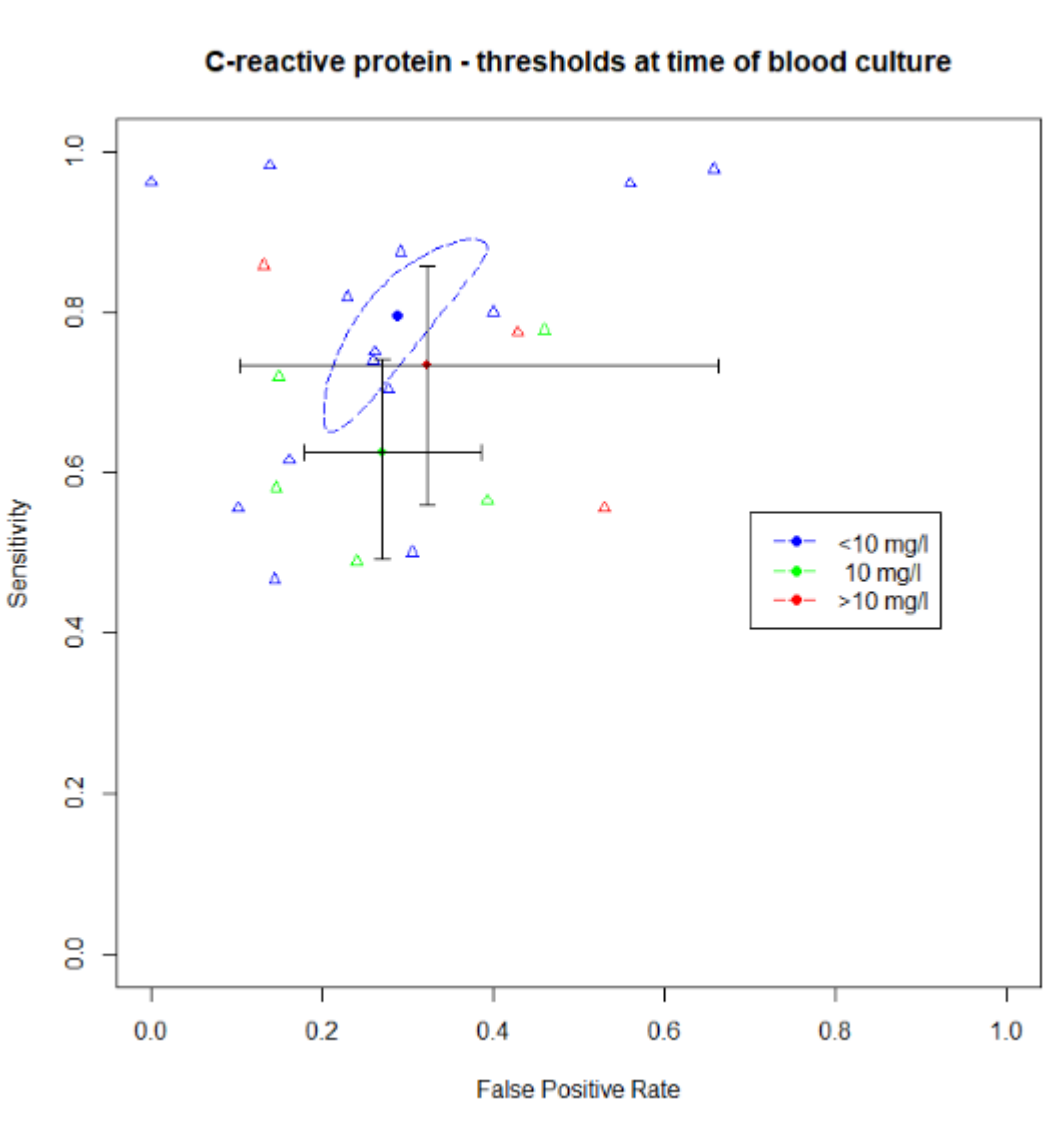
1 Likelihood ratios

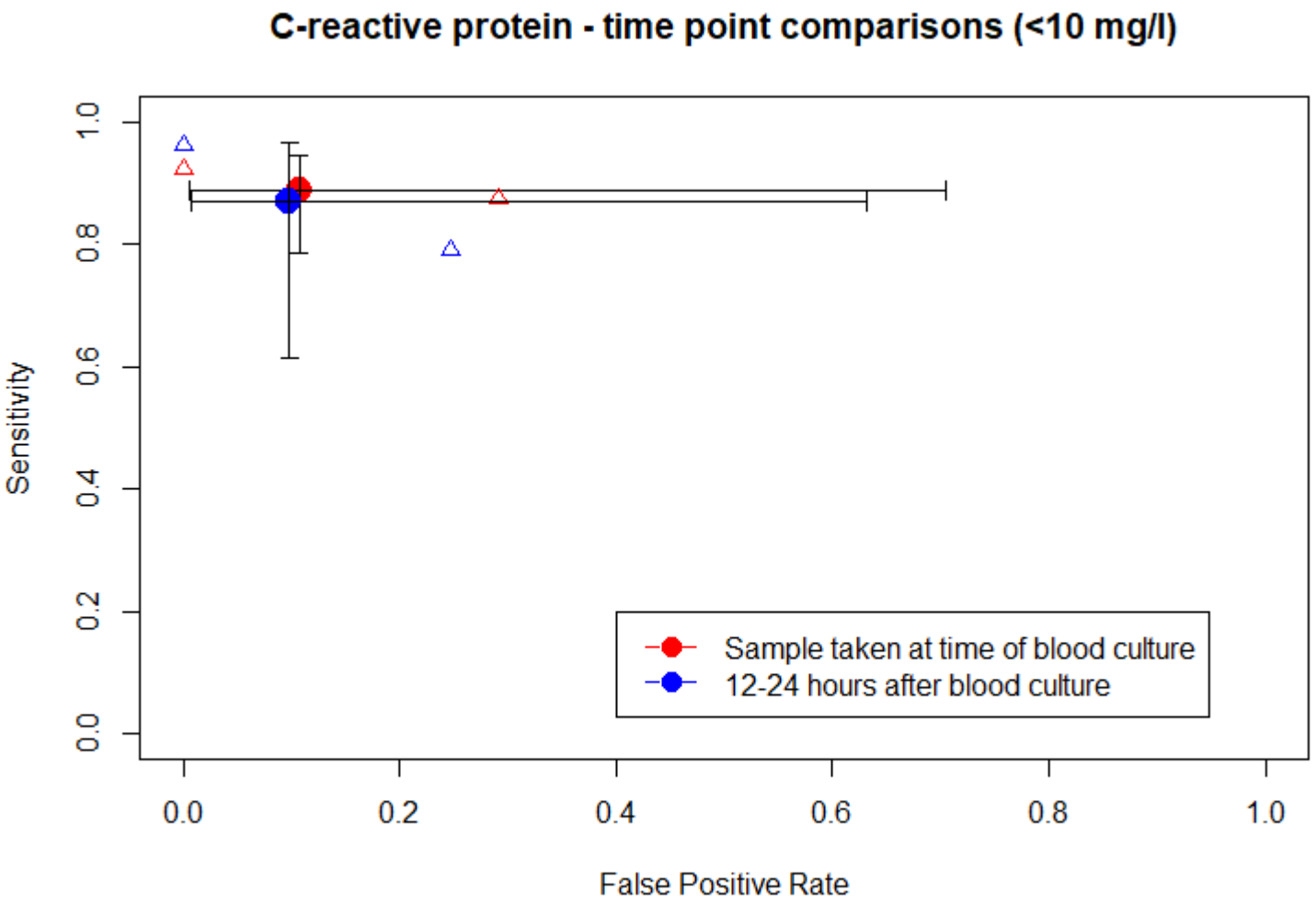




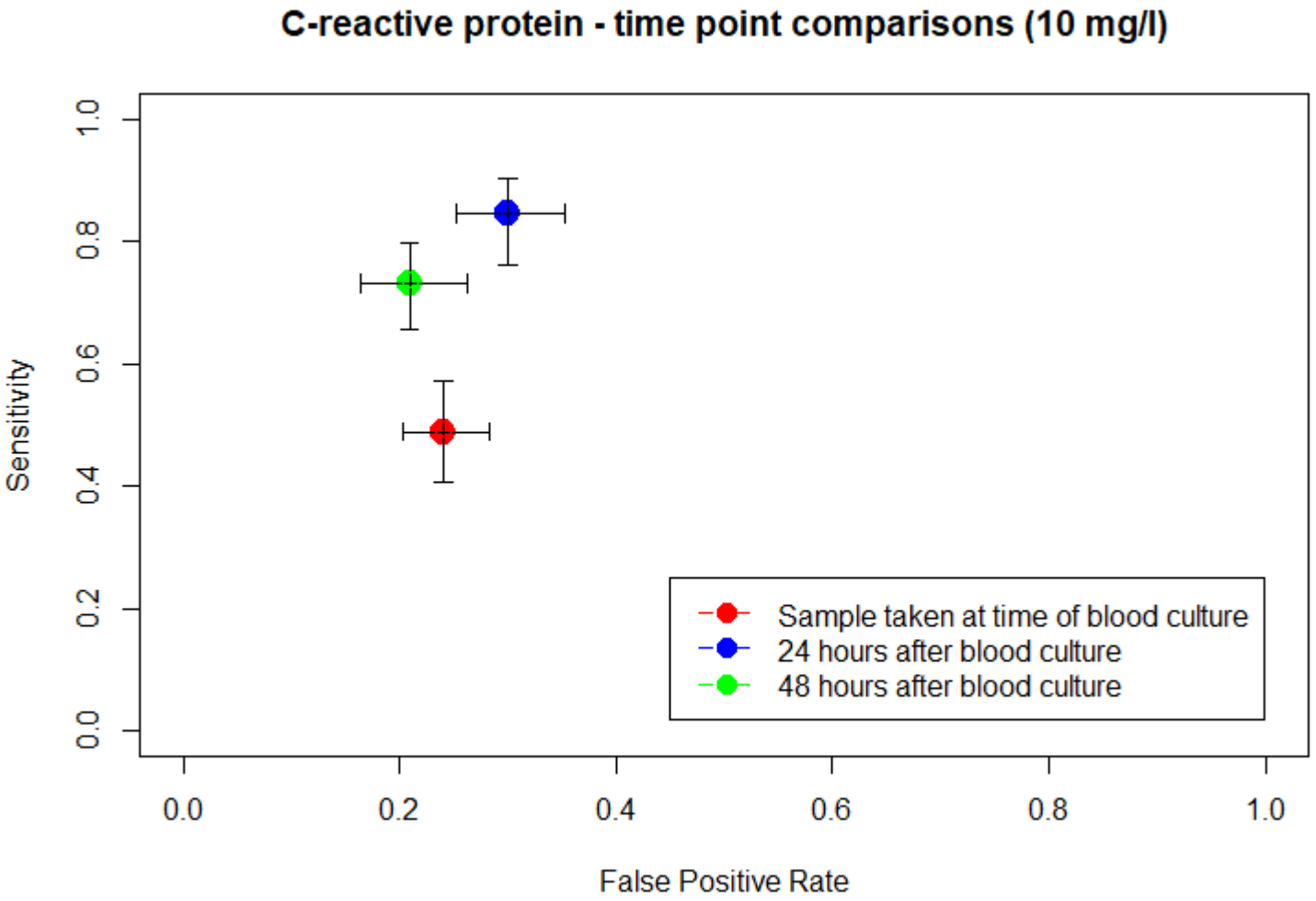
2

3


C-reactive protein - thresholds at time of blood culture
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
<10 mg/l
10 mg/l
>10 mg/l


C-reactive protein - time point comparisons (<10 mg/l)
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
Sample taken at time of blood culture
12-24 hours after blood culture

1

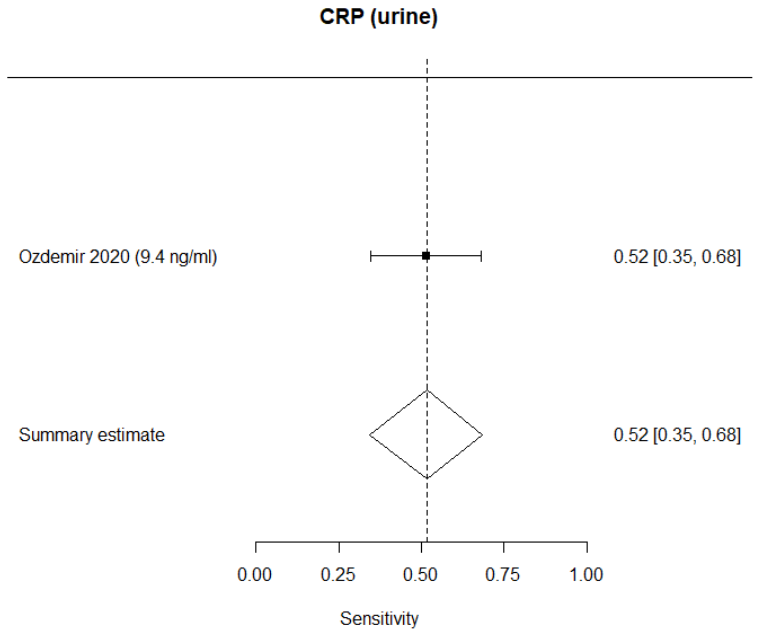

C-reactive protein - time point comparisons (10 mg/l)
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
Sample taken at time of blood culture
24 hours after blood culture
48 hours after blood culture

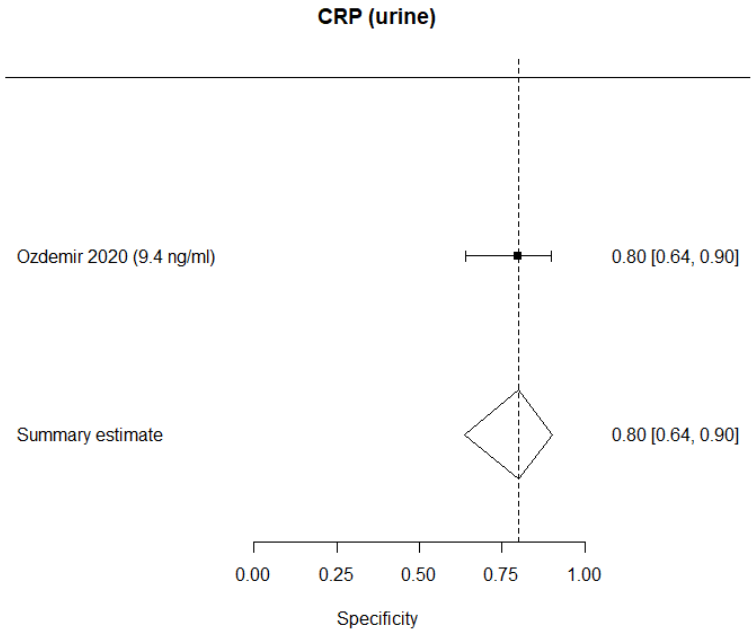
1

2

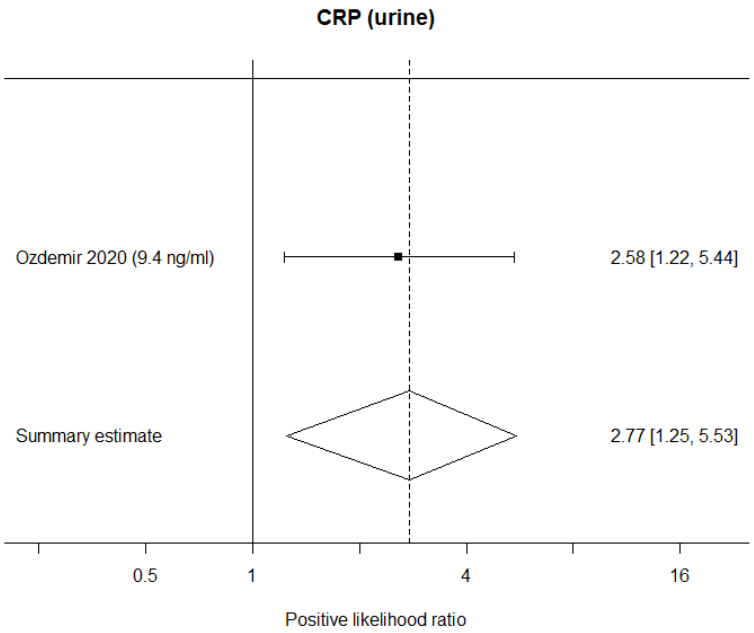
C-reactive protein (from urine sample– 9.4 ng/ml)

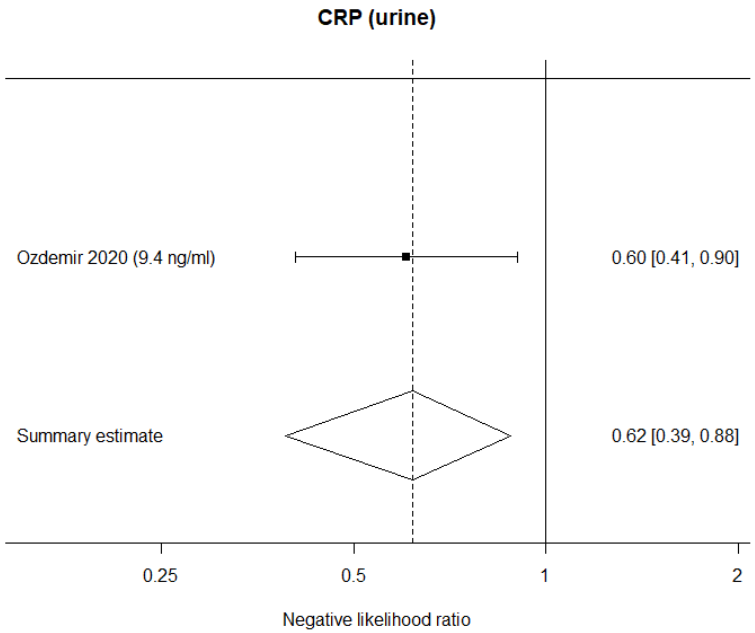
Sensitivity and specificity





1 Likelihood ratios

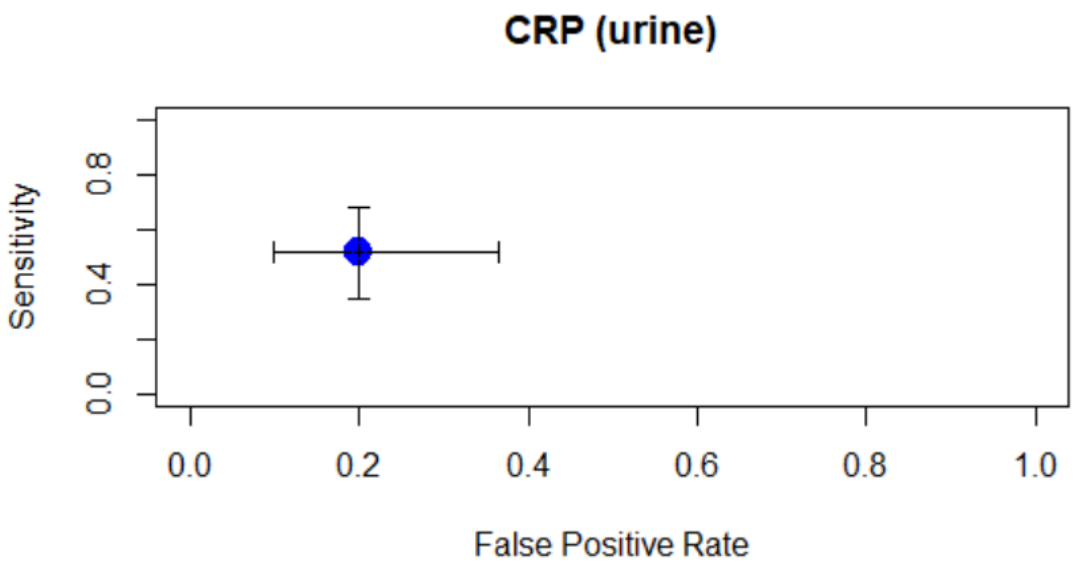




2

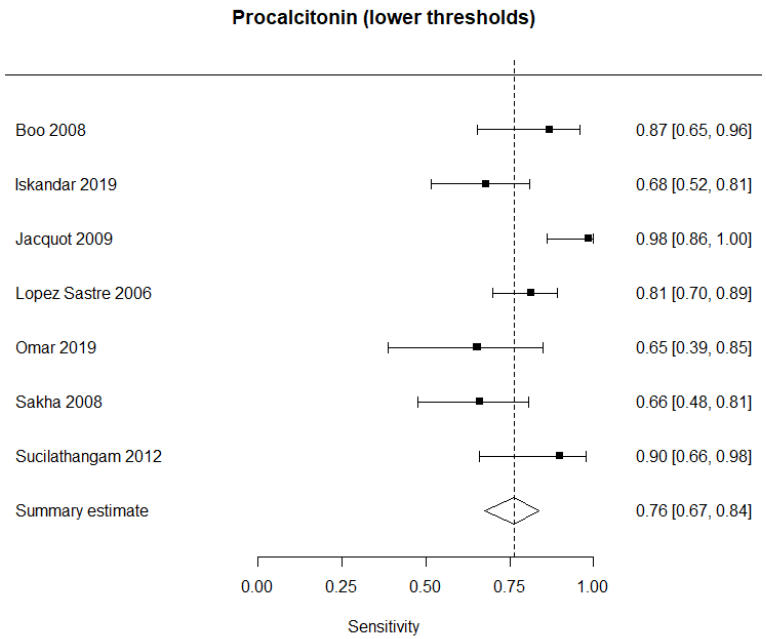
3

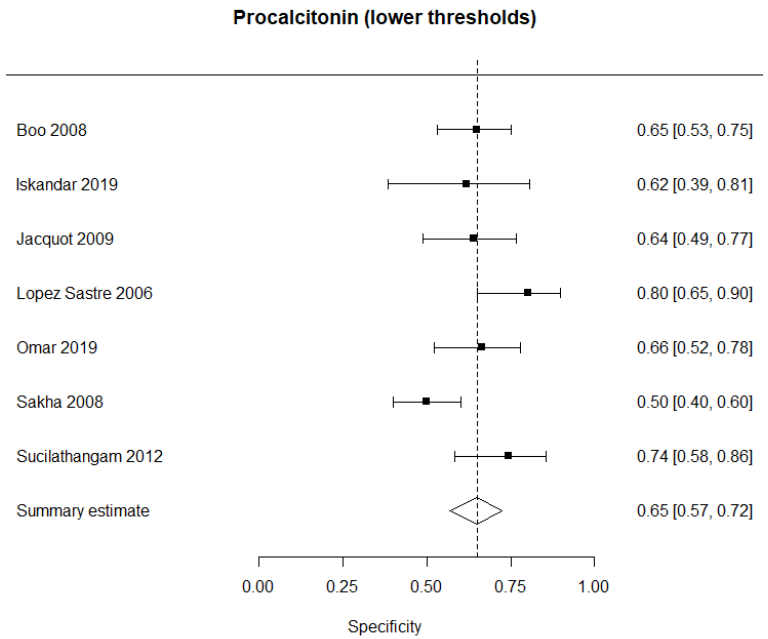
4


CRP (urine)
Sensitivity
0.0
0.4
0.8
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate

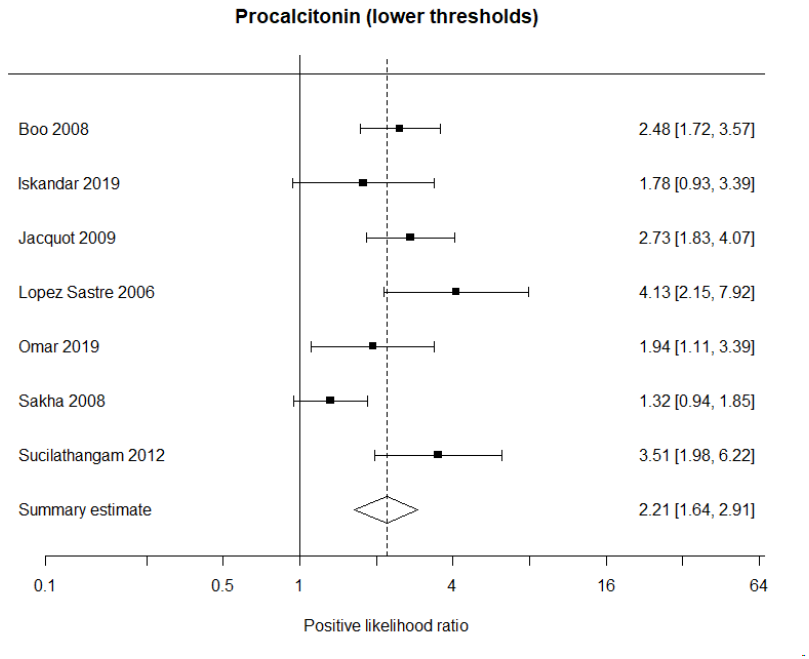
Procalcitonin (lower thresholds - ≤10 ng/ml)

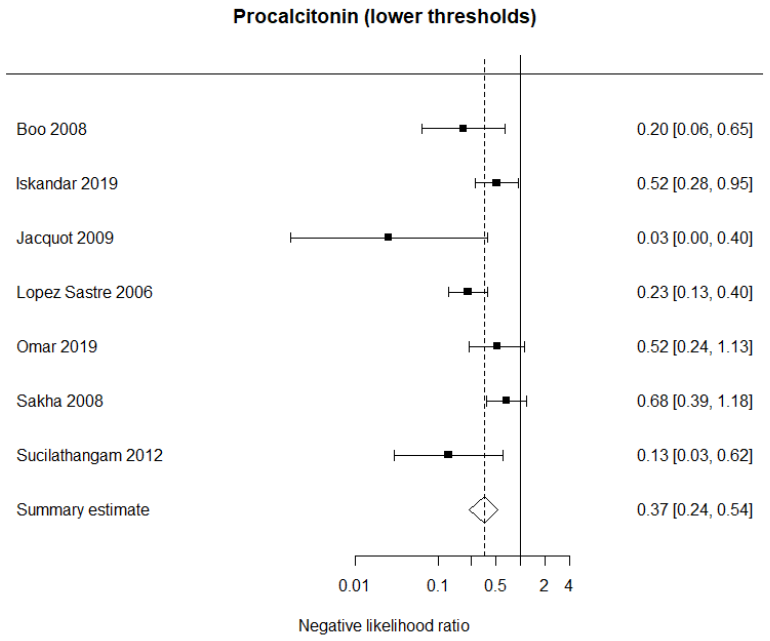
Sensitivity and specificity





1 Likelihood ratios





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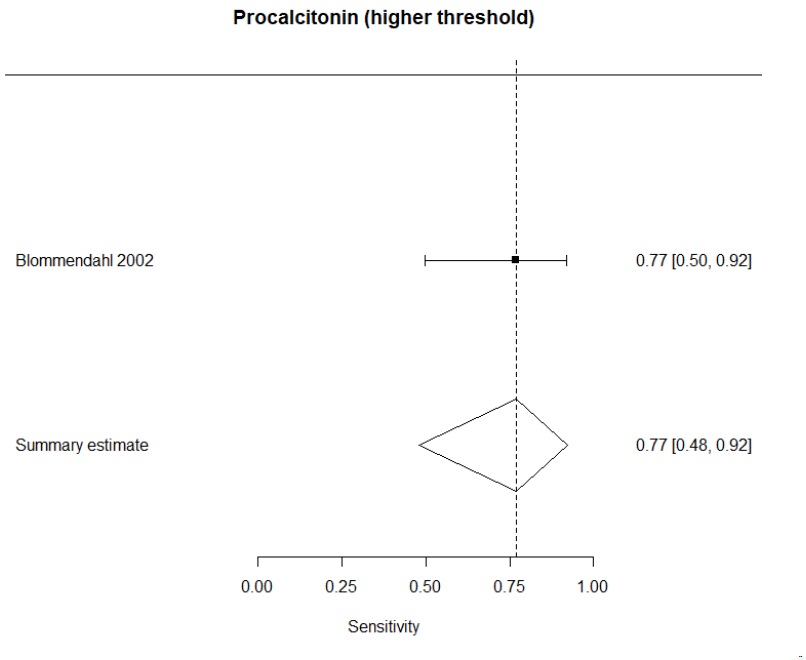
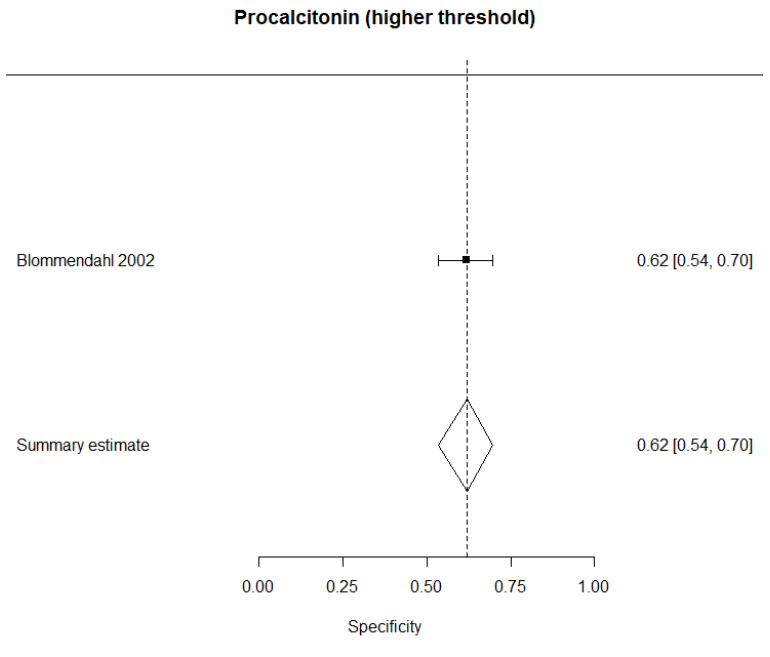
9

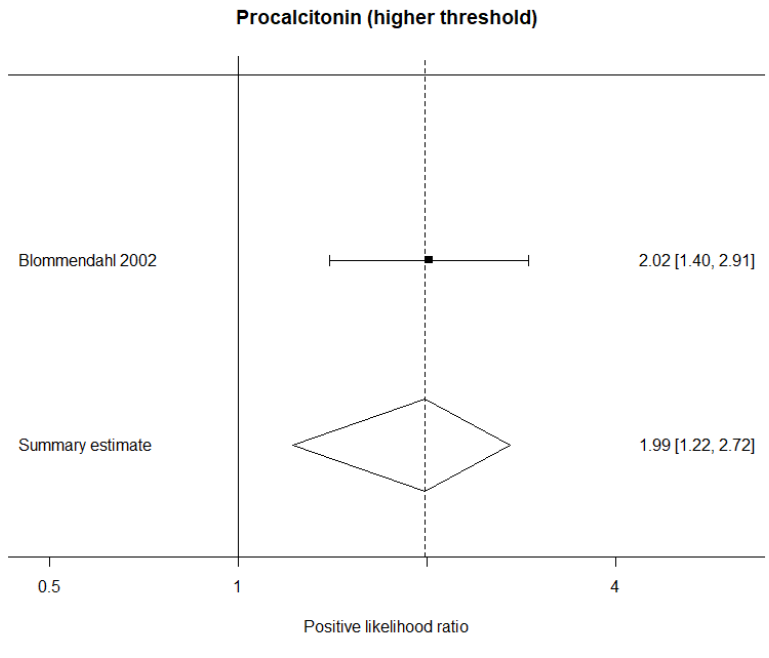
Procalcitonin (higher threshold - 1000 ng/ml)

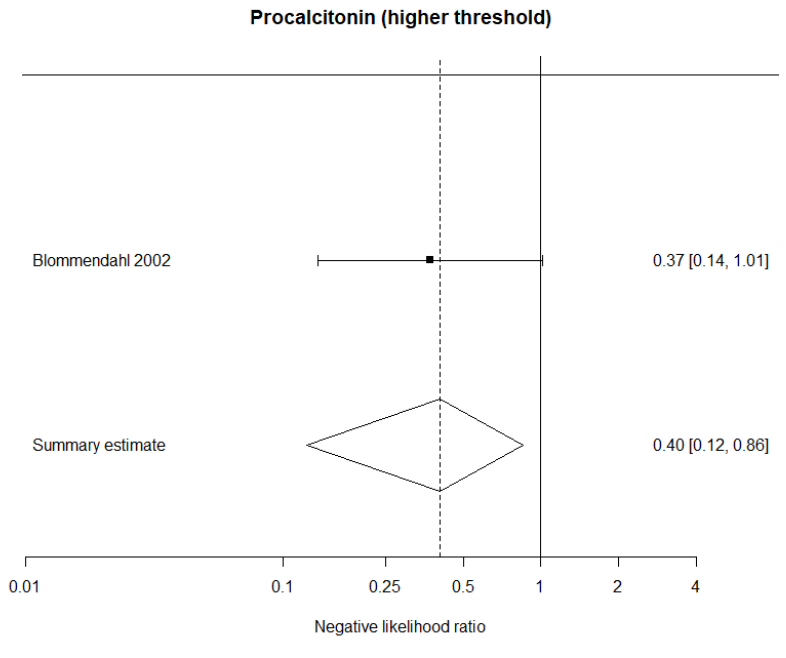
Sensitivity and specificity





1 Likelihood ratios

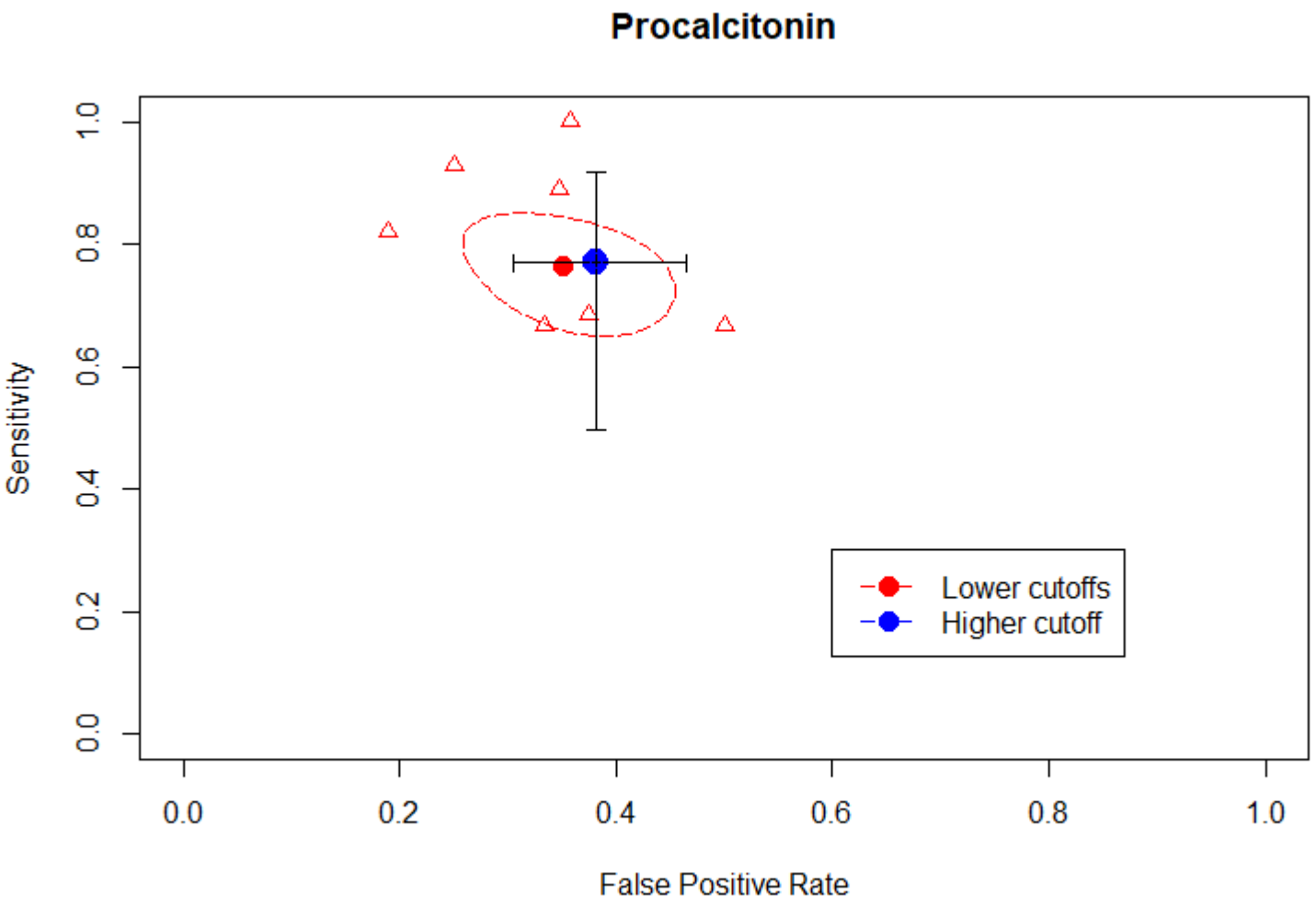




2

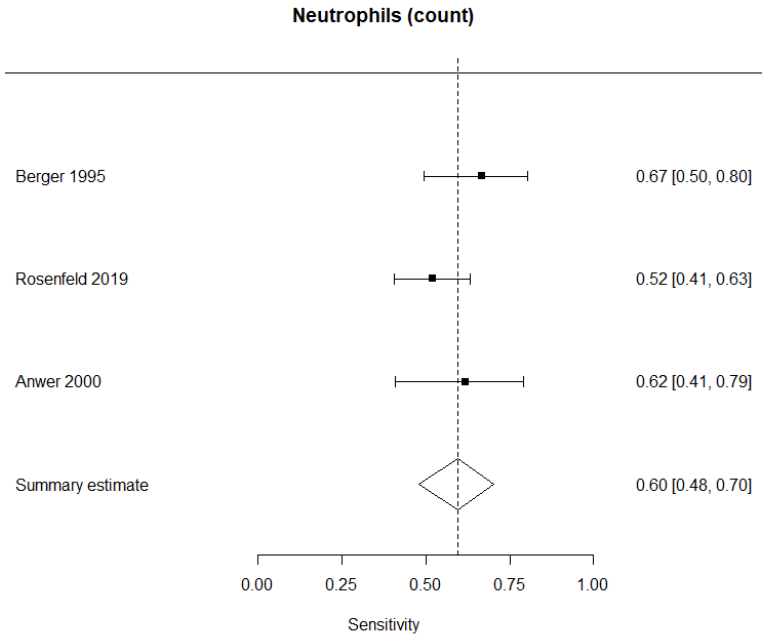
3

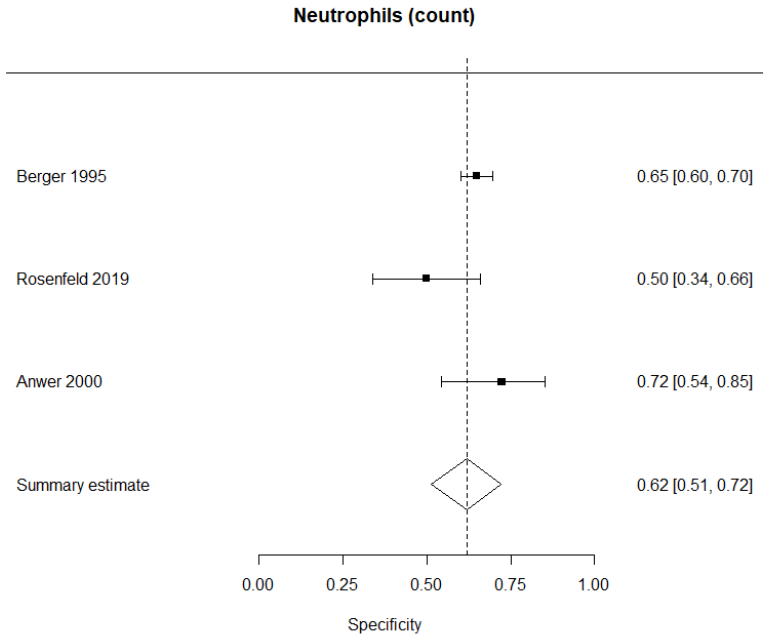
4


Procalcitonin
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
Lower cutoffs
Higher cutoff

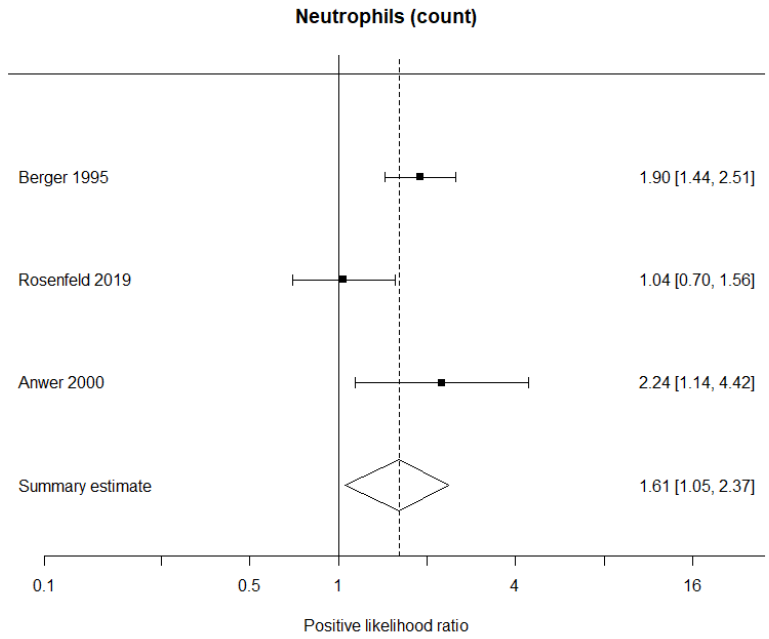
Neutrophils (count)

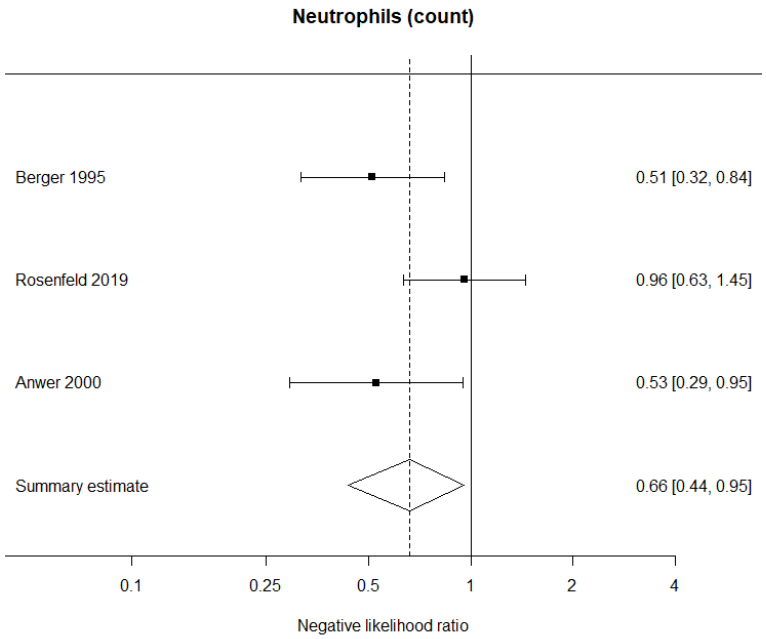
Sensitivity and specificity





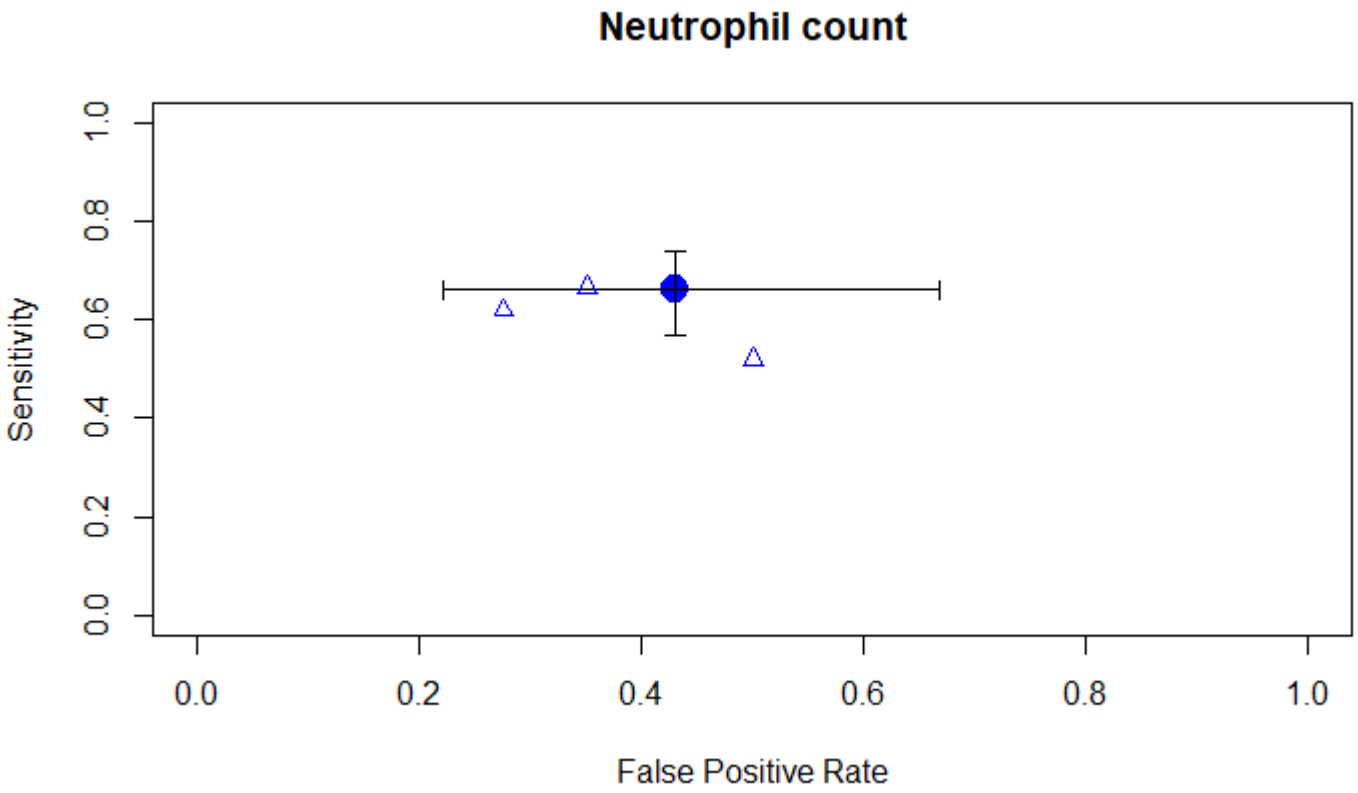
1 Likelihood ratios





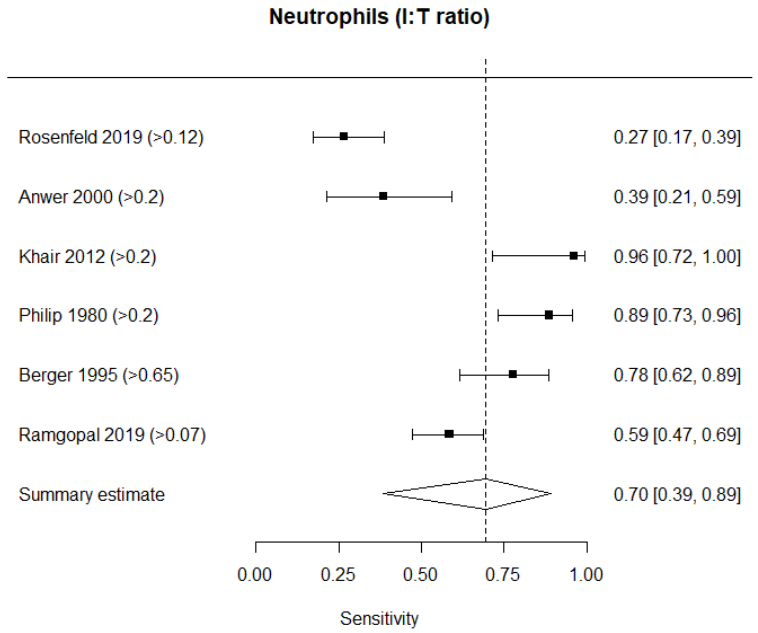
2

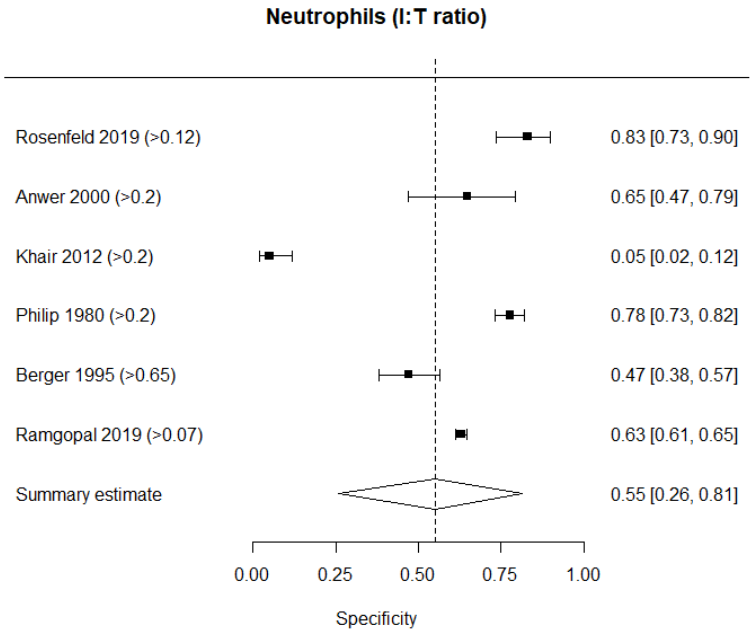
3


Neutrophil count
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate

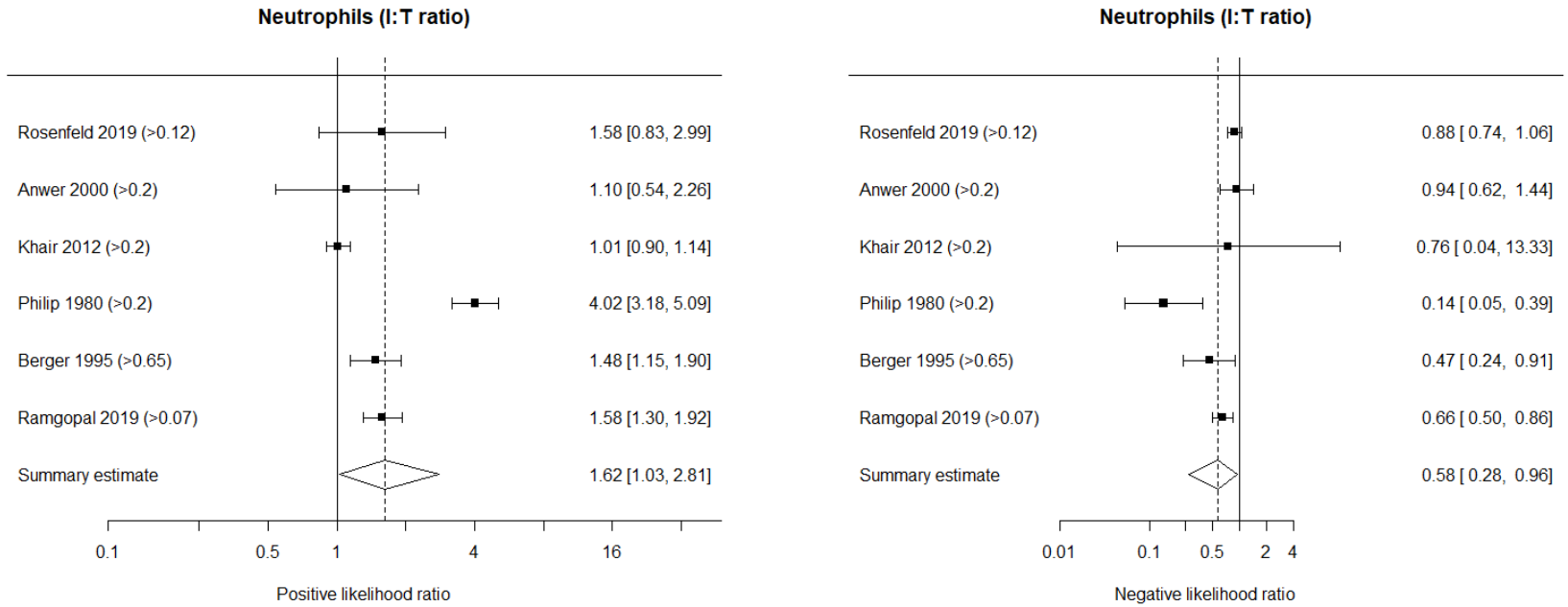
Neutrophils (I:T ratio)

Sensitivity and specificity





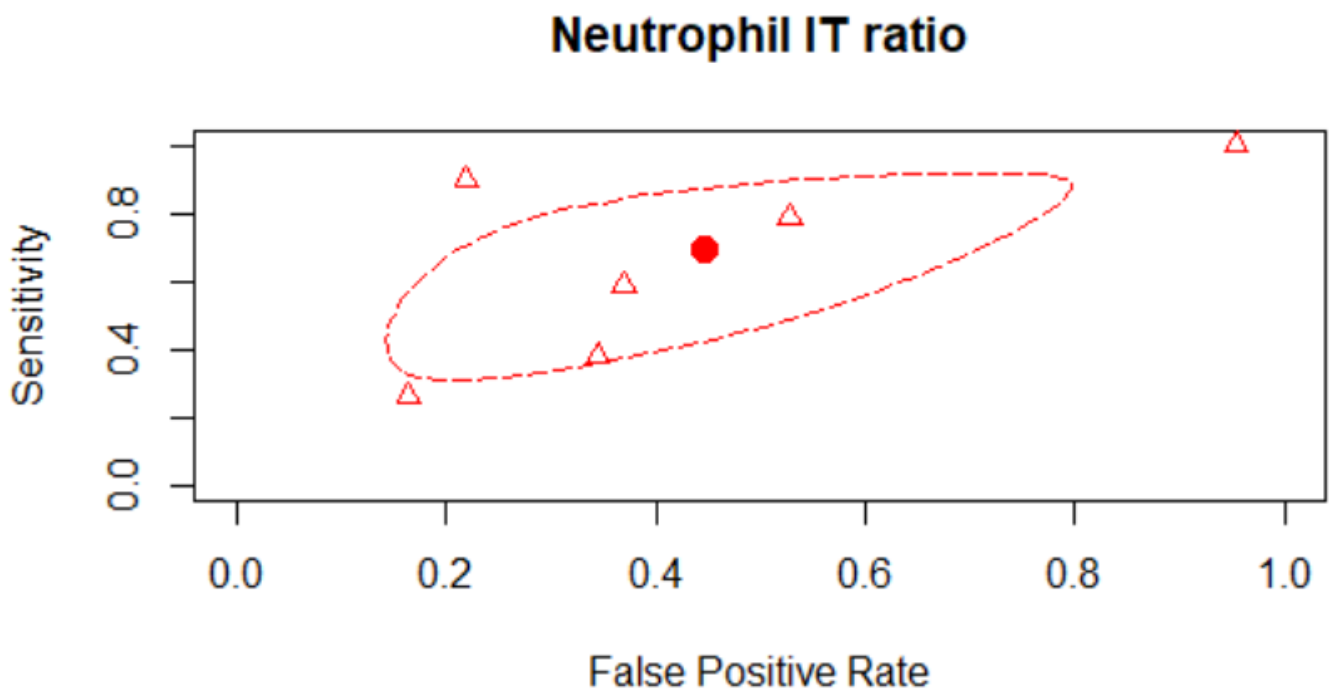
1 Likelihood ratios



2

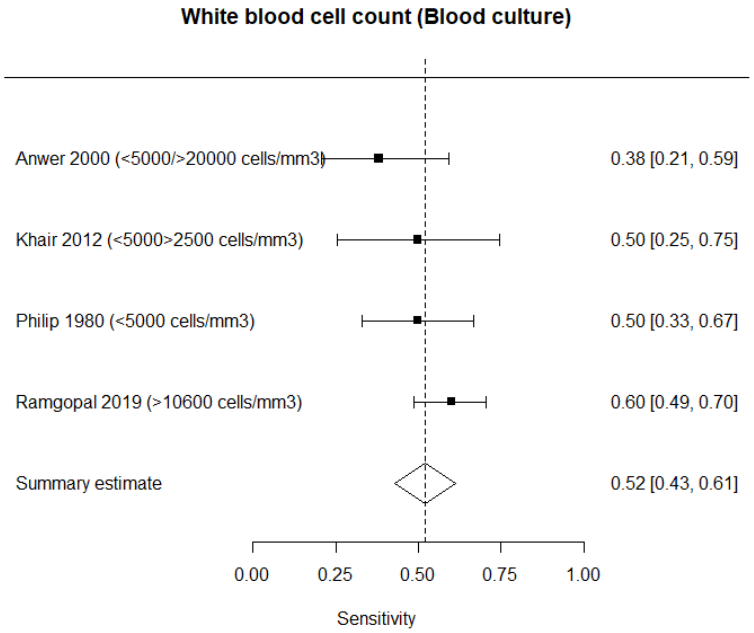
3

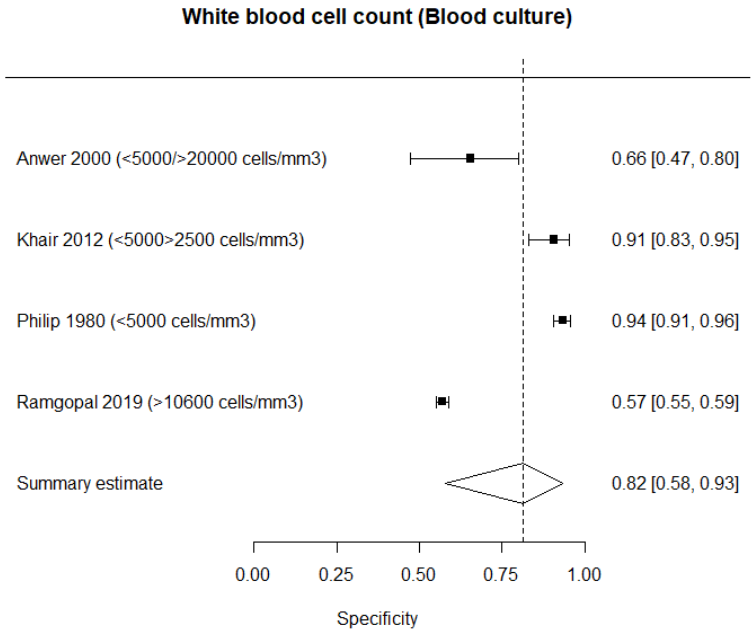
4


Neutrophil IT ratio
Sensitivity
0.0
0.4
0.8
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate

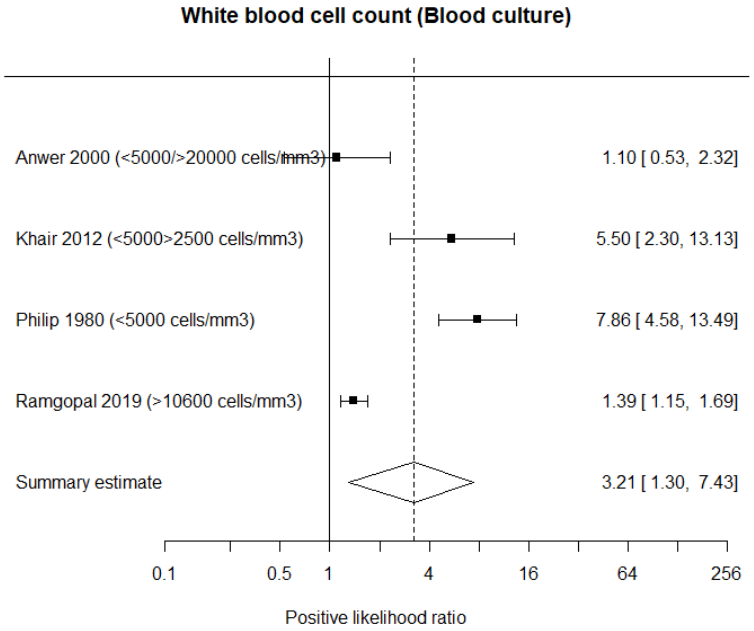
White blood cell count (from blood culture)

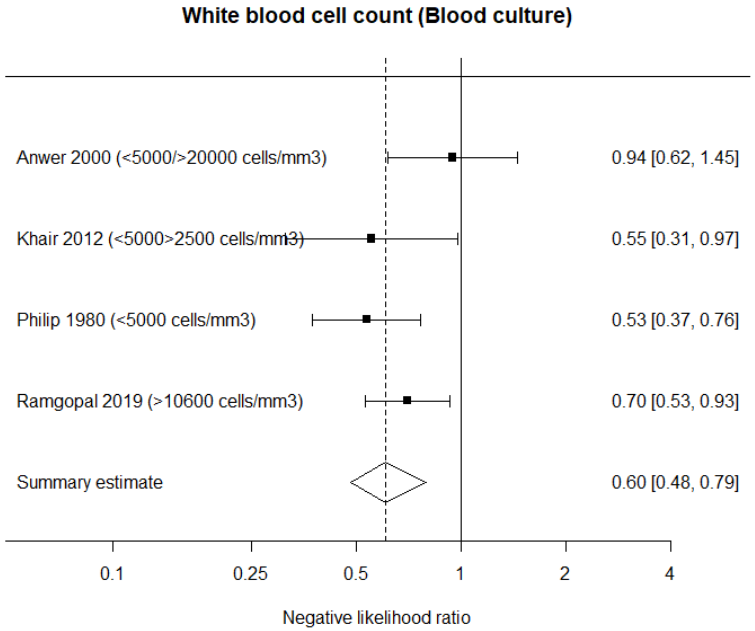
Sensitivity and specificity





1 Likelihood ratios





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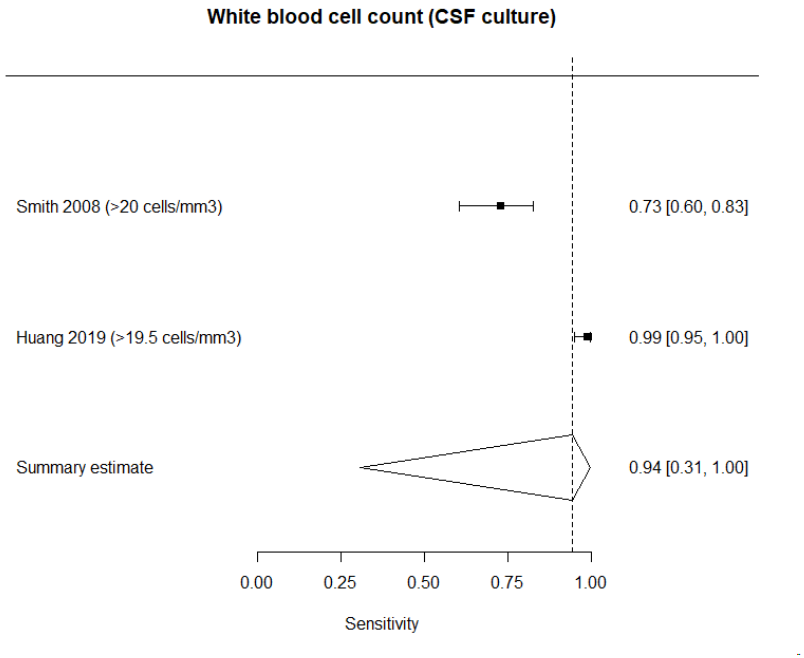
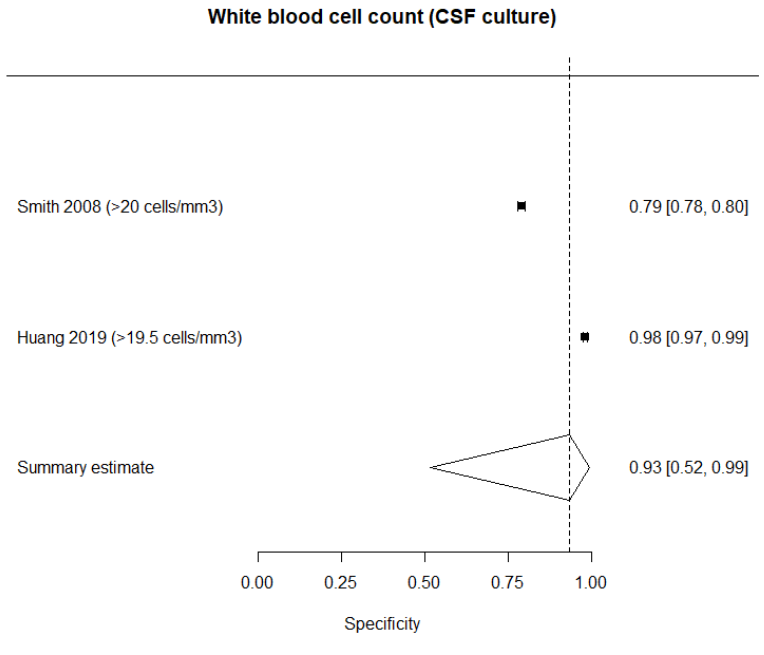
7
8

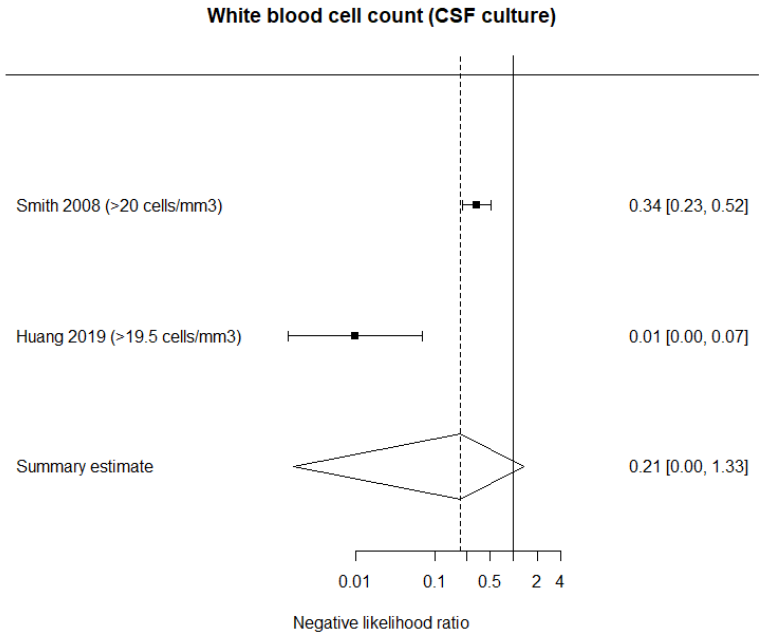
White blood cell count (from CSF sample)

Sensitivity and specificity



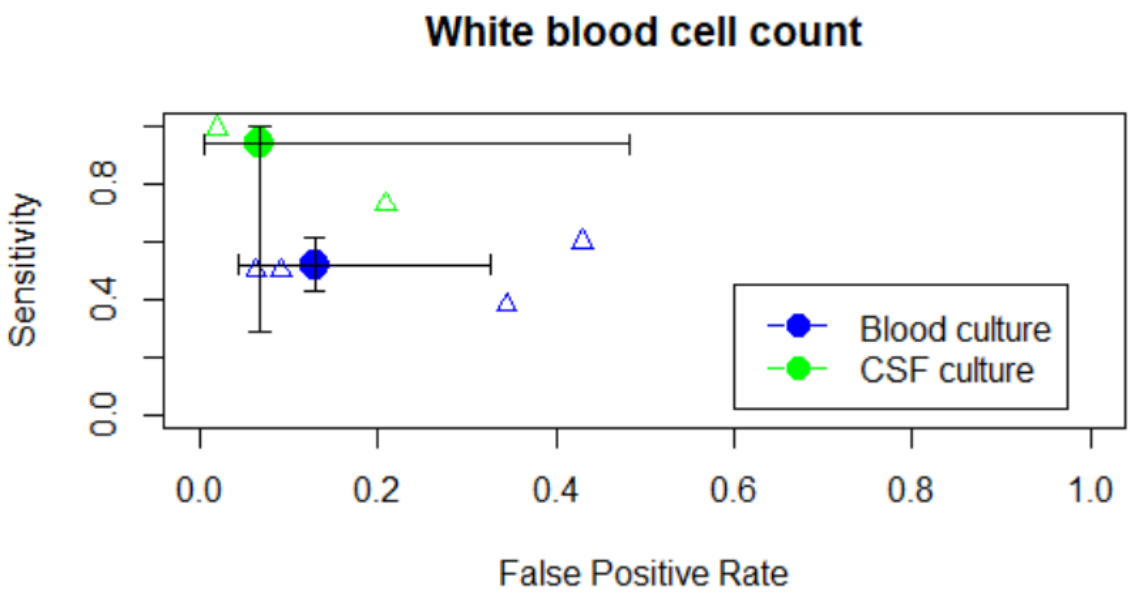


1 Likelihood ratios



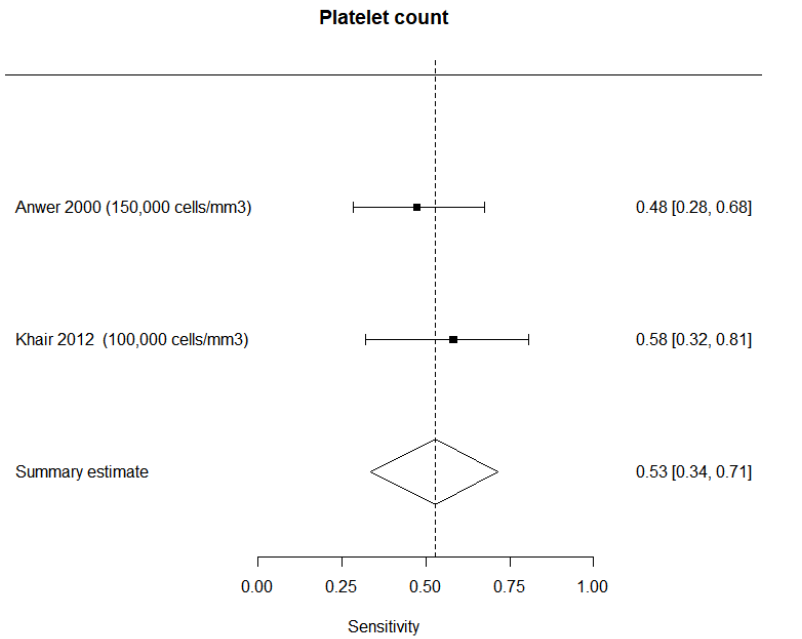
2 LR+ not calculable

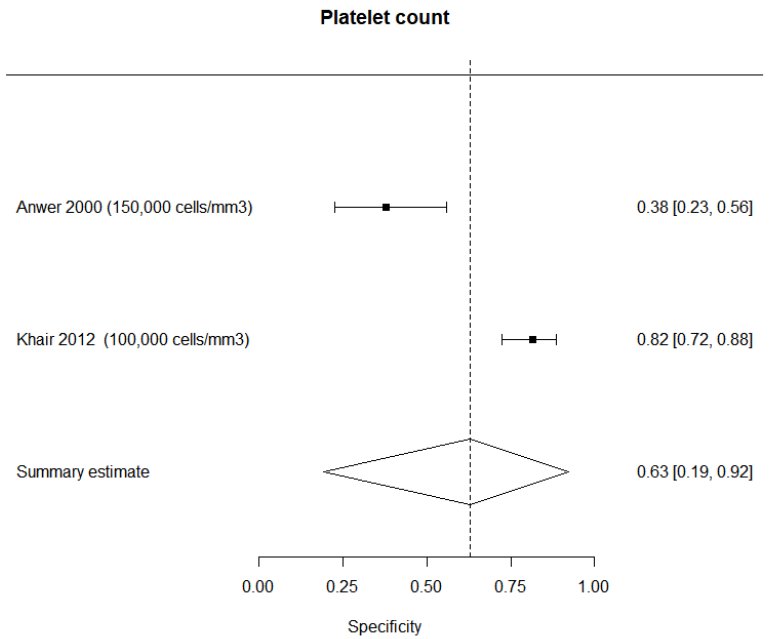
3


White blood cell count
Sensitivity
0.0
0.4
0.8
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate
Blood culture
CSF culture

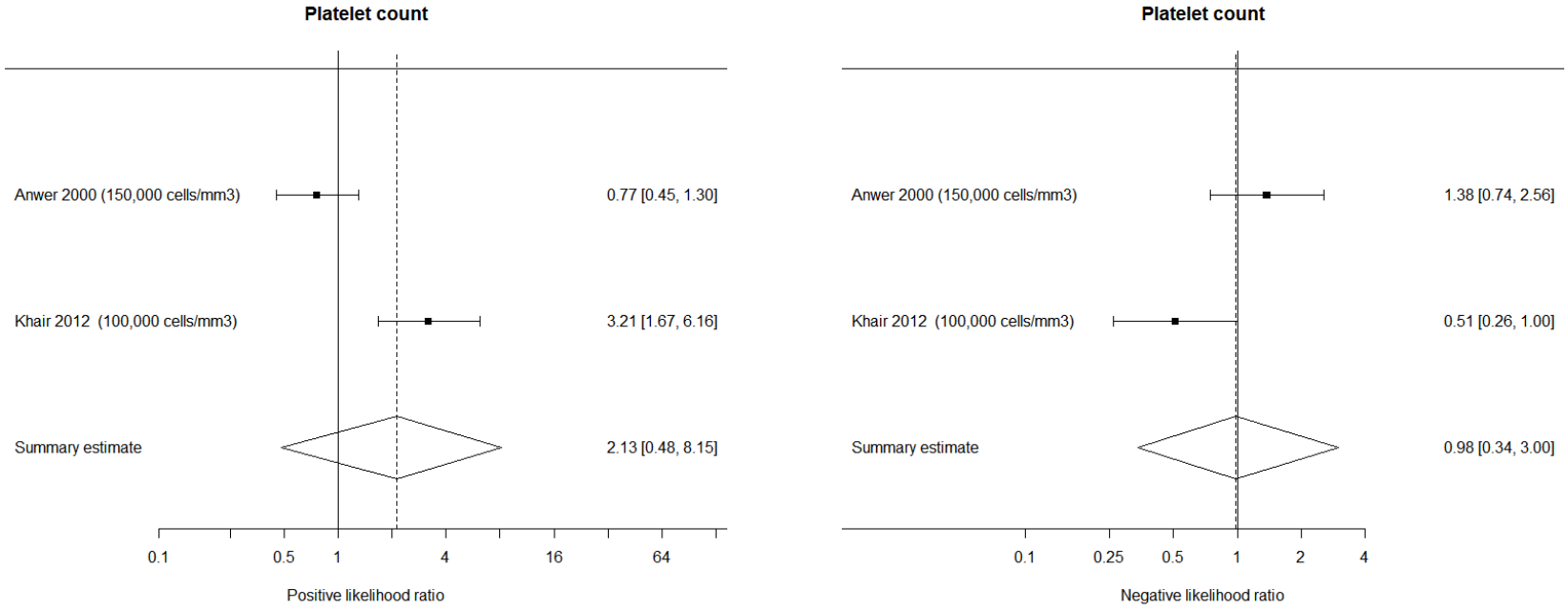
Platelet count

Sensitivity and specificity





1 Likelihood ratios



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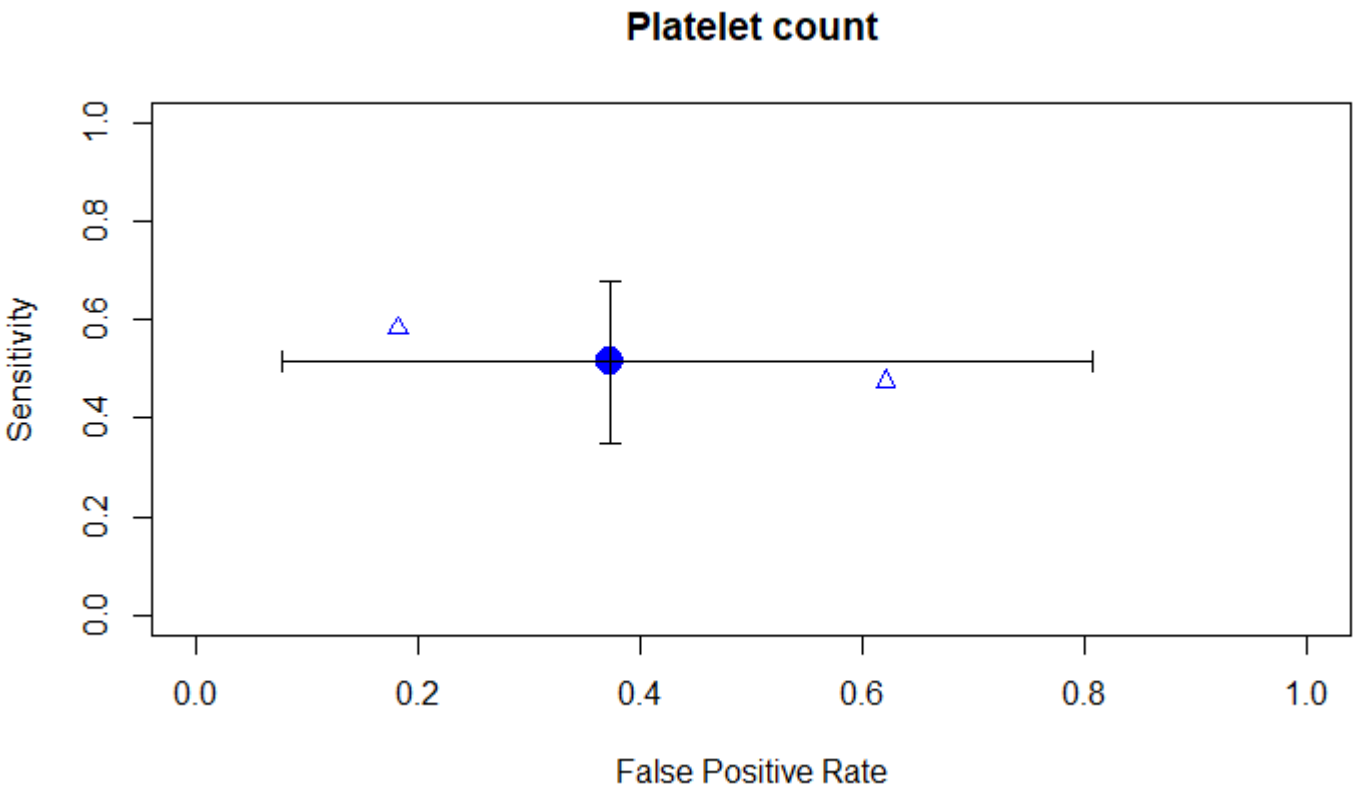
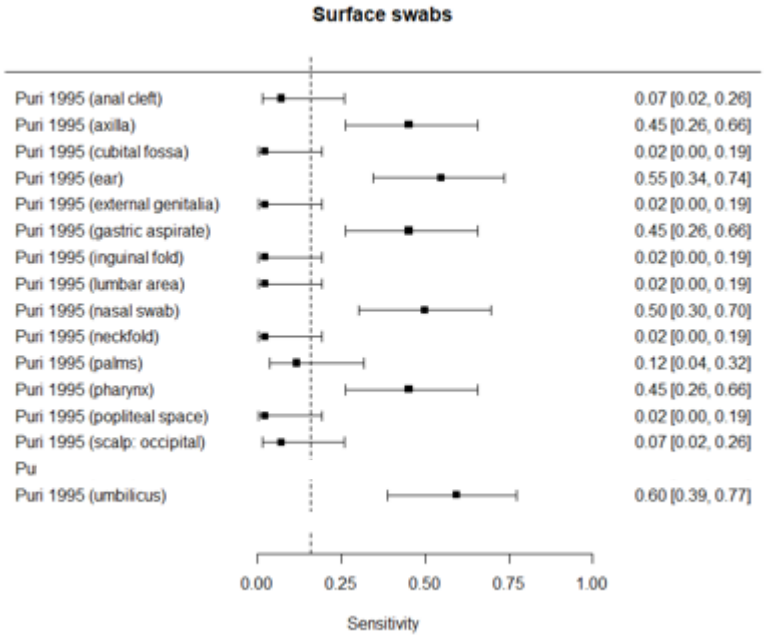
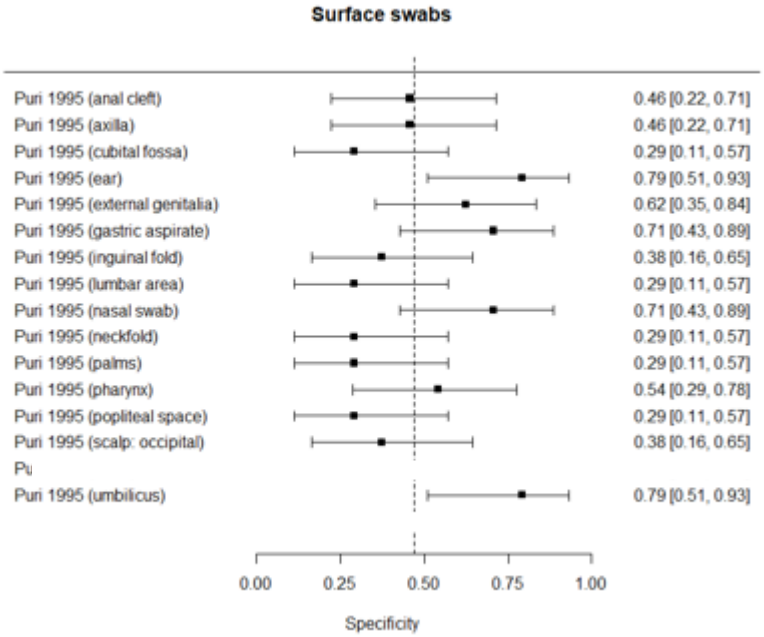

Platelet count
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate

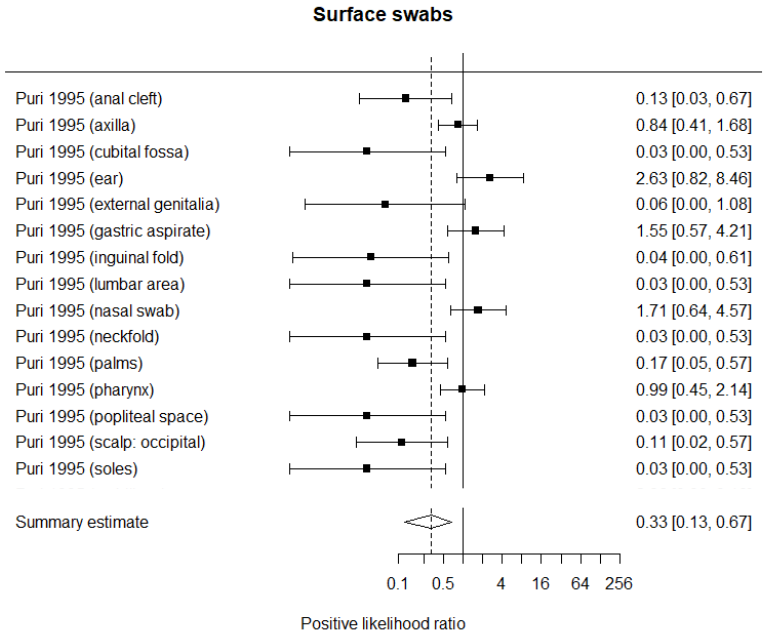
Surface swabs

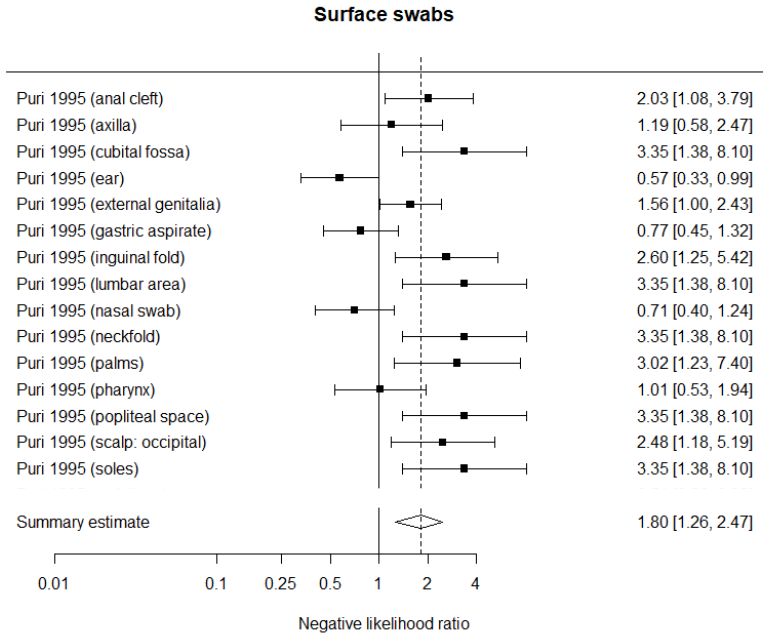
Sensitivity and specificity





1 Likelihood ratios





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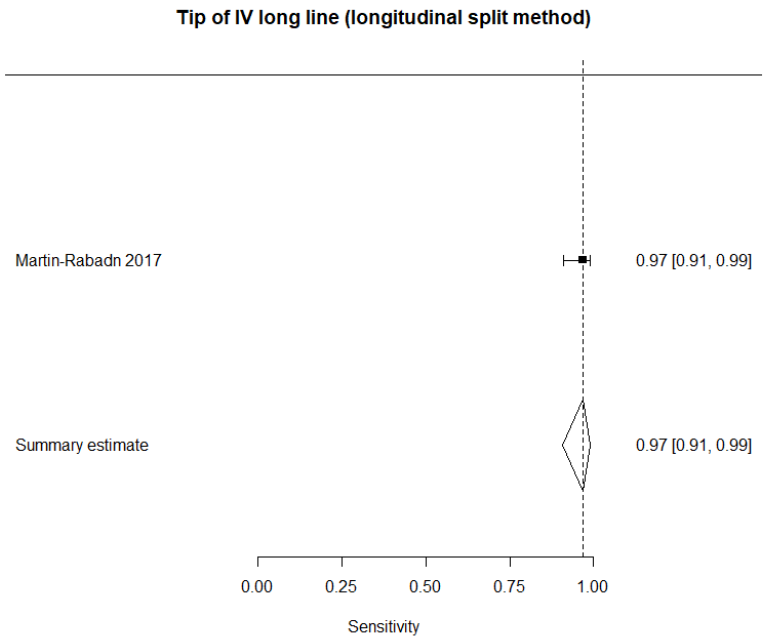
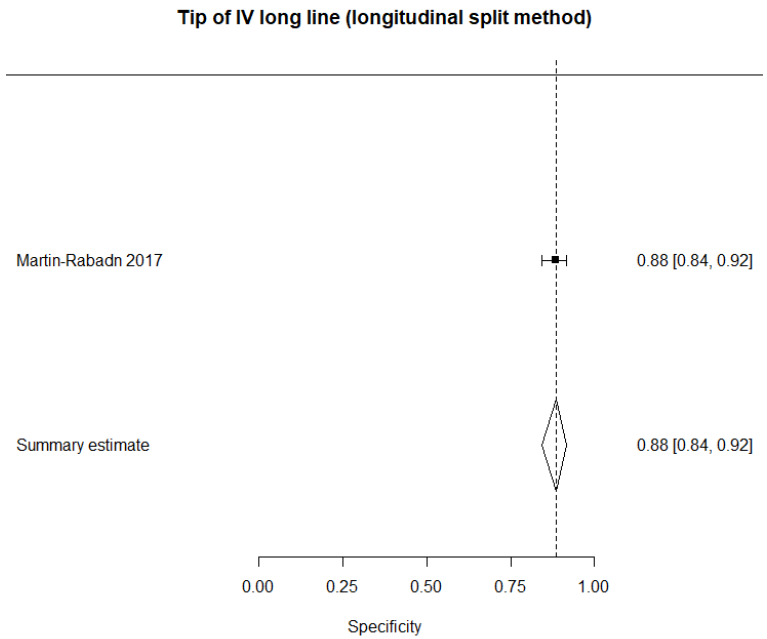
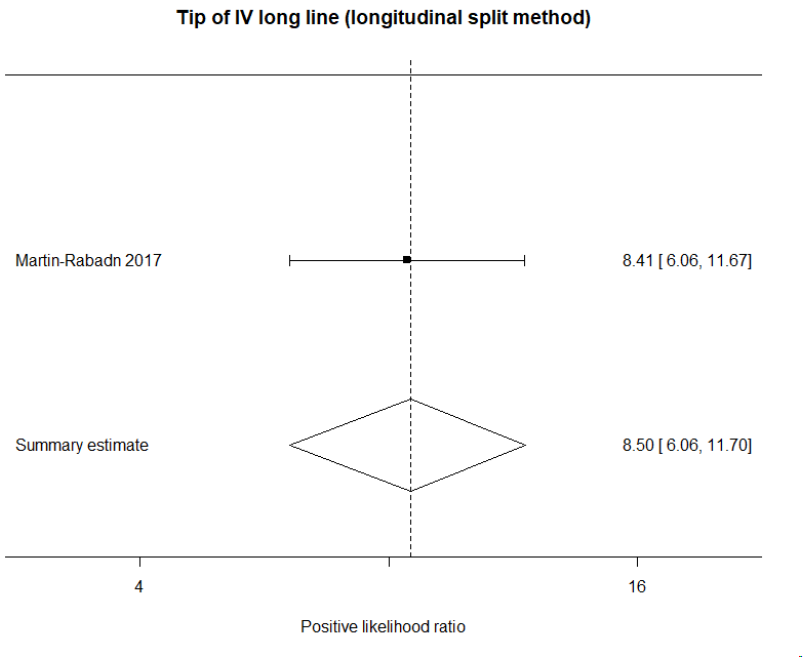
Tip of IV long line (longitudinal split method)

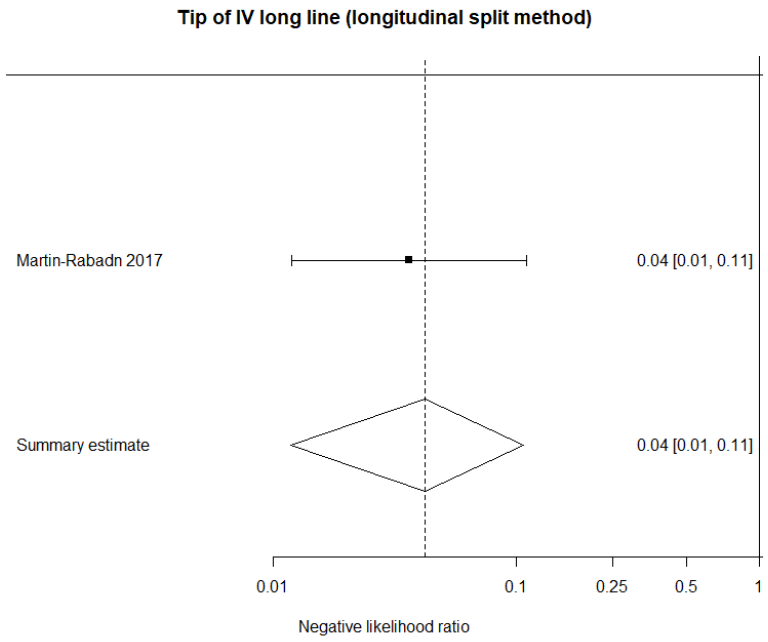
Sensitivity and specificity





1 Likelihood ratios





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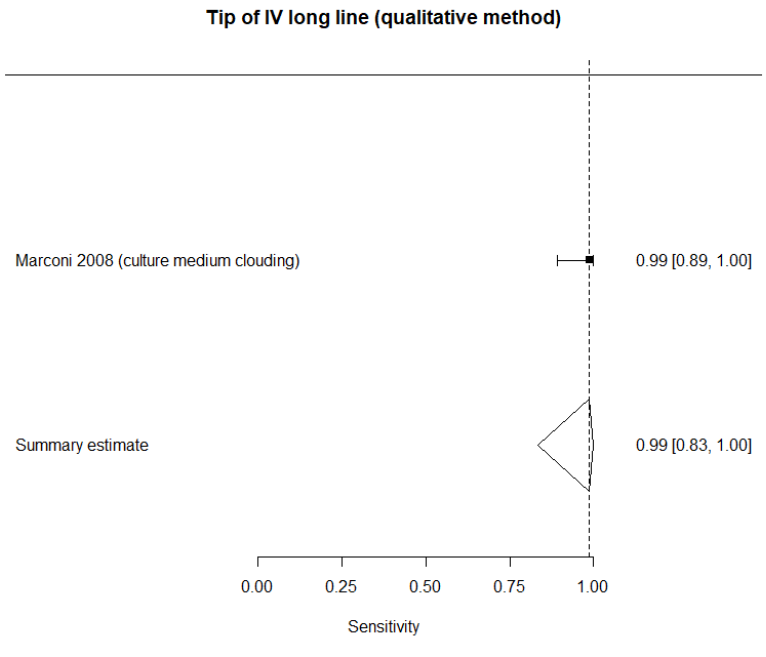
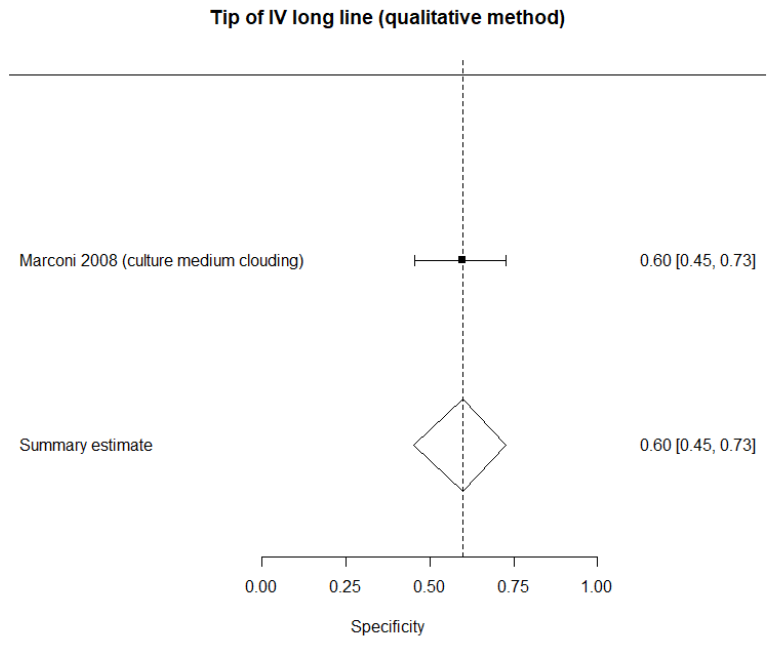
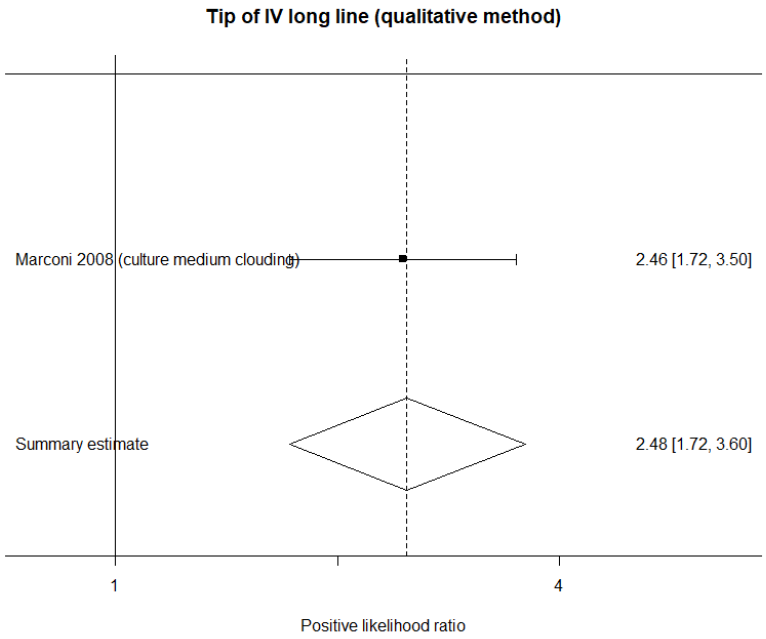
Tip of IV long line (qualitative method)

Sensitivity and specificity





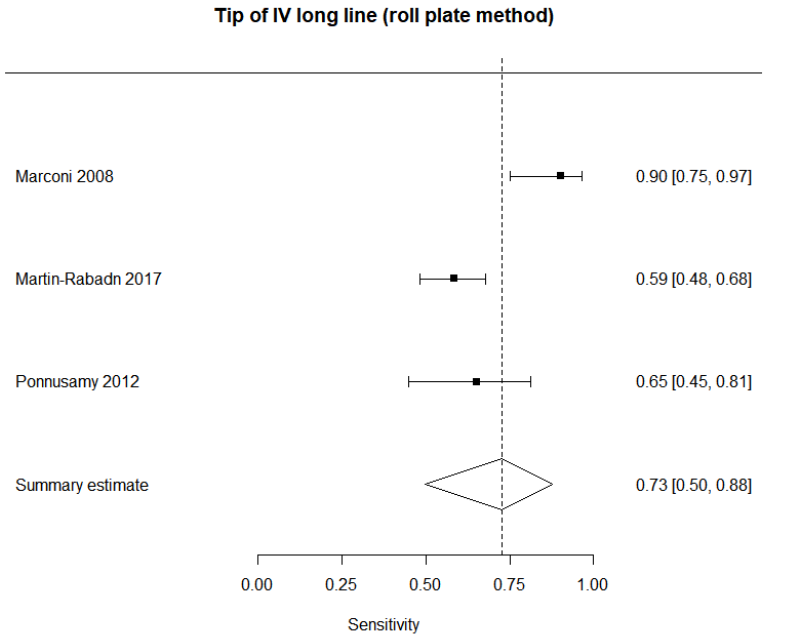
Likelihood ratios

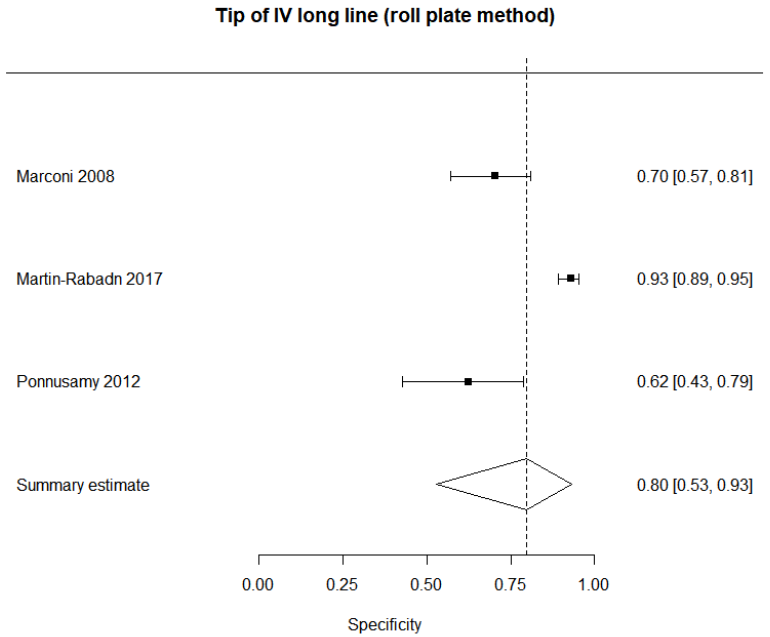


Negative LR: not calculable

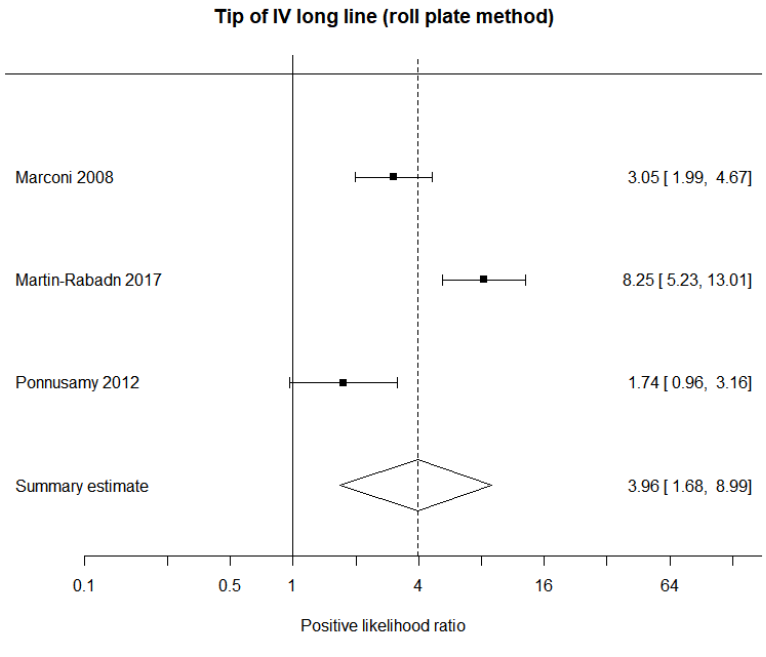
Tip of IV long line (roll plate method)

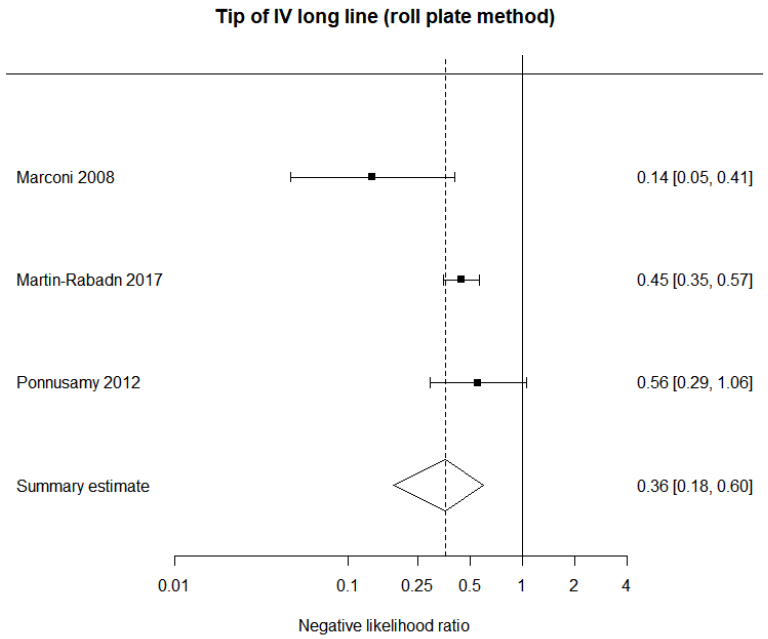
Sensitivity and specificity





1 Likelihood ratios





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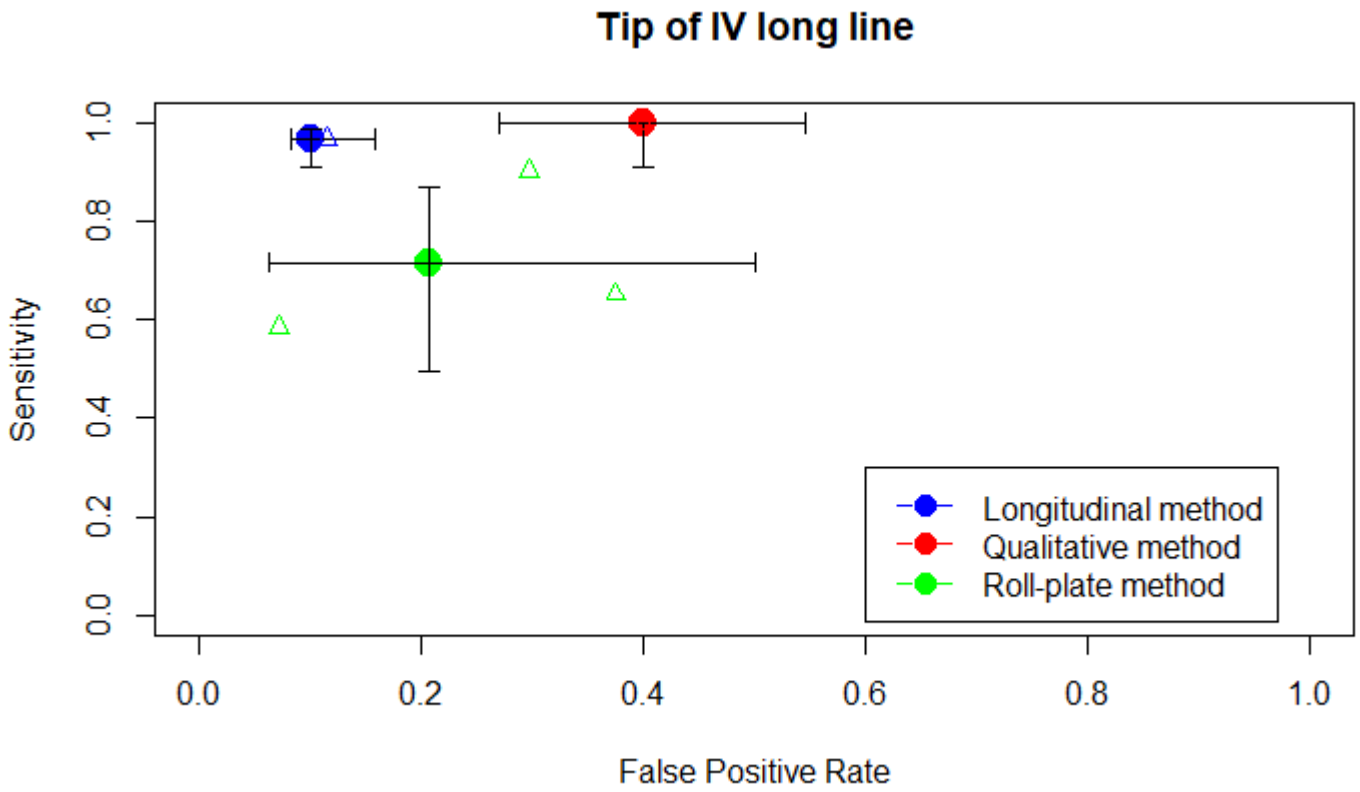

Tip of IV long line
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate
Longitudinal method
Qualitative method
Roll-plate method

1

Appendix F – GRADE tables

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
C-reactive protein (≤10 mg/l): Sample at time of blood culture										
14	13 cross-sectional	2083	0.80 (0.68, 0.88)	0.71 (0.63, 0.78)	LR+ 2.77 (2.33, 3.29)	Serious[1]	Not serious	Very serious[5]	Not serious	Very low
					LR- 0.29 (0.19, 0.41)	Serious[1]	Not serious	Very serious[5]	Not serious	Low
C-reactive protein (10 mg/l): Sample at time of blood culture										
5	Cross-sectional	928	0.62 (0.50, 0.73)	0.73 (0.59, 0.83)	LR+ 2.33 (1.55, 3.49)	Very serious[2]	Not serious	Serious[6]	Serious[8]	Very low
					LR- 0.53 (0.38, 0.69)	Serious[1]	Not serious	Serious[6]	Serious[9]	Very low
C-reactive protein (≥10 mg/l): Sample at time of blood culture										
3	Cross-sectional	325	0.77 (0.56, 0.90)	0.69 (0.38, 0.89)	LR+ 2.93 (0.95, 7.75)	Serious[1]	Not serious	Very serious[5]	Very serious[10]	Very low
					LR- 0.40 (0.12, 1.08)	Serious[1]	Not serious	Very serious[5]	Very serious[11]	Very low
C-reactive protein (≤10 mg/l): Sample taken 12-24 hours after blood culture										
2	Cross-sectional	257	0.88 (0.59, 0.97)	0.91 (0.38, 0.99)	LR+ not calculable	Serious[1]	Not serious	Serious[6]	N/A[16]	Low
					LR- 0.23 (0.03, 0.99)	Serious[1]	Not serious	Serious[6]	Serious[9]	Very low
C-reactive protein (10 mg/l): Sample taken 24 hours after blood culture										
1 (Beltempo 2018)	Cross-sectional	416	0.84 (0.76, 0.90)	0.70 (0.65, 0.75)	LR+ 2.82 (2.32, 3.39)	Serious[1]	Serious[3]	N/A[7]	Not serious	Moderate
					LR- 0.23 (0.14, 0.34)	Serious[1]	Serious[3]	N/A[7]	Not serious	Moderate

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
C-reactive protein (10 mg/l): Sample taken 48 hours after blood culture										
1 (Beltempo 2018)	Cross-sectional	416	0.73 (0.66, 0.80)	0.79 (0.74, 0.84)	LR+ 3.52 (2.72, 4.52)	Serious[1]	Serious[3]	N/A[7]	Not serious	Moderate
					LR- 0.34 (0.26, 0.44)	Serious[1]	Serious[3]	N/A[7]	Not serious	Moderate
C-reactive protein (from urine sample – 9.4 ng/ml): Sample taken when infection was diagnosed										
1 (Ozdemir 2020)	Cross-sectional	66	0.52 (0.35, 0.68)	0.80 (0.64, 0.90)	LR+ 2.58 (1.22, 5.44)	Serious[1]	Not serious	N/A[7]	Serious[8]	Low
					LR- 0.62 (0.39, 0.88)	Serious[1]	Not serious	N/A[7]	Serious[9]	Low
Procalcitonin (lower threshold) (≤10 ng/ml)										
7	Cross-sectional	535	0.76 (0.67, 0.84)	0.65 (0.57, 0.72)	LR+ 2.21 (1.64, 2.91)	Serious[1]	Not serious	Not serious	Serious[8]	Low
					LR- 0.37 (0.24, 0.54)	Serious[1]	Not serious	Serious[6]	Serious[9]	Very low
Procalcitonin (higher threshold) (1000 ng/ml)										
1 (Blommendahl 2002)	Cross-sectional	169	0.77 (0.50, 0.92)	0.62 (0.54, 0.70)	LR+ 2.02 (1.40, 2.91)	Very serious[2]	Serious[3]	N/A[7]	Serious[8]	Very low
					LR- 0.37 (0.14, 1.01)	Very serious[2]	Serious[3]	N/A[7]	Very serious[11]	Very low
Neutrophil count (>5000 / ≤1800 ≥5400 / age-adjusted count)										
3	Cross-sectional	329	0.60 (0.48, 0.70)	0.62 (0.51, 0.72)	LR+ 1.61 (1.05, 2.37)	Serious[1]	Not serious	Serious[5]	Serious[8]	Very low
					LR- 0.66 (0.44, 0.95)	Serious[1]	Not serious	Very serious[6]	Serious[9]	Very low
Neutrophils (I:T ratio) (>0.07, >0.12 / >0.2 / >0.65)										
6	Cross-sectional	961	0.70	0.55	LR+ 1.62 (1.03, 2.81)	Serious[1]	Not serious	Very serious[5]	Serious[9]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			(0.39, 0.89)	(0.26, 0.81)	LR- 0.58 (0.28, 0.96)	Serious[1]	Not serious	Very serious[5]	Serious[9]	Very low
White blood cell count (blood culture) (<5000 cells/mm^3 / <5000 >20000 cells/mm^3)										
3	Cross-sectional	526	0.46 (0.32, 0.60)	0.87 (0.66, 0.96)	LR+ 4.37 (1.10, 12.70)	Serious[1]	Not serious	Very serious[5]	Serious[8]	Very low
					LR- 0.64 (0.43, 0.95)	Serious[1]	Not serious	Serious[6]	Serious[9]	Very low
White blood cell count (CSF culture) (>19.5 cells/mm^3 / >20 cells/mm^3)										
2	Cross-sectional	6462	0.94 (0.31, 1.00)	0.93 (0.52, 0.99)	LR+ Not calculable	Serious[1]	Serious[4]	Very serious[5]	N/A[16]	Very low
					LR- 0.21 (0.00, 1.33)	Serious[1]	Serious[4]	Very serious[5]	Very serious[11]	Very low
Platelet count (100 cells/mm^3 / 150 cells/mm^3)										
2	Cross-sectional	150	0.53 (0.34, 0.71)	0.63 (0.19, 0.92)	LR+ 2.13 (0.48, 8.15)	Serious[1]	Not serious	Very serious[5]	Very serious[10]	Very low
					LR- 0.98 (0.34, 3.00)	Serious[1]	Not serious	Very serious[5]	Very serious[11]	Very low
Surface swabs (anal cleft)										
1 (Puri 1995)	Cross-sectional	31	0.07 (0.02, 0.26)	0.46 (0.22, 0.71)	LR+ 0.13 (0.03, 0.67)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 2.03 (1.08, 3.79)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (axilla)										
1 (Puri 1995)	Cross-sectional	31	0.45 (0.26, 0.66)	0.46 (0.22, 0.71)	LR+ 0.84 (0.41, 1.68)	Serious[1]	Not serious	N/A[7]	Very serious[14]	Very low
					LR- 1.19 (0.58, 2.47)	Serious[1]	Not serious	N/A[7]	Very serious[15]	Very low
Surface swabs (cubital fossa)										

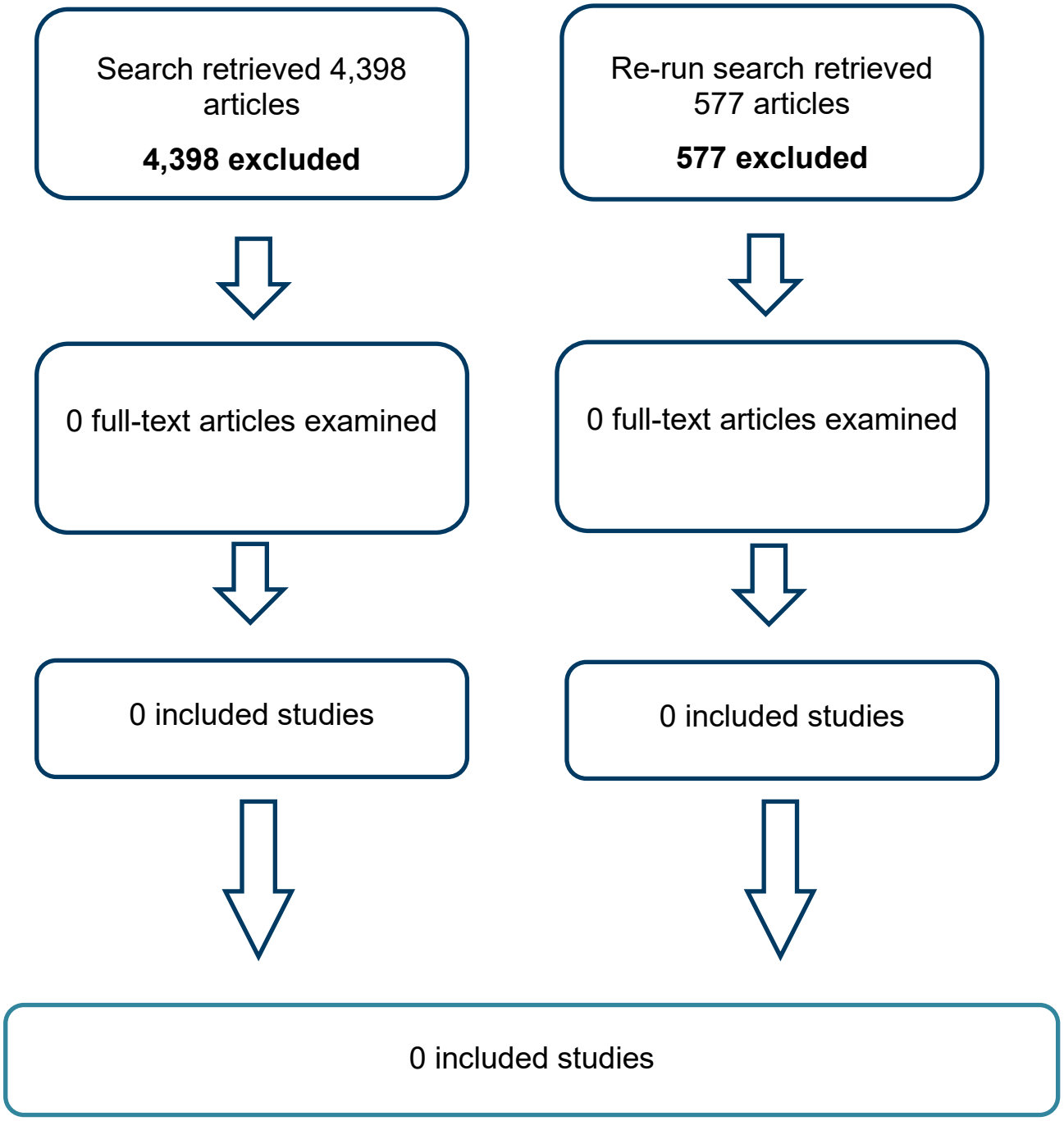
No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 3.35 (1.38, 8.10)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (ear)										
1 (Puri 1995)	Cross-sectional	31	0.55 (0.34, 0.74)	0.79 (0.51, 0.93)	LR+ 2.63 (0.82, 8.46)	Serious[1]	Not serious	N/A[7]	Very serious[10]	Very low
					LR- 0.57 (0.33, 0.99)	Serious[1]	Not serious	N/A[7]	Serious[9]	Low
Surface swabs (external genitalia)										
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.62 (0.35, 0.84)	LR+ 0.06 (0.00, 1.08)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 1.56 (1.00, 2.43)	Serious[1]	Not serious	N/A[7]	Very serious[15]	Very low
Surface swabs (gastric aspirate)										
1 (Puri 1995)	Cross-sectional	31	0.45 (0.26, 0.66)	0.71 (0.43, 0.89)	LR+ 1.55 (0.57, 4.21)	Serious[1]	Not serious	N/A[7]	Very serious[10]	Very low
					LR- 0.77 (0.45, 1.32)	Serious[1]	Not serious	N/A[7]	Very serious[11]	Very low
Surface swabs (inguinal fold)										
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.38 (0.16, 0.65)	LR+ 0.04 (0.00, 0.61)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 2.60 (1.25, 5.42)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (lumbar area)										
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Serious[1]	Not serious	N/A[7]	Serious[14]	Low
					LR- 3.35	Serious[1]	Not serious	N/A[7]	Serious[15]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
					(1.38, 8.10)					
Surface swabs (nasal swab)										
1 (Puri 1995)	Cross-sectional	31	0.50 (0.30, 0.70)	0.71 (0.43, 0.89)	LR+ 1.71 (0.64, 4.57)	Serious[1]	Not serious	N/A[7]	Very serious[10]	Very low
					LR- 0.71 (0.40, 1.24)	Serious[1]	Not serious	N/A[7]	Very serious[11]	Very low
Surface swabs (neckfold)										
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 3.35 (1.38, 8.10)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (palms)										
1 (Puri 1995)	Cross-sectional	31	0.12 (0.04, 0.32)	0.29 (0.11, 0.57)	LR+ 0.17 (0.05, 0.57)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 3.02 (1.23, 7.40)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (pharynx)										
1 (Puri 1995)	Cross-sectional	31	0.45 (0.26, 0.66)	0.54 (0.29, 0.78)	LR+ 0.99 (0.45, 2.14)	Serious[1]	Not serious	N/A[7]	Very serious[14]	Very low
					LR- 1.01 (0.53, 1.94)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (popliteal space)										
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 3.35 (1.38, 8.10)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (scalp: occipital)										
		31	0.07	0.38	LR+ 0.11	Serious[1]	Not serious	N/A[7]	Serious[12]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Puri 1995)	Cross-sectional		(0.02, 0.26)	(0.16, 0.65)	(0.02, 0.57)					
					LR- 2.48 (1.18, 5.19)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (soles)										
1 (Puri 1995)	Cross-sectional	31	0.02 (0.00, 0.19)	0.29 (0.11, 0.57)	LR+ 0.03 (0.00, 0.53)	Serious[1]	Not serious	N/A[7]	Serious[12]	Low
					LR- 3.35 (1.38, 8.10)	Serious[1]	Not serious	N/A[7]	Serious[13]	Low
Surface swabs (umbilicus)										
1 (Puri 1995)	Cross-sectional	31	0.60 (0.39, 0.77)	0.79 (0.51, 0.93)	LR+ 2.86 (0.90, 9.10)	Serious[1]	Not serious	N/A[7]	Very serious[10]	Very low
					LR- 0.51 (0.28, 93)	Serious[1]	Not serious	N/A[7]	Serious[9]	Low
Tip of the IV long line (longitudinal split method) (Culture of tip yielded ≥15 colony forming units of the same colony type)										
1 (Martin-Rabdn 2017)	Cross-sectional	277	0.97 (0.91, 0.99)	0.88 (0.84, 0.92)	LR+ 8.41 (6.06, 11.67)	Serious[1]	Not serious	N/A[7]	Not serious[10]	Moderate
					LR- 0.04 (0.01, 0.11)	Serious[1]	Not serious	N/A[7]	Not serious[11]	Moderate
Tip of the IV long line (qualitative method) (Culture of tip yielded ≥15 colony forming units of the same colony type)										
1 (Marconi 2008)	Cross-sectional	85	0.99 (0.89, 1.00)	0.60 (0.45, 0.73)	LR+ 2.48 (1.72, 3.60)	Serious[1]	Not serious	N/A[7]	Serious[8]	Low
					LR- not calculable	Serious[1]	Not serious	N/A[7]	N/A[17]	Moderate
Tip of the IV long line (roll plate method) (Culture of tip yielded ≥15 colony forming units of the same colony type)										
3	Cross-sectional	387	0.73 (0.50, 0.88)	0.80 (0.53, 0.93)	LR+ 3.96 (1.68, 8.99)	Serious[1]	Not serious	Very serious[5]	Serious[8]	Very low
					LR- 0.36 (0.18, 0.60)	Serious[1]	Not serious	Serious[6]	Serious[9]	Very low

1. >33.3% of weight of meta-analysis at moderate or high risk of bias. Quality downgraded 1 level
2. Single study at high risk of bias. Quality downgraded 2 levels
3. Single study which is partially directly applicable. Quality downgraded 1 level
4. >33.3% of weight of meta-analysis from partially directly applicable studies. Quality downgraded 1 level
5. I^2 >66.7%. Quality downgraded 2 levels
6. I^2 >33.3% but <66.7%. Quality downgraded 1 level
7. Single study. Inconsistency not applicable
8. Positive likelihood ratio crossed 1 end of the defined MIDs (1 or 2). Quality downgraded 1 level
9. Negative likelihood ratio crossed 1 end of the defined MIDs (0.5 or 1). Quality downgraded 1 level
10. Positive likelihood ratio crossed both ends of the defined MIDs (1 and 2). Quality downgraded 2 levels
11. Negative likelihood ratio crossed both ends of the defined MIDs (0.5 and 1). Quality downgraded 2 levels
12. Positive likelihood ratio crossed 1 end of the defined MIDs for negative likelihood ratio (0.5 or 1). Quality downgraded 1 level
13. Negative likelihood ratio crossed 1 end of the defined MIDs for positive likelihood ratio (1 or 2). Quality downgraded 1 level
14. Positive likelihood ratio crossed both ends of the defined MIDs for negative likelihood ratio (0.5 and 1). Quality downgraded 2 levels
15. Negative likelihood ratio crossed both ends of the defined MIDs for positive likelihood ratio (1 and 2). Quality downgraded 2 levels
16. Likelihood ratio not calculable. Imprecision not applicable

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence is available as none of the studies in the economic search results was found to be relevant.

Appendix I – Health economic model

This question was not prioritised for original economic analysis.

Appendix J – Excluded studies

Clinical studies

Study	Reason for exclusion
Abdollahi A, Shoar S, Nayyeri F et al. (2012) Diagnostic Value of Simultaneous Measurement of Procalcitonin, Interleukin-6 and hs-CRP in Prediction of Early-Onset Neonatal Sepsis. Mediterranean journal of hematology and infectious diseases 4(1): e2012028	- Early-onset neonatal infection
Aboud, M.I.; Waise, M.M.A.; Shakerdi, L.A. (2010) Procalcitonin as a marker of neonatal sepsis in intensive care units. Iranian Journal of Medical Sciences 35(3): 205-210	- Study design does not match those specified in the protocol [Case-control]
Adib, M., Bakhshiani, Z., Navaei, F. et al. (2012) Procalcitonin: A reliable marker for the diagnosis of Neonatal sepsis. Iranian Journal of Basic Medical Sciences 15(2): 777-782	- Case-control study
Ahmed, Ejaz; Rehman, Abdur; Ali, Muhammad Asghar (2017) Validation of serum C-reactive protein for the diagnosis and monitoring of antibiotic therapy in neonatal sepsis. Pakistan journal of medical sciences 33(6): 1434-1437	- Study design does not match those specified in the protocol
Al-Zwaini, E J (2009) C-reactive protein: a useful marker for guiding duration of antibiotic therapy in suspected neonatal septicaemia?. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 15(2): 269-75	- Reference standard in study does not match that specified in protocol [Suspected infection]
Ammo, K. and Salacity, G. (2008) CRP and ESR as a diagnostic marker in detection of neonatal sepsis. Pakistan Paediatric Journal 32(1): 15-22	- Not possible to calculate a contingency table from the data specified in the protocol
Ang, A T; Ho, N K; Chia, S E (1990) The usefulness of CRP and I/T ratio in early diagnosis of infections in Asian newborns. The Journal of the Singapore Paediatric Society 32(34): 159-63	- Reference standard in study does not match that specified in protocol [Positive blood, CSF or urine culture]
Armanian, A.-M.; Farajollahi, M.; Salehimehr, N. (2019) Positive Culture Samples of Infants with Neonatal Infections in a Tertiary Neonatal Center in Isfahan, Iran. Archives of Iranian medicine 22(11): 659-662	- Outcome to be predicted does not match that specified in the protocol *Antibiotic susceptibility*
Auriti, Cinzia, Fiscarelli, Ersilia, Ronchetti, Maria Paola et al. (2012) Procalcitonin in detecting neonatal nosocomial sepsis. Archives of disease in childhood. Fetal and neonatal edition 97(5): f368-70	- Outcome to be predicted do not match that specified in the protocol [Reports number with suspected infection and with confirmed infection but statistical outcomes are for both groups combined]
Aydemir, C, Aydemir, H, Kokturk, F et al. (2018) The cut-off levels of procalcitonin and C-reactive protein and the kinetics of mean platelet volume in preterm neonates with sepsis. BMC pediatrics 18(1): 253	- Study design does not match those specified in the protocol [Case control]

Bach, P.R., Davis, B.W., Loughmiller, D. et al. (2007) C-reactive protein (CRP) in neonates: Comparing VITROS slide and high-sensitivity CRP methods [3]. Clinical Chemistry 53(11): 1979-1981	- Article commentary
Ballot, Daynia E, Perovic, Olga, Galpin, Jacky et al. (2004) Serum procalcitonin as an early marker of neonatal sepsis. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 94(10): 851-4	- Early-onset neonatal infection
Benitz, W E, Han, M Y, Madan, A et al. (1998) Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics 102(4): e41	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]
Billetop, A., Grant, K., Beasmore, J. et al. (2019) Clinical evaluation of point-of-care testing for wide-range C-reactive protein (wr-CRP) in neonates with suspected sepsis. Journal of Laboratory Medicine 43(3): 135-140	- Early-onset neonatal infection
Bohnhorst, Bettina, Lange, Matthias, Bartels, Dorothee B et al. (2012) Procalcitonin and valuable clinical symptoms in the early detection of neonatal late-onset bacterial infection. Acta paediatrica (Oslo, Norway : 1992) 101(1): 19-25	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]
Bressan, Silvia, Andreola, Barbara, Cattelan, Francesca et al. (2010) Predicting severe bacterial infections in well-appearing febrile neonates: laboratory markers accuracy and duration of fever. The Pediatric infectious disease journal 29(3): 227-32	- Reference standard in study does not match that specified in protocol [Blood, CSF, urine or stool culture or any aspirated fluid]
Brown, Jennifer Valeska Elli, Meader, Nicholas, Cleminson, Jemma et al. (2019) C-reactive protein for diagnosing late-onset infection in newborn infants. The Cochrane database of systematic reviews 1: cd012126	- Systematic review. Reference list checked for possible includes [1 article ordered for full text review]
Brown, J.V.E., Meader, N., Wright, K. et al. (2020) Assessment of C-Reactive Protein Diagnostic Test Accuracy for Late-Onset Infection in Newborn Infants: A Systematic Review and Meta-analysis. JAMA Pediatrics 174(3): 260-268	- Systematic review. Reference list checked for possible includes
Burgoine, K., Ikiror, J., Naizuli, K. et al. (2019) Reagent Strips as an Aid to Diagnosis of Neonatal Meningitis in a Resource-limited Setting. Journal of Tropical Pediatrics 65(1): 9-13	- Reference standard in study does not match that specified in protocol [Leukocyte count, protein and glucose]
Cetinkaya, M, Ozkan, H, Koksal, N et al. (2009) Comparison of serum amyloid A concentrations with those of C-reactive protein and procalcitonin in diagnosis and follow-up of neonatal sepsis in premature infants. Journal of perinatology : official journal of the California Perinatal Association 29(3): 225-31	- Outcome to be predicted do not match that specified in the protocol [Probable sepsis, not culture confirmed]
Chacha, Flora, Mirambo, Mariam M, Mushi, Martha F et al. (2014) Utility of qualitative C- reactive protein assay and white blood cells counts in the diagnosis of neonatal septicaemia at Bugando Medical Centre, Tanzania. BMC pediatrics 14: 248	- Outcome to be predicted do not match that specified in the protocol [Majority of babies have early onset neonatal infection]

Chan, D K and Ho, L Y (1997) Usefulness of C-reactive protein in the diagnosis of neonatal sepsis. Singapore medical journal 38(6): 252-5	- Reference standard in study does not match that specified in protocol [Positive blood or CSF cultures or joint aspirate]
Chan, Kathy Y Y, Lam, Hugh S, Cheung, Hon M et al. (2009) Rapid identification and differentiation of Gram-negative and Gram-positive bacterial bloodstream infections by quantitative polymerase chain reaction in preterm infants. Critical care medicine 37(8): 2441-7	- Not used in current practice
Chen, Hsiu-Lin, Hung, Chih-Hsing, Tseng, Hsing-I et al. (2009) Circulating chemokine levels in febrile infants with serious bacterial infections. The Kaohsiung journal of medical sciences 25(12): 633-9	- Reference standard in study does not match that specified in protocol [Positive blood, CSF or urine culture]
Chiesa, C, Panero, A, Rossi, N et al. (1998) Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 26(3): 664-72	- Study design does not match those specified in the protocol [Case-control for late-onset]
Choi, Yoonjoung, Saha, Samir K, Ahmed, A S M Nawshad Uddin et al. (2008) Routine skin cultures in predicting sepsis pathogens among hospitalized preterm neonates in Bangladesh. Neonatology 94(2): 123-31	- Study design does not match those specified in the protocol
Da Silva, O; Ohlsson, A; Kenyon, C (1995) Accuracy of leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis: a critical review. The Pediatric infectious disease journal 14(5): 362-6	- Systematic review. Reference list checked for possible includes [2 articles ordered for full-text review]
Dai, Ji, Jiang, Wenjie, Min, Zhigang et al. (2017) Neutrophil CD64 as a diagnostic marker for neonatal sepsis: Meta-analysis. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 26(2): 327-332	- Systematic review. Reference list checked for possible includes
Davis, Jonathan, Christie, Sharon, Fairley, Derek et al. (2015) Performance of a Novel Molecular Method in the Diagnosis of Late-Onset Sepsis in Very Low Birth Weight Infants. PloS one 10(8): e0136472	- Reference standard in study does not match that specified in protocol
Diar, H A, Nakwa, F L, Thomas, R et al. (2012) Evaluating the QuikRead C-reactive protein test as a point-of-care test. Paediatrics and international child health 32(1): 35-42	- Study does not contain any relevant index tests
Dillenseger, Laurence, Langlet, Claire, Iacobelli, Silvia et al. (2018) Early Inflammatory Markers for the Diagnosis of Late-Onset Sepsis in Neonates: The Nosodiag Study. Frontiers in pediatrics 6: 346	- Outcome to be predicted do not match that specified in the protocol [Reports number with probable infection and with certain infection but statistical outcomes are for both groups combined]
Dilli, Dilek, Oguz, S Suna, Dilmen, Ugur et al. (2010) Predictive values of neutrophil CD64 expression compared with interleukin-6 and C-reactive protein in early diagnosis of neonatal sepsis. Journal of clinical laboratory analysis 24(6): 363-70	- Case-control study

Dollner, H; Vatten, L; Austgulen, R (2001) Early diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6, soluble tumour necrosis factor receptors and soluble adhesion molecules. Journal of clinical epidemiology 54(12): 1251-7	- Outcome to be predicted do not match that specified in the protocol [Not all sepsis was culture confirmed]
Draz, N.I., Taha, S.E., Abou Shady, N.M. et al. (2013) Comparison of broad range 16S rDNA PCR to conventional blood culture for diagnosis of sepsis in the newborn. Egyptian Journal of Medical Human Genetics 14(4): 403-411	- Not used in current practice
Ehl, S, Gering, B, Bartmann, P et al. (1997) C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics 99(2): 216-21	- Outcome to be predicted do not match that specified in the protocol [Duration of antibiotics. No information on accuracy]
El-Sonbaty, M.M., AlSharany, W., Youness, E.R. et al. (2016) Diagnostic utility of biomarkers in diagnosis of early stages of neonatal sepsis in neonatal intensive care unit in Egypt. Egyptian Pediatric Association Gazette 64(2): 91-96	- Reference standard in study does not match that specified in protocol [Sensitivity and specificity calculated based on confirmed or suspected sepsis]
Elwan, A.E. and Zarouk, W.A. (2009) Diagnosis of neonatal bacterial sepsis by polymerase chain reaction. Journal of Biological Sciences 9(6): 533-540	- Not used in current practice
Enguix, A, Rey, C, Concha, A et al. (2001) Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. Intensive care medicine 27(1): 211-5	- Case-control study
Ertugrul, Sabahattin, Annagur, Ali, Kurban, Sevil et al. (2013) Comparison of urinary neutrophil gelatinase-associated lipocalin, C-reactive protein and procalcitonin in the diagnosis of late onset sepsis in preterm newborns. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 26(4): 430-3	- Conference abstract
Evans, M E, Schaffner, W, Federspiel, C F et al. (1988) Sensitivity, specificity, and predictive value of body surface cultures in a neonatal intensive care unit. JAMA 259(2): 248-52	- Reference standard in study does not match that specified in protocol
Faix, R.G. (2009) Adjustment of cerebrospinal fluid cell counts for a traumatic lumbar puncture does not aid diagnosis of meningitis in neonates. Journal of Pediatrics 155(1): 148-149	- Conference abstract
Fattah, M A, Omer, Al Fadhil A, Asaif, S et al. (2017) Utility of cytokine, adhesion molecule and acute phase proteins in early diagnosis of neonatal sepsis. Journal of natural science, biology, and medicine 8(1): 32-39	- Case-control study
Fendler, Wojciech M and Piotrowski, Andrzej J (2008) Procalcitonin in the early diagnosis of nosocomial sepsis in preterm neonates. Journal of paediatrics and child health 44(3): 114-8	- Outcome to be predicted do not match that specified in the protocol [Suspected sepsis]

Ferrera, P C; Bartfield, J M; Snyder, H S (1997) Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections. The American journal of emergency medicine 15(3): 299-302	- Assessment tool do not match that specified in the protocol
Fida, Nadia M; Al-Mughales, Jamil A; Fadelallah, Mohamed F (2006) Serum concentrations of interleukin-1 alpha, interleukin-6 and tumor necrosis factor-alpha in neonatal sepsis and meningitis. Saudi medical journal 27(10): 1508-14	- Case-control study
Fleischer, Eduardo, Neuman, Mark I, Wang, Marie E et al. (2019) Cerebrospinal Fluid Profiles of Infants <=60 Days of Age With Bacterial Meningitis. Hospital pediatrics 9(12): 979-982	- Outcome to be predicted does not match that specified in the protocol *CSF profiles*
Forest JC, Larivière F, Dolcé P et al. (1986) C-reactive protein as biochemical indicator of bacterial infection in neonates. Clinical biochemistry 19(3): 192-194	- Case-control study
Francis, S T, Rawal, S, Roberts, H et al. (2010) Detection of meticillin-resistant staphylococcus aureus (MRSA) colonization in newborn infants using real-time polymerase chain reaction (PCR). Acta paediatrica (Oslo, Norway : 1992) 99(11): 1691-4	- Reference standard in study does not match that specified in protocol [Reference standard is unclear]
Franz, A R, Kron, M, Pohlandt, F et al. (1999) Comparison of procalcitonin with interleukin 8, C-reactive protein and differential white blood cell count for the early diagnosis of bacterial infections in newborn infants. The Pediatric infectious disease journal 18(8): 666-71	- Outcome to be predicted do not match that specified in the protocol [Reports number with culture proven infection and with clinical infection but statistical outcomes are for both groups combined]
Franz, A R, Steinbach, G, Kron, M et al. (1999) Reduction of unnecessary antibiotic therapy in newborn infants using interleukin-8 and C-reactive protein as markers of bacterial infections. Pediatrics 104(3pt1): 447-53	- Outcome to be predicted do not match that specified in the protocol [Reports number with suspected infection and with culture confirmed infection but statistical outcomes are for both groups combined]
Fukuzumi, N., Osawa, K., Sato, I. et al. (2020) Detection of bacterial infection based on age-specific percentile-based reference curve for serum procalcitonin level in preterm infants. Clinical Laboratory 66(12): 105-112	- Outcome to be predicted does not match that specified in the protocol *Diagnostic accuracy calculated from infection including dermatitis and pneumonia. Results for sepsis not reported separately*
Gerdes, L U, Jorgensen, P E, Nexo, E et al. (1998) C-reactive protein and bacterial meningitis: a meta-analysis. Scandinavian journal of clinical and laboratory investigation 58(5): 383-93	- Systematic review. Reference list checked for possible includes [1 study ordered for full text review]

Ghosh, S; Mittal, M; Jaganathan, G (2001) Early diagnosis of neonatal sepsis using a hematological scoring system. Indian journal of medical sciences 55(9): 495-500	- Not used in current practice
Golden, Stephen M, Stamilio, David M, Faux, Brian M et al. (2004) Evaluation of a real-time fluorescent PCR assay for rapid detection of Group B Streptococci in neonatal blood. Diagnostic microbiology and infectious disease 50(1): 7-13	- Population does not match that specified in the protocol [Population not clearly identified]
Goldfinch, Christopher D, Korman, Tony, Kotsanas, Despina et al. (2018) C-reactive protein and immature-to-total neutrophil ratio have no utility in guiding lumbar puncture in suspected neonatal sepsis. Journal of paediatrics and child health 54(8): 848-854	- Outcome to be predicted do not match that specified in the protocol [Reports number with culture proven infection and with suspected infection but statistical outcomes are for both groups combined]
Goldfinch, Christopher D, Korman, Tony, Kotsanas, Despina et al. (2018) C-reactive protein and immature-to-total neutrophil ratio have no utility in guiding lumbar puncture in suspected neonatal sepsis. Journal of paediatrics and child health 54(8): 848-854	- Outcome to be predicted does not match that specified in the protocol *Reports number with suspected infection and with confirmed infection but statistical outcomes are for both groups combined*
Gomez, Borja, Diaz, Haydee, Carro, Alba et al. (2019) Performance of blood biomarkers to rule out invasive bacterial infection in febrile infants under 21 days old. Archives of disease in childhood 104(6): 547-551	- Study does not contain any relevant index tests
Greenberg, Rachel G, Smith, P Brian, Cotten, C Michael et al. (2008) Traumatic lumbar punctures in neonates: test performance of the cerebrospinal fluid white blood cell count. The Pediatric infectious disease journal 27(12): 1047-51	- Population does not match that specified in the protocol [Traumatic lumbar punctures]
Groselj-Grenc, Mojca, Ihan, Alojz, Pavcnik-Arnol, Maja et al. (2009) Neutrophil and monocyte CD64 indexes, lipopolysaccharide-binding protein, procalcitonin and C-reactive protein in sepsis of critically ill neonates and children. Intensive care medicine 35(11): 1950-8	- Outcome to be predicted do not match that specified in the protocol [Includes suspected sepsis] - Reference standard in study does not match that specified in protocol [Includes cultures other than blood and CSF]
Hedegaard, Sofie Sommer; Wisborg, Kirsten; Hvas, Anne-Mette (2015) Diagnostic utility of biomarkers for neonatal sepsis--a systematic review. Infectious diseases (London, England) 47(3): 117-24	- Systematic review. Reference list checked for possible includes
Hisamuddin, E., Hisam, A., Wahid, S. et al. (2015) Validity of c-reactive protein (CRP) for diagnosis of neonatal sepsis. Pakistan Journal of Medical Sciences 31(3): 527-531	- Outcome to be predicted do not match that specified in the protocol [Suspected sepsis]

Hornik, Christoph P, Benjamin, Daniel K, Becker, Kristian C et al. (2012) Use of the complete blood cell count in late-onset neonatal sepsis. The Pediatric infectious disease journal 31(8): 803-7	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]
Hristeva, L, Bowler, I, Booy, R et al. (1993) Value of cerebrospinal fluid examination in the diagnosis of meningitis in the newborn. Archives of disease in childhood 69(5specno): 514-7	- Reference standard in study does not match that specified in protocol [Reference standard unclear]
Hsu, Kai-Hsiang, Chiang, Ming-Chou, Lien, Reyin et al. (2014) Limited diagnostic value of routine screening of neonates with the urinary group B streptococcal antigen tests. Pediatrics and neonatology 55(6): 480-6	- Study does not contain any relevant index tests [Urine culture assessing agglutination (GBS antigen test – not test of bacterial culture)
Isidor, Betrand, Caillaux, Gaelle, Gilquin, Valerie et al. (2007) The use of procalcitonin in the diagnosis of late-onset infection in neonatal intensive care unit patients. Scandinavian journal of infectious diseases 39(1112): 1063-6	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]
Jaswal, R S, Kaushal, R K, Goel, Asha et al. (2003) Role of C-reactive protein in deciding duration of antibiotic therapy in neonatal septicemia. Indian pediatrics 40(9): 880-3	- Reference standard in study does not match that specified in protocol
Kamiab, Z., Hassan, M.R.M., Hassanshahi, G. et al. (2019) The cut-off point of ferritin, procalcitonin, and serum CRP levels in the peripheral blood of neonates suffering from sepsis. Journal of Kerman University of Medical Sciences 26(1): 12-21	- Assessment tool do not match that specified in the protocol [Units of the cut-off for each test not reported]
Kasper, David C, Altiok, Ipek, Mechtler, Thomas P et al. (2013) Molecular detection of late-onset neonatal sepsis in premature infants using small blood volumes: proof-of-concept. Neonatology 103(4): 268-73	- Reference standard in study does not match that specified in protocol
Khassawneh, M, Hayajneh, W A, Kofahi, H et al. (2007) Diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6 and immunoglobulin M. Scandinavian journal of immunology 65(2): 171-5	- Reference standard in study does not match that specified in protocol [Blood, CSF, urine or other relevant cultures]
Khosravi, N., Khalesi, N., Noorbakhsh, S. et al. (2014) The relationship between cerebrospinal fluid C-reactive protein and neonatal meningitis. Tehran University Medical Journal 71(11): 723-728	- Study not reported in English
Kisban, G; Bartalics, L; Koranyi, G (1985) Diagnostic value of C-reactive protein in premature babies weighing less than 1500 g. Acta paediatrica Hungarica 26(4): 335-40	- Not possible to calculate a contingency table from the data specified in the protocol
Kocabas, Emine, Sarikcioglu, Aysun, Aksaray, Necmi et al. (2007) Role of procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-alpha in the diagnosis of neonatal sepsis. The Turkish journal of pediatrics 49(1): 7-20	- Case-control study
Kordek, Agnieszka, Loniewska, Beata, Podraza, Wojciech et al. (2014) Usefulness of estimation of blood procalcitonin concentration versus C-reactive protein concentration and white blood cell count for therapeutic monitoring of sepsis in	- Case-control study

neonates. Postepy higieny i medycyny doswiadczalnej (Online) 68: 1516-23	
Krediet, T, Gerards, L, Fleer, A et al. (1992) The predictive value of CRP and I/T-ratio in neonatal infection. Journal of perinatal medicine 20(6): 479-85	- Not possible to calculate a contingency table from the data specified in the protocol
Kuppermann, Nathan, Dayan, Peter S, Levine, Deborah A et al. (2019) A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections. JAMA pediatrics 173(4): 342-351	- Study does not contain any relevant index tests
Laborada, Gary, Rego, Maria, Jain, Ajey et al. (2003) Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis. American journal of perinatology 20(8): 491-501	- Outcome to be predicted do not match that specified in the protocol [Definition of sepsis did not fully match the criteria in the protocol]
Lacour, A G, Gervaix, A, Zamora, S A et al. (2001) Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. European journal of pediatrics 160(2): 95-100	- Population does not match that specified in the protocol [Neonates and children. Results for neonates not reported separately]
Liu, Y.; Zhao, L.; Wu, Z. (2019) Accuracy of C-reactive protein test for neonatal septicemia: A diagnostic meta-analysis. Medical Science Monitor 25: 4076-4081	- Systematic review. Reference list checked for possible includes [1 study ordered for full text review]
Mathers, N J and Pohlandt, F (1987) Diagnostic audit of C-reactive protein in neonatal infection. European journal of pediatrics 146(2): 147-51	- Outcome to be predicted do not match that specified in the protocol [Sensitivity and specificity results include suspected infection]
Meehan, M, Cafferkey, M, Corcoran, S et al. (2015) Real-time polymerase chain reaction and culture in the diagnosis of invasive group B streptococcal disease in infants: a retrospective study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 34(12): 2413-20	- Early-onset neonatal infection
Meem, Mahbuba, Modak, Joyanta K, Mortuza, Roman et al. (2011) Biomarkers for diagnosis of neonatal infections: A systematic analysis of their potential as a point-of-care diagnostics. Journal of global health 1(2): 201-9	- Systematic review. Reference list checked for possible includes
Mustafa, S., Farooqui, S., Waheed, S. et al. (2005) Evaluation of C-reactive protein as early indicator of blood culture positivity in neonates. Pakistan Journal of Medical Sciences 21(1): 69-73	- Assessment tool do not match that specified in the protocol [C-reactive protein but does not state the cut-off value used]
Naher, B S, Mannan, M A, Noor, K et al. (2011) Role of serum procalcitonin and C-reactive protein in the diagnosis of neonatal sepsis. Bangladesh Medical Research Council bulletin 37(2): 40-6	- Reference standard in study does not match that specified in protocol
Nasir, I.A., Mele, H.U., Babayo, A. et al. (2015) Serum Procalcitonin Assay for Investigations and Clinical Management of Neonatal Sepsis: A Review. Journal of Pediatric Infectious Diseases 10(1): 3-11	- Review article but not a systematic review

Natarajan, Girija, Johnson, Yvette R, Zhang, Fan et al. (2006) Real-time polymerase chain reaction for the rapid detection of group B streptococcal colonization in neonates. Pediatrics 118(1): 14-22	- Early-onset neonatal infection
Ng, P C, Cheng, S H, Chui, K M et al. (1997) Diagnosis of late onset neonatal sepsis with cytokines, adhesion molecule, and C-reactive protein in preterm very low birthweight infants. Archives of disease in childhood. Fetal and neonatal edition 77(3): f221-7	- Reference standard in study does not match that specified in protocol
Nnanna, I.I., Ehis, O.J., Sidiquo, I.I. et al. (2011) Serum procalcitonin: Early detection of neonatal bacteremia and septicemia in a tertiary healthcare facility. North American Journal of Medical Sciences 3(3): 157-160	- Reference standard in study does not match that specified in protocol
Numbenjapon, Nawapom, Chamnanwanakij, Sangkae, Sangaroon, Preeyapan et al. (2015) C-reactive protein as a single useful parameter for discontinuation of antibiotic treatment in Thai neonates with clinical sepsis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 98(4): 352-7	- Study design does not match those specified in the protocol
Nuntnarumit, Pracha; Pinkaew, Orawan; Kitiwanwanich, Sureewan (2002) Predictive values of serial C-reactive protein in neonatal sepsis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 85suppl4: 1151-8	- Reference standard in study does not match that specified in protocol [Included suspected sepsis]
Olaciregui, I, Hernandez, U, Munoz, J A et al. (2009) Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. Archives of disease in childhood 94(7): 501-5	- Outcome to be predicted do not match that specified in the protocol [Multiple sepsis definitions]
Pacifico, L, Chiesa, C, Cianfrano, V et al. (1989) Body surface cultures in the neonatal intensive care unit. JAMA 261(1): 46	- Conference abstract
Pammi, Mohan, Flores, Angela, Leeflang, Mariska et al. (2011) Molecular assays in the diagnosis of neonatal sepsis: a systematic review and meta-analysis. Pediatrics 128(4): e973-85	- Conference abstract
Pammi, Mohan, Flores, Angela, Versalovic, James et al. (2017) Molecular assays for the diagnosis of sepsis in neonates. The Cochrane database of systematic reviews 2: cd011926	- Systematic review. Reference list checked for possible includes
Park, I.H., Lee, S.H., Yu, S.T. et al. (2014) Serum procalcitonin as a diagnostic marker of neonatal sepsis. Korean Journal of Pediatrics 57(10): 440-445	- Outcome to be predicted do not match that specified in the protocol [Sensitivity and specificity results include suspected infection]
Paule, Suzanne M, Pasquariello, Anna C, Hacek, Donna M et al. (2004) Direct detection of Staphylococcus aureus from adult and neonate nasal swab specimens using real-time polymerase chain reaction. The Journal of molecular diagnostics : JMD 6(3): 191-6	- Reference standard in study does not match that specified in protocol [Reference standard unclear]
Pavcnik-Arnol, Maja; Hojker, Sergej; Derganc, Metka (2004) Lipopolysaccharide-binding protein in critically ill neonates and children with suspected infection: comparison with	- Population does not match that specified in the protocol [Neonates and children. Neonatal results not reported separately]

procalcitonin, interleukin-6, and C-reactive protein. Intensive care medicine 30(7): 1454-60	
Philip AG and Baker CJ (1983) Cerebrospinal fluid C-reactive protein in neonatal meningitis. The Journal of pediatrics 102(5): 715-717	- Reference standard in study does not match that specified in protocol [No clear definition of confirmed infection]
Pourcyrous, M, Bada, H S, Korones, S B et al. (1993) Significance of serial C-reactive protein responses in neonatal infection and other disorders. Pediatrics 92(3): 431-5	- Outcome to be predicted do not match that specified in the protocol [Does not include accuracy data]
Pravin Charles, Marie Victor, Kalaivani, Ramakrishnan, Venkatesh, Soma et al. (2018) Evaluation of procalcitonin as a diagnostic marker in neonatal sepsis. Indian journal of pathology & microbiology 61(1): 81-84	- Reference standard in study does not match that specified in protocol [Unclear whether reference standard includes suspected sepsis as well as confirmed]
Prince, K.; Omar, F.; Joolay, Y. (2019) A Comparison of Point of Care C-Reactive Protein Test to Standard C-Reactive Protein Laboratory Measurement in a Neonatal Intensive Care Unit Setting. Journal of Tropical Pediatrics 65(5): 498-504	- Full text paper not available
Pugni, Lorenza, Pietrasanta, Carlo, Milani, Silvano et al. (2015) Presepsin (Soluble CD14 Subtype): Reference Ranges of a New Sepsis Marker in Term and Preterm Neonates. PloS one 10(12): e0146020	- Not used in current practice
Quadir, Ashfaque F and Britton, Philip N (2018) Procalcitonin and C-reactive protein as biomarkers for neonatal bacterial infection. Journal of paediatrics and child health 54(6): 695-699	- Systematic review. Reference list checked for possible includes
Rashwan, Nagwan I, Hassan, Mohammed H, Mohey El-Deen, Zeinab M et al. (2019) Validity of biomarkers in screening for neonatal sepsis - A single center -hospital based study. Pediatrics and neonatology 60(2): 149-155	- Case-control study
Raul Bustos, B. and Heriberto Araneda, C. (2012) Procalcitonin for the diagnosis of late onset sepsis in newborns of very low birth weight. Revista Chilena de Infectologia 29(5): 511-516	- Study not reported in English
Reshi, Z, Nazir, M, Wani, W et al. (2017) Cerebrospinal fluid procalcitonin as a biomarker of bacterial meningitis in neonates. Journal of perinatology : official journal of the California Perinatal Association 37(8): 927-931	- Outcome to be predicted do not match that specified in the protocol [Neonates with sepsis who developed meningitis]
Rodwell, R L; Leslie, A L; Tudehope, D I (1988) Early diagnosis of neonatal sepsis using a hematologic scoring system. The Journal of pediatrics 112(5): 761-7	- Assessment tool do not match that specified in the protocol
Rohit, Anusha, Maiti, Biswajit, Shenoy, Shalini et al. (2016) Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) for rapid diagnosis of neonatal sepsis. The Indian journal of medical research 143(1): 72-8	- Not used in current practice

Russell, G A; Smyth, A; Cooke, R W (1992) Receiver operating characteristic curves for comparison of serial neutrophil band forms and C reactive protein in neonates at risk of infection. Archives of disease in childhood 67(7specno): 808-12	- Outcome to be predicted do not match that specified in the protocol [Includes clinical infection as well as confirmed]
Saied, D.A. (2018) Can we rely on the neutrophil left shift for the diagnosis of neonatal sepsis? Need for re-evaluation. Egyptian Pediatric Association Gazette 66(1): 22-27	- Reference standard in study does not match that specified in protocol [Positive blood cultures or laboratory findings that were not specified in protocol]
Shaat, Samar S, El Shazly, Soraya A, Badr Eldin, Mohamed M et al. (2013) Role of polymerase chain reaction as an early diagnostic tool for neonatal bacterial sepsis. The Journal of the Egyptian Public Health Association 88(3): 160-4	- Not used in current practice
Shabuj, K H, Hossain, J, Moni, S C et al. (2017) C-reactive Protein (CRP) as a Single Biomarker for Diagnosis of Neonatal Sepsis: A Comprehensive Meta-analysis. Mymensingh medical journal : MMJ 26(2): 364-371	- Systematic review. Reference list checked for possible includes
Sharma, Deepak, Farahbakhsh, Nazanin, Shastri, Sweta et al. (2018) Biomarkers for diagnosis of neonatal sepsis: a literature review. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 31(12): 1646-1659	- Systematic review. Reference list checked for possible includes
Shi, Jing; Tang, Jun; Chen, Dapeng (2016) Meta-analysis of diagnostic accuracy of neutrophil CD64 for neonatal sepsis. Italian journal of pediatrics 42(1): 57	- Systematic review. Reference list checked for possible includes
Sorsa, A. (2018) Diagnostic significance of white blood cell count and C-reactive protein in neonatal sepsis; Asella referral hospital, south east Ethiopia. Open Microbiology Journal 12(1): 209-217	- Reference standard in study does not match that specified in protocol [Risk factors or clinical features but not culture confirmed]
Srinivasan, Lakshmi, Kilpatrick, Laurie, Shah, Samir S et al. (2018) Elevations of novel cytokines in bacterial meningitis in infants. PloS one 13(2): e0181449	- Case-control study
Topuz, S. and Ovali, F. (2012) Comparison of C-reactive protein and procalcitonin in the diagnosis of neonatal sepsis. Nobel Medicus 8(1): 72-76	- Study not reported in English
Turner, Dan, Hammerman, Cathy, Rudensky, Bernard et al. (2006) The role of procalcitonin as a predictor of nosocomial sepsis in preterm infants. Acta paediatrica (Oslo, Norway : 1992) 95(12): 1571-6	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]
van den Brand, Marre, van den Dungen, Frank A M, Bos, Martine P et al. (2018) Evaluation of a real-time PCR assay for detection and quantification of bacterial DNA directly in blood of preterm neonates with suspected late-onset sepsis. Critical care (London, England) 22(1): 105	- Outcome to be predicted do not match that specified in the protocol [Sensitivity and specificity results include suspected infection]

Vazzalwar R, Pina-Rodrigues E, Puppala BL et al. (2005) Procalcitonin as a screening test for late-onset sepsis in preterm very low birth weight infants. Journal of perinatology : official journal of the California Perinatal Association 25(6): 397-402	- Reference standard in study does not match that specified in protocol [Positive blood, urine or CSF culture]
Vouloumanou, Evridiki K, Plessa, Eleni, Karageorgopoulos, Drosos E et al. (2011) Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. Intensive care medicine 37(5): 747-62	- Systematic review. Reference list checked for possible includes
Wagle, S, Grauaug, A, Kohan, R et al. (1994) C-reactive protein as a diagnostic tool of sepsis in very immature babies. Journal of paediatrics and child health 30(1): 40-4	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]
Wasunna, A, Whitelaw, A, Gallimore, R et al. (1990) C-reactive protein and bacterial infection in preterm infants. European journal of pediatrics 149(6): 424-7	- Early-onset neonatal infection
Wen, N., Shi, J., Wu, J. et al. (2019) The application of PCT and CRP combined with 16s rRNA in the early diagnosis of neonatal septicemia. International Journal of Clinical and Experimental Medicine 12(11): 12861-12867	- Study does not contain any relevant index tests *Index test not used in UK*
Xu, L., Li, Q., Mo, Z. et al. (2016) Diagnostic value of C-reactive protein in neonatal sepsis: A meta-analysis. European Journal of Inflammation 14(2): 100-108	- Systematic review. Reference list checked for possible includes
Ye, Qing, Du, Li-Zhong, Shao, Wen-Xia et al. (2017) Utility of cytokines to predict neonatal sepsis. Pediatric research 81(4): 616-621	- Case-control study
Yu, Zhangbin, Liu, Jiebo, Sun, Qing et al. (2010) The accuracy of the procalcitonin test for the diagnosis of neonatal sepsis: a meta-analysis. Scandinavian journal of infectious diseases 42(10): 723-33	- Systematic review. Reference list checked for possible includes
Zawar, M P, Tambekar, R G, Deshpande, N M et al. (2003) Early diagnosis of neonatal septicemia by sepsis screen. Indian journal of pathology & microbiology 46(4): 610-2	- Reference standard in study does not match that specified in protocol [Definition for infection is unclear]
Zecca, Enrico, Barone, Giovanni, Corsello, Mirta et al. (2009) Reliability of two different bedside assays for C-reactive protein in newborn infants. Clinical chemistry and laboratory medicine 47(9): 1081-4	- Reference standard in study does not match that specified in protocol [Blood, CSF or urine culture]

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