National Institute for Health and Care Excellence

Final

Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management

[B2] Evidence review for investigating and diagnosing suspected meningococcal disease with blood and urine investigations

NICE guideline NG240

Evidence review underpinning recommendations 1.5.2 to 1.5.5 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Review question

What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Introduction

Meningococcal disease is a rare but serious infection, which can occur in any age group. Early recognition of the condition requires a high index of suspicion.

Accurately diagnosing meningococcal disease in a timely manner ensures that appropriate antibiotic therapy is given, and close contacts of the index case can be offered chemoprophylaxis. There are several tests that may assist in the diagnosis of meningococcal disease. 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 meningococcal disease.

Summary of the protocol

See Table 1 for a summary of the Population, Index tests, Reference standard and Target condition characteristics of this review.

Table 1: Summary of the protocol

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis)
Index tests	Use of the following investigations, individually or in combination: **Blood** • white cell count • neutrophil count • C-reactive protein (CRP) • lactate • procalcitonin • molecular diagnosis for *Neisseria meningitidis* • platelets **Urine** • Meningococcal antigen

Reference standard	• Cerebrospinal fluid (CSF) bacterial culture for Neisseria meningitidis • Blood culture for Neisseria meningitidis • Polymerase chain reaction (PCR; in blood or CSF) for Neisseria meningitidis (using laboratory based techniques)
Target condition	Meningococcal disease (excluding meningococcal meningitis alone)

CRP: c-reactive protein; CSF: cerebrospinal fluid; PCR: polymerase chain reaction

For further details see the review protocol in appendix A.

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 and the methods document (supplementary document 1).

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

Diagnostic evidence

Included studies

Nine studies were included for this review, 1 systematic review and meta-analysis of individual patient data (Bell 2015), and 8 single-gate, cross-sectional, diagnostic test accuracy (DTA) studies that were published after the systematic review or did not meet the inclusion criteria of the systematic review but were relevant to this review (Baker 1989, Borchsenius 1991, Bourke 2015, Bugden 2004, Marzouk 1993, McKenna 2011, Paize 2011, Wells 2001). No evidence from test and treat randomised controlled trials were identified.

The included studies are summarised in Table 2.

Five studies looked at the DTA of white cell count (WCC; Baker 1989, Bell 2015, Borchsenius 1991, Bourke 2015, Wells 2001), 2 studies looked at the DTA of neutrophil count (Bourke 2015, Wells 2001), 7 studies looked at the DTA of C-reactive protein (CRP; Bell 2015, Borchsenius 1991, Bourke 2015, Bugden 2004, Marzouk 1993, Paize 2011, Wells 2001), 3 studies looked at the DTA of procalcitonin (PCT; Bell 2015, Bugden 2004, Paize 2011), 2 studies looked at the DTA of loop-mediated isothermal amplification (LAMP; Bourke 2015, McKenna 2011), 1 study looked at platelets (Wells 2001), and 1 study looked at the combination of CRP and WCC (Bell 2015). There was no evidence identified for blood lactate or urine meningococcal antigen.

Five studies used culture (from blood or CSF) and/or polymerase chain reaction (PCR) for Neisseria meningitidis as the reference standard (Bell 2015, Bourke 2015, Bugden 2004, Paize 2011, Wells 2001), 1 study used blood and/or CSF culture for Neisseria meningitidis (Baker 1989), 1 study used blood PCR (McKenna 2011), 1 study used blood and/or CSF culture and gram staining and/or antigen detection (Marzouk 1993), and 1 study used blood and/or CSF culture and/or CSF leukocyte count (Borchsenius 1991).

Six studies included babies and children (Baker 1989, Bell 2015, Bourke 2015, Marzouk 1993, Paize 2011, Wells 2001), 1 study did not clearly define the age range for the data included in this review but it was predominantly from babies and children aged under 13 years (at least 92%) so this study is included in the babies and children group (McKenna

2011), 1 study (Bugden 2004) included young adults (aged 14 to 40 years), and 1 study did not define the age range of participants (Borchsenius 1991).

Three studies compared people with meningococcal disease to a mixed comparison group including both those with no meningitis/septicaemia and those with other types of meningitis (Baker 1989, Borchsenius 1991, Marzouk 1993). For 6 studies the comparison was between people with meningococcal disease and an undefined non-meningococcal disease control group (Bell 2015, Bourke 2015, Bugden 2004, McKenna 2011, Paize 2011, Wells 2001).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
Baker 1989 Single-gate cross-sectional DTA study USA	N=54 Children and young people aged <21 years old with presence/history of fever >38°C and a petechial rash Meningococcal disease n=15: Age in months (median; range in parentheses): 41 (6-180) Sex not reported No meningitis/septicaemia/viral meningitis n=39: Age in months (median; range in parentheses): 45 (3-132) Sex not reported	WCC Elevated threshold defined as >15,000/µl (converted to 15 x 10^9/l for consistency with other studies)	Blood or CSF culture	• Sensitivity • Specificity	4/15 in MD group (27%) meningococcal meningitis and bacteraemia; 4/15 (27%) meningococcal meningitis without bacteraemia; and 7/15 (47%) bacteraemia without meningitis
Bell 2015	6 studies	WCC	Blood or CSF	• Sensitivity	Sample sizes or

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
Systematic review and meta-analysis of individual patient data Review conducted in UK; included studies restricted to middle-high income countries	(N=881) included in SR (N=518-671 included in analysis) Children aged 1 month to 16 years admitted to hospital with suspected meningococcal disease (fever>38°C, without source after clinical history/examination) No further details reported	Thresholds for individual studies not reported; optimal threshold defined as 16 x 10^9/l <u>CRP</u> Thresholds for individual studies not reported; optimal threshold defined as 28mg/l <u>PCT</u> Thresholds ranged from 0.2ng/ml to 2ng/ml; optimal threshold defined as 1.93ng/ml <u>Combined CRP & WCC</u> Optimal thresholds defined as CRP 28 mg/l and WCC 16 x 10^9/l	culture or PCR	• Specificity • AUC	demographic details not reported for those with meningococcal disease or non-meningococcal disease control group across all included studies. For data included in analysis, MD n=104-201 and non-MD n=414-474 (variation due to differing amounts of data available for each index test)
Borchsenius 1991 Single-gate cross-sectional DTA study Norway	N=120 People with suspected systemic meningococcal disease admitted to hospital (those with meningitis only are not included in this review*) Meningococcal disease (n=59): Age: Reported for whole MD	<u>CRP</u> Elevated threshold defined as ≥20 mg/l <u>WCC</u> Threshold defined as <4000 or ≥11000 cells/mm^3 (converted to x 10^9/l for consistency with other studies)	CSF and/or blood culture, clinical picture, meningococcal antigen in CSF, or growth of N. meningitidis in pharyngeal swab specimens	• Sensitivity • Specificity	*Those with meningococcal meningitis only are included in the review on blood and urine investigations for suspected bacterial meningitis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	group only; Mean/median not reported; 50% aged < 12 years Sex not reported No meningococcal disease (n=61): Age: Mean/median not reported; 79% aged < 12 years Sex not reported				
Bourke 2015 Single-gate cross-sectional DTA study UK	N=148 Children aged 0-13 years old presenting to emergency department with suspected meningitis or septicaemia (fever, unwell appearance, non-blanching rash, signs of meningitis, or signs of septicaemia) Meningococcal disease group n=27: Age/sex not reported by arm Non-meningococcal disease group n=121: No further details reported for control group Whole sample (N=148): Age (median;	<u>CRP</u> Elevated threshold defined as >60mg/l <u>WCC</u> Abnormal WCC defined as outside the normal range (<5 or >13 × 10^9/l) <u>Neutrophils</u> Abnormal neutrophil count defined as outside the normal range (<2 or >8 × 10^9/l) <u>Molecular diagnosis for Neisseria meningitidis</u> Loop-mediated isothemal amplification (LAMP)	Blood culture or PCR	• Sensitivity • Specificity	Serogroup of N. meningitidis: B n=26 (96%); Y n=1 (4%) Culture was also performed on CSF but all these results were negative (presumed due to antibiotics prior to lumbar puncture) Antibiotics prior to lumbar puncture: 148 (100%) Paper also reports CRP at threshold >10mg/l but only data for >60mg/l threshold included in review as this is more consistent with other studies

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	range in parentheses): 11 months (17 days-12.5 years) Sex: male: 84 (57%); female: 64 (43%)				
Bugden 2004 Single-gate cross-sectional DTA study New Zealand	N=183 Young adults aged 14-40 years presenting to the emergency department with temperature ≥38°C (or history of fever and use of antipyretic medicine) or symptoms consistent with meningococcal disease (referred by GP) Meningococcal disease group n=9: No further details reported Negative for meningococcal disease group n=174: No further details reported	PCT Elevated threshold defined as ≥0.5 ng/ml CRP Elevated threshold defined as ≥20mg/l	Blood and/or CSF culture and meningococcal PCR on blood and/or CSF	• Sensitivity • Specificity	Very small number of people diagnosed with meningococcal disease; therefore confidence intervals are wide 9/9 MD group had history of fever; only 4/9 had a recorded temperature > 38° at the initial presentation Prior antibiotics: 25/183 (14%)
Marzouk 1993 Single-gate cross-sectional DTA study UK	N=180 Children who presented with suspected clinical diagnosis of meningococcal disease Meningococcal disease group	CRP Elevated threshold defined as ≥60mg/l	CSF culture, blood culture, Gram stain and/or meningococcal antigen detected in blood or CSF	• Sensitivity • Specificity	MD group included 15/124 with meningococcal meningitis only but disaggregated data not reported for this group Serogroup of N. meningitidis:

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	n=124: Age in months (median; range in parentheses): 18 (1-182) Sex not reported No meningitis/viral meningitis group n=56: Age in months (median; no measure of variance reported): 14 Sex not reported				B n=78 (63%); C n=36 (29%); unknown n=10 (8%) Paper also reports CRP at thresholds of ≥40mg/l and ≥100mg/l, but data only extracted for ≥60mg/l threshold as this is more consistent with other studies
McKenna 2011 Single-gate cross-sectional DTA study UK	N=213 Residual clinical specimens (serum and EDTA blood), predominantly from children presenting to the emergency department with suspected meningitis or septicaemia Meningococcal disease group n=18: No further details reported Non-meningococcal disease group n=195: No further details reported	Molecular diagnosis for Neisseria meningitidis Loop-mediated isothemal amplification (LAMP)	Blood PCR	• Sensitivity • Specificity	Study also reports LAMP data for other specimen types (throat swab, CSF, respiratory secretions, faeces) but data only extracted for serum (n=141) and EDTA blood (n=72)
Paize 2011 Single-gate cross-sectional DTA study	N=36 Children attending A&E with suspected meningococcal	CRP Threshold not specified PCT	Blood or CSF culture or PCR	• Sensitivity • Specificity	Paper also reports PCT at 11.5ng/ml threshold but only data for 0.5ng/ml

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
UK	disease or transferring from regional hospitals with diagnosed meningococcal disease Meningococcal disease n=24: Age/sex not available by arm Non-meningococcal disease n=12: Presumed viral illness, no further details reported Whole sample (N=36): Age in years (median; range in parentheses): 2 (0-4.5) Sex: male: 13 (36%); female: 23 (64%)	Elevated threshold defined as >0.5ng/ml			threshold included in review as it is more consistent with other studies
Wells 2001 Single-gate cross-sectional DTA study UK	N=218 Children aged ≤15 years presenting to emergency department with non-blanching rash Meningococcal disease n=24: Age/sex not reported Non-meningococcal disease n=194: No further details reported	<u>WCC</u> Abnormal WCC defined as outside the normal range (<4 or >11 × 10^9/l) <u>Neutrophils</u> Abnormal neutrophil count defined as outside the normal range (<2 or >7.5 × 10^9/l) <u>Platelets</u> Low platelet count defined as <150 × 10^9/l	CSF culture, blood culture, and/or positive PCR	• Sensitivity • Specificity	Serogroup of N. meningitidis: B n=12 (50%); C n=11 (46%); unknown n=1 (4%)

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
		CRP Elevated threshold defined as >6mg/l			

A&E: accident and emergency; AUC: area under the curve; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; EDTA: ethylenediaminetetraacetic acid; GP: general practitioner; LAMP: loop-mediated isothermal amplification; MD: meningococcal disease; N. meningitidis: Neisseria meningitides; PCR: polymerase chain reaction; PCT: procalcitonin; WCC: white cell count

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

This section is a narrative summary of the findings of the review, as presented in the GRADE tables in appendix F. For details of the committee's confidence in the evidence and how this affected recommendations, see The committee's discussion and interpretation of the evidence.

The evidence was assessed as being high to low quality. Downgrading of the evidence was due to 95% confidence intervals crossing decision making thresholds and risk of bias in the evidence. No meta-analyses were conducted for any of the index tests because of the high level of heterogeneity between studies in terms of populations, thresholds and reference standards used. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

For interpreting the sensitivity and specificity estimates, the following rules of thumb were used (as outlined in the review protocol in Appendix A): sensitivity/specificity estimates of at least 90% were considered as very sensitive/specific; at least 50% as moderately sensitive/specific; and less than 50% as not sensitive/specific.

Overall, the evidence showed that white cell count (WCC) and neutrophil count were both moderately sensitive and moderately specific for a diagnosis of meningococcal disease in babies and children. There was some evidence from an undefined age range that showed moderate sensitivity of WCC for a diagnosis of meningococcal disease, although specificity fell below the moderate threshold.

C-reactive protein (CRP) was both moderately to very sensitive and specific for a diagnosis of meningococcal disease in babies and children. There was some evidence showing CRP to be very sensitive and moderately specific for a diagnosis of meningococcal disease in young adults. There was also some evidence from an undefined age range that CRP was moderately sensitive but not specific for a diagnosis of meningococcal disease.

Procalcitonin (PCT) was moderately to very sensitive and moderately specific for a diagnosis of meningococcal disease in babies and children. PCT was also very sensitive and moderately specific for a diagnosis of meningococcal disease in young adults.

Loop-mediated isothermal amplification (LAMP) was moderately to very sensitive and very specific for a diagnosis of meningococcal disease in babies and children.

There was some evidence that low platelet count was very specific but not sensitive for a diagnosis of meningococcal disease in babies and children.

The combination of WCC and CRP was moderately specific (and just below threshold for moderate sensitivity) for a diagnosis of meningococcal disease in babies and children.

No evidence was available for blood lactate or urine meningococcal antigen.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline. One economic study was identified which was relevant to this question (Bell 2015).

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Table 3: Economic evidence profile of procalcitonin test plus standard testing versus standard testing in the diagnosis of meningococcal disease in children

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Bell 2015 Clinical and Cost-Effectiveness of Procalcitonin Test for Prodromal Meningococcal Disease–A Meta-Analysis	Potentially serious limitations[1]	Directly applicable[2]	**Type of economic analysis**: Cost-effectiveness analysis – decision analytic model **Time horizon:** < 1-year **Primary measure of outcome:** Correctly treated patient	-£464[3]	0.051	Dominant (PCT + standard testing is cheaper and more effective than standard testing alone)	One-way sensitivity analysis was undertaken by varying the diagnostic thresholds for each test, using the hierarchical summary receiver operating characteristics (HSROC) statistics. This suggested that PCT plus standard testing was cost-saving except when the PCT threshold approached 0.2ng/ml

[1] Outcome does not capture differences in long-term health related quality of life and a different prevalence was used in the model for procalcitonin plus standard testing than for standard testing
[2] QALYs are not used as an outcome measure
[3] Costs from a 2017-18 price year were updated for inflation to 2019/20 using an inflator of 1.05 derived from the hospital & community health services (HCHS) index and NHS Cost Inflation Index (NHSCII).

Economic model

The cost-effectiveness of procalcitonin for the diagnosis of meningococcal disease was originally prioritised for economic analysis for this review question. However, following the presentation of the clinical evidence it was decided that health economic modelling would not aid the committee decision making given the data from the many included studies could not be synthesised because of the heterogeneity across them. Furthermore, the committee were not persuaded that the clinical evidence was sufficiently strong to make an offer recommendation for PCT given its higher cost when compared to CRP.

Evidence statements

Economic

One cost effectiveness analysis found that procalcitonin plus standard testing dominated (cheaper and more effective) standard testing alone for the diagnosis of meningococcal disease in children presenting with fever without source at the emergency department. The evidence was directly applicable but with potentially serious limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee agreed that they would prioritise sensitivity over specificity for this diagnostic test accuracy review. They considered the impact of true positives (correctly identifying meningococcal disease and starting the appropriate management), true negatives (reassuring patients and carers that the person does not have meningococcal disease), false positives (potentially starting unnecessary treatments) and false negatives (failing to identify people that require further interventions and intensive management). The committee noted that false negatives could be particularly impactful as they could lead to treatment being delayed until the condition worsens, which would likely result in worse outcomes for the person affected – hence a particular need to focus on the sensitivity of tests. The committee considered the positive and negative predictive values as additional information alongside sensitivity and specificity to allow them to understand what the impact of a system that recommended a certain action for all positive or negative test results would have.

The quality of the evidence

The quality of the evidence was assessed with GRADE and was rated as high to low quality and evidence was typically downgraded due to imprecision (95% confidence intervals crossing decision making thresholds) and risk of bias in the evidence (mainly due to missing data or the exclusion of participants from analyses).

No meta-analyses were conducted for any of the index tests because of the high level of heterogeneity between studies in terms of populations, thresholds and reference standards used. No evidence was available for blood lactate or urine meningococcal antigen.

Benefits and harms

The committee noted that none of the blood tests were shown to be both very sensitive and very specific across studies in the evidence reviewed and agreed that no individual blood test would be sufficient to make a diagnosis of meningococcal disease. The committee also agreed that meningococcal disease should not be ruled out based on a normal CRP, PCT or white blood cell count alone. However, the committee agreed that blood tests can be an important tool to support diagnosis (when considered alongside the clinical features) and

these tests are simple, cheap, and widely used in current practice. The committee considered the evidence on sensitivity and specificity, together with their clinical knowledge and experience, to recommend blood tests that might support a diagnosis of meningococcal disease.

There was evidence that both procalcitonin (PCT) and C-reactive protein (CRP) were at least moderately sensitive and moderately specific for a diagnosis of meningococcal disease. The evidence showed that, overall, PCT was moderately to very sensitive and moderately specific for diagnosing meningococcal disease in babies and children, and very sensitive and moderately specific for young adults (aged 14-40 years). CRP was both moderately to very sensitive and specific for a diagnosis of meningococcal disease in babies and children, very sensitive and moderately specific in young adults, and moderately sensitive (but not specific) in an undefined age range. The committee discussed the higher costs associated with PCT and agreed that the difference in diagnostic accuracy was not sufficient to warrant recommending PCT over CRP. The committee therefore recommended that CRP, or PCT if CRP is not available, should be included in the blood tests performed for people with suspected meningococcal disease.

The evidence showed that white cell count (WCC) and neutrophil count were both moderately sensitive and moderately specific for diagnosing meningococcal disease in babies and children. There was also some evidence from an undefined age range that showed moderate sensitivity of WCC, although specificity fell below the moderate threshold. The committee agreed that white blood cell count (including neutrophils) may inform treatment decisions when considered alongside clinical presentation and could guide healthcare professionals in deciding if further investigations are required, and on this basis the committee recommended that this test should be performed.

The accuracy of blood culture and blood polymerase chain reaction (PCR) for Neisseria meningitidis were not investigated as part of this review as they were included in the reference standard rather than index tests. The committee agreed that it was important to specify that these tests should be performed, and their clinical benefit (based on committee consensus) to support a diagnosis was recognised by including them in the list of gold standards for diagnosis specified in the review protocol. The committee recommended a whole-blood diagnostic PCR and gave examples of PCR for meningococcal and pneumococcal as these are the more widely available tests in clinical practice. The PCR was not restricted to meningococcal to allow for differential diagnosis, and the recommendation was left open to allow for other PCR tests as this is an area of active research and development.

No evidence was identified for the diagnostic accuracy of lactate. The committee agreed that it was important to specify that this test should be performed as the absence of lactate from the recommended list of tests could have the unintended consequence that this test would no longer be performed, and the committee agreed it is important and part of routine practice.

Only one study investigated a combination of index tests, which was the combination of WCC and CRP. This combination was moderately specific, and just below the threshold for moderate sensitivity, for a diagnosis of meningococcal disease in babies and children. The committee did not recommend diagnosis of meningococcal disease based on any specific combination of tests, but recommended a comprehensive list of blood tests should be performed to support a diagnosis.

The committee considered the accuracy of loop-mediated isothermal amplification (LAMP). The evidence base was small but showed LAMP was moderately to very sensitive and very specific for a diagnosis of meningococcal disease in babies and children. However, the committee did not consider it appropriate to include LAMP in the recommendations because it is not routinely available outside of the research setting in the UK, and the committee did

not find the evidence sufficiently compelling to recommend a change to current clinical practice.

The committee discussed that a bacterial throat swab should be taken from all cases with suspected meningococcal disease. Positive meningococcal isolate would provide additional information about the strain of N. meningitidis. The committee acknowledged that the throat swab should be taken before the administration of antibiotics and on the request form it should be specified that the swab is for meningococcal culture. Furthermore, the committee agreed that it is important to include this recommendation as it is in line with Guidance for public health management of meningococcal disease in the UK.

Cost effectiveness and resource use

An included study (Bell 2015) suggested that procalcitonin (PCT) plus standard care (CRP and WCC) dominated standard care alone for the diagnosis of meningococcal disease in a population of children with fever without source. The study reported that costs were lower, despite additional expenditure on PCT, as better diagnostic accuracy resulted in less unnecessary treatment in false positives and a reduction in treatment delays from a reduction in false negatives. However, the committee noted the potentially serious limitations in the study. First, the study results were not based on the same prevalence between the diagnostic strategies being compared. Second, the analysis did not address uncertainty in parameter point estimates for sensitivity, specificity, and prevalence. Third, whilst the analysis stated that it was a comparison of PCT plus standard care against standard care, the diagnostic accuracy of PCT plus standard care did not seem to be based on those tests used in combination but rather of PCT as a standalone test. Finally, it was not clear what the probabilities were or how they were derived for disease severity following a particular diagnostic outcome (true positive, false positive, false negative and true negative) which were fundamental in driving the differences in costs between the diagnostic strategies compared. Therefore, given the potential serious limitations of this analysis, the committee did not use the results from this study to inform their recommendations.

The committee did not think the clinical evidence was sufficiently strong to conclude that the additional costs of PCT would represent a cost-effective use of NHS resources. Therefore, they only recommended its use when CRP was not available (for example, if a local decision was made to prefer PCT over CRP, this would be acceptable, and it would not be necessary to perform both tests). While the committee acknowledged that no one single blood test could be used to diagnose meningococcal disease they believed several inexpensive blood tests could help support diagnosis and therefore in addition to CRP or PCT, they also recommended blood culture, white blood cell count, lactate, and whole-blood diagnostic polymerase chain reaction (PCR). The considered these useful tests would be cost-effective given their low cost.

The committee believed that their recommendations for investigating and diagnosing suspected meningococcal disease are in line with current practice and would not result in a significant resource impact to the NHS.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.2 to 1.5.5.

References – included studies

Diagnostic

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Economic

Bell 2015

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42020227019
Review title	Investigating and diagnosing suspected meningococcal disease with blood and urine investigations.
Review question	What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?
Objective	To determine the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease.
Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: Date limitations: 1960 English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Meningococcal disease

Field	Content
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis). Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis.
Test	The use of the following investigations, individually or in combination: Blood: • white cell count • neutrophil count • C-reactive protein (CRP) • lactate • procalcitonin • molecular diagnosis for Neisseria meningitidis • platelets Urine: • meningococcal antigen
Comparator/Reference standard/Confounding factors	Reference standard: any of the following, alone or in combination: • Cerebrospinal fluid (CSF) bacterial culture for Neisseria meningitidis • Blood culture for Neisseria meningitidis • PCR (in blood or CSF) for Neisseria meningitidis (using laboratory based techniques)
Types of study to be included	• Systematic reviews of test-and-treat RCTs and/or diagnostic accuracy studies. • Individual diagnostic accuracy studies including:

Field	Content
	• Test-and-treat RCTs • If insufficient test-and-treat RCTs: Cross-sectional diagnostic test accuracy studies (Studies with prospective and retrospective data collection will be included. Two-gate studies will only be included if there are insufficient single-gate studies.) Conference abstracts will not be considered.
Other exclusion criteria	Countries other than OECD high income countries Studies conducted prior to 1960 as evidence pertaining to laboratory tests such as white cell count and CRP date back to this period and unlikely to be a significant amount of recent evidence on these tests Studies published not in English-language
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	**Population: adults** **1. Test and Treat RCTs** • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) **2. Cross-sectional diagnostic test accuracy studies** • Sensitivity • Specificity **Population: infants and children** **1. Test and Treat RCTs** • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding

Field	Content
	hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age. **2. Cross-sectional diagnostic test accuracy studies** • Sensitivity • Specificity
Secondary outcomes (important outcomes)	**Population: adults** **1. Test and Treat RCTs** • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation Length of hospitalisation **2. Cross-sectional diagnostic test accuracy studies** • Area under the curve **Population: infants and children** **1. Test and Treat RCTs** • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1

Field	Content
	year after discharge) • Functional impairment (measured by any validated scale at any time point) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation **2. Cross-sectional diagnostic test accuracy studies** • Area under the curve
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. 5% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the tests, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklist: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for test-and-treat RCTs • QUADAS-2 tool for diagnostic test accuracy studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Where data is available from two or more studies for the same parameter and is sufficiently consistent, meta-analysis of diagnostic test accuracy will be performed using the metandi and midas applications in STATA/winbugs and Cochrane Review Manager software. Sensitivity, specificity, and area under the curve (AUC) with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies.

Field	Content

	The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/"
	
	Minimally important differences:
	Test and Treat RCTs:
	• All-cause mortality: statistical significance
	• Serious intervention-related adverse effects: statistical significance
	• Length of hospitalisation: 1 day
	• Validated scales: Published MIDs where available; if not GRADE default MIDs
	• All other outcomes: GRADE default MIDs
	
	Decision making thresholds:
	Diagnostic accuracy studies:
	• Sensitivity:
	  ○ Very useful test: ≥90%
	  ○ Moderately useful test: ≥50%
	  ○ Not a useful test <50%
	• Specificity:
	  ○ Very useful test: ≥90%
	  ○ Moderately useful test: ≥50%
	  ○ Not a useful test <50%
	• AUC:
	  ○ Very useful test: >0.80
	  ○ Moderately useful test: >0.70
	  ○ Not a useful test: ≤0.70

Analysis of sub-groups	Evidence will be stratified by:

Field	Content
	Age: • Younger Infants: >28 days to ≤3 months of age • Older infants: >3 months to <1 year of age • Children: ≥1 year of age to <18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children. Different thresholds for the index test Reference standard used (alone or in combination): • Cerebrospinal fluid (CSF) bacterial culture for Neisseria meningitidis • Blood culture for Neisseria meningitidis • PCR (in blood or CSF) for Neisseria meningitidis (using laboratory based techniques) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Young and middle aged adults • Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group

Field	Content			
	compared with others.			
Type and method of review	☒	Intervention		
	☒	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	12/01/2021			
Anticipated completion date	07/12/2023			
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		☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk			

Field	Content
	Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
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.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.
Other registration details	None
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=227019
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.
Keywords	Meningococcal disease, diagnosis, sensitivity, specificity, white cell count, neutrophil count, C-reactive protein (CRP), procalcitonin, polymerase chain reaction, blood culture, mortality, impairments
Details of existing review of same topic by same	None

Field	Content	
authors		
Current review status	☐	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

AUC: area under the curve; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CRP: c-reactive protein; CSF: cerebrospinal fluid; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MDI: mental development index; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PCR: polymerase chain reaction; PDI: psychomotor development index; PRESS: Peer Review of Electronic Search Strategies; QUADAS: quality assessment of diagnostic accuracy studies; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Clinical Search

This was a combined search to cover both this review (evidence review B2) and also evidence review B1.

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2020 December 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to December 08, 2020
Date of last search: 10 December 2020
Multifile database codes: emczd = Embase Classic+Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	9 or 17
19	exp Blood Cell Count/ or exp Leukocytes/ or Lymphocytes/ or Neutrophils/ or C Reactive Protein/ or Calcitonin/ or Procalcitonin/ or Molecular Diagnostic Techniques/ or Polymerase Chain Reaction/ or Latex Fixation Tests/ or Agglutination Tests/ or Blood Culture/ or Platelet Count/ or L-Lactate Dehydrogenase/ or Lactic Acid/ or Lactates/ or Antigens, Bacterial/ or *Cerebrospinal Fluid/ or Urinalysis/
20	19 use ppez
21	exp blood cell count/ or leukocyte/ or lymphocyte/ or leukocytosis/ or neutrophil/ or c reactive protein/ or calcitonin/ or procalcitonin/ or molecular diagnostics/ or polymerase chain reaction/ or loop mediated isothermal amplification/ or latex agglutination test/ or agglutination test/ or blood culture/ or platelet count/ or lactate dehydrogenase/ or lactic acid/ or lactate blood level/ or bacterial antigen/ or antigen blood level/ or *cerebrospinal fluid/ or urinalysis/
22	21 use emczd
23	neutrophil?.ti,ab.
24	((c-reactiv* or reactiv*) adj3 protein*).ti,ab.
25	CRP.ti,ab.
26	(procalcitonin* or pro calcitonin* or calcitonin*).ti,ab.
27	(white adj3 cell? adj3 (count* or number*)).ti,ab.
28	((white or WBC* or WBCC* or WCC* or CBC* or ALC*) adj2 count*).ti,ab.
29	(complete* adj3 (blood* and count*)).ti,ab.
30	(WBC or WBCC or WCC or CBC or ALC).ti,ab.
31	(leukocytosis or lymphocytosis).ti,ab.
32	((leukocyt* or lymphocyt*) adj3 (count* or number*)).ti,ab.
33	(molecul* adj diagnos*).mp.
34	(polymer* adj3 chain* adj3 reaction*).ti,ab.
35	PCR.ti,ab.

#	Searches
36	(loop* adj3 isotherm* adj3 amplif*).ti,ab.
37	LAMP.ti,ab.
38	(direct* adj3 sequenc*).ti,ab.
39	(latex* adj3 agglutinat*).mp.
40	((latex or agglutinat*) adj3 (test* or immunoassay* or assay* or method* or slide or kit or kits or typing)).ti,ab.
41	((blood? or urin*) adj3 (culture? or investigat*)).ti,ab.
42	(platelet* adj count*).ti,ab.
43	lactate* dehydrogenase*.mp.
44	(("cerebrospinal fluid" or CSF) adj5 (lactat* or lactic*)).ti,ab.
45	((lactate* or lactic*) adj3 (level* or value* or count* or concentration* or distribution* or serum or CSF)).ti,ab.
46	((pathogen or antigen) adj detect*).ti,ab.
47	or/20,22-46
48	exp "SENSITIVITY AND SPECIFICITY"/ or LIKELIHOOD FUNCTIONS/ or DIAGNOSIS, DIFFERENTIAL/
49	48 use ppez
50	"SENSITIVITY AND SPECIFICITY"/ or STATISTICAL MODEL/ or *DIAGNOSTIC ACCURACY/ or DIAGNOSTIC TEST ACCURACY STUDY/ or DIFFERENTIAL DIAGNOSIS/
51	50 use emczd
52	(sensitivity or specificity).ti,ab.
53	((pre test or pretest or post test or posttest) adj probability).ti,ab.
54	(predictive value* or PPV or NPV).ti,ab.
55	likelihood ratio*.ti,ab.
56	(ROC curve* or AUC).ti,ab.
57	diagnos*.ti.
58	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
59	gold standard.ab.
60	di.fs.
61	or/49,51-60
62	letter/
63	editorial/
64	news/
65	exp historical article/
66	Anecdotes as Topic/
67	comment/
68	case report/
69	(letter or comment*).ti.
70	62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71	randomized controlled trial/ or random*.ti,ab.
72	70 not 71
73	animals/ not humans/
74	exp Animals, Laboratory/
75	exp Animal Experimentation/
76	exp Models, Animal/
77	exp Rodentia/
78	(rat or rats or mouse or mice).ti.
79	72 or 73 or 74 or 75 or 76 or 77 or 78
80	letter.pt. or letter/
81	note.pt.
82	editorial.pt.
83	case report/ or case study/
84	(letter or comment*).ti.
85	80 or 81 or 82 or 83 or 84
86	randomized controlled trial/ or random*.ti,ab.
87	85 not 86
88	animal/ not human/
89	nonhuman/ not human/
90	exp Animal Experiment/
91	exp Experimental Animal/
92	animal model/
93	exp Rodent/
94	(rat or rats or mouse or mice).ti.
95	87 or 88 or 89 or 90 or 91 or 92 or 93 or 94
96	79 use ppez
97	95 use emczd
98	96 or 97
99	18 and 47 and 61
100	99 not 98
101	limit 100 to English language
102	limit 101 to yr="1960 -Current"
103	Meningitis/di or Meningitis, Bacterial/di or Meningitis, Escherichia Coli/di or Meningitis, Haemophilus/di or Meningitis, Listeria/di or Meningitis, Meningococcal/di or Meningitis, Pneumococcal/di or Meningoencephalitis/di

#	Searches
104	103 use ppez
105	meningitis/di or bacterial meningitis/di or haemophilus meningitis/di or hemophilus influenzae meningitis/di or listeria meningitis/di or meningococcal meningitis/di or pneumococcal meningitis/di or meningoencephalitis/di
106	105 use emczd
107	meta-analysis/
108	meta-analysis as topic/
109	systematic review/
110	meta-analysis/
111	(meta analy* or metanaly* or metaanaly*).ti,ab.
112	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
113	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
114	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
115	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
116	(search* adj4 literature).ab.
117	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
118	cochrane.jw.
119	((pool* or combined) adj2 (data or trials or studies or results)).ab.
120	(or/107-108,111,113-118) use ppez
121	(or/109-112,114-119) use emczd
122	120 or 121
123	104 or 106
124	122 and 123
125	124 not 98
126	limit 125 to English language
127	limit 126 to yr="1960 -Current"
128	102 or 127

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 12 of 12, December 2020, **Cochrane Central Register of Controlled Trials**, Issue 12 of 12, December 2020
Date of last search: 10 December 2020

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	(((bacter* or infect*) NEAR/3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))):ti,ab,kw
#10	((meningit* NEAR/3 (“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or “gram negativ* bacill*” or streptococc* or “group B streptococc*” or GBS or “streptococcus pneumon*” or “s pneumon*” or septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#11	((“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or “gram negativ* bacill*” or streptococc* or “group B streptococc*” or GBS or “streptococcus pneumon*” or “s pneumon*”) NEAR/3 (septic* or sepsis* or bacteraemia* or bacteremia*))
#12	(meningencephalitis* or meningoencephalitis* or meningit*)
#13	MeSH descriptor: [Meningococcal Infections] this term only
#14	MeSH descriptor: [Neisseria meningitidis] explode all trees
#15	((meningococc* NEAR/3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))):ti,ab,kw
#16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)):ti,ab,kw
#17	((Neisseria* NEXT mening*)):ti,ab,kw
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	MeSH descriptor: [Sensitivity and Specificity] explode all trees
#20	MeSH descriptor: [Likelihood Functions] this term only
#21	((sensitivity or specificity)):ti,ab,kw
#22	((("pre test" or pretest or "post test" or posttest) NEXT probability)):ti,ab,kw
#23	(("predictive value*" or PPV or NPV)):ti,ab,kw
#24	("likelihood ratio*"):ti,ab,kw
#25	(("ROC curve*" or AUC)):ti,ab,kw
#26	(diagnos*):ti
#27	((diagnos* NEAR/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness))):ti,ab,kw
#28	("gold standard"):ti,ab,kw
#29	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28

#	Searches
#30	#18 AND #29

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface

Date of last search: 10 December 2020

#	Searches
1	MeSH DESCRIPTOR Meningitis IN DARE,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))) IN DARE, HTA
10	((meningencephalitis* or meningoencephalitis* or meningit*)) IN DARE, HTA
11	MeSH DESCRIPTOR Meningococcal Infections IN DARE,HTA
12	MeSH DESCRIPTOR Neisseria meningitidis IN DARE,HTA
13	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))) IN DARE, HTA
14	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN DARE, HTA
15	((Neisseria* NEXT mening*)) IN DARE, HTA
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Sensitivity and Specificity IN DARE,HTA
18	MeSH DESCRIPTOR Likelihood Functions IN DARE,HTA
19	((sensitivity or specificity)) IN DARE, HTA
20	((("pre test" or pretest or "post test" or posttest) NEXT probability)) IN DARE, HTA
21	(("predictive value*" or PPV or NPV)) IN DARE, HTA
22	("likelihood ratio*") IN DARE, HTA
23	(("ROC curve*" or AUC)) IN DARE, HTA
24	((diagnos*)):TI IN DARE, HTA
25	((diagnos* NEAR2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness))) IN DARE, HTA
26	(("gold standard")) IN DARE, HTA
27	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28	#16 AND #27

Economic Search

One global search was conducted for economic evidence across the guideline.

Database(s): NHS Economic Evaluation Database (NHS EED), HTA Database – CRD interface

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA

#	Searches
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2021 March 10, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to March 09, 2021
Date of last search: 11 March 2021
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.

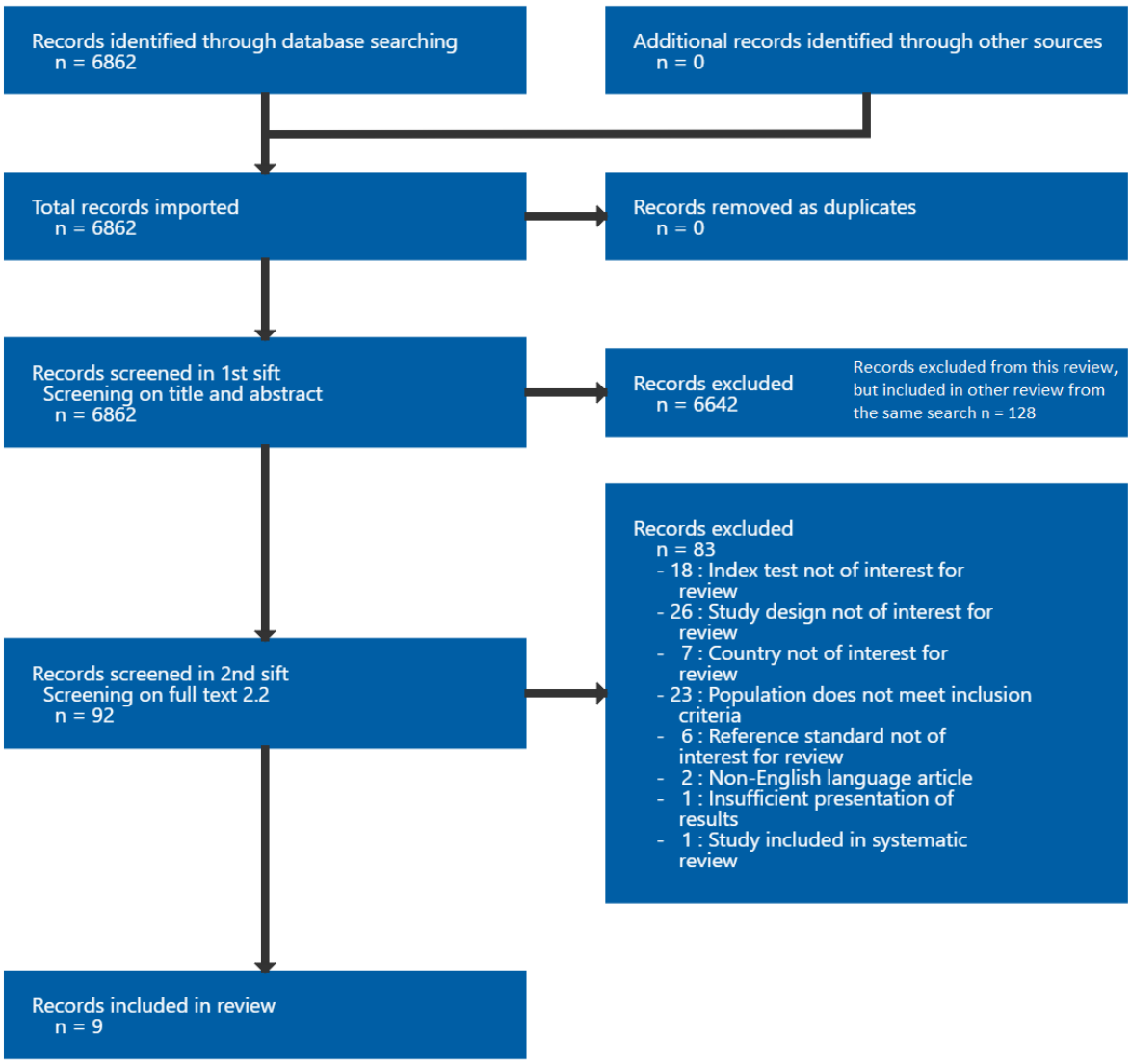
#	Searches
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language

#	Searches
117	114 or 116

Appendix C Diagnostic evidence study selection

Study selection for: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Table 5: Evidence tables - diagnostic evidence

Baker, 1989

Bibliographic Reference Baker, R.C; Seguin, J.H; Leslie, N; Gilchrist, M.J; Myers, M.G.; Fever and petechiae in children; Pediatrics; 1989; vol. 84 (no. 6); 1051-1055

Study details

Country/ies where study was carried out	USA
Study type	Single-gate cross-sectional DTA study
Study dates	November 1982-October 1983
Inclusion criteria	Children and young people aged <21 years old with presence/history of fever >38°C and a petechial rash (detected before venepuncture or lumbar puncture)
Exclusion criteria	Neonates and those with purpura fulminans or known bleeding diatheses
Patient characteristics	N=54 Meningococcal disease n=15: Age in months (median; range in parentheses): 41 (6-180) Sex not reported n=4 (27%) meningococcal meningitis and bacteraemia; n=4 (27%) meningococcal meningitis without bacteraemia; and n=7 (47%) bacteraemia without meningitis (5 with N. meningitidis, 1 with H. influenzae type b, and 1 with S. pneumoniae) No meningitis/septicaemia/viral meningitis n=39: Age in months (median; range in parentheses): 45 (3-132) Sex not reported n=34 (87%) pharyngitis/upper respiratory tract infection; n=3 (8%) urinary tract infection/acute gastroentereitis; n=2 (5%) viral meningitis

Index test(s)	WCC Elevated threshold defined as >15,000/µl (converted to 15 x 10^9/l for consistency with other studies)
Reference standard(s)	Blood or CSF culture
Sources of funding	No sources of funding reported
Results	WCC, threshold 15,000/µl (n=54): TP 10; FP 6; FN 5; TN 33 N.B. 2x2 tables and relevant outcomes calculated in RevMan For consistency across studies, results have been reported as follows in forest plots and GRADE tables: WCC – 10^9/l. Calculated as 10^9/l = cells/µl divided by 1000.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; S. pneumoniae; streptococcus pneumonia; TN: true negative; TP: true positive; WCC: white cell count

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low (*Single-gate study, consecutive sample enrolled*)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear (*No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias. No information about whether threshold was 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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low (*No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias*)

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 (*Target condition for this study included invasive disease with causes other than Neisseria meningitides. However, this only accounted for 13% of the population*)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High (*Only those with identified infective organisms were included in the analysis. Excludes 85 patients where no organism was isolated*)

Bell, 2015

Bibliographic Reference Bell, J. M; Shields, M. D; Agus, A; Dunlop, K; Bourke, T; Kee, F; Lynn, F.; Clinical and cost-effectiveness of procalcitonin test for prodromal Meningococcal Disease - A meta-analysis; PLoS ONE; 2015; vol. 10 (no. 6)

Study details

Country/ies where study was carried out	Review conducted in UK; included studies restricted to middle-high income countries
Study type	Systematic review and meta-analysis of individual patient data
Study dates	Articles published up to August 2011
Inclusion criteria	RCTs and prospective and retrospective studies that included children aged 1 month to 16 years admitted to hospital with suspected meningococcal disease (fever>38°C, without source after clinical history/examination)
Exclusion criteria	Insufficient raw data provided to include in pooled individual patient level analysis
Patient characteristics	6 studies (N=881) included in SR (N=518-671 included in analysis): No further details reported

Index test(s)	WCC Thresholds for individual studies not reported; optimal threshold defined as 16 x 10^9/l CRP Thresholds for individual studies not reported; optimal threshold defined as 28mg/l PCT Thresholds ranged from 0.2ng/ml to 2ng/ml; optimal threshold defined as 1.93ng/ml Combined CRP & WCC Optimal thresholds defined as CRP 28 mg/l and WCC 16 x 10^9/l
Reference standard(s)	Blood or CSF culture or PCR
Sources of funding	Not industry funded
Other information	Sample sizes or demographic details not reported for those with meningococcal disease or non-meningococcal disease control group across all included studies. For data included in analysis, MD n=104-201 and non-MD n=414-474 (variation due to differing amounts of data available for each index test)
Results	WCC, threshold >16 x 10^9/l (n=592): TP 59; FP 152; FN 59; TN 322. AUC: 0.67 (95% CI 0.61-0.72) CRP, threshold >28mg/l (n=519): TP 77; FP 191; FN 27; TN 224. AUC: 0.83 (95% CI 0.79-0.87) PCT, threshold >1.93ng/ml (n=671): TP 179; FP 122; FN 22; TN 348. AUC: 0.95 (95% CI 0.93-0.97) Combined CRP & WCC, thresholds CRP >28 mg/l and WCC >16 x 10^9/l (n=518): TP 49; FP 83; FN 55; TN 331 N.B. 2x2 tables and relevant outcomes calculated in RevMan

AUC: area under the curve; CI: confidence interval; CRP: c-reactive protein; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; MD: meningococcal disease; PCR: polymerase chain reaction; PCT: procalcitonin; TN: true negative; TP: true positive; WCC: white cell count

Critical appraisal - ROBIS

Section	**Answer**
Study eligibility criteria	Low (*Considerable effort had been made to specify review question, objectives and eligibility criteria. Eligibility criteria has been adhered to*)
Identification and selection of studies	Unclear (*No information about mitigating/checking for errors in study selection*)
Data collection and study appraisal	Unclear (*No information about mitigating/checking for errors in data extraction or risk of bias assessment*)

Section	Answer
Synthesis and findings	High (*Important between-study variation was not accounted for (outliers/heterogeneity not explored in analysis)*)

Borchsenius, 1991

Bibliographic Reference Borchsenius, F; Bruun, J. N; Tonjum, T.; Systemic meningococcal disease: the diagnosis on admission to hospital; NIPH annals; 1991; vol. 14 (no. 1); Nov-22

Study details

Country/ies where study was carried out	Norway
Study type	Single-gate cross-sectional DTA study (a very small number of patients [5% of full sample that included those with meningitis only] included retrospectively)
Study dates	December 1981 - April 1982
Inclusion criteria	People with suspected systemic meningococcal disease admitted to hospital (those with meningococcal meningitis only are included in the review on blood and urine investigations for suspected bacterial meningitis)
Exclusion criteria	Not reported

Patient characteristics	N=120 Meningococcal disease (n=59): Age: Reported for whole MD group only; Mean/median not reported; 50% aged < 12 years Sex not reported Septicaemia (arterial hypotension or cutaneous haemorrhages; n=21, 36%); meningitis and septicaemia (both meningitis and septicaemia; n=17, 29%); other (other systemic meningococcal infections; n=21, 36%). No meningococcal disease (n=61): Age: Mean/median not reported; 79% aged < 12 years Sex not reported Bacterial meningitis or septicaemia, excluding those due to N. meningitidis (n=16, 26%); bacterial infection (with known bacterial aetiology; n=9, 15% [pneumonia, n=4; urinary tract infection, n=1; toxic shock syndrome, n=1; systemic bacterial infections, n=3); viral infections (positive viral isolation or serious meningitis; n=14, 23%); other diseases (n=22, 36%; includes n=15 with upper respiratory tract infections of unknown aetiology). n=2 who were difficult to categorize included in the control group as meningitis of unknown microbiological aetiology)
Index test(s)	CRP Elevated threshold defined as ≥20 mg/l WCC Threshold defined as <4000 or ≥11000 cells/mm³ (converted to x 10^9/l for consistency with other studies)
Reference standard(s)	CSF and/or blood culture, clinical picture, meningococcal antigen in CSF, or growth of N. meningitidis in pharyngeal swab specimens
Sources of funding	Not reported
Results	CRP, threshold ≥20 mg/L (n=68): TP 29; FP 21; FN 7; TN 11 WCC, threshold <4000 or ≥11000 mm³/L (n=102): TP 34; FP 29; FN 17; TN 22 N.B. 2x2 tables and relevant outcomes calculated in RevMan For consistency across studies, results have been reported as follows in forest plots and GRADE tables: WCC – 10^9/l. Calculated as 10^9/l = mm³/L divided by 1000.

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; MD: meningococcal disease; N. meningitidis: Neisseria meningitides; TN: true negative; TP: true positive; WCC: white cell count

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Generally a consecutive sample enrolled (5% included retrospectively), but exclusion criteria not reported. Inclusion criteria limited to patients hospitalized with suspected systemic meningococcal disease, but no further details reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias. No information about whether thresholds were 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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Study includes patients without bacteriological proof (N=44, 38% of the full sample that includes those with meningococcal disease); and unclear if reference standard results interpreted without knowledge of the 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	Could the patient flow have introduced bias?	High *(High for CRP: Only 64% of population had data available for CRP (serum drawn later at different site compared to FBC on admission))* Unclear *(Unclear for WCC: Some missing data but results available for 90% of population)*

Bourke, 2015

Bibliographic Reference Bourke, T. W; McKenna, J. P; Coyle, P. V; Shields, M. D; Fairley, D. J.; Diagnostic accuracy of loop-mediated isothermal amplification as a near-patient test for meningococcal disease in children: an observational cohort study; The Lancet Infectious DiseasesLancet Infect Dis; 2015; vol. 15 (no. 5); 552-8

Study details

Country/ies where study was carried out	UK
Study type	Single-gate cross-sectional DTA study
Study dates	November 2009 - January 2012
Inclusion criteria	Children aged 0-13 years old presenting to emergency department with suspected meningitis or septicaemia (fever, unwell appearance, non-blanching rash, signs of meningitis, or signs of septicaemia)
Exclusion criteria	No additional criteria reported
Patient characteristics	N=148 Meningococcal disease group n=27: Age/sex not reported by arm Serogroup of N. meningitidis: B n=26 (96%); Y n=1 (4%) Non-meningococcal disease group n=121: No further details reported for control group Whole sample (N=148): Age (median; range in parentheses): 11 months (17 days-12.5 years) Sex: male: 84 (57%); female: 64 (43%)
Index test(s)	CRP Elevated threshold defined as >60mg/l WCC Abnormal WCC defined as outside the normal range (<5 or >13 × 10^9/l) Neutrophils Abnormal neutrophil count defined as outside the normal range (<2 or >8 × 10^9/l) Molecular diagnosis for Neisseria meningitidis Loop-mediated isothemal amplification (LAMP)
Reference standard(s)	Blood culture of N meningitidis and/or detection of N meningitidis DNA by PCR from blood or CSF Note: culture was also performed on CSF but all these results were negative (presumed due to antibiotics prior to lumbar puncture)

Sources of funding	Not industry funded
Other information	Authors acknowledge that rates of meningococcal disease were low compared to historical rates, resulting in wide confidence intervals for estimates of accuracy. Antibiotics prior to lumbar puncture: 148 (100%). Paper also reports CRP at threshold >10mg/l but only data for >60mg/l threshold included in review as this is more consistent with other studies.
Results	CRP, threshold >60mg/l (n=148): TP 17; FP 11; FN 10; TN 110 WCC, outside normal range <5 or >13 × 10^9/l (n=148): TP 21; FP 42; FN 6; TN 79 Neutrophils, outside normal range <2 or >8 × 10^9/l (n=148): TP 23; FP 58; FN 4; TN 63 Molecular diagnosis: Blood LAMP test (n=144): TP 22; FP 0; FN 4; TN 118 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CRP: c-reactive protein; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; LAMP: loop-mediated isothermal amplification; N. meningitidis: Neisseria meningitides; PCR: polymerase chain reaction; TN: true negative; TP: true positive; WCC: white cell count

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Single-gate study, consecutive sample enrolled)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard; however, tests are objective so unlikely that knowledge of results would introduce bias. No information about whether thresholds were pre-specified)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
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	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

Bugden, 2004

Bibliographic Reference Bugden, S. A; Coles, C; Mills, G. D.; The potential role of procalcitonin in the emergency department management of febrile young adults during a sustained meningococcal epidemic; EMA - Emergency Medicine Australasia; 2004; vol. 16 (no. 2); 114-119

Study details

Country/ies where study was carried out	New Zealand
Study type	Single-gate cross-sectional DTA study
Study dates	June 2002-March 2003
Inclusion criteria	Young adults aged 14-40 years presenting to the emergency department with temperature ≥38°C (or history of fever and use of antipyretic medicine) or symptoms consistent with meningococcal disease (referred by GP)
Exclusion criteria	Diagnosis of pneumonia, urinary tract infection, purulent tonsillitis, soft tissue infection, acute abdomen or other pre-existing medical condition that could account for fever (for example, post-chemotherapy or neutropenia)

Patient characteristics	N=183 Meningococcal disease group n=9: No further details reported Negative for meningococcal disease group n=174: No further details reported
Index test(s)	PCT Elevated threshold defined as ≥0.5 ng/ml CRP Elevated threshold defined as ≥20mg/l
Reference standard(s)	Blood and/or CSF culture and meningococcal PCR on blood and/or CSF
Sources of funding	No sources of funding reported
Other information	Very small number of people diagnosed with meningococcal disease; therefore confidence intervals are wide. 9/9 MD group had history of fever; only 4/9 had a recorded temperature > 38° at the initial presentation. Prior antibiotics: 25/183 (14%)
Results	PCT, threshold ≥0.5 ng/ml (n=183): TP 9; FP 19; FN 0; TN 155 CRP, threshold ≥20mg/l (n=137): TP 6; FP 62; FN 0; TN 69 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GP: general practitioner; MD: meningococcal disease; PCR: polymerase chain reaction; PCT: procalcitonin; TN: true negative; TP: true positive

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(A number of conditions were excluded but the authors noted that they did not exclude upper respiratory tract infections and gastroenteritis due to these having a similar presentation to meningococcal disease)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index tests were interpreted without knowledge of the reference standard; however, tests are objective so unlikely that knowledge of results would introduce bias and threshold 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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(Results of index test were not available immediately, so would not have been available at time of reference standard)*
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	Could the patient flow have introduced bias?	Low

Marzouk, 1993

Bibliographic Reference Marzouk, O; Bestwick, K; Thomson, A. P. J; Sills, J. A; Hart, C. A.; Variation in serum C-reactive protein across the clinical spectrum of meningococcal disease; Acta Paediatrica, International Journal of Paediatrics; 1993; vol. 82 (no. 9); 729-733

Study details

Country/ies where study was carried out	UK
Study type	Single-gate cross-sectional DTA study
Study dates	November 1988 - August 1990
Inclusion criteria	Children who presented with suspected clinical diagnosis of meningococcal disease
Exclusion criteria	Not reported

Patient characteristics	N=180 Meningococcal disease group n=124: Age in months (median; range in parentheses): 18 (1-182) Sex not reported Meningococcal septicaemia n=30 (24%); n=79 (64%) meningococcal septicaemia and meningococcal meningitis; n=15 (12%) meningococcal meningitis Serogroup of N. meningitidis: B n=78 (63%); C n=36 (29%); unknown n=10 (8%) No meningitis/viral meningitis group n=56: Age in months (median; no measure of variance reported): 14 Sex not reported Diagnoses: Viral meningitis n=3; chest infection n=6; tonsillitis n=4; otitis media n=2; Kawasaki disease n=1; suspected viral illness n=40
Index test(s)	CRP Elevated threshold defined as ≥60mg/l
Reference standard(s)	CSF culture, blood culture, Gram stain and/or meningococcal antigen detected in blood or CSF
Sources of funding	Not industry funded
Other information	The study included n=4 children with other types of bacterial meningitis and n=28 who were thought to have MD clinically but MD not confirmed bacteriologically, data for these participants (n=32) not included in this review. MD group included 15/124 with meningococcal meningitis only but disaggregated data not reported for this group. Paper also reports CRP at thresholds of ≥40mg/l and ≥100mg/l, but data only extracted for ≥60mg/l threshold as this is more consistent with other studies.
Results	CRP, threshold ≥60mg/l (n=151): TP 67; FP 6; FN 28; TN 50 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; MD: meningococcal disease; N. meningitidis: Neisseria meningitides; TN: true negative; TP: true positive

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Single-gate study, consecutive sample enrolled)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias. No information about whether threshold was 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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Some cases identified based on gram staining and/or antigen detection by counter-immunoelectrophoresis and/or latex agglutination)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Blood samples and CRP tests were taken/performed at admission, but unclear when CSF samples were taken. DTA data only available for 84% of sample)*

McKenna, 2011

Bibliographic Reference McKenna, J. P; Fairley, D. J; Shields, M. D; Cosby, S. L; Wyatt, D. E; McCaughey, C; Coyle, P. V.; Development and clinical validation of a loop-mediated isothermal amplification method for the rapid detection of Neisseria meningitidis; Diagnostic microbiology and infectious disease; 2011; vol. 69 (no. 2); 137-144

Study details

Country/ies where study was carried out	UK

Study type	Single-gate cross-sectional DTA study
Study dates	April 2007-February 2009
Inclusion criteria	Residual clinical specimens (serum and EDTA blood), predominantly from children presenting to the emergency department with suspected meningitis or septicaemia (although some samples from people aged over 13 years suspected of meningococcal infection were also included)
Exclusion criteria	No additional criteria reported
Patient characteristics	N=213 Meningococcal disease group n=18: No further details reported Non-meningococcal disease group n=195: No further details reported
Index test(s)	Molecular diagnosis for Neisseria meningitidis Loop-mediated isothemal amplification (LAMP)
Reference standard(s)	Blood PCR
Sources of funding	No sources of funding reported
Other information	Study also reports LAMP data for other specimen types (throat swab, CSF, respiratory secretions, faeces) but data only extracted for serum (n=141) and EDTA blood (n=72)
Results	Molecular diagnosis: LAMP (n=213): TP 18; FP 2; FN 0; TN 193 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; EDTA: ethylenediaminetetraacetic acid; FN: false negative; FP: false positive; LAMP: loop-mediated isothermal amplification; PCR: polymerase chain reaction; TN: true negative; TP: true positive

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
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	Could the patient flow have introduced bias?	Low *(Index test and reference standard analysed at the same time (and from the same sample))*

Paize, 2011

Bibliographic Reference Paize, F; Carrol, E; Downey, C; Parry, C. M; Green, G; Diggle, P; Newland, P; Riordan, F. A. I; Thomson, A; Hart, C. A; Toh, C. H.; Diagnostic efficacy of activated partial thromboplastin time waveform and procalcitonin analysis in pediatric meningococcal sepsis; Pediatric Critical Care Medicine; 2011; vol. 12 (no. 6); e322-e329

Study details

Country/ies where study was carried out	UK
Study type	Single-gate cross-sectional DTA study
Study dates	January 2007-January 2008

Inclusion criteria	Children attending A&E with suspected meningococcal disease or transferring from regional hospitals with diagnosed meningococcal disease
Exclusion criteria	No additional criteria reported
Patient characteristics	N=36 Meningococcal disease n=24: Age/sex not available by arm Non-meningococcal disease n=12: Presumed viral illness, no further details reported Whole sample (N=36): Age in years (median; range in parentheses): 2 (0-4.5) Sex: male: 13 (36%); female: 23 (64%)
Index test(s)	CRP Threshold not specified PCT Elevated threshold defined as >0.5ng/ml
Reference standard(s)	Blood or CSF culture or PCR
Sources of funding	Not industry funded
Other information	Paper also reports PCT at 11.5ng/ml threshold but only data for 0.5ng/ml threshold included in review as it is more consistent with other studies
Results	CRP, threshold not defined (n=36): TP 21; FP 2; FN 3; TN 10 PCT, threshold >0.5ng/ml (n=36): TP 24; FP 2; FN 0; TN 10 N.B. 2x2 tables and relevant outcomes calculated in RevMan

A&E: accident and emergency; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; PCR: polymerase chain reaction; PCT: procalcitonin; TN: true negative; TP: true positive

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	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	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard; however, tests are objective so unlikely that knowledge of results would introduce bias. No information about whether thresholds were pre-specified and threshold for CRP undefined)*
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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
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	Could the patient flow have introduced bias?	Low

Wells, 2001

Bibliographic Reference Wells, L.C; Smith, J.C; Weston, V.C; Collier, J; Rutter, N.; The child with a non-blanching rash: how likely is meningococcal disease?; Archives of Disease in Childhood; 2001; vol. 85 (no. 3); 218-222

Study details

Country/ies where study was carried out	UK

Study type	Single-gate cross-sectional DTA study
Study dates	November 1998-October 1999
Inclusion criteria	Children aged ≤15 years presenting to emergency department with non-blanching rash
Exclusion criteria	Not explicitly reported, but excluded those with a clear alternative diagnosis (11 with Henoch–Schonlein purpura, 1 with idiopathic thrombocytopenic purpura, 1 with haemolytic uraemic syndrome, 1 with acute leukaemia, and 1 with a previously recognised clotting disorder)
Patient characteristics	N=218 Meningococcal disease n=24: Age/sex not reported Serogroup of N. meningitidis: B n=12 (50%); C n=11 (46%); unknown n=1 (4%) Non-meningococcal disease n=194: No further details reported
Index test(s)	WCC Abnormal WCC defined as outside the normal range (<4 or >11 × 10^9/l) Neutrophils Abnormal neutrophil count defined as outside the normal range (<2 or >7.5 × 10^9/l) Platelets Low platelet count defined as <150 × 10^9/l CRP Elevated threshold defined as >6mg/l
Reference standard(s)	CSF culture, blood culture, and/or positive PCR
Sources of funding	No sources of funding reported
Results	WCC, outside of normal 4 -11 × 10^9/l range (n=211): TP 14; FP 83; FN 10; TN 104 Neutrophils, outside of normal 2 - 7.5 × 10^9/l range (n=211): TP 15; FP 71; FN 9; TN 116 Platelets, threshold <150 × 10^9/l (n=203): TP 6; FP 14; FN 18; TN 165 CRP, threshold >6mg/l (n=183): TP 17; FP 76; FN 0; TN 90 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitides; PCR: polymerase

chain reaction; TN: true negative; TP: true positive; WCC: white cell count

Critical appraisal - QUADAS-2

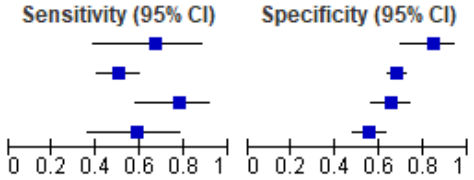
Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled but excluded children with clear alternative diagnoses)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard; however, tests are objective so unlikely that knowledge of results would introduce bias. No information about whether thresholds were 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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
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	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards, and some missing data although this is limited (3-16%))*

Appendix E Forest plots

Forest plots for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Figure 2: Forest plot for sensitivity and specificity of white cell count (WCC) for diagnosis of meningococcal disease in babies and children

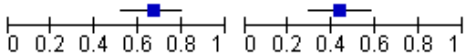
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Baker 1989	10	6	5	33	MD VM NM	>15 x 10⁹/l	CB	0.67 [0.38, 0.88]	0.85 [0.69, 0.94]
Bell 2015	59	152	59	322	MD U	>16 x 10⁹/l	CBP	0.50 [0.41, 0.59]	0.68 [0.64, 0.72]
Bourke 2015	21	42	6	79	MD U	<5 x 10⁹/l or >13 x 10⁹/l	BP	0.78 [0.58, 0.91]	0.65 [0.56, 0.74]
Wells 2001	14	83	10	104	MD U	<4 x10⁹/l or >11 x10⁹/l	CBP	0.58 [0.37, 0.78]	0.56 [0.48, 0.63]



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; NM: non-meningitis/septicaemia; P: PCR; TN: true negative; TP: true positive; U: undefined; VM: viral meningitis

Figure 3: Forest plot for sensitivity and specificity of white cell count (WCC) for diagnosis of meningococcal disease in an undefined age

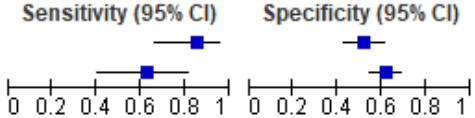
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Borchsenius 1991	34	29	17	22	MD VM NM	<4 x10⁹/l or >11 x10⁹/l	CBO	0.67 [0.52, 0.79]	0.43 [0.29, 0.58]



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; NM: non-meningitis/septicaemia; O: other reference standard not specified in review protocol; TN: true negative; TP: true positive; VM: viral meningitis

Figure 4: Forest plot for sensitivity and specificity of neutrophil count for diagnosis of meningococcal disease in babies and children

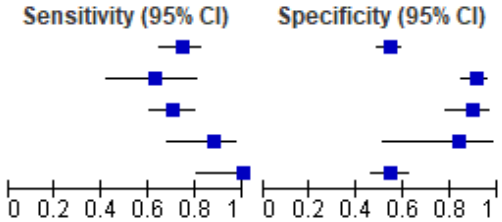
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bourke 2015	23	58	4	63	MD U	<2 or >8 × 10⁹/l	BP	0.85 [0.66, 0.96]	0.52 [0.43, 0.61]
Wells 2001	15	71	9	116	MD U	<2 x 10⁹/l or >7.5 x 10⁹/l	CBP	0.63 [0.41, 0.81]	0.62 [0.55, 0.69]



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Figure 5: Forest plot for sensitivity and specificity of C-reactive protein (CRP) for diagnosis of meningococcal disease in babies and children

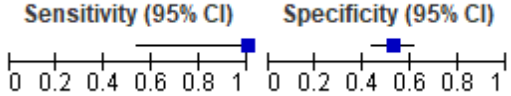
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bell 2015	77	191	27	224	MD U	>028mg/l	CBP	0.74 [0.65, 0.82]	0.54 [0.49, 0.59]
Bourke 2015	17	11	10	110	MD U	>060mg/l	BP	0.63 [0.42, 0.81]	0.91 [0.84, 0.95]
Marzouk 1993	67	6	28	50	MD VM NM	>060mg/l	CBAO	0.71 [0.60, 0.79]	0.89 [0.78, 0.96]
Paize 2011	21	2	3	10	MD U	undefined	CBP	0.88 [0.68, 0.97]	0.83 [0.52, 0.98]
Wells 2001	17	76	0	90	MD U	>006mg/l	CBP	1.00 [0.80, 1.00]	0.54 [0.46, 0.62]



A: antigen detection; B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; NM: non-meningitis/septicaemia; O: other reference standard not specified in review protocol; P: PCR; TN: true negative; TP: true positive; U: undefined; VM: viral meningitis

Figure 6: Forest plot for sensitivity and specificity of C-reactive protein (CRP) for diagnosis of meningococcal disease in young adults

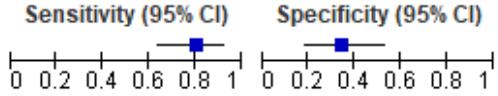
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bugden 2004	6	62	0	69	MD U	>020mg/l	CBP	1.00 [0.54, 1.00]	0.53 [0.44, 0.61]



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Figure 7: Forest plot for sensitivity and specificity of C-reactive protein (CRP) for diagnosis of meningococcal disease in an undefined age

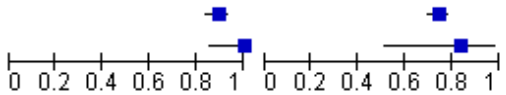
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Borchsenius 1991	29	21	7	11	MD VM NM	>020mg/l	CBO	0.81 [0.64, 0.92]	0.34 [0.19, 0.53]



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; NM: non-meningitis/septicaemia; O: other reference standard not specified in review protocol; TN: true negative; TP: true positive; VM: viral meningitis

Figure 8: Forest plot for sensitivity and specificity of procalcitonin (PCT) for diagnosis of meningococcal disease in babies and children

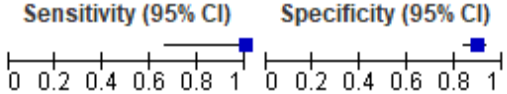
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bell 2015	179	122	22	348	MD U	>1.93ng/ml	CBP	0.89 [0.84, 0.93]	0.74 [0.70, 0.78]		
Paize 2011	24	2	0	10	MD U	>0.5ng/ml	CBP	1.00 [0.86, 1.00]	0.83 [0.52, 0.98]		



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Figure 9: Forest plot for sensitivity and specificity of procalcitonin (PCT) for diagnosis of meningococcal disease in young adults

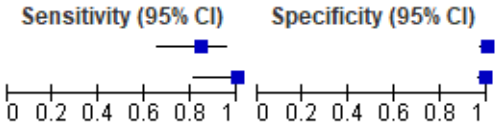
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bugden 2004	9	19	0	155	MD U	>0.5ng/ml	CBP	1.00 [0.66, 1.00]	0.89 [0.83, 0.93]		



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Figure 10: Forest plot for sensitivity and specificity of loop-mediated isothemal amplification (LAMP) for diagnosis of meningococcal disease in babies and children

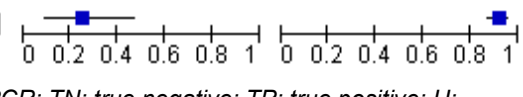
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bourke 2015	22	0	4	118	MD U	not applicable	BP	0.85 [0.65, 0.96]	1.00 [0.97, 1.00]		
McKenna 2011	18	2	0	193	MD U	not applicable	P	1.00 [0.81, 1.00]	0.99 [0.96, 1.00]		



B: blood culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Figure 11: Forest plot for sensitivity and specificity of platelets for diagnosis of meningococcal disease in babies and children

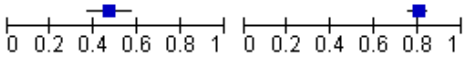
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wells 2001	6	14	18	165	MD U	<150 × 10⁹/l	CBP	0.25 [0.10, 0.47]	0.92 [0.87, 0.96]		



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Figure 12: Forest plot for sensitivity and specificity of combination of white cell count (WCC) and C-reactive protein (CRP) for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bell 2015	49	83	55	331	MD U	WCC >16 x 10⁹/l; CRP 28mg/l	CBP	0.47 [0.37, 0.57]	0.80 [0.76, 0.84]		



B: blood culture; C: CSF culture; CI: confidence interval; FN: false negative; FP: false positive; MD: meningococcal disease; P: PCR; TN: true negative; TP: true positive; U: undefined

Appendix F GRADE tables

GRADE tables for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Table 6: White cell count (WCC) for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Baker 1989)	Population: MD VM NM Threshold: >15 x 10^9/l Reference standard: CB	54	Sensitivity: 0.67 (0.38 to 0.88)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.63	0.87
			Specificity: 0.85 (0.69 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Bell 2015)	Population: MD U Threshold: >16 x 10^9/l Reference standard: CBP	592	Sensitivity: 0.50 (0.41 to 0.59)	No serious	No serious	No serious	Serious[2]	MODERATE	0.28	0.85
			Specificity: 0.68 (0.64 to 0.72)	No serious	No serious	No serious	No serious	HIGH		
			AUC: 0.67 (0.61 to 0.72)	No serious	No serious	No serious	Serious[2]	MODERATE		

1 (Bourke 2015)	Population: MD U Threshold: <5 or ≥13 x 10^9/l Reference standard: BP	148	Sensitivity: 0.78 (0.58 to 0.91)	No serious	No serious	No serious	Serious[2]	MODERATE	0.33	0.93
			Specificity: 0.65 (0.56 to 0.74)	No serious	No serious	No serious	No serious	HIGH		
1 (Wells 2001)	Population: MD U Threshold: <4 or >11 x 10^9/l Reference standard: CBP	211	Sensitivity: 0.58 (0.37 to 0.78)	No serious	No serious	No serious	Serious[2]	MODERATE	0.14	0.91
			Specificity: 0.56 (0.48 to 0.63)	No serious	No serious	No serious	Serious[2]	MODERATE		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NM: non-meningitis/septicaemia; NPV: negative predictive value; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined; VM: viral meningitis
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold

Table 7: White cell count (WCC) for diagnosis of meningococcal disease in an undefined age

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD VM NM Threshold: <4000 or ≥11000 x 10^9/l Reference standard: CBO	102	Sensitivity: 0.67 (0.52 to 0.79)	No serious	No serious	No serious	No serious	HIGH	0.54	0.56
			Specificity: 0.43 (0.29 to 0.58)	No serious	No serious	No serious	Serious[1]	MODERATE		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NM: non-meningitis/septicaemia; NPV: negative predictive value; O: other reference standard not specified in the review protocol; PPV: positive predictive value; VM: viral meningitis
[1] 95% CI crosses 1 decision making threshold

Table 8: Neutrophil count for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bourke 2015)	Population: MDU Threshold: <2 or >8 × 10⁹/l Reference standard: BP	148	Sensitivity: 0.85 (0.65 to 0.96)	No serious	No serious	No serious	Serious[1]	MODERATE	0.28	0.94
			Specificity: 0.52 (0.43 to 0.61)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Wells 2001)	Population: MDU Threshold: <2 or >7.5 × 10⁹/l Reference standard: CBP	211	Sensitivity: 0.63 (0.41 to 0.81)	No serious	No serious	No serious	Serious[1]	MODERATE	0.17	0.93
			Specificity: 0.62 (0.55 to 0.69)	No serious	No serious	No serious	No serious	HIGH		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined
[1] 95% CI crosses 1 decision making threshold

Table 9: C-reactive protein (CRP) for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV

1 (Bell 2015)	Population: MDU Threshold: >28mg/l Reference standard: CBP	519	Sensitivity: 0.74 (0.65 to 0.82)	No serious	No serious	No serious	No serious	HIGH	0.29	0.89
			Specificity: 0.54 (0.49 to 0.59)	No serious	No serious	No serious	Serious[1]	MODERATE		
			AUC: 0.83 (0.79 to 0.87)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Bourke 2015)	Population: MDU Threshold: >60mg/l Reference standard: BP	148	Sensitivity: 0.63 (0.42 to 0.81)	No serious	No serious	No serious	Serious[1]	MODERATE	0.61	0.92
			Specificity: 0.91 (0.84 to 0.95)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Marzouk 1993)	Population: MDVM NM Threshold: >60mg/l Reference standard: CBAO	151	Sensitivity: 0.71 (0.60 to 0.79)	Serious[2]	No serious	No serious	No serious	MODERATE	0.92	0.64
			Specificity: 0.89 (0.78 to 0.96)	Serious[2]	No serious	No serious	Serious[1]	LOW		
1 (Paize 2011)	Population: MDU Threshold: Undefined Reference standard: CBP	36	Sensitivity: 0.88 (0.68 to 0.97)	No serious	No serious	No serious	Serious[1]	MODERATE	0.91	0.77
			Specificity: 0.83 (0.52 to 0.98)	No serious	No serious	No serious	Serious[1]	MODERATE		

1 (Wells 2001)	Population: MD U Threshold: >6mg/l Reference standard: CBP	183	Sensitivity: 1.00 (0.80 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.18	1.00
			Specificity: 0.54 (0.46 to 0.62)	No serious	No serious	No serious	Serious[1]	MODERATE		

A: antigen detection; A: AUC: area under the curve; B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NM: non-meningitis/septicaemia; NPV: negative predictive value; O: other reference standard not specified in the review protocol; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined; VM: viral meningitis

[1] 95% CI crosses 1 decision making threshold

[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 10: C-reactive protein (CRP) for diagnosis of meningococcal disease in young adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bugden 2004)	Population: MD U Threshold: >20mg/l Reference standard: CBP	137	Sensitivity: 1.00 (0.54 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.09	1.00
			Specificity: 0.53 (0.44 to 0.61)	No serious	No serious	No serious	Serious[1]	MODERATE		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction; PPV: positive predictive value; U: undefined

[1] 95% CI crosses 1 decision making threshold

Table 11: C-reactive protein (CRP) for diagnosis of meningococcal disease in an undefined age

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD VM NM Threshold: >20mg/l Reference standard: CBO	68	Sensitivity: 0.81 (0.64 to 0.92)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.58	0.61
			Specificity: 0.34 (0.19 to 0.53)	Serious[1]	No serious	No serious	Serious[2]	LOW		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NM: non-meningitis/septicaemia; NPV: negative predictive value; O: other reference standard not specified in review protocol; PPV: positive predictive value; VM: viral meningitis
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold

Table 12: Procalcitonin (PCT) for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bell 2015)	Population: MDU Threshold: >1.93 ng/l Reference standard: CBP	671	Sensitivity: 0.89 (0.84 to 0.93)	No serious	No serious	No serious	Serious[1]	MODERATE	0.59	0.94
			Specificity: 0.74 (0.70 to 0.78)	No serious	No serious	No serious	No serious	HIGH		
			AUC: 0.95 (0.93 to 0.97)	No serious	No serious	No serious	No serious	HIGH		
1 (Paize 2011)	Population: MDU Threshold: >0.5 ng/l Reference standard: CBP	36	Sensitivity: 1.00 (0.86 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.92	1.00
			Specificity: 0.83 (0.52 to 0.98)	No serious	No serious	No serious	Serious[1]	MODERATE		

AUC: area under the curve; B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined
[1] 95% CI crosses 1 decision making threshold

Table 13: Procalcitonin (PCT) for diagnosis of meningococcal disease in young adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bugden 2004)	Population: MDU Threshold: >0.5 ng/l Reference standard: CBP	183	Sensitivity: 1.00 (0.66 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.32	1.00
			Specificity: 0.89 (0.83 to 0.93)	No serious	No serious	No serious	Serious[1]	MODERATE		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined
[1] 95% CI crosses 1 decision making threshold

Table 14: Loop-mediated isothermal amplification (LAMP) for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bourke 2015)	Population: MDU Threshold: NA Reference standard: BP	144	Sensitivity: 0.85 (0.65 to 0.96)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	0.97
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (McKenna 2011)	Population: MDU Threshold: NA Reference	213	Sensitivity: 1.00 (0.81 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.90	1.00

	standard: P		Specificity: 0.99 (0.96 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

B: blood culture; CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined

[1] 95% CI crosses 1 decision making threshold

Table 15: Platelet count for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Wells 2001)	Population: MD U Threshold: <150 × 10⁹/l Reference standard: CBP	203	Sensitivity: 0.25 (0.10 to 0.47)	No serious	No serious	No serious	No serious	HIGH	0.30	0.90
			Specificity: 0.92 (0.87 to 0.96)	No serious	No serious	No serious	Serious[1]	MODERATE		

B: blood culture; C: CSF culture; CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction (PCR); PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined

[1] 95% CI crosses 1 decision making threshold

Table 16: Combination of WCC and CRP for diagnosis of meningococcal disease in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bell 2015)	Population: MD U Threshold: CRP >28 mg/l and WCC >16 x 10⁹/l Reference standard: CBP	518	Sensitivity: 0.47 (0.37 to 0.57)	No serious	No serious	No serious	Serious[1]	MODERATE	0.37	0.86
			Specificity: 0.80 (0.76 to 0.84)	No serious	No serious	No serious	No serious	HIGH		

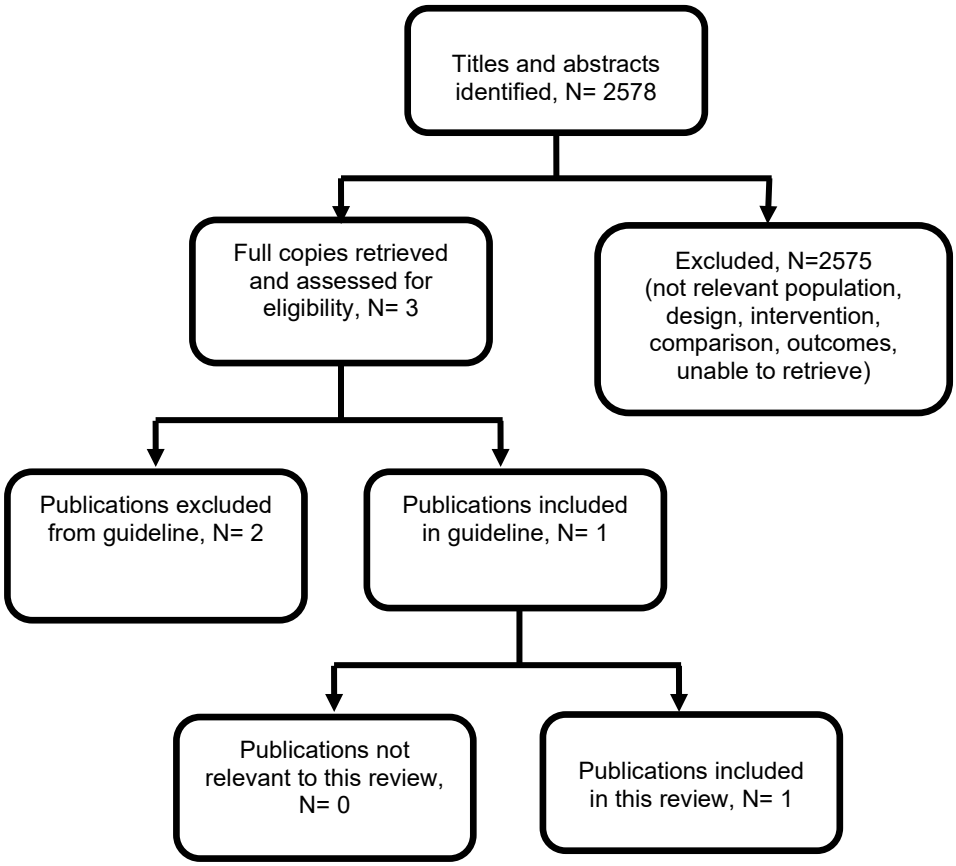
B: blood culture; C: CSF culture; CI: confidence interval; CRP: C-reactive protein; MD: meningococcal disease; NPV: negative predictive value; P: polymerase chain reaction (PCR); PPV: positive predictive value; U: undefined; WCC: white cell count

[1] 95% CI crosses 1 decision making threshold

Appendix G Economic evidence study selection

Study selection for: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Figure 13: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Table 17: Economic evidence tables

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Bell 2015 UK **Study type:** Cost-effectiveness analysis **Source of funding:** This study was supported by Improving Children's Lives Initiative, Queen's University Belfast and The Atlantic Philanthropies.	**Intervention** Procalcitonin test + standard testing (WCC + CRP) **Comparator:** Standard testing (WCC + CRP)	Children presenting with fever without source at the emergency department **Modelling approach:** Decision analysis **Source of baseline data:** Meta-analysis and summary point statistics of HSROC analysis **Source of effectiveness data:** Meta-analysis and summary point statistics of HSROC analysis **Source of resource use data:** Derived using meta-analysis of diagnostic test accuracy and Bourke (2010). **Source of unit cost data:** • NHS Reference Costs 2011-12	**Primary analysis** **Mean cost per participant:** **Intervention:** £3,477 **Control:** £3,062 **Difference:** -£415 **Primary measure of outcome:** Correct diagnosis **Mean outcome per participant** **Intervention:** 0.785 **Control:** 0.734 **Difference:** 0.051	**Primary analysis** **ICERs:** -£8,137 (PCT + standard testing dominates) **Sensitivity analysis:** *PCT max 2ng/ml:* PCT + standard testing dominates *PCT min 0.2ng/ml:* ICER: £2,330 *Combined CRP&WCC Max. 40mg/l & 15x10^9/l:* PCT + standard testing dominates *Combined CRP&WCC Min. 17.7mg/l & 14.1 x10^9/l*: PCT + standard testing dominates	**Currency:** GBP **Cost year:** 2011-12 **Time horizon:** <1 year **Discounting:** None (N/A) **Applicability:** Directly applicable **Limitations:** Potentially serious limitations **Other comments:** No probabilistic sensitivity analysis

HSROC = hierarchical summary receiver operating characteristic; ICER = incremental cost-effectiveness ratio; PCT = procalcitonin test

Appendix I Economic model

Economic model for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

Diagnostic studies

Table 18: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Alliluev, A. P, Koroleva, I. S, Vengerov, Yu Ya, Kotel'nikova, O. V et al. (1999) Latex agglutination test for rapid and retrospective diagnosis of meningococcal infection. Bulletin of Experimental Biology and Medicine 128(5): 1128-1131	- Country not of interest for review *Not a high-income OECD country*
Baethgen, L. F, Moraes, C, Weidlich, L et al. (2003) Direct-test PCR for detection of meningococcal DNA and its serogroup characterization: Standardization and adaptation for use in a public health laboratory. Journal of Medical Microbiology 52(9): 793-799	- Index test not of interest for review *CSF sample*
Bas Suarez, M. P, Sebastian Garcia, I, Mendoza Alamo, P et al. (2010) Febrile neonates: Reliability of low risk criteria for serious bacterial infection. Journal of Maternal-Fetal and Neonatal Medicine 1: 399	- Study design not of interest for review *Conference abstract*
Baspinar, E. O, Dayan, S, Bekcibasi, M et al. (2017) Comparison of culture and PCR methods in the diagnosis of bacterial meningitis. Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology] 48(2): 232-236	- Index test not of interest for review *Only CSF samples tested*
Benito, J, Luaces-Cubells, C, Mintegi, S et al. (2013) Lack of value of midregional pro-adrenomedullin and C-terminal pro-endothelin-1 for prediction of severe bacterial infections in infants with fever without a source. European Journal of Pediatrics 172(11): 1441-9	- Population does not meet inclusion criteria *0.8% with bacterial meningitis*
Bennett, D. E; Mulhall, R. M; Cafferkey, M. T. PCR-based assay for detection of Neisseria meningitidis capsular serogroups 29E, X, and Z. Journal of clinical microbiology 42(4): 1764-5	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Borrow, R, Claus, H, Guiver, M et al. (1997) Non-culture diagnosis and serogroup determination of meningococcal B and C infection by a sialyltransferase (siaD) PCR ELISA. Epidemiology & InfectionEpidemiol Infect 118(2): 111-7	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Borrow, R, Guiver, M, Sadler, F et al. (1998)	- Study design not of interest for review

Study	Reason for Exclusion
False positive diagnosis of meningococcal infection by the IS1106 PCR ELISA. FEMS Microbiology Letters 162(2): 215-218	*Not enough data to construct 2 x 2 tables for review*
Bourke, T. W; Fairley, D. J; Shields, M. D. (2010) Rapid diagnosis of meningococcal disease. Expert Review of Anti-Infective Therapy 8(12): 1321-1323	- Study design not of interest for review *Editorial*
Breeding, K. M, Ragipani, B, Lee, K. U. D et al. (2016) Real-time PCR-based serotyping of Streptococcus agalactiae. Scientific reports 6: 38523	- Population does not meet inclusion criteria *Population undefined (GBS infection)- no details whether population had meningitis or age of population*
Bromberger, P. I, Chandler, B, Gezon, H et al. (1980) Rapid detection of neonatal group B streptococcal infections by latex agglutination. Journal of pediatrics 96(1): 104-6	- Population does not meet inclusion criteria *Neonates*
Bronska, E, Dzupova, O, Krizova, P et al. (2005) Invasive meningococcal disease and latex agglutination test - Is it still beneficial for diagnosis?. Folia Microbiologica 50(5): 453-456	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Bronska, E, Kalmusova, J, Dzupova, O et al. (2006) Dynamics of PCR-based diagnosis in patients with invasive meningococcal disease. Clinical Microbiology and Infection 12(2): 137-141	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Browne, K; Miegel, J; Stottmeier, K. D. (1984) Detection of pneumococci in blood cultures by latex agglutination. Journal of clinical microbiology 19(5): 649-650	- Population does not meet inclusion criteria *Population undefined (septic pneumococcal episode)- no details whether population had meningitis*
Carcamo Yanez, V. A, Gopfert, J. C, Otto, M et al. (2017) Development and Validation of an Ultrasensitive Procalcitonin Sandwich Immunoassay. HighthroughputHigh-throughput 6(4): 16	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Chiu, I. M, Huang, L. C, Chen, I. L et al. (2019) Diagnostic values of C-reactive protein and complete blood cell to identify invasive bacterial infection in young febrile infants. Pediatrics and Neonatology 60(2): 197-200	- Population does not meet inclusion criteria *48% of population bacterial meningitis*
Clarke, S. C, Reid, J, Thom, L et al. (2001) Confirmation of meningococcal disease by urinary antigen testing. Clinical Microbiology and Infection 7(10): 565-567	- Reference standard not of interest for review *PCR urine*
Claxton, P. M and Masterton, R. G. (1994) Rapid organism identification from Bactec NR blood culture media in a diagnostic microbiology laboratory. Journal of Clinical Pathology 47(9): 796-8	- Reference standard not of interest for review *Blood culture*

Study	Reason for Exclusion
Congeni, B. L; Igel, H. J; Platt, M. S. (1984) Evaluation of a latex particle agglutination kit in pneumococcal disease. Pediatric infectious disease 3(5): 417-9	- Index test not of interest for review *Latex agglutination*
Coonrod, J. D and Rylko, Bauer (1976) Latex agglutination in the diagnosis of pneumococcal infection. Journal of clinical microbiology 4(2): 168-174	- Reference standard not of interest for review *LA of CSF*
Corless, C. E, Guiver, M, Borrow, R et al. (2001) Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. Journal of clinical microbiology 39(4): 1553-1558	- Study design not of interest for review *Insufficient data to construct 2 x 2 table*
Cruciani, M and Mengoli, C. (2009) An Overview of Meta-analyses of Diagnostic Tests in Infectious Diseases. Infectious Disease Clinics of North America 23(2): 225-267	- Study design not of interest for review *Review of diagnostic systematic review methods*
de Paz, H. D, Brotons, P, Esteva, C et al. (2020) Validation of a Loop-Mediated Isothermal Amplification Assay for Rapid Diagnosis of Invasive Pneumococcal Disease. Frontiers in Cellular and Infection Microbiology 10 (no pagination)	- Reference standard not of interest for review *PCR of various clinical samples (only 0.8% were of CSF)*
Deghmane, A. E; Hong, E; Taha, M. K. (2019) Diagnosis of Meningococcal Infection Using Internally Controlled Multiplex Real-Time PCR. Methods in Molecular BiologyMethods Mol Biol 1969: 17-31	- Study design not of interest for review *Editorial*
Demissie, D. E, Kaplan, S. L, Romero, J. R et al. (2013) Altered neutrophil counts at diagnosis of invasive meningococcal infection in children. Pediatric infectious disease journal 32(10): 1070-1072	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Dillon, J. R; Carballo, M; Pauze, M. (1988) Evaluation of eight methods for identification of pathogenic Neisseria species: Neisseria-Kwik, RIM-N, Gonobio-Test, Minitek, Gonochek II, GonoGen, Phadebact Monoclonal GC OMNI Test, and Syva MicroTrak Test. Journal of clinical microbiology 26(3): 493-7	- Population does not meet inclusion criteria *Population does not meet the inclusion criteria*
Doyle, C. J and Jennison, A. V. (2013) Novel real-time polymerase chain reactions for serogroup specific gene detection of Neisseria meningitidis serogroups B, C, W-135 and Y. Journal of Microbiological Methods 94(2): 83-85	- Index test not of interest for review *PCR of blood or CSF (distribution not reported)*
Ferguson, B. L. (1966) Significance of the blood white cell count in the diagnosis of hemophilus	- Study design not of interest for review

Study	Reason for Exclusion
influenzae meningitis. North Carolina medical journal (Durham, N.C.) 27(6): 286-287	*Case report*
Florea, D, Otelea, D, Bnica, L et al. (2012) PCR and mass spectrometry - A new diagnostic method for infectious diseases. Journal of Gastrointestinal and Liver Diseases 4: 44	- Study design not of interest for review *Conference abstract*
Fretzayas, A, Moustaki, M, Stefos, E et al. (2010) Differential diagnosis of meningococcal meningitis based on common clinical and laboratory findings: Are there criterion standards?. Infectious Diseases in Clinical Practice 18(4): 253-257	- Index test not of interest for review *Diagnostic data on signs and symptoms only*
Friedland, L. R, Menon, A. G, Reising, S. F et al. (1994) Development of a polymerase chain reaction assay to detect the presence of Streptococcus pneumoniae DNA. Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis 20(4): 187-93	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Friedman, C. A; Wender, D. F; Rawson, J. E. (1984) Rapid diagnosis of group B streptococcal infection utilizing a commercially available latex agglutination assay. Pediatrics 73(1): 27-30	- Population does not meet inclusion criteria *Neonates*
Gartzonika, C; Vrioni, G; Levidiotou, S. (2005) Evaluation of a commercially available reverse transcription-PCR enzyme immunoassay (Enterovirus Consensus kit) for the diagnosis of enterovirus central nervous system infections. Clinical Microbiology and Infection 11(2): 131-137	- Index test not of interest for review *Only CSF samples tested*
Ge, X; Li, P; Wu, Z. (2019) Clinical diagnostic value of combined detection of serum C-reactive protein and procalcitonin for bacterial infectious diseases in children. Journal of the College of Physicians and Surgeons Pakistan 29(2): 189-190	- Country not of interest for review *Not a high-income OECD country*
Gooch, Iii W. M. (1985) Immunologic diagnosis of infectious disease by antigen detection in urine. Journal of Medical Technology 2(12): 762-765	- Study design not of interest for review *Discussion paper*
Gunduz, A, Tekin, M, Konca, C et al. (2018) Effectiveness of Laboratory Markers in Determining Serious Bacterial Infection in Children with Fever without Source. Journal of Pediatric Infectious Diseases 13(4): 287-292	- Population does not meet inclusion criteria *Population does not meet the inclusion criteria*
Hanson, L. A, Jodal, U, Sabel, K. G et al. (1983) The diagnostic value of C-reactive protein. Pediatric infectious disease 2(2): 87-9	- Study design not of interest for review *Editorial*
Hatherill, M, Tibby, S.M, Sykes, K et al. (1999) Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and	- Population does not meet inclusion criteria *Diagnostic data available for serious bacterial*

Study	Reason for Exclusion
leucocyte count. Archives of Disease in Childhood 81(5): 417-421	*infection defined as a combined category of septic shock and bacterial meningitis (only 10% of which were bacterial meningitis)*
Hill, R. B, Adams, S, Gunn, B. A et al. (1994) The effects of nonclassic pediatric bacterial pathogens on the usefulness of the Directigen latex agglutination test. American Journal of Clinical Pathology 101(6): 729-732	- Index test not of interest for review *LA on CSF or urine (80% of bacterial meningitis group in urine; no details on comparator group)*
Hirvonen, J. J, Seiskari, T, Harju, I et al. (2015) Use of an automated PCR assay, the GenomEra S. pneumoniae , for rapid detection of Streptococcus pneumoniae in blood cultures. Infectious Diseases 47(11): 796-800	- Population does not meet inclusion criteria *Not meningococcal disease*
Hong, E, Barraud, O, Bidet, P et al. (2012) Proficiency of PCR in hospital settings for nonculture diagnosis of invasive meningococcal infections. Clinical Laboratory 58(03apr): 343-346	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Hoshina, T, Takimoto, T, Nanishi, E et al. (2015) The uselessness of procalcitonin in the diagnosis of focal bacterial central nervous system infection. Journal of infection and chemotherapy 21(8): 620-622	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Jordens, J. Z, Williams, J. N, Jones, G. R et al. (2002) Detection of meningococcal carriage by culture and PCR of throat swabs and mouth gargles. Journal of clinical microbiology 40(1): 75-79	- Population does not meet inclusion criteria *Meningococcal carriage in healthy volunteers*
Kalmusova, J; Bronska, E; Krizova, P. (2004) [Diagnostics of invasive meningococcal, haemophilus and pneumococcal disease by PCR assay]. Klinicka Mikrobiologie a Infekcni Lekarstvi 10(3): 130-3	- Non-English language article *Article in Czech/Slovak*
Kimura, K, Yanagisawa, H, Wachino, J et al. (2013) Rapid and reliable loop-mediated isothermal amplification method for detecting Streptococcus agalactiae. Japanese Journal of Infectious Diseases 66(6): 546-8	- Study design/index test not of interest for review *Development of LAMP method for GBS detection*
Kline, M. W, O'Brian Smith, E, Kaplan, S. L et al. (1988) Effects of causative organism and presence or absence of meningitis on white blood cell counts in children with bacteremia. Journal of emergency medicine 6(1): 33-35	- Insufficient presentation of results *Only mean/SD white blood cell counts of those with and without meningitis are reported*
Kohli, V, Singhi, S, Sharma, P et al. (1993) Value of serum C-reactive protein concentrations in febrile children without apparent focus. Annals of Tropical Paediatrics 13(4): 373-378	- Country not of interest for review *Not a high-income OECD country*
Koller, R. F, Barbani, M. T, Zurcher, S et al.	- Study design not of interest for review

Study	Reason for Exclusion
(2016) Expanding the spectrum of microbiological diagnostics by FilmArray multiplex PCR. Clinical Chemistry and Laboratory Medicine 54 (7): ea113	*Conference abstract*
Lai, C. C, Chen, S. Y, Wang, C. Y et al. (2010) Diagnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. Journal of the American Geriatrics Society 58(3): 518-522	- Country not of interest for review *Not a high-income OECD country*
Lorrot, M, Moulin, F, Coste, J et al. (2000) Procalcitonin in pediatric emergencies: comparison with C-reactive protein, interleukin-6 and interferon alpha in the differentiation between bacterial and viral infections. Presse medicale (paris, france : 1983) 29(3): 128-134	- Non-English language article *Article in French*
Luaces-Cubells, C, Mintegi, S, Garcia-Garcia, J.J et al. (2012) Procalcitonin to detect invasive bacterial infection in non-toxic-appearing infants with fever without apparent source in the emergency department. Pediatric Infectious Disease Journal 31(6): 645-647	- Population does not meet inclusion criteria *Invasive bacterial infection (only 50% were bacterial meningitis, no sub-group analysis conducted)*
Mandl, K.D; Stack, A.M; Fleisher, G.R. (1997) Incidence of bacteremia in infants and children with fever and petechiae. Journal of Pediatrics 131(3): 398-404	- Study design not of interest for review *Not diagnostic accuracy study*
Marcos, M. A, Martinez, E, Almela, M et al. (2001) New rapid antigen test for diagnosis of pneumococcal meningitis. Lancet 357(9267): 1499-1500	- Study design not of interest for review *Research letter*
Matos, J. D. A, Madureira, D. J, Rebelo, M. C et al. (2006) Diagnosis of Streptococcus pneumoniae meningitis by polymerase chain reaction amplification of the gene for pneumolysin. Memorias do Instituto Oswaldo Cruz 101(5): 559-563	- Country not of interest for review *Not a high-income OECD country*
Mauffrey, F, Fournier, E, Demczuk, W et al. (2017) Comparison of sequential multiplex PCR, sequetyping and whole genome sequencing for serotyping of Streptococcus pneumoniae. PLoS ONE [Electronic Resource]PLoS ONE 12(12): e0189163	- Study design not of interest for review *Comparison of different serotyping methods*
Milcent, K, Faesch, S, Guen, C. G. L et al. (2016) Use of Procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants. JAMA Pediatrics 170(1): 62-69	- Population does not meet inclusion criteria *Invasive bacterial illness (results for meningitis not reported separately and <50% of those with invasive bacterial illness had meningitis)*
Mills, G.D, Lala, H.M, Oehley, M.R et al. (2006) Elevated procalcitonin as a diagnostic marker in meningococcal disease. European Journal of Clinical Microbiology and Infectious Diseases	- Study included in systematic review *Included in Bell 2015*

Study	Reason for Exclusion
25(8): 501-509	
Mohamed, N, Elfaitouri, A, Fohlman, J et al. (2004) A sensitive and quantitative single-tube real-time reverse transcriptase-PCR for detection of enteroviral RNA. Journal of clinical virology 30(2): 150-156	- Index test not of interest for review *Only CSF samples tested*
Murphy, J, O'Rourke, S, Corcoran, M et al. (2018) Evaluation of the clinical utility of a real-time PCR assay for the diagnosis of streptococcus pneumoniae bacteremia in children: A retrospective diagnostic accuracy study. Pediatric infectious disease journal 37(2): 153-156	- Population does not meet inclusion criteria *Pneumococcal bacteraemia*
Newcombe, J, Cartwright, K, Palmer, W. H et al. (1996) PCR of peripheral blood for diagnosis of meningococcal disease. Journal of Clinical MicrobiologyJ Clin Microbiol 34(7): 1637-40	- Index test not of interest for review *No index test of interest (lab-based PCR)*
Nielsen, M, Sheikh, N, Fitzgerald, E et al. (2017) Screening for early-onset invasive group B Streptococcal disease in neonates in an Irish hospital (2001-2014): a retrospective audit. Infectious Diseases 49(6): 466-470	- Population does not meet inclusion criteria *Infants less than 28 days old without suspected bacterial meningitis*
Olaciregui Echenique, 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): 501-505	- Population does not meet inclusion criteria *Serious bacterial infection/unspecified sepsis/bacteraemia (results for meningitis or meningococcal disease not reported separately and unclear what proportion of those with serious bacterial infection/unspecified sepsis/bacteraemia these conditions accounted for)*
Payne, M, Champagne, S, Lowe, C et al. (2018) Evaluation of the filmarray blood culture identification panel compared to direct MALDI-TOF MS identification for rapid identification of pathogens. Journal of Medical Microbiology 67(9): 1253-1256	- Population does not meet inclusion criteria *Unclear what proportion, if any, of the sample had meningitis. Only the pathogens, and not the condition caused by them, are reported*
Petti, C. A; Woods, C. W; Reller, L. B. (2005) Streptococcus pneumoniae antigen test using positive blood culture bottles as an alternative method to diagnose pneumococcal bacteremia. Journal of clinical microbiology 43(5): 2510-2512	- Population does not meet inclusion criteria *Pneumococcal bacteraemia*
Picazo, J. J, Contreras, J. R, Rios, E et al. (2013) Rapid diagnosis of invasive pneumococcal disease in pediatric population. Journal of Microbiological Methods 93(2): 116-20	- Index test not of interest for review *Pleural and cerebrospinal fluid*
Rench, M. A; Metzger, T. G; Baker, C. J. (1984) Detection of group B streptococcal antigen in body fluids by a latex-coupled monoclonal antibody assay. Journal of clinical microbiology 20(5): 852-854	- Index test not of interest for review *Latex agglutination*

Study	Reason for Exclusion
Richardson, D. C, Louie, L, Louie, M et al. (2003) Evaluation of a rapid PCR assay for diagnosis of meningococcal meningitis. Journal of clinical microbiology 41(8): 3851-3853	- Index test not of interest for review *Only CSF samples tested*
Saha, S. K, Darmstadt, G. L, Yamanaka, N et al. (2005) Rapid diagnosis of pneumococcal meningitis: Implications for treatment and measuring disease burden. Pediatric infectious disease journal 24(12): 1093-1098	- Country not of interest for review *Not a high-income OECD country*
Sheppard, C. L, Harrison, T. G, Kearns, A. M et al. (2003) Diagnosis of invasive pneumococcal infection by PCR amplification of Streptococcus pneumoniae genomic fragments in blood: a multi-centre comparative study. Communicable disease and public health / PHLS 6(3): 221-227	- Population does not meet inclusion criteria *Pneumococcal pneumonia*
Smith, M. D, Derrington, P, Evans, R et al. (2003) Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW Streptococcus pneumoniae urinary antigen test: A prospective, controlled clinical evaluation. Journal of clinical microbiology 41(7): 2810-2813	- Population does not meet inclusion criteria *Pneumococcal bacteraemia*
Smith, M. D, Sheppard, C. L, Hogan, A et al. (2009) Diagnosis of Streptococcus pneumoniae infections in adults with bacteremia and community-acquired pneumonia: Clinical comparison of pneumococcal PCR and urinary antigen detection. Journal of clinical microbiology 47(4): 1046-1049	- Population does not meet inclusion criteria *Pneumococcal bacteraemia*
Su, G, Fu, Z, Hu, L et al. (2015) 16S ribosomal ribonucleic acid gene polymerase chain reaction in the diagnosis of bloodstream infections: A systematic review and meta-analysis. PloS one 10 (5)	- Population does not meet inclusion criteria *Unspecified sepsis/bacteraemia/bloodstream infections. Checked included studies. No new studies identified*
Tansarli, G. S and Chapin, K. C. (2020) Diagnostic test accuracy of the BioFire FilmArray meningitis/encephalitis panel: a systematic review and meta-analysis. Clinical Microbiology and Infection 26(3): 281-290	- Index test not of interest for review *BioFire FilmArray on CSF*
Trippella, G, Galli, L, De Martino, M et al. (2017) Procalcitonin performance in detecting serious and invasive bacterial infections in children with fever without apparent source: a systematic review and meta-analysis. Expert Review of Antiinfective TherapyExpert Rev Anti Infect Ther 15(11): 1041-1057	- Reference standard not of interest for review *No comparator of interest*
Tzanakaki, G, Tsolia, M, Vlachou, V et al. (2003) Evaluation of non-culture diagnosis of invasive meningococcal disease by polymerase chain reaction (PCR). FEMS Immunology and Medical	- Index test not of interest for review *Lab-based PCR*

Study	Reason for Exclusion
Microbiology 39(1): 31-36	
Van Den Bruel, A, Thompson, M. J, Haj-Hassan, T et al. (2011) Diagnostic value of laboratory tests in identifying serious infections in febrile children: Systematic review. BMJ 342(7810): d3082	- Population does not meet inclusion criteria *Serious infection (includes mixed population of which meningitis is included, no proportion breakdown)*
Wakhle, L and Saigal, S. R. (1997) Rapid and specific diagnosis of group B streptococcal infection by the polymerase chain reaction (PCR). Advances in Experimental Medicine & BiologyAdv Exp Med Biol 418: 347-9	- Study design not of interest for review *Discussion paper*
Waterfield, T, Fairley, D, Blackwood, B et al. (2019) A systematic review of the diagnostic accuracy of Loop-mediated-isothermal AMPlification (LAMP) in the diagnosis of invasive meningococcal disease in children. BMC PediatricsBMC Pediatr 19(1): 49	- Country not of interest for review *Includes studies from countries that are not high-income OECD countries. No new relevant studies identified*
Waterfield, T, Lyttle, M. D, McKenna, J et al. (2020) Loop-mediated isothermal amplification for the early diagnosis of invasive meningococcal disease in children. Archives of Disease in Childhood.	- Index test not of interest for review *LAMP on oropharynx swab*
Waterfield, T, Maney, J. A, Lyttle, M. D et al. (2020) Diagnostic test accuracy of point-of-care procalcitonin to diagnose serious bacterial infections in children. BMC Pediatrics 20 (1)	- Population does not meet inclusion criteria *Serious bacterial infection (10% diagnosed as bacterial meningitis)*
Waterfield, T, Patenall, B, McKenna, J et al. (2017) 52 Loop-mediated isothermal amplification PCR (LAMP) for the rapid identification of invasive meningococcal disease in the emergency department. Emergency medicine journal : EMJ 34(12): a895	- Study design not of interest for review *Conference abstract*
Webb, B. J and Baker, C. J. (1980) Commercial latex agglutination test for rapid diagnosis of group B streptococcal infection in infants. Journal of clinical microbiology 12(3): 442-444	- Index test not of interest for review *LA in CSF*
Wood, A. L and Gill, M. J. (2001) PCR and the investigation of meningococcal infection. Epidemiology and Infection 127(2): 269-274	- Index test not of interest for review *No index test of interest*

CSF: cerebrospinal fluid; LA: latex agglutination; PCR: polymerase chain reaction; PCT: procalcitonin; OECD: Organisation for Economic Co-operation and Development; RCT: randomised controlled trial

Excluded economic studies

No studies were identified which were applicable to this review question.

Appendix J Research recommendations – full details

Research recommendations for review question: What is the accuracy and effectiveness of blood and urine investigations in diagnosing meningococcal disease?

No research recommendation was made for this review.