National Institute for Health and Care Excellence

Final

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

[B1] Evidence review for investigating and diagnosing suspected bacterial meningitis with blood and urine investigations

NICE guideline NG240

Evidence review underpinning recommendations 1.4.2 to 1.4.5 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Investigating and diagnosing suspected bacterial meningitis with blood and urine investigations

Review question

What is the accuracy and effectiveness of blood and urine investigations in diagnosing bacterial meningitis?

Introduction

Bacterial meningitis 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 bacterial meningitis in a timely manner ensures that appropriate antibiotic therapy can be initiated, and subsequently adjusted according to the bacterial aetiology and antibiotic sensitivity results. There are a number of tests that may be used to assist in the diagnosis of bacterial meningitis. 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 (B1) is to evaluate these tests and determine which are the most effective for the diagnosis of bacterial meningitis.

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 bacterial meningitis
Index tests	Use of the following investigations, individually or in combination: **Blood** white cell count neutrophil count C-reactive protein (CRP) procalcitonin molecular diagnosis for bacterial pathogens blood culture for bacterial pathogens **Urine** Antigen detection for bacterial pathogens
Reference standard	Either of the following, alone or in combination: Cerebrospinal fluid (CSF) bacterial culture Molecular diagnosis in the CSF for bacterial pathogens
Target condition	Bacterial meningitis (including meningococcal meningitis alone)

CRP: c-reactive protein; CSF: cerebrospinal fluid

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

Twenty five studies were included in this review, 15 single-gate cross-sectional diagnostic accuracy (DTA) studies (Benjamin 1984, Bonsu 2003, Borchsenius 1991, Hansson 1993, Knudsen 2007, Lembo 1991a, Lembo 1991b, Morales Casado 2016, Peltola 1982, Ray 2007, Roine 1991, Santotoribo 2018, Schwarz 2000, Tzanakaki 2015, Viallon 2011), 3 single-gate retrospective DTA studies (De Cauwer 2007, Dubos 2008, Morrissey 2017), and 7 two-gate cross-sectional DTA studies (Dagan 1998, Dubos 2006, Jereb 2001, Paradowski 1995, Park 2011, Sormunen 1999, Tatara 2000). No evidence from test and treat randomised controlled trials were identified.

The included studies are summarised in Table 2.

Two studies included babies only (Bonsu 2003, Morrissey 2017); 11 studies included babies and children (Benjamin 1984, Dagan 1998, De Cauwer 2007, Dubos 2006, Dubos 2008, Lembo 1991a, Lembo 1991b, Peltola 1982, Roine 1999, Sormunen 1999, Tatara 2000); 4 studies included children and adults (Hansson 1993, Knudsen 2007, Morales Casado 2016, Santotoribo 2018); 6 studies included adults (Jereb 2001, Paradowski 1995, Park 2017, Ray 2007, Schwarz 2000, Viallon 2011); and 2 studies did not define the age range of participants (Borchsenius 1991, Tzanakaki 2005).

Seven studies looked at the DTA of white cell count (WCC; Bonsu 2003, Borchsenius 1991, Dubos 2006, Dubos 2008, Lembo 1991a, Lembo 1991b, Sormunen 1999); 2 studies looked at the DTA for neutrophil count (Dubos 2006, Dubos 2008); 19 studies looked at the DTA of C-reactive protein (CRP; Benjamin 1984, Borchsenius 1991, De Cauwer 2007, Dubos 2006, Dubos 2008, Hansson 1993, Jereb 2001, Knudsen 2007, Lembo 1991b, Morales Casado 2016, Paradowski 1995, Peltola 1982, Ray 2007, Roine 1991, Santotoribo 2018, Schwarz 2000, Sormunen 1999, Tatara 2000, Viallon 2011); 10 studies looked at the DTA of procalcitonin (PCT; Dubos 2006, Dubos 2008, Jereb 2001, Knudsen 2007, Morales Casado 2016, Park 2017, Ray 2007, Santotoribo 2018, Schwarz 2000, Viallon 2011); and 3 studies looked at molecular diagnosis for bacterial pathogens, specifically the DTA of polymerase chain reaction (PCR) for Neisseria meningitides (Tzanakaki 2005), Streptococcus pneumonia (Dagan 1998, Tzanakaki 2005), Group B streptococcus (Morrissey 2017) and Haemophilus influenza (Tzanakaki 2005). There was no evidence identified for antigen detection for bacterial pathogens in urine, blood culture of bacterial pathogens or any molecular diagnosis techniques apart from PCR.

Six studies used cerebrospinal fluid (CSF) culture as the reference standard (Benjamin 1984, Bonsu 2003, Morrissey 2017, Sormunen 1999, Tatara 2000, Viallon 2011); 2 studies used CSF culture and/or antigen for bacterial pathogens (Hansson 1993, Morales Casado 2016); 6 studies used CSF culture and/or CSF antigen for bacterial pathogens and/or other reference standard not listed in protocol including other CSF findings (Knudsen 2007, Lembo 1991a, Lembo 1991b, Paradowski 1995, Park 2017, Santotoribo 2018); 2 studies used CSF culture and/or CSF antigen and/or blood culture (Dubos 2006, Dubos 2008); 1 study used CSF cultures and/or CSF antigen and/or blood culture and/or other CSF findings (Ray 2007); 4 studies used CSF culture and/or blood culture (Dagan 1998, Peltola 1982, Roine 1991,

Tzanakaki 2005); and 4 studies used CSF culture and/or blood culture and/or other reference standard not listed in protocol including other CSF findings as the reference standard (Borchsenius 1991, De Cauwer 2007, Jereb 2001, Schwarz 2000).

Seventeen studies compared people with bacterial meningitis to those with viral meningitis (De Cauwer 2007, Dubos 2006, Dubos 2008, Hansson 1993, Jereb 2001, Morales Casado 2016, Paradowski 1995, Park 2017, Peltola 1982, Ray 2007, Roine 1991, Santotoribo 2018, Schwarz 2000, Sormunen 1999, Tatara 2000, Tzanakaki 2005, Viallon 2011). For 5 studies, the comparison was between those with bacterial meningitis and a mixed comparison group including both those without meningitis and those with other types of meningitis (Benjamin 1984, Borchsenius 1991, Knudsen 2007, Lembo 1991a, Lembo 1991b). One study compared a bacterial meningitis group to a mixed comparison group including those with non-meningitis illnesses and healthy controls (Dagan 1998). For 2 studies the comparison was between people with bacterial meningitis and an undefined non-bacterial meningitis control group (Bonsu 2003, Morrissey 2017).

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
Benjamin 1984 Single-gate cross-sectional DTA study USA	N=79 CSF samples submitted to laboratory during study period, including all cases of bacterial and viral meningitis Bacterial meningitis n=21: Age/sex not reported by arm Viral meningitis (n=8)/no meningitis (n=50) n=58: Age/sex not reported by arm	CRP Elevated threshold defined as >1mg/dL (converted to mg/l for consistency with other studies)	CSF bacterial culture	Sensitivity Specificity	Causative organisms: n=14 H. influenzae type b, n=2 S. pneumoniae, n=3 N. meningitidis, n=1 M. tuberculosis, n=1 Salmonella species n=40 with leukaemia excluded from the analysis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Whole sample (N=79): Age (range): 1 week-18 years (mean/median not reported)				
Bonsu 2003 Single-gate cross-sectional DTA study USA	N=5353 Babies evaluated for serious bacterial infection in the ED (presenting with a temperature ≥ 38°C) Bacterial meningitis (n=22): Age and sex not reported for BM group Non-bacterial meningitis (5331): No further details reported for control group Whole sample (N=5353): Age in days (range): 3-89 (mean/median not reported)	WCC Elevated threshold defined as ≥15000 cells/mm³ (converted to cells/µl for consistency with other studies)	CSF bacterial culture	Sensitivity Specificity	Causative organisms: n= 11 E. coli, n=9 group B streptococcus, n=1 S. pneumoniae, n=1 C. koseri Data also reported for WCC thresholds of <5000, ≥10000, ≥20000, ≥25000, <5000 or ≥15000, and <5000 or ≥20000 cells/mm³, but data only extracted for the ≥15000 threshold as this is most consistent with other studies
Borchsenius 1991 Single-gate cross-sectional DTA study Norway	N=92 People with suspected systemic meningococcal disease admitted to hospital (those with meningitis only are included in this review, and those with septicaemia or	CRP Elevated threshold defined as ≥20 mg/l WCC Threshold defined as <4,000 or ≥11,000 cells/mm³ (converted to cells/µl for consistency with other	CSF and/or blood culture, clinical picture, meningococcal antigen in CSF, or growth of N. meningitidis in pharyngeal swab specimens	Sensitivity Specificity	Study includes patients without bacteriological proof (N=44, 38% of the full sample that includes those with meningococcal disease)

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	meningitis and septicaemia are included in the review on blood and urine investigations for meningococcal disease) Meningococcal meningitis (n=56): Age: Reported for whole sample only (including those with meningococcal disease); Mean/median not reported; 50% aged < 12 years No meningococcal or bacterial infection (n=36): Age: Reported for whole sample only (including control participants not included in this review; Mean/median not reported; 79% aged < 12 years	studies)			
Dagan 1998 Two-gate cross-sectional DTA study Israel	N=281 Babies and children with meningitis and other conditions recruited from the ED. Healthy controls recruited from Maternal Child Health Centres	<u>Molecular diagnosis</u> Specific PCR for S. pneumoniae	CSF and serum culture for pneumococcal isolates	Sensitivity Specificity	

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	(primary care) Pneumococcal meningitis n= 4: Age/sex not reported by arm No meningitis (n=75)/ healthy controls (n=202) n=277: Age/sex not reported by arm Whole sample (N=281): Age (range): 10 months to 16 years				
De Cauwer 2007 Single-gate retrospective DTA study Belgium	N=92 Children (0-15 years old) admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of viral or bacterial meningitis Bacterial meningitis (n=21): Age in years (mean; range in parentheses): 3.9 (0-13) Sex: male 12 (57%); female: 9 (43%) Viral meningitis (n=71): Age in years (mean; range	CRP Elevated threshold defined as ≥2mg/L	CSF culture or pleocytosis in the CSF and a positive blood culture for a bacterial disease	Sensitivity Specificity	Bacterial aetiology: Meningococcal meningitis (n=16; 76%); pneumococcal meningitis (n=5; 24%) CSF cultures were positive in 14/21 and negative in 7/21

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	in parentheses): 6.1 (0-15) Sex: male 46 (65%); female: 25 (35%)				
Dubos 2006 Two-gate cross-sectional DTA study France	N=167 Children (aged 28 days to 16 years) admitted to hospital with a diagnosis of acute meningitis Children with BM admitted to hospital 1995-2004 compared to children admitted to hospital with VM 2000-2004 Bacterial meningitis n=21: Age/sex not reported by arm Viral meningitis n=146: Age/sex not reported by arm Whole sample (N=167): Age in years (median; range in parentheses): 4.6 (0.2-14.9) Sex: male: 117 (70%); female: 50 (30%)	PCT Elevated threshold defined as ≥0.5 ng/ml CRP Elevated threshold defined as ≥20mg/L WCC Elevated threshold defined as ≥15000/mm³ (converted to cells/µl for consistency with other studies) Neutrophils Elevated threshold defined as ≥10000/mm³ (converted to cells/µl for consistency with other studies)	Bacterial infection in CSF (direct examination, culture, latex agglutination, or PCR) or blood culture	Sensitivity Specificity	Causative organism: n=10 S. pneumonia, n=9 N. meningitidis, n=1 H. influenzae b, n=1 Streptococcus group B
Dubos 2008 Single-gate retrospective	N=198 People aged 29 days to 18 years who	WCC Elevated threshold defined as ≥15000/mm³	Bacterial infection in CSF (direct examination, culture,	Sensitivity Specificity	Causative organisms: n=45 N. meningitidis, n=32 S. pneumoniae, n=7

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
DTA study 5 European countries (France, Spain, Switzerland, Turkey, & Poland)	were admitted for bacterial or viral meningitis and had measurements of the main inflammatory markers (including PCT) in blood and CSF taken in the ED Bacterial meningitis n=96: Age in years (mean; range in parentheses): 3.2 (0.1-14) Viral meningitis n=102: Age not reported for this arm separately Whole sample (N=198): Age in years (mean; range in parentheses): 4.8 (0.1-15.9)	(converted to cells/µl for consistency with other studies) <u>Neutrophils</u> Elevated threshold defined as ≥10000/mm³ (converted to cells/µl for consistency with other studies) <u>CRP</u> Elevated threshold defined as ≥20 mg/l <u>PCT</u> Elevated threshold defined as ≥0.5 ng/ml	latex agglutination, or PCR) or blood culture		H. influenzae, n=4 S. agalactiae 76/96 (79%) diagnosed on the basis of positive CSF culture
Hansson 1993 Single-gate cross-sectional DTA study Sweden	N=206 Children and adults undergoing lumbar puncture due to suspected CNS infection Bacterial meningitis n=60: Age/sex not available Viral meningitis n=146:	<u>CRP</u> Elevated threshold defined as ≥50 mg/l	CSF culture or bacterial antigen in CSF	Sensitivity Specificity	Causative organisms: not reported Total of 235 patients enrolled but 2x2 table can only be calculated based on those with bacterial meningitis (n=60) and those with viral meningitis (n=146) due to insufficient presentation of results

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Age/sex not available				
Jereb 2001 Two-gate cross-sectional DTA study Slovenia	N=45 Adults admitted to hospital with bacterial meningitis compared to adults admitted with viral meningitis (tick-borne encephalitis) Bacterial meningitis n=20: Age in years (median; range in parentheses): 55 (16-77) Sex: male: 9 (45%); female: 11 (55%) Viral meningitis (tick-borne encephalitis) n=25: Age in years (median; range in parentheses): 49 (22-66) Sex: male: 13 (52%); female: 12 (48%)	CRP Elevated threshold defined as ≥50mg/L PCT Elevated threshold defined as ≥0.5 ng/ml	CSF and/or blood culture or CSF gram-stained smear	Sensitivity Specificity	Causative organisms: n=9 S. pneumonia, n=4 Staphylococcus aureus, n=2 Listeria monocytogenes, n=2 N. meningitides, n=1 H. influenzae b, n=1 Clostridium perfringens, n=1 CSF and blood cultures negative but positive Gram smear (gram positive cocci)
Knudsen 2007 Single-gate cross-sectional DTA study Denmark	N=52 People suspected of meningitis on admission to hospital, who received a lumbar puncture Bacterial meningitis n=10: Age/sex not	CRP Elevated threshold defined as ≥40 mg/l PCT Elevated threshold defined as ≥0.25 ng/ml	>800 leukocytes/l of which >80% are neutrophilic granulocytes in CSF and/or CSF culture or bacterial antigens in CSF	Sensitivity Specificity	Causative organism: n=5 pneumococci; n=3 meningococci; n=1 E.coli; n=1 unknown n=21 had antibiotic treatment before LP (median time for initiation of antibiotic treatment prior to

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	reported by arm Viral meningitis (n=12)/no meningitis (n=30) n=42: Age/sex not reported by arm Whole sample (N=52): Age in years (median; range in parentheses): 36.1 (12.8-92.3) Sex: male: 25 (48%); female: 27 (52%)				LP: 1 day, range 0-6 day)
Lembo 1991a Single-gate cross-sectional DTA study USA	N=232 (included in analysis) Babies and children with suspected meningitis who had lumbar puncture Bacterial meningitis n=46: Age in months (median; range in parentheses): 11 (0-157) Sex: male: 28 (61%); female: 18 (39%) Viral meningitis/no meningitis n=186: Viral meningitis n=130: Age in months (median; range in parentheses):	<u>WCC</u> Elevated threshold defined as ≥ 15,000/mm³ (converted to cells/µl for consistency with other studies)	CSF culture or bacterial antigen in CSF or urine in combination with CSF pleocytosis and a positive gram strain of CSF	Sensitivity Specificity	Causative organism: n=29 H. influenza type b; n=6 S. pneumoniae; n=3 N. meningitidis; n=3 streptococcus group b; n=2 streptococcus group a; n=1 listeria monocytogenes; n=1 E. coli; n=1 P. mirabilis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	2 (0-219) Sex: male: 69 (53%); female: 61 (47%) No meningitis n=56: Age in months (median; range in parentheses): 6.5 (0-79) Sex: male: 25 (45%); female: 31 (55%)				
Lembo 1991b Single-gate cross-sectional DTA study USA	N=160 Babies and children presenting with an acute febrile episode who had a lumbar puncture Bacterial meningitis n=10: Age/sex not reported by arm Viral meningitis/no meningitis n=150: Viral meningitis n=14; other bacterial infection n=10; other illnesses n=126 Age/sex not reported by arm Whole sample (N=160): Age in months (median; no measure of variance reported): 60 Sex: male: 84 (52.5%);	<u>WCC</u> Elevated threshold defined as ≥ 15,000/mm³ (converted to cells/µl for consistency with other studies) <u>CRP</u> Elevated threshold defined as >1mg/dl (converted to mg/l for consistency with other studies)	CSF culture or bacterial antigen in combination with a positive gram strain of CSF	Sensitivity Specificity	Causative organism: n=5 H. influenza type b, n=3 S. pneumoniae, n=1 group A streptococci, n=1 listeria monocytogenes

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	female: 76 (47.5%)				
Morales Casado 2016 Single-gate cross-sectional DTA study Spain	N=71 People aged >15 years old with acute meningitis who underwent lumbar punctures, blood culture tests, CRP and PCT Bacterial meningitis n=38: Age in years (mean; SD in parentheses): 56 (22) Sex: male: 28 (74%); female: 10 (26%) Viral meningitis n=33: Age in years (mean; SD in parentheses): 38 (16) Sex: male: 20 (61%); female 13 (39%)	CRP Elevated threshold defined as ≥90 mg/l PCT Elevated threshold defined as ≥0.74 ng/ml	CSF culture or bacterial antigen in CSF	Sensitivity Specificity AUC	Causative organism: n=18 S. pneumoniae; n=7 N. meningitidis; n=7 L. monocytogenes; n=4 H. influenzae; n=2 E. coli Data for n=27 not included in analysis: n=15 probable VM with negative results from cultures; n=12 presumptively diagnosed partially-treated acute meningitis (history of antibiotic treatment and negative results from cultures) Immunosuppression: 5/38 (13%) in BM group; 1/33 (3%) in VM group Antibiotic use in previous 72 hours: 4/38 (11%) in BM group; 4/33 (12%) in VM group
Morrissey 2017 Single-gate retrospective DTA study Ireland	N=827 (data only included for those with CSF samples) Babies (aged 7–90 days) that had a blood or CSF sample tested by GBS PCR Bacterial meningitis n=5: Age/sex not	Molecular diagnosis Specific PCR for group B streptococcus	CSF culture	Sensitivity Specificity	Causative organism: n=5 late onset group B streptococcal (GBS) disease

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	reported by arm Non-GBS group n=822: No further details reported Whole sample (N=827): Age in days (median; IQR in parentheses): 35 (20.75-57) Sex: male: 478 (58%); female: 340 (41%)				
Paradowski 1995 Two-gate cross-sectional DTA study Poland	N=60 Adults hospitalised with acute meningitis Bacterial meningitis n=30: Age in years (mean; range in parentheses): 49 (19-82) Sex: male: 22 (73%); female: 8 (27%) Viral meningitis n=30: Age in years (mean; range in parentheses): 38 (23-75) Sex: male: 16 (53%); female: 14 (47%)	CRP Elevated threshold defined as >40 mg/l	CSF culture, bacterial antigen in CSF, or clinical picture	Sensitivity Specificity	Causative organism: n=10 N. meningitidis; n=7 S. pneumoniae; n=4 H. influenzae; n=3 Streptococcus group B; n=3 Streptococcus aureus; n=1 Pseudomonas aeruginosa; n=2 bacteria not identified Study also included healthy controls but data is not extractable for this group The majority of BM cases (93%) were confirmed through microbiological techniques
Park 2017 Two-gate cross-sectional DTA study	N=138 Adults admitted to hospital with a clinical	PCT Elevated threshold defined as >0.12 ng/ml	CSF culture, smear, or PCR for bacterial pathogens or good	Sensitivity Specificity	Causative organism identified (n=47): n=24 streptococcus species; n=8 staphylococcus

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
Korea	suspicion of bacterial meningitis compared to those admitted with viral meningitis during a similar time period Bacterial meningitis n=80 Age in years (median; IQR in parentheses): 66 (16-91) Sex: male: 49 (61%); female: 31 (39%) Viral meningitis n=58 Age in years (median; IQR in parentheses): 37 (15-81) Sex: male: 30 (52%); female: 28 (48%)		specific response to antibacterial therapy, clinical features, or other positive CSF findings		species; n=6 klebsiella species; n=5 listeria species; n=4 other species 47/80 (59%) had positive CSF culture, smear, or PCR for bacterial pathogens
Peltola 1982 Single-gate cross-sectional DTA study Finland	N=31 Babies and children diagnosed with bacterial meningitis, viral meningitis, or meningoencephalitis Bacterial meningitis n=16: Age in years (mean; standard deviation in parentheses): 1.69 (1.97) Sex not	CRP Elevated threshold defined as ≥10mg/l	CSF culture and/or blood culture	Sensitivity Specificity	Causative organism: n=11 H. influenzae; n=2 meningococci; n=2 pneumococci; n=1 ß-haemolytic streptococcus n=2 adults in viral illness group but study categorised as babies and children as all other participants aged 0.04-9 years

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	reported Viral illness n=15: n=14 viral meningitis or meningoencephalitis; n=1 encephalitis Age in years (mean; standard deviation in parentheses): 8.24 (14.01) Sex not reported				
Ray 2007 Single-gate cross-sectional DTA study France	N=151 Adults (aged at least 16 years) presenting to the emergency department and hospitalised with acute meningitis, with initial gram staining negative for bacteria Bacterial meningitis n=18: Age in years (mean; SD in parentheses): 52 (20) Sex: male: 9 (50%); female: 9 (50%) Viral meningitis n=133: Age in years (mean; SD in parentheses): 33 (13) Sex: male: 66 (50%); female: 67 (50%)	PCT Elevated threshold defined as ≥2.13 ng/ml CRP Elevated threshold defined as ≥22 mg/l	CSF culture, CSF antigen test or blood culture, or CSF pleocytosis	Sensitivity Specificity AUC	Causative organism: n=4 Streptococcus species other than pneumonia; n=2 S. pneumoniae; n=2 N. meningitidis; n=1 Fusobacterium; n=1 Klebsiella pneumoniae; n=1 Mycobacterium tuberculosis; n=7 unknown 61% of diagnoses made on a positive CSF culture, antigen test or blood culture n=2 HIV positive, and n=2 daily steroid treatment Previous antibiotics: 4/18 (23%) in BM group; 8/133 (6%) in VM group
Roine 1991	N=83	CRP Elevated	CSF culture or blood	Sensitivity Specificity	Causative organism: n=31

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
Single-gate cross-sectional DTA study Chile	Babies and children diagnosed with bacterial or viral meningitis Bacterial meningitis n=67: Age in months (mean; SD in parentheses): 23 (34) Sex not reported Viral meningitis n=16: Age in months (mean; SD in parentheses): 24 (32) Sex not reported	threshold defined as ≥20 mg/l	culture		H. influenzae type b; n=18 S. pneumoniae; n=10 N. meningitidis; n=4 beta haemolytic streptococcus B; n=1 enterococcus; n=1 staphylococcus aureus; n=1 klebsiella pneumonia Diagnosis made on basis of CSF culture for 60/67 (90%)
Santotoribo 2018 Single-gate cross-sectional DTA study Spain	N=30 Children and adults diagnosed with bacterial or viral meningitis Bacterial meningitis n=18 Age/sex not reported by arm Viral meningitis n=12 Age/sex not reported by arm Whole sample (N=30): Age in years (median; range in parentheses): 52 (6-86) Sex: male: 24	CRP Elevated threshold defined as ≥14mg/l PCT Elevated threshold defined as ≥0.18 ng/ml	CSF culture, or signs/symptoms of acute infectious meningitis together with CSF showing intense PMN pleocytosis, elevated total protein and a marked glucose consumption	Sensitivity Specificity AUC	Causative organism (identified for 10/18): n=3 S. pneumoniae; n=2 N. meningitidis; n=2 Klebsiella pneumoniae; n=2 Staphylococcus aureus; n=1 Staphylococcus hominis Diagnosis made on basis of CSF culture for 10/18 (56%)

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	(80%); female: 6 (20%)				
Schwarz 2000 Single-gate cross-sectional DTA study Germany	N=30 Adults (aged at least 16 years) hospitalised with acute meningitis Bacterial meningitis n=16 Age in years (mean; range in parentheses): 61 (16-87) Sex not reported Viral meningitis n=14 Age in years (mean; range in parentheses): 42 (19-48) Sex not reported	PCT Elevated threshold defined as >0.5ng/ml CRP Elevated threshold defined as >8mg/l	Microscopy of CSF, CSF culture, or blood culture	Sensitivity Specificity	Causative organism (identified in 11/16): n=6 S. pneumoniae; n=1 H. influenzae; n=1 Staphylococcus aureus; n=1 mycobacterium tuberculosis; n=1 borrelia burgdorferi; n=1 klebsiella pneumonia Diagnosis made on basis of CSF culture for 11/16 (69%)
Sormunen 1999 Two-gate cross-sectional DTA study Finland	N=237 Babies and children with bacterial meningitis with initial gram staining negative for bacteria, compared to children diagnosed with viral meningitis during a similar time period (hospital charts reviewed) Bacterial meningitis n=55 (gram stain	WCC Elevated threshold defined as >15,0000 cells/mm³ (converted to cells/µl for consistency with other studies) CRP Elevated threshold defined as >20 mg/l	CSF culture	Sensitivity Specificity	Causative organism: n=26 N. meningitidis; n=23 H. influenzae type b; n=3 S. pneumoniae; n=1 Listeria monocytogenes; n=1 E. coli; n=1 S. agalactiae Paper also reports WCC thresholds of >20,000 and >25,000 cells/mm³, but data only extracted for the >15,0000 threshold as this is consistent with other studies

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	negative): Age/sex not available for those included in the analysis Viral meningitis n=182: Age/sex not available				Paper also reports CRP for threshold >40mg/l, but data only extracted for the >20 mg/l threshold, as this is most consistent with other studies
Tatara 2000 Two-gate cross-sectional DTA study Japan	N=192 Babies and children (aged 1 month to 15 years) with a diagnosis of acute meningitis. Babies and children with BM compared to those with VM Bacterial meningitis n=66: Age in years (mean; SD in parentheses): 1.6 (1.8) Sex not reported Viral meningitis n=126: Age in years (mean; SD in parentheses): 3.8 (3.4) Sex not reported	<u>CRP</u> Elevated threshold defined as ≥2 mg/dL (converted to mg/l for consistency with other studies)	CSF culture	Sensitivity Specificity	Causative organism: n=45 H. influenzae; n=13 S. pneumoniae; n=3 group B streptococcus; n=3 E. coli; n=2 Listeria monocytogeneous; n=1 N. meningitidis
Tzanakaki 2005 Single-gate cross-sectional DTA study Greece	N=217 People diagnosed with bacterial or viral meningitis based on blood and/or CSF samples submitted to laboratory	<u>Molecular diagnosis</u> Specific PCR for N. meningitidis Specific PCR for S. pneumoniae Specific PCR for H.	CSF culture and/or blood culture	Sensitivity Specificity	Data not extracted for n=54 suspected bacterial meningitis (clinically suspected cases of bacterial meningitis, but with culture and other tests

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	N. meningitidis n=33: No further details reported S. pneumoniae n=26: No further details reported H. influenzae type B n=8: No further details reported Viral meningitis n=150: No further details reported	influenzae			yielding negative results)
Viallon 2011 Single-gate cross-sectional DTA study France	N=253 Adults admitted to the ED with acute meningitis and a negative direct CSF examination Bacterial meningitis n=35 (negative direct CSF examination): Age in years (mean; SD in parentheses): 55 (20) Sex: male: 17 (49%); female: 18 (51%) Viral meningitis n=218: Age in years (mean; SD in parentheses): 35 (18)	CRP Elevated threshold defined as ≥37mg/l PCT Elevated threshold defined as ≥0.28 ng/ml	CSF culture (but only those with negative direct CSF examination included)	Sensitivity Specificity AUC	Causative organism: n=14 S. pneumoniae; n=6 Listeria monocytogenes; n=5 N. meningitidis; n=4 Streptococcus species; n=2 H. influenzae; n=2 Staphylococcus aureus; n=2 other species

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Sex: male: 116 (53%); female: 102 47%)				

AUC: area under the curve; BM: bacterial meningitis; C. koseri: citrobacter koseri; CNS: central nervous system; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia coli; ED: emergency department; GBS: group B streptococcal; H. influenza: haemophilus influenza; IQR: interquartile range; L. monocytogenes: listeria monocytogenes; LP: lumbar puncture; M. tuberculosis: mycobacterium tuberculosis; N. meningitidis: Neisseria meningitides; P. mirabilis: proteus mirabilis; PCR: polymerase chain reaction; PCT: procalcitonin; PMN: polymorphonuclear; S. agalactiae: streptococcus agalactiae; S. pneumoniae; streptococcus pneumonia; SD: standard deviation; VM: viral meningitis; 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.

No meta-analyses were conducted for any of the index tests because of the high level of heterogeneity between studies in terms of study design, population, threshold, and reference standard. The evidence was stratified by age, different thresholds for the index test and infective organism diagnosed as a result of testing polymerase chain reaction (PCR).

The evidence was assessed as being high to very low quality. Downgrading of the evidence was commonly due to risk of bias and imprecision (95% confidence intervals crossing decision making thresholds). 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.

White cell count (WCC)

In babies and children, there was evidence that white cell count (WCC) at a threshold of 15000 cells/µl was moderately specific for a diagnosis of bacterial meningitis, although estimates of sensitivity varied they were also largely moderately sensitive.

There was also some evidence showing WCC to be moderately specific (but not sensitive) for a diagnosis of bacterial meningitis in babies at a threshold of 15000 cells/µl.

One study from an undefined age range showed that WCC outside of the normal range (less than 4000 or more than 11000 cells/µl) was moderately sensitive but not specific for a diagnosis of meningococcal meningitis. No evidence was available for the accuracy of WCC in adults.

Neutrophil count

Neutrophil count was moderately sensitive and moderately specific for a diagnosis of bacterial meningitis in babies and children at thresholds of 10,000 cells/µl. No evidence was available for the accuracy of neutrophil count in adults.

C-reactive protein (CRP)

Overall, c-reactive protein (CRP) was both moderately to highly sensitive and specific for a diagnosis of bacterial meningitis in babies and children at thresholds of 2mg/l, 10mg/l and 20mg/l.

In children and adults, CRP was also largely both moderately to highly sensitive and specific for a diagnosis of bacterial meningitis at thresholds of 14mg/l, 40mg/l, 50mg/l and 90mg/l.

CRP was both moderately to highly sensitive and specific for a diagnosis of bacterial meningitis in adults at thresholds of 8mg/l, 22mg/l, 37mg/l, 40mg/l, and 50mg/l.

There was also some evidence showing CRP to be very sensitive and moderately specific for a diagnosis of bacterial meningitis, at a threshold of 20mg/l, in an undefined age range.

Procalcitonin (PCT)

Overall, procalcitonin (PCT) was very sensitive and very specific for a diagnosis of bacterial meningitis in babies and children, children and adults, and adults. Thresholds ranged from 0.12 ng/ml to 2.13 ng/ml, with the majority of studies using a threshold of 0.5ng/ml.

Polymerase chain reaction (PCR)

Overall, polymerase chain reaction (PCR) for N. meningitides, S. pneumonia, and H. influenzae was highly specific and moderately to highly sensitive in an undefined age. PCR for S. pneumonia in babies and children was very sensitive and moderately specific. PCR for group B streptococcus in babies was both very sensitive and very specific.

No evidence was available for urine detection of bacterial pathogens, blood culture of bacterial pathogens or any molecular diagnosis techniques apart from PCR.

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, but no economic studies were identified which were applicable to this review question.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Appendix J.

Economic model

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

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 bacterial meningitis and starting the appropriate management), true negatives (reassuring

patients and carers that the person does not have bacterial meningitis), false positives (potentially promoting further investigations that are unnecessary, such as lumbar puncture, or starting unnecessary treatments) and false negatives (failing to identify people that require further interventions and intensive management) and noted that false negatives could be particularly impactful as they could lead to treatment being delayed until 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 very low. Generally, evidence was downgraded due to imprecision of effect estimates (95% confidence intervals crossing decision making thresholds) and risk of bias (for example, non-consecutive patient selection, lack of details on population, two-gate study design, lack of information about whether thresholds for index tests were pre-specified, and differences between the reference standard used and the gold standard specified in the protocol). Despite there being a significant body of evidence, meta-analyses could not be conducted because of heterogeneity between studies (for example, different populations included in the studies and different criteria for diagnosing bacterial meningitis).

The committee noted that no evidence was available for urine detection of bacterial pathogens, blood culture of bacterial pathogens or any molecular diagnosis techniques apart from PCR.

Benefits and harms

The committee noted that all the evidence was based on individual blood tests and agreed that none of these blood tests alone would be sufficient to make a diagnosis of bacterial meningitis, nor should any of these tests be used to rule out bacterial meningitis. However, the committee agreed that blood tests can be an important tool when used alongside clinical features and lumbar puncture results, 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 bacterial meningitis.

The evidence showed that, overall, procalcitonin (PCT) was very sensitive and very specific for diagnosing bacterial meningitis in babies, children, and adults. C-reactive protein (CRP) was largely both moderately to highly sensitive and specific for a diagnosis of bacterial meningitis in babies, children, and adults. 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 bacterial meningitis.

The evidence showed that white cell count (WCC) at a threshold of greater than or equal to 15000 cells/µl was moderately specific for diagnosing bacterial meningitis in babies and children, although estimates of sensitivity varied they were also largely moderately sensitive. There was also some evidence from an undefined age range that abnormal WCC (either below 4000 or above 11000 cells/µl) was moderately sensitive (but not specific) for diagnosing meningococcal meningitis. Neutrophil count was shown to be both moderately sensitive and moderately specific for a diagnosis of bacterial meningitis in babies and children. The committee agreed that white blood cell count (including neutrophils) may be valuable to 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.

There was limited evidence on the accuracy of polymerase chain reaction (PCR), mainly from an undefined age range. However, the evidence that was available showed that, overall, PCR for N. meningitidis, S. pneumoniae, and H. influenzae were both moderately to highly sensitive and specific for diagnosing bacterial meningitis. PCR for group B streptococcus in babies was both very sensitive and very specific. Based on the evidence, and their clinical knowledge and experience, the committee recommended that whole-blood diagnostic PCR should be included in the battery of blood tests performed. The committee agreed to give examples of PCR for meningococcal and pneumococcal as these are the more widely available tests in clinical practice, however, they did not want to restrict the recommendation to these tests as this is an area of active research and development.

There was no evidence available on the accuracy of blood culture for diagnosing bacterial meningitis. The committee agreed that it was important to specify that this should be performed as the absence of blood culture from the recommended list of tests could have the unintended consequence that this test would no longer be performed, and the committee agreed the test is important and part of routine practice. Additionally, the committee acknowledged that it is standard practice to take blood sugar and agreed to include blood glucose test to avoid situations where this test could be missed.

The committee were aware of the Guidance for public health management of meningococcal disease in the UK, and that meningococcal meningitis (without septicaemia) is included in this review. The committee agreed to reflect this guidance and recommend that a bacterial throat swab for meningococcal culture should be performed for people with suspected bacterial meningitis. The committee also noted that this should preferably be performed before starting antibiotics as antibiotics can affect the likelihood of obtaining a positive culture result, and that the request form should be explicit that this is specifically for meningococcal culture.

The committee also agreed that a HIV test should be performed in adults with suspected bacterial meningitis because HIV is a risk factor for serious infections. This is also in line with current practice.

No evidence was identified for urine detection of bacterial pathogens, and the committee agreed that it was not appropriate to make recommendations in this area.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of 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). The committee believed that their recommendations for investigating and diagnosing suspected meningitis are low cost and reflect current NHS practice. Therefore, the committee did not anticipate that their recommendations would result in a significant resource impact to the NHS.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.2 to 1.4.5.

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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 bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42020227017
Review title	Investigating and diagnosing suspected bacterial meningitis with blood and urine investigations
Review question	What is the accuracy and effectiveness of blood and urine investigations in diagnosing bacterial meningitis?
Objective	To determine the accuracy and effectiveness of blood and urine investigations in diagnosing bacterial meningitis
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	Bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis

Field	Content
	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. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Test	The use of the following investigations, alone or in combination: Blood: • white cell count • neutrophil count • C-reactive protein (CRP) • procalcitonin • molecular diagnosis for bacterial pathogens: • Blood culture for bacterial pathogens Urine: • Antigen detection for bacterial pathogens
Comparator/Reference standard/Confounding factors	Reference standard – either of the following, alone or in combination: • Cerebrospinal fluid (CSF) bacterial culture • Molecular diagnosis in the CSF for bacterial pathogens
Types of study to be included	• Systematic reviews of test-and-treat RCTs and/or diagnostic accuracy studies. • Individual diagnostic accuracy studies including: • Test-and-treat RCTs • If insufficient test-and-treat RCTs: Cross-sectional diagnostic test accuracy studies (Studies with

Field	Content
	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 hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge)

Field	Content
	• 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** • Seizures or epilepsy • 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 or that are life threatening or otherwise considered medically significant • Length of hospitalisation **2. Cross-sectional diagnostic test accuracy studies** • Area under the curve **Population: infants and children** **1. Test and Treat RCTs** • Seizures or epilepsy • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point)

Field	Content
	• Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant **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. 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)

Field	Content

	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: Age: • Younger Infants: >28 days to ≤3 months of age • Older infants: >3 months to <1 year of age

Field	Content
	• 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 Infective organism diagnosed as a result of testing: • Neisseria meningitidis • Streptococcus pneumonia • Haemophilus influenza • group B streptococcus • Gram-negative bacilli • Listeria monocytogenes Reference standard used: • Cerebrospinal fluid (CSF) bacterial culture • Molecular diagnosis in the CSF for bacterial pathogens • CSF bacterial culture and molecular diagnosis for bacterial pathogens 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

Field	Content			
	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 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		☑	☑

Field	Content
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk 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?ID=CRD42020227017
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	Bacterial meningitis, 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	None

Field	Content	
same 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 bacterial meningitis?

Clinical Search

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

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
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA

#	Searches
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

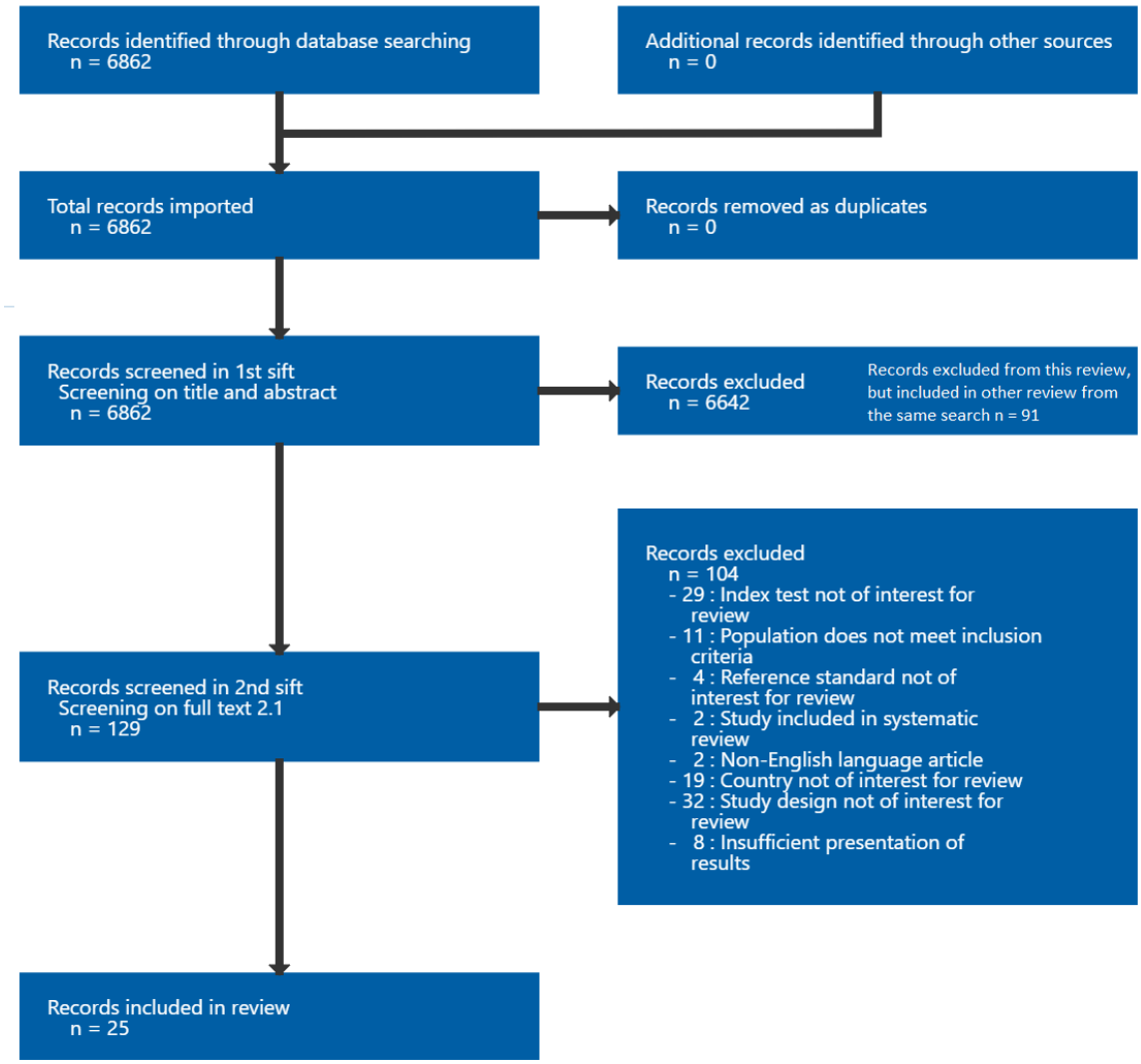
#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or 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.
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

#	Searches
	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
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 bacterial meningitis?

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 bacterial meningitis?

Table 4: Evidence tables - diagnostic evidence

Benjamin, 1984

Bibliographic Reference Benjamin, D. R; Opheim, K. E; Brewer, L.; Is C-reactive protein useful in the management of children with suspected bacterial meningitis?; American Journal of Clinical Pathology; 1984; vol. 81 (no. 6); 779-782

Study details

Country/ies where study was carried out	USA
Study type	Single-gate cross-sectional DTA study
Study dates	Not reported (within a 6 month period)
Inclusion criteria	CSF samples submitted to laboratory during study period, including all cases of bacterial and viral meningitis
Exclusion criteria	Not reported
Patient characteristics	N=79 Bacterial meningitis n=21: Age/sex not reported by arm Causative organisms: n=14 H. influenzae type b, n=2 S. pneumoniae, n=3 N. meningitidis, n=1 M. tuberculosis, n=1 Salmonella species Viral meningitis/no meningitis n=58: Viral meningitis n=8; no meningitis n=50 Age/sex not reported by arm Whole sample (N=79): Age (range): 1 week-18 years (mean/median not reported)

Index test(s)	CRP Elevated threshold defined as >1mg/dL (converted to mg/l for consistency with other studies)
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Other information	n=40 with leukaemia excluded from the analysis
Results	CRP, threshold >1 mg/dL (n=79): TP 20; FP 25; FN 1; 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: Serum CRP – mg/l. Calculated as 1 mg/dL = 10mg/l.

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; M. tuberculosis: mycobacterium tuberculosis; N. meningitidis: Neisseria meningitides; S. pneumoniae; streptococcus pneumonia; TN: true negative; TP: true positive

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear (*All CSF samples submitted to laboratory during study period; exclusion criteria not reported*)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low (*n=40 with leukaemia who had CSF samples taken as part the routine protocol or assessment of leukaemia included in study but not included in the analysis for this review*)
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
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Bonsu, 2003

Bibliographic Reference	Bonsu, B. K; Harper, M. B.; Utility of the peripheral blood white blood cell count for identifying sick young infants who need lumbar puncture; Annals of emergency medicine; 2003; vol. 41 (no. 2); 206-214

Study details

Country/ies where study was carried out	USA
Study type	Single-gate cross-sectional DTA study
Study dates	January 1992 - July 1999
Inclusion criteria	Babies evaluated for serious bacterial infection in the emergency department (presenting with a temperature of 38°C or greater)
Exclusion criteria	All CSF samples that were blood contaminated (RBC count ≥10,000 cells/mm³); babies given a diagnosis of leukaemia
Patient characteristics	N=5353 Bacterial meningitis (n=22): Age and sex not reported for BM group Causative organisms: n= 11 E. coli, n=9 group B streptococcus, n=1 S. pneumoniae, n=1 C. koseri Non-bacterial meningitis (5331): No further details reported for control group Whole sample (N=5353): Age in days (range): 3-89 (mean/median not reported)

Index test(s)	WCC Elevated threshold defined as ≥15000 cells/mm³ (converted to cells/µl for consistency with other studies)
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Other information	Data also reported for WCC thresholds of <5000, ≥10000, ≥20000, ≥25000, <5000 or ≥15000, and <5000 or ≥20000 cells/mm³, but data only extracted for the ≥15000 threshold as this is most consistent with other studies
Results	WCC, threshold ≥15000/mm³ (n=5353): TP 6; FP 1221; FN 15; TN 4110 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 – cells/µl. Equivalent to cells/mm³

BM: bacterial meningitis; C. koseri: citrobacter koseri; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia coli; FN: false negative; FP: false positive; RBC: red blood cell; S. pneumoniae; streptococcus pneumonia; TN: true negative; TP: true positive; WCC: white cell count

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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?	Low (*Thresholds pre-specified; 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*.)

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

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 meningitis only are included in this review, and those with septicaemia or meningitis and septicaemia are included in the review on blood and urine investigations for meningococcal disease). The control group (n=61) included those where meningococcal disease could be ruled out (with n=2 who were difficult to categorize included in the control group as meningitis of unknown microbiological aetiology). For this review, the control participants (n=25) with bacterial meningitis or septicaemia (excluding those due to N. meningitidis) and other bacterial infections were not included.
Exclusion criteria	Not reported

Patient characteristics	N=92 Meningococcal meningitis (n=56): Age: Reported for whole sample only (including those with meningococcal disease); Mean/median not reported; 50% aged < 12 years. No meningococcal or bacterial infection (n=36): Age: Reported for whole sample only (including control participants not included in this review; Mean/median not reported; 79% aged < 12 years Viral infections (positive viral isolation or serious meningitis; N=14); other diseases (N=22; 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 <4,000 or ≥11,000 cells/mm³ (converted to cells/µl 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
Other information	Study includes patients without bacteriological proof (N=44, 38% of the full sample that includes those with meningococcal disease)
Results	CRP, threshold ≥20 mg/L (n=59): TP 36; FP 9; FN 4; TN 10 WCC, threshold <4000 or ≥11000 mm³/L (n=83): TP 47; FP 17; FN 6; TN 13 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 – cells/µl. Equivalent to cells/mm³

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N. 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*)

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?	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*)

Dagan, 1998

Bibliographic Reference Dagan, R; Shriker, O; Hazan, I; Leibovitz, E; Greenberg, D; Schlaeffer, F; Levy, R.; Prospective study to determine clinical relevance of detection of pneumococcal DNA in sera of children by PCR; Journal of clinical microbiology; 1998; vol. 36 (no. 3); 669-73

Study details

Country/ies where study was carried out	Israel

Study type	Two-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	Not clearly reported Babies and children with meningitis and other conditions (pneumococcal bacteraemia, lobar or segmental pneumococcal pneumonia and acute otitis media) were recruited from the emergency department (and blood samples were obtained during the acute phase of the disease). Healthy controls were recruited from Maternal Child Health Centres (primary care) and blood samples were obtained during regular visits
Exclusion criteria	Not reported
Patient characteristics	N=281 Pneumococcal meningitis n= 4: Age/sex not reported by arm No meningitis/healthy controls n=277: Age/sex not reported by arm n=75 non-meningitis: n= 9 pneumococcal bacteraemia; n= 34 lobar or segmental pneumococcal pneumonia; n= 32 acute otitis media with middle ear fluid and nasopharyngeal swab culture positive for S. pneumoniae; n= 202 healthy controls Whole sample (N=281): Age (range): 10 months to 16 years
Index test(s)	Molecular diagnosis Specific PCR for S. pneumoniae
Reference standard(s)	CSF and serum culture for pneumococcal isolates
Sources of funding	No sources of funding reported
Other information	Poor reporting of inclusion and exclusion criteria
Results	Molecular diagnosis: PCR for S. pneumoniae (n=281): TP 4; FP 71; FN 0; TN 206 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; PCR: polymerase chain reaction; S. pneumoniae; streptococcus pneumonia; 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?	High (*Case-control design, and unclear if the study avoided inappropriate exclusions*)
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 (*The index test was interpreted without knowledge of the reference standard*)
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*)

De Cauwer, 2007

Bibliographic Reference De Cauwer, H. G; Eykens, L; Hellinckx, J; Mortelmans, L. J. M.; Differential diagnosis between viral and bacterial meningitis in children; European Journal of Emergency Medicine; 2007; vol. 14 (no. 6); 343-347

Study details

Country/ies where study was carried out	Belgium

Study type	Single-gate retrospective DTA study
Study dates	1997 to 2005
Inclusion criteria	Children (0-15 years old) admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of viral or bacterial meningitis
Exclusion criteria	Patients with Lyme's disease
Patient characteristics	N=92 Bacterial meningitis (n=21): Age in years (mean; range in parentheses): 3.9 (0-13) Sex: male 12 (57%); female: 9 (43%) Bacterial aetiology: Meningococcal meningitis (n=16; 76%); pneumococcal meningitis (n=5; 24%) Viral meningitis (n=71): Age in years (mean; range in parentheses): 6.1 (0-15) Sex: male 46 (65%); female: 25 (35%)
Index test(s)	CRP Elevated threshold defined as ≥2mg/L
Reference standard(s)	CSF culture or pleocytosis in the CSF and a positive blood culture for a bacterial disease. Blood cultures were positive in 18/21, negative in 2/21 and not performed in 1/21. In the same group, CSF cultures were positive in 14/21 and negative in 7/21.
Sources of funding	No sources of funding reported
Results	CRP, threshold ≥2 mg/L (n=91): TP 20; FP 12; FN 1; TN 58 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; 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 (*Consecutive sample enrolled but only patients diagnosed with bacterial meningitis or viral meningitis were included*)

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?	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 (*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?	High (*Reference standard defined as positive CSF culture or blood culture (only 14/21 patients with positive CSF culture*))
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear (*No information about interval between index tests and reference standards*)

Dubos, 2006

Bibliographic Reference Dubos, F; Moulin, F; Gajdos, V; De Suremain, N; Biscardi, S; Lebon, P; Raymond, J; Breart, G; Gendrel, D; Chalumeau, M.; Serum procalcitonin and other biologic markers to distinguish between bacterial and aseptic meningitis; Journal of pediatrics; 2006; vol. 149 (no. 1); 72-76

Study details

Country/ies where study was carried out	France
Study type	Two-gate cross-sectional DTA study

Study dates	For bacterial meningitis cohort: January 1995 - October 2004 For viral meningitis cohort: January 2000 - April 2004
Inclusion criteria	Children (aged 28 days to 16 years) admitted to hospital with a diagnosis of acute meningitis. Children with bacterial meningitis admitted to hospital between January 1995 and October 2004 compared to children admitted to hospital with viral meningitis between January 2000 and April 2004.
Exclusion criteria	Neurosurgical disease; immunodepression; traumatic lumbar puncture (defined as CSF RBC>10,000/mm³); antibiotics given within the 48 hours preceding lumbar puncture; referral from another hospital after diagnosis; incomplete medical records
Patient characteristics	N=167 Bacterial meningitis n=21: Age/sex not reported by arm Causative organism: n=10 S. pneumonia, n=9 N. meningitidis, n=1 H. influenzae b, n=1 Streptococcus group B Viral meningitis n=146: Age/sex not reported by arm Whole sample (N=167): Age in years (median; range in parentheses): 4.6 (0.2-14.9) Sex: male: 117 (70%); female: 50 (30%)
Index test(s)	PCT Elevated threshold defined as ≥0.5 ng/ml CRP Elevated threshold defined as ≥20mg/L WCC Elevated threshold defined as ≥15000/mm³ (converted to cells/µl for consistency with other studies) Neutrophils Elevated threshold defined as ≥10000/mm³ (converted to cells/µl for consistency with other studies)
Reference standard(s)	Bacterial infection in CSF (direct examination, culture, latex agglutination, or PCR) or blood culture
Sources of funding	No sources of funding reported

Results	PCT, threshold ≥0.5 ng/ml (n=152): TP 16; FP 15; FN 2; TN 119 CRP, threshold ≥20 mg/l (n=167): TP 19; FP 42; FN 2; TN 104 WCC, threshold ≥15000/mm³ (n=165): TP 13; FP 26; FN 8; TN 118 Neutrophils, threshold ≥10000/mm³ (n=153): TP 12; FP 39; FN 8; TN 94 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 – cells/µl. Equivalent to cells/mm³

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; PCR: polymerase chain reaction; PCT: procalcitonin; RBC: red blood cell; 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?	High (*Case-control design (different recruitment periods for cases and controls)*)
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?	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

Dubos, 2008

Bibliographic Reference Dubos, F; Korczowski, B; Aygun, D.A; Martinot, A; Prat, C; Galetto-Lacour, A; Casado-Flores, J; Taskin, E; Leclerc, F; Rodrigo, C; Gervaix, A; Leroy, S; Gendrel, D; Breart, G; Chalumeau, M.; Serum procalcitonin level and other biological markers to distinguish between bacterial and aseptic meningitis in children: A European multicenter case cohort study; Archives of Pediatrics and Adolescent Medicine; 2008; vol. 162 (no. 12); 1157-1163

Study details

Country/ies where study was carried out	5 European countries (France, Spain, Switzerland, Turkey, & Poland)
Study type	Single-gate retrospective DTA study
Study dates	Varied by centre, across centres covered 1996-2005
Inclusion criteria	People aged 29 days to 18 years who were admitted for bacterial or viral meningitis and had measurements of the main inflammatory markers (including PCT) in blood and CSF taken in the emergency department
Exclusion criteria	Any neurosurgical disease; immunosuppression; traumatic lumbar puncture (defined as CSF red blood cell count >10 000/µL); previously treated meningitis; referred from another hospital because of a diagnosis of meningitis
Patient characteristics	N=198 Bacterial meningitis n=96: Age in years (mean; range in parentheses): 3.2 (0.1-14) Causative organisms: n=45 N. meningitidis, n=32 S. pneumoniae, n=7 H. influenzae, n=4 Streptococcus agalactiae Viral meningitis n=102: Age not reported for this arm separately Whole sample (N=198): Age in years (mean; range in parentheses): 4.8 (0.1-15.9)

Index test(s)	WCC Elevated threshold defined as ≥15000/mm³ *(*converted to cells/µl for consistency with other studies) Neutrophils Elevated threshold defined as ≥10000/mm³ *(*converted to cells/µl for consistency with other studies) CRP Elevated threshold defined as ≥20 mg/l PCT Elevated threshold defined as ≥0.5 ng/ml
Reference standard(s)	Bacterial infection in CSF (direct examination, culture, latex agglutination, or PCR) or blood culture
Sources of funding	Not industry funded
Other information	76/96 (79%) diagnosed on the basis of positive CSF culture
Results	WCC, threshold ≥15000/mm³ (n=198): TP 46; FP 22; FN 50; TN 80 Neutrophils, threshold ≥10000/mm³ (n=188): TP 49; FP 25; FN 37; TN 77 CRP, threshold ≥20 mg/l (n=197): TP 79; FP 34; FN 16; TN 68 PCT, threshold ≥0.5 ng/ml (n=190): TP 89; FP 17; FN 1; TN 83 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 – cells/µl. Equivalent to cells/mm³

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; PCR: polymerase chain reaction; PCT: procalcitonin; 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
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*)

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	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?	High (*79% of population with bacterial meningitis diagnosed via bacterial infection in CSF*)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Hansson, 1993

Bibliographic Reference	Hansson, L. O; Axelsson, G; Linne, T; Aurelius, E; Lindquist, L.; Serum C-reactive protein in the differential diagnosis of acute meningitis; Scandinavian Journal of Infectious Diseases; 1993; vol. 25 (no. 5); 625-630

Study details

Country/ies where study was carried out	Sweden
Study type	Single-gate cross-sectional DTA study
Study dates	1983 - 1986
Inclusion criteria	Children and adults undergoing lumbar puncture due to suspected CNS infection
Exclusion criteria	Neonates; people with HIV

Patient characteristics	N=206 Bacterial meningitis n=60: Age/sex not available Viral meningitis n=146: Age/sex not available
Index test(s)	CRP Elevated threshold defined as ≥50 mg/l
Reference standard(s)	CSF culture or bacterial antigen in CSF
Sources of funding	No sources of funding reported
Other information	Total of 235 patients enrolled but 2x2 table can only be calculated based on those with bacterial meningitis (n=60) and those with viral meningitis (n=146) due to insufficient presentation of results
Results	CRP, threshold ≥50 mg/l (n=206): TP 53; FP 15; FN 7; TN 131 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CNS: central nervous system; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; HIV: human immunodeficiency virus; TN: true negative; TP: true positive

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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 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*)

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	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 antigen detection in CSF*)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High (*It was not possible to include all cases in the analysis due to insufficient presentation of results*)

Jereb, 2001

Bibliographic Reference Jereb, M; Muzlovic, I; Hojker, S; Strle, F.; Predictive value of serum and cerebrospinal fluid procalcitonin levels for the diagnosis of bacterial meningitis; Infection; 2001; vol. 29 (no. 4); 209-212

Study details

Country/ies where study was carried out	Slovenia
Study type	Two-gate cross-sectional DTA study
Study dates	1998
Inclusion criteria	Adults admitted to hospital with bacterial meningitis compared to adults admitted with viral meningitis (tick-borne encephalitis)
Exclusion criteria	Not reported

Patient characteristics	N=45 Bacterial meningitis n=20: Age in years (median; range in parentheses): 55 (16-77) Sex: male: 9 (45%); female: 11 (55%) Causative organisms: n=9 S. pneumonia, n=4 Staphylococcus aureus, n=2 Listeria monocytogenes, n=2 N. meningitides, n=1 H. influenzae b, n=1 Clostridium perfringens, n=1 CSF and blood cultures negative but positive Gram smear (gram positive cocci) Viral meningitis (tick-borne encephalitis) n=25: Age in years (median; range in parentheses): 49 (22-66) Sex: male: 13 (52%); female: 12 (48%)
Index test(s)	CRP Elevated threshold defined as ≥50mg/L PCT Elevated threshold defined as ≥0.5 ng/ml
Reference standard(s)	CSF and/or blood culture or CSF gram-stained smear
Sources of funding	No sources of funding reported
Results	CRP, threshold ≥50mg/L (n=45): TP 18; FP 2; FN 2; TN 23 PCT, threshold ≥0.5 ng/ml (n=45): TP 18; FP 0; FN 2; TN 25 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; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; PCT: procalcitonin; S. pneumoniae; streptococcus pneumonia; 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?	High (*Case control design*)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
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?	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?	High (*Reference standard CSF and/or blood culture or CSF gram-stained smear. No proportions of population diagnosed via CSF culture*)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low (*Index tests and reference standard both conducted on admission*)

Knudsen, 2007

Bibliographic Reference Knudsen, T.B; Larsen, K; Kristiansen, T.B; Moller, H.J; Tvede, M; Eugen-Olsen, J; Kronborg, G.; Diagnostic value of soluble CD163 serum levels in patients suspected of meningitis: comparison with CRP and procalcitonin; Scandinavian Journal of Infectious Diseases; 2007; vol. 39 (no. 06jul); 542-553

Study details

Country/ies where study was carried out	Denmark
Study type	Single-gate cross-sectional DTA study
Study dates	February 2001 - February 2005
Inclusion criteria	People suspected of meningitis on admission to hospital, who received a lumbar puncture

Exclusion criteria	People transferred from other hospitals who had already been diagnosed or lumbar puncture had been performed as part of a routine investigation
Patient characteristics	N=52 Bacterial meningitis n=10: Age/sex not reported by arm Causative organism: n=5 pneumococci; n=3 meningococci; n=1 E.coli; n=1 unknown Viral meningitis/no meningitis n=42: n=12 viral meningitis; n=30 non-meningitis Age/sex not reported by arm Whole sample (N=52): Age in years (median; range in parentheses): 36.1 (12.8-92.3) Sex: male: 25 (48%); female: 27 (52%)
Index test(s)	CRP Elevated threshold defined as ≥40 mg/l PCT Elevated threshold defined as ≥0.25 ng/ml
Reference standard(s)	>800 leukocytes/l of which >80% are neutrophilic granulocytes in CSF and/or CSF culture or bacterial antigens in CSF
Sources of funding	No sources of funding reported
Other information	n=21 had antibiotic treatment before LP (median time for initiation of antibiotic treatment prior to LP: 1 day, range 0-6 day). Lumbar puncture and blood samples carried out at the same time (on admission).
Results	CRP, threshold ≥40 mg/l (n=52): TP 9; FP 25; FN 1; TN 17 PCT, threshold ≥0.25 ng/ml (n=52): TP 9; FP 18; FN 1; TN 24 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia coli; FN: false negative; FP: false positive; LP: lumbar puncture; 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 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?	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

Lembo, 1991a

Bibliographic Reference Lembo, R. M; Rubin, D. H; Krowchuk, D. P; McCarthy, P. L.; Peripheral white blood cell counts and bacterial meningitis: Implications regarding diagnostic efficacy in febrile children; Pediatric Emergency Care; 1991; vol. 7 (no. 1); 04-Nov

Study details

Country/ies where study was carried out	USA
Study type	Single-gate cross-sectional DTA study

Study dates	July 1979 - June 1980; February 1984 - August 1985; January 1986 - December 1987
Inclusion criteria	Babies and children with suspected meningitis who had lumbar puncture
Exclusion criteria	No complete blood cell count within 12 hours of the initial lumbar puncture; history of intracranial surgery; underlying malignancy; receiving immunosuppressive therapy
Patient characteristics	N=232 (included in analysis) Bacterial meningitis n=46: Age in months (median; range in parentheses): 11 (0-157) Sex: male: 28 (61%); female: 18 (39%) Causative organism: n=29 H. influenza type b; n=6 S. pneumoniae; n=3 N. meningitidis; n=3 streptococcus group b; n=2 streptococcus group a; n=1 listeria monocytogenes; n=1 E. coli; n=1 P. mirabilis Viral meningitis/no meningitis n=186: Viral meningitis n=130: Age in months (median; range in parentheses): 2 (0-219) Sex: male: 69 (53%); female: 61 (47%) No meningitis n=56: Age in months (median; range in parentheses): 6.5 (0-79) Sex: male: 25 (45%); female: 31 (55%) Extra-meningeal infections: n=22 urinary tract infection; n=13 occult bacteremia; n=7 cellulitis/abscess; n=7 enteritis; n=4 otitis media; n=2 pneumonia; n=1 septic arthritis
Index test(s)	WCC Elevated threshold defined as ≥ 15,000/mm³ (converted to cells/µl for consistency with other studies)
Reference standard(s)	CSF culture or bacterial antigen in CSF or urine in combination with CSF pleocytosis and a positive gram strain of CSF
Sources of funding	No sources of funding reported
Results	WCC, threshold ≥15000/mm³ (n=232): TP 10; FP 50; FN 36; TN 136 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 – cells/µl. Equivalent to cells/mm³

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia coli; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; P. mirabilis: proteus mirabilis; 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?	Unclear (*Unclear if 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 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?	High (*Detection of pathogen-specific antigen in the CSF or urine*)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Lembo, 1991b

Bibliographic Reference Lembo, R.M; Marchant, C.D.; Acute phase reactants and risk of bacterial meningitis among febrile infants and children; Annals of Emergency Medicine,Ann.Emerg.Med.; 1991; vol. 20 (no. 1); 36-40

Study details

Country/ies where study was carried out	USA

Study type	Single-gate cross-sectional DTA study
Study dates	February 1984 - August 1985
Inclusion criteria	Babies and children presenting with an acute febrile episode who had a lumbar puncture
Exclusion criteria	History of malignancy; immunodeficiency; intracranial surgery; receiving immunosuppressive therapy
Patient characteristics	N=160 Bacterial meningitis n=10: Age/sex not reported by arm Causative organism: n=5 H. influenza type b, n=3 S. pneumonia, n=1 group A streptococci, n=1 listeria monocytogenes Viral meningitis/no meningitis n=150: Viral meningitis n=14; other bacterial infection n=10; other illnesses n=126 Whole sample (N=160): Age in months (median; no measure of variance reported): 60 Sex: male: 84 (52.5%); female: 76 (47.5%)
Index test(s)	WCC Elevated threshold defined as ≥ 15,000/mm³ (converted to cells/µl for consistency with other studies) CRP Elevated threshold defined as >1mg/dl (converted to mg/l for consistency with other studies)
Reference standard(s)	CSF culture or bacterial antigen in combination with a positive gram strain of CSF
Sources of funding	No sources of funding reported
Results	WCC, threshold ≥15000/mm³ (n=160): TP 4; FP 54; FN 6; TN 96 CRP, threshold >1 mg/dL (n=160): TP 8; FP 67; FN 2; TN 83 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 – cells/µl. Equivalent to cells/mm³. CRP – mg/l. Calculated as 1 mg/dL = 10mg/l.

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; 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?	Unclear (*Not clear if consecutive sample was 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 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*)

Morales Casado, 2016

Bibliographic Reference Morales Casado, M. I; Moreno Alonso, F; Juarez Belaunde, A. L; Heredero Galvez, E; Talavera Encinas, O; Julian-Jimenez, A.; Ability of procalcitonin to predict bacterial meningitis in the emergency department; Neurologia; 2016; vol. 31 (no. 1); Sep-17

Study details

Country/ies where study was carried out	Spain

Study type	Single-gate cross-sectional DTA study
Study dates	August 2009 - July 2013
Inclusion criteria	People aged >15 years old with acute meningitis who underwent lumbar punctures, blood culture tests, CRP and PCT
Exclusion criteria	People with a different potential primary focus of bacterial infection; a second episode of acute meningitis during the study period; a second episode of tuberculous or autoimmune meningitis during follow-up
Patient characteristics	N=71 Bacterial meningitis n=38: Age in years (mean; SD in parentheses): 56 (22) Sex: male: 28 (74%); female: 10 (26%) Causative organism: n=18 S. pneumoniae; n=7 N. meningitidis; n=7 L. monocytogenes; n=4 H. influenzae; n=2 E. coli Viral meningitis n=33: Age in years (mean; SD in parentheses): 38 (16) Sex: male: 20 (61%); female 13 (39%) Viral meningitis: n=30 enteroviruses; n=3 with herpes simplex virus
Index test(s)	CRP Elevated threshold defined as ≥90 mg/l PCT Elevated threshold defined as ≥0.74 ng/ml
Reference standard(s)	CSF culture or bacterial antigen in CSF
Sources of funding	No sources of funding reported
Other information	Data for n=27 not included in analysis: n=15 probable VM with negative results from cultures; n=12 presumptively diagnosed partially-treated acute meningitis (history of antibiotic treatment and negative results from cultures). Immunosuppression: 5/38 (13%) in BM group; 1/33 (3%) in VM group. Antibiotic use in previous 72 hours: 4/38 (11%) in BM group; 4/33 (12%) in VM group
Results	CRP, threshold ≥90 mg/l (n=71): TP 26; FP 5; FN 12; TN 28. AUC 0.916 (95% CI: 0.838-0.994) PCT, threshold ≥0.74 ng/ml (n=): TP 36; FP 0; FN 2; TN 33. AUC 0.996 (95% CI: 0.987-1) N.B. 2x2 tables and relevant outcomes calculated in RevMan

AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia

coli; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; L. monocytogenes: listeria monocytogenes; N. meningitidis: Neisseria meningitides; PCT: procalcitonin; S. pneumoniae;

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 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?	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*)

Morrissey, 2017

Bibliographic Reference Morrissey, S. M; Nielsen, M; Ryan, L; Al Dhanhani, H; Meehan, M; McDermott, S; Doyle, M; Gavin, P; O'Sullivan, N; Cunney, R; Drew, R. J.; Group B streptococcal PCR testing in comparison to culture for diagnosis of late onset bacteraemia and meningitis in infants aged 7-90 days: a multi-centre diagnostic accuracy study; European Journal of Clinical Microbiology and Infectious Diseases; 2017; vol. 36 (no. 7); 1317-1324

Study details

Country/ies where study was carried out	Ireland
Study type	Single-gate retrospective DTA study
Study dates	March 2010 - December 2014
Inclusion criteria	Babies (aged 7–90 days) that had a blood or CSF sample tested by GBS PCR
Exclusion criteria	Not reported
Patient characteristics	N=827 (data only included for those with CSF samples) Bacterial meningitis n=5: Age/sex not reported by arm Causative organism: n=5 late onset group B streptococcal (GBS) disease Non-GBS group n=822: No further details reported Whole sample (N=827): Age in days (median; IQR in parentheses): 35 (20.75-57) Sex: male: 478 (58%); female: 340 (41%)
Index test(s)	Molecular diagnosis Specific PCR for group B streptococcus
Reference standard(s)	CSF culture
Sources of funding	No sources of funding
Results	Molecular diagnosis: PCR for group B streptococcus (n=827): TP 5; FP 17; FN 0; TN 805 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GBS: group B streptococcal; IQR: interquartile range; 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 reported if consecutive sample enrolled*)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High (*Population age ranges from 7-90 days, median age 39 days. Significant proportion of population are neonates which are excluded from review*)
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?	High (*Reference standard stated as blood culture or definite/probable clinical case (undefined). Unclear if CSF culture is part of the definite clinical case definition*)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Paradowski, 1995

Bibliographic Reference Paradowski, M; Lobos, M; Kuydowicz, J; Krakowiak, M; Kubasiewicz-Ujma, B.; Acute phase proteins in serum and cerebrospinal fluid in the course of bacterial meningitis; Clinical Biochemistry; 1995; vol. 28 (no. 4); 459-466

Study details

Country/ies where study was carried out	Poland
Study type	Two-gate cross-sectional DTA study

Study dates	April 1992 - May 1994
Inclusion criteria	Adults hospitalised with acute meningitis. People with bacterial meningitis compared to those with viral meningitis
Exclusion criteria	Not reported
Patient characteristics	N=60 Bacterial meningitis n=30: Age in years (mean; range in parentheses): 49 (19-82) Sex: male: 22 (73%); female: 8 (27%) Causative organism: n=10 N. meningitidis; n=7 S. pneumoniae; n=4 H. influenzae; n=3 Streptococcus group B; n=3 Streptococcus aureus; n=1 Pseudomonas aeruginosa; n=2 bacteria not identified. Viral meningitis n=30: Age in years (mean; range in parentheses): 38 (23-75) Sex: male: 16 (53%); female: 14 (47%)
Index test(s)	CRP Elevated threshold defined as >40 mg/l
Reference standard(s)	CSF culture, bacterial antigen in CSF, or clinical picture
Sources of funding	No sources of funding reported
Other information	The study also included healthy controls but data is not extractable for this group. The majority of BM cases (93%) were confirmed through microbiological techniques
Results	CRP, threshold >40 mg/l (n=60): TP 25; FP 0; FN 5; TN 30 N.B. 2x2 tables and relevant outcomes calculated in RevMan

BM: bacterial meningitis; CRP: c-reactive protein; 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

Critical appraisal - QUADAS-2

Section	Question	Answer

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Case control study)*
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?	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

Park, 2017

Bibliographic Reference Park, B. S; Park, S. H; Kim, J; Shin, K. J; Ha, S. Y; Park, J; Kim, S. E; Lee, B. I; Park, K. M.; Procalcitonin as a potential predicting factor for prognosis in bacterial meningitis; Journal of Clinical Neuroscience; 2017; vol. 36; 129-133

Study details

Country/ies where study was carried out	Korea
Study type	Two-gate cross-sectional DTA study

Study dates	January 2009 - May 2016
Inclusion criteria	Adults admitted to hospital with a clinical suspicion of bacterial meningitis compared to those admitted with viral meningitis during a similar time period
Exclusion criteria	No assessment of blood PCT levels
Patient characteristics	N=138 Bacterial meningitis n=80 Age in years (median; IQR in parentheses): 66 (16-91) Sex: male: 49 (61%); female: 31 (39%) 47/80 (59%) had positive CSF culture, smear, or PCR for bacterial pathogens. Causative organism identified (n=47): n=24 streptococcus species; n=8 staphylococcus species; n=6 klebsiella species; n=5 listeria species; n=4 other species Viral meningitis n=58 Age in years (median; IQR in parentheses): 37 (15-81) Sex: male: 30 (52%); female: 28 (48%) 25/58 (43%) had viral pathogens identified using PCR of the CSF: n=16 with enterovirus; n=5 herpes simplex virus; n=3 herpes zoster virus; n=1 Epstein-Barr virus
Index test(s)	PCT Elevated threshold defined as >0.12 ng/ml
Reference standard(s)	CSF culture, smear, or PCR for bacterial pathogens or good specific response to antibacterial therapy, clinical features, or other positive CSF findings
Sources of funding	No sources of funding reported
Results	PCT, threshold >0.12 ng/ml (n=138): TP 71; FP 15; FN 9; TN 43 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; IQR: interquartile range; 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?	High *(Case control design)*

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?	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?	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?	High *(Only 59% of diagnoses made on a positive CSF culture, smear, or PCR for bacterial pathogens)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Peltola, 1982

Bibliographic Reference Peltola, H. O.; C-reactive protein for rapid monitoring of infections of the central nervous system; Lancet; 1982; vol. 1 (no. 8279); 980-2

Study details

Country/ies where study was carried out	Finland
Study type	Single-gate cross-sectional DTA study
Study dates	January 1979 - October 1981

Inclusion criteria	Babies and children diagnosed with bacterial meningitis, viral meningitis, or meningoencephalitis
Exclusion criteria	Not reported
Patient characteristics	N=31 Bacterial meningitis n=16: Age in years (mean; standard deviation in parentheses): 1.69 (1.97) Sex not reported Causative organism: n=11 H. influenzae; n=2 meningococci; n=2 pneumococci; n=1 ß-haemolytic streptococcus Viral illness n=15: n=14 viral meningitis or meningoencephalitis; n=1 encephalitis Age in years (mean; standard deviation in parentheses): 8.24 (14.01) Sex not reported Viral aetiology: n=4 coxsachie B; n=3 parotitis; n=2 ECHO 30; n=1 cytomegalovirus; n=1 HSV 2; n=4 unknown
Index test(s)	CRP Elevated threshold defined as ≥10mg/l
Reference standard(s)	CSF culture and/or blood culture
Sources of funding	No sources of funding reported
Other information	n=2 adults in viral illness group but study categorised as babies and children as all other participants aged 0.04-9 years
Results	CRP, threshold ≥10 mg/l (n=31): TP 16; FP 1; FN 0; TN 14 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; H. influenza: haemophilus influenza; HSV: herpes simplex virus; 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 *(Consecutive sample enrolled but only patients diagnosed with bacterial meningitis, viral meningitis or meningoencephalitis were included)*

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?	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?	High *(Reference standard was CSF culture and/or blood culture, no further details on proportions diagnosed via each method)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

Ray, 2007

Bibliographic Reference Ray, P; Badarou-Acossi, G; Viallon, A; Boutoille, D; Arthaud, M; Trystram, D; Riou, B.; Accuracy of the cerebrospinal fluid results to differentiate bacterial from non bacterial meningitis, in case of negative gram-stained smear; American journal of emergency medicine; 2007; vol. 25 (no. 2); 179-184

Study details

Country/ies where study was carried out	France
Study type	Single-gate cross-sectional DTA study
Study dates	January 2001 - December 2002

Inclusion criteria	Adults (aged at least 16 years) presenting to the emergency department and hospitalised with acute meningitis, with initial gram staining negative for bacteria
Exclusion criteria	Gram-stained smears showing presence of bacteria
Patient characteristics	N=151 Bacterial meningitis n=18: Age in years (mean; SD in parentheses): 52 (20) Sex: male: 9 (50%); female: 9 (50%) Causative organism: n=4 Streptococcus species other than pneumonia; n=2 S. pneumoniae; n=2 N. meningitidis; n=1 Fusobacterium; n=1 Klebsiella pneumoniae; n=1 Mycobacterium tuberculosis; n=7 unknown Viral meningitis n=133: Age in years (mean; SD in parentheses): 33 (13) Sex: male: 66 (50%); female: 67 (50%) Viral pathogens identified: n=13 enterovirus; n=10 echovirus; n=5 herpes simplex virus; n=3 varicella-zoster virus
Index test(s)	PCT Elevated threshold defined as ≥2.13 ng/ml CRP Elevated threshold defined as ≥22 mg/l
Reference standard(s)	CSF culture, CSF antigen test or blood culture, or CSF pleocytosis
Sources of funding	No sources of funding reported
Other information	61% of diagnoses made on a positive CSF culture, antigen test or blood culture n=2 HIV positive, and n=2 daily steroid treatment Previous antibiotics: 4/18 (23%) in BM group; 8/133 (6%) in VM group
Results	PCT, threshold ≥2.13 ng/ml (n=151): TP 16; FP 0; FN 2; TN 133. AUC 0.98 (95% CI: 0.83-1.00) CRP, threshold ≥22 mg/l (n=151): TP 14; FP 35; FN 4; TN 98. AUC 0.81 (95% CI: 0.58-0.92) N.B. 2x2 tables and relevant outcomes calculated in RevMan

AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; HIV: human immunodeficiency virus; N. meningitidis: Neisseria meningitides; PCT: procalcitonin; S. pneumoniae; streptococcus pneumonia; SD: standard deviation; TN: true negative; TP: true positive; VM: viral meningitis

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 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?	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?	High *(Reference standard included CSF culture, CSF antigen test or blood culture, or CSF pleocytosis. Only 61% of diagnoses made on a positive CSF culture, antigen test or blood culture)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(10/18 patients with BM not included in the PCT analysis, without any explanation)*

Roine, 1991

Bibliographic Reference Roine, I; Banfi, A; Bosch, P; Ledermann, W; Contreras, C; Peltola, H.; Serum C-reactive protein in childhood meningitis in countries with limited laboratory resources: a Chilean experience; Pediatric infectious disease journal; 1991; vol. 10 (no. 12); 923-8

Study details

Country/ies where study was carried out	Chile
Study type	Single-gate cross-sectional DTA study
Study dates	1987-1989
Inclusion criteria	Babies and children diagnosed with bacterial or viral meningitis
Exclusion criteria	Not reported
Patient characteristics	N=83 Bacterial meningitis n=67: Age in months (mean; SD in parentheses): 23 (34) Sex not reported Causative organism: n=31 H. influenzae type b; n=18 S. pneumoniae; n=10 N. meningitidis; n=4 beta haemolytic streptococcus B; n=1 enterococcus; n=1 staphylococcus aureus; n=1 klebsiella pneumoniae Viral meningitis n=16: Age in months (mean; SD in parentheses): 24 (32) Sex not reported
Index test(s)	CRP Elevated threshold defined as ≥20 mg/l
Reference standard(s)	CSF culture or blood culture
Sources of funding	No sources of funding reported
Other information	Diagnosis made on basis of CSF culture for 60/67 (90%)
Results	CRP, threshold ≥20 mg/l (n=83): TP 64; FP 2; FN 3; TN 14 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; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; S. pneumoniae; streptococcus pneumonia; SD: standard deviation; 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?	High *(Small comparative group to bacterial meningitis. Unclear if consecutive sample adopted)*
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?	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

Santotoribio, 2018

Bibliographic Reference Santotoribio, J. D; Cuadros-Munoz, J. F; Garcia-Casares, N.; Comparison of C reactive protein and procalcitonin levels in cerebrospinal fluid and serum to differentiate bacterial from viral meningitis; Annals of Clinical and Laboratory Science; 2018; vol. 48 (no. 4); 506-510

Study details

Country/ies where study was carried out	Spain

Study type	Single-gate cross-sectional DTA study
Study dates	2015 - 2016
Inclusion criteria	Children and adults diagnosed with bacterial or viral meningitis
Exclusion criteria	Other primary bacterial focus; chronic inflammatory diseases; previous antibiotic treatment
Patient characteristics	N=30 Bacterial meningitis n=18 Age/sex not reported by arm Causative organism (identified for 10/18): n=3 S. pneumoniae; n=2 N. meningitidis; n=2 Klebsiella pneumoniae; n=2 Staphylococcus aureus; n=1 Staphylococcus hominis Viral meningitis n=12 Age/sex not reported by arm Viral pathogen (identified for 4/12): n=2 Herpes simplex; n=2 enterovirus Whole sample (N=30): Age in years (median; range in parentheses): 52 (6-86) Sex: male: 24 (80%); female: 6 (20%)
Index test(s)	CRP Elevated threshold defined as ≥14mg/l PCT Elevated threshold defined as ≥0.18 ng/ml
Reference standard(s)	CSF culture, or signs/symptoms of acute infectious meningitis together with CSF showing intense PMN pleocytosis, elevated total protein and a marked glucose consumption
Sources of funding	No sources of funding reported
Other information	Diagnosis made on basis of CSF culture for 10/18 (56%)
Results	CRP, threshold ≥14 mg/l (n=30): TP 18; FP 2; FN 0; TN 10. AUC 0.926 (95% CI: 0.769-0.988) PCT, threshold ≥0.18 ng/ml (n=30): TP 16; FP 0; FN 2; TN 12. AUC 0.963 (95% CI: 0.822-0.995) 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; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N.

meningitidis: Neisseria meningitides; PCT: procalcitonin; PMN: polymorphonuclear; S. pneumoniae; streptococcus pneumonia; 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 *(Consecutive sample enrolled but patients with other primary bacterial focus were excluded to avoid false positives from CRP and PCT, along with patients with chronic inflammatory diseases. Patients previously treated with antibiotics were also excluded)*
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?	High *(56% of population with bacterial meningitis had positive bacterial infection in CSF)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

Schwarz, 2000

Bibliographic Reference	Schwarz, S; Bertram, M; Schwab, S; Andrassy, K; Hacke, W.; Serum procalcitonin levels in bacterial and abacterial meningitis; Critical care medicine; 2000; vol. 28 (no. 6); 1828-1832

Study details

Country/ies where study was carried out	Germany
Study type	Single-gate cross-sectional DTA study
Study dates	December 1997 - September 1998
Inclusion criteria	Adults (aged at least 16 years) hospitalised with acute meningitis
Exclusion criteria	Antibiotic treatment prior to hospital admission
Patient characteristics	N=30 Bacterial meningitis n=16 Age in years (mean; range in parentheses): 61 (16-87) Sex not reported Causative organism (identified in 11/16): n=6 S. pneumoniae; n=1 H. influenzae; n=1 Staphylococcus aureus; n=1 mycobacterium tuberculosis; n=1 borrelia burgdorferi; n=1 klebsiella pneumoniae Viral meningitis n=14 Age in years (mean; range in parentheses): 42 (19-48) Sex not reported Viral pathogen (identified in 7/14): n=2 Herpes simplex 1; n=1 Herpes simplex 2; n=1 Epstein-Barr; n=1 Enterovirus; n=2 Central European encephalitis
Index test(s)	PCT Elevated threshold defined as >0.5ng/ml CRP Elevated threshold defined as >8mg/l
Reference standard(s)	Microscopy of CSF, CSF culture, or blood culture
Sources of funding	No sources of funding reported

Other information	Diagnosis made on basis of CSF culture for 11/16 (69%)
Results	PCT, threshold >0.5ng/ml (n=30): TP 11; FP 0; FN 5; TN 14 CRP, threshold >8 mg/l (n=30): TP 15; FP 6; FN 1; TN 8 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; H. influenza: haemophilus influenza; PCT: procalcitonin; S. pneumoniae; streptococcus pneumonia; 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 *(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 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?	High *(69% of population with bacterial meningitis diagnosed via CSF culture)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Sormunen, 1999

Bibliographic Reference	Sormunen, P; Kallio, M. J. T; Kilpi, T; Peltola, H.; C-reactive protein is useful in distinguishing Gram stain-negative bacterial meningitis from viral meningitis in children; Journal of pediatrics; 1999; vol. 134 (no. 6); 725-729

Study details

Country/ies where study was carried out	Finland
Study type	Two-gate cross-sectional DTA study
Study dates	1984-1991 for BM 1977-1992 for VM
Inclusion criteria	Babies and children with bacterial meningitis with initial gram staining negative for bacteria, compared to children diagnosed with viral meningitis during a similar time period (hospital charts reviewed)
Exclusion criteria	Immunocompromised; prosthetic device (such as a ventriculo-peritoneal shunt); received more than 1 dose of parenteral antimicrobial agents before the diagnosis of bacterial meningitis
Patient characteristics	N=237 Bacterial meningitis n=55 (gram stain negative): Age/sex not available for those included in the analysis Causative organism: n=26 N. meningitidis; n=23 H. influenzae type b; n=3 S. pneumoniae; n=1 Listeria monocytogenes; n=1 E. coli; n=1 S. agalactiae Viral meningitis n=182: Age/sex not available Viral pathogen (identified in 92/182): n=46 enteroviruses; n=18 mumps (n = 18); n=10 varicella-zoster; n=6 adenovirus; n=4 cytomegalovirus; n=3 influenza; n=2 herpesvirus; n=2 rubella, n=1 measles. For 90/182 the specific aetiology was not identified, but no other (non-viral) cause of meningitis was found, and these people recovered without antimicrobial therapy
Index test(s)	WCC Elevated threshold defined as >15,0000 cells/mm³ (converted to cells/µl for consistency with other studies) CRP Elevated threshold defined as >20 mg/l
Reference standard(s)	CSF culture

Sources of funding	No sources of funding reported
Other information	Paper also reports WCC thresholds of >20,000 and >25,000 cells/mm³, but data only extracted for the >15,0000 threshold as this is consistent with other studies. Paper also reports CRP for threshold >40mg/l, but data only extracted for the >20 mg/l threshold, as this is most consistent with other studies.
Results	WCC, threshold >15000/mm³ (n=237): TP 34; FP 27; FN 21; TN 155 CRP, threshold >20 mg/l (n=237): TP 53; FP 13; FN 2; TN 169 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 – cells/µl. Equivalent to cells/mm³

BM: bacterial meningitis; CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia coli; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; S. agalactiae: streptococcus agalactiae; S. pneumoniae; streptococcus pneumonia; TN: true negative; TP: true positive; VM: viral meningitis; WCC: white cell count

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Case control)*
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)*
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

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(94% of patients diagnosed with bacterial meningitis underwent gram staining)*

Tatara, 2000

Bibliographic Reference	Tatara, R; Imai, H.; Serum C-reactive protein in the differential diagnosis of childhood meningitis; Pediatrics International; 2000; vol. 42 (no. 5); 541-546

Study details

Country/ies where study was carried out	Japan
Study type	Two-gate cross-sectional DTA study
Study dates	July 1988 to June 1998
Inclusion criteria	Babies and children (aged 1 month to 15 years) with a diagnosis of acute meningitis. Babies and children with bacterial meningitis compared to those with viral meningitis.
Exclusion criteria	Blood not drawn at the same time as lumbar puncture; those judged to have probable bacterial meningitis (for example, where prior antibiotic treatment might have sterilised the CSF); other non-viral or known underlying diseases including Kawasaki disease or other collagen vascular diseases

Patient characteristics	N=192 Bacterial meningitis n=66: Age in years (mean; SD in parentheses): 1.6 (1.8) Sex not reported Causative organism: n=45 H. influenzae; n=13 S. pneumoniae; n=3 group B streptococcus; n=3 E. coli; n=2 Listeria monocytogeneous; n=1 N. meningitidis Viral meningitis n=126: Age in years (mean; SD in parentheses): 3.8 (3.4) Sex not reported
Index test(s)	CRP Elevated threshold defined as ≥2 mg/dL (converted to mg/l for consistency with other studies)
Reference standard(s)	CSF culture
Sources of funding	Not industry funded
Results	CRP, threshold ≥2 mg/dL (n=192): TP 61; FP 20; FN 5; TN 106 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: Serum CRP – mg/l. Calculated as 1 mg/dL = 10mg/l.

CRP: c-reactive protein; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E.coli: escherichia coli; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; S. pneumoniae; streptococcus pneumonia; SD: standard deviation; 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 known if cases were consecutive)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
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?	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

Tzanakaki, 2005

Bibliographic Reference Tzanakaki, G; Tsophanomichalou, M; Kesanopoulos, K; Matzourani, R; Sioumala, M; Tabaki, A; Kremastinou, J.; Simultaneous single-tube PCR assay for the detection of Neisseria meningitidis, Haemophilus influenzae type b and Streptococcus pneumoniae; Clinical Microbiology and Infection; 2005; vol. 11 (no. 5); 386-390

Study details

Country/ies where study was carried out	Greece
Study type	Single-gate cross-sectional DTA study
Study dates	2002-2003
Inclusion criteria	People diagnosed with bacterial or viral meningitis based on blood and/or CSF samples submitted to laboratory

Exclusion criteria	Not reported
Patient characteristics	N=217 N. meningitidis n=33: No further details reported S. pneumoniae n=26: No further details reported H. influenzae type B n=8: No further details reported Viral meningitis n=150: No further details reported
Index test(s)	Molecular diagnosis Specific PCR for N. meningitidis Specific PCR for S. pneumoniae Specific PCR for H. influenzae
Reference standard(s)	CSF culture and/or blood culture
Sources of funding	No sources of funding reported
Other information	Data not extracted for n=54 suspected bacterial meningitis (clinically suspected cases of bacterial meningitis, but with culture and other tests yielding negative results)
Results	Molecular diagnosis: PCR for N. meningitidis (n=183): TP 31; FP 0; FN 2; TN 150 Molecular diagnosis: PCR for S. pneumoniae (n=176): TP 24; FP 0; FN 2; TN 150 Molecular diagnosis: PCR for H. influenzae (n=158): TP 7; FP 0; FN 1; TN 150 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; PCR: polymerase chain reaction; S. pneumoniae; streptococcus pneumonia; 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?	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?	High *(Reference standard CSF culture or blood culture. No proportions of population with bacterial meningitis diagnosed via CSF culture)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

Viallon, 2011

Bibliographic Reference Viallon, A; Desseigne, N; Marjollet, O; Birynczyk, A; Belin, M; Guyomarch, S; Borg, J; Pozetto, B; Bertrand, J. C; Zeni, F.; Meningitis in adult patients with a negative direct cerebrospinal fluid examination: Value of cytochemical markers for differential diagnosis; Critical Care; 2011; vol. 15 (no. 3)

Study details

Country/ies where study was carried out	France
Study type	Single-gate cross-sectional DTA study

Study dates	January 1997 - December 2009
Inclusion criteria	Adults admitted to the emergency department with acute meningitis and a negative direct CSF examination
Exclusion criteria	Presence of bacteria in the CSF evidenced by direct examination and/or detection of bacterial antigens in the CSF; antibiotic treatment before admission (>2 successive doses of prescribed antibiotic); presence of another focus of infection in addition to meningitis; meningitis assumed to be of bacterial origin, despite the absence of microbiologic documentation, and treated with antibiotics during hospitalisation
Patient characteristics	N=253 Bacterial meningitis n=35 (negative direct CSF examination): Age in years (mean; SD in parentheses): 55 (20) Sex: male: 17 (49%); female: 18 (51%) Causative organism: n=14 S. pneumoniae; n=6 Listeria monocytogenes; n=5 N. meningitidis; n=4 Streptococcus species; n=2 H. influenzae; n=2 Staphylococcus aureus; n=2 other species Viral meningitis n=218: Age in years (mean; SD in parentheses): 35 (18) Sex: male: 116 (53%); female: 102 47%) Viral pathogen (identified in 85/218): n=53 enterovirus; n=25 herpes virus; n=5 varicella zoster virus; n=2 Paramyxovirus
Index test(s)	CRP Elevated threshold defined as ≥37mg/l PCT Elevated threshold defined as ≥0.28 ng/ml
Reference standard(s)	CSF culture (but only those with negative direct CSF examination included)
Sources of funding	No sources of funding reported
Results	CRP, threshold ≥37mg/l (n=253): TP 30; FP 35; FN 5; TN 183. AUC 0.92 (95% CI: 0.92- 0.98) PCT, threshold ≥0.28 ng/ml (n=253): TP 34; FP 0; FN 1; TN 218. AUC 0.99 (95% CI: 0.99-1) 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; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenza: haemophilus influenza; N. meningitidis: Neisseria meningitides; PCT: procalcitonin; S. pneumoniae; streptococcus pneumonia; SD: standard deviation; TN: true negative; TP: true positive

Critical appraisal - QUADAS-2

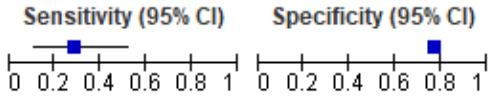
Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled however only patients diagnosed with bacterial meningitis or viral meningitis were included)*
Patient selection: applicability	Are there concerns that included 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?	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 *(62/97 patients with bacterial meningitis excluded due to presence of bacteria in the CSF evidenced by direct examination, additional focus of infection, and absence of microbiological documentation)*

Appendix E Forest plots

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

Figure 2: **Forest plot for sensitivity and specificity of white cell count (WCC) for diagnosis of bacterial meningitis in babies**

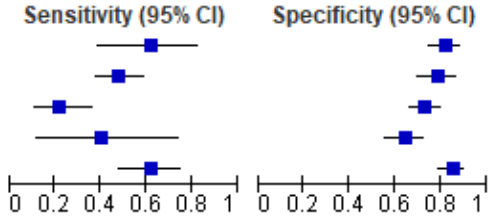
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003	6	1221	15	4110	BM U	15000 cells/µl	C	0.29 [0.11, 0.52]	0.77 [0.76, 0.78]



BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; U: undefined population

Figure 3: **Forest plot for sensitivity and specificity of white cell count (WCC) for diagnosis of bacterial meningitis in babies and children**

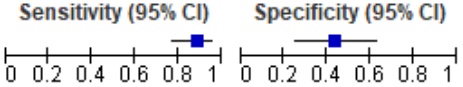
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2006	13	26	8	118	BM VM	15000 cells/µl	CAB	0.62 [0.38, 0.82]	0.82 [0.75, 0.88]
Dubos 2008	46	22	50	80	BM VM	15000 cells/µl	CAB	0.48 [0.38, 0.58]	0.78 [0.69, 0.86]
Lembo 1991a	10	50	36	136	BM VM NM	15000 cells/µl	CAO	0.22 [0.11, 0.36]	0.73 [0.66, 0.79]
Lembo 1991b	4	54	6	96	BM VM NM	15000 cells/µl	CAO	0.40 [0.12, 0.74]	0.64 [0.56, 0.72]
Sormunen 1999	34	27	21	155	BM VM	15000 cells/µl	C	0.62 [0.48, 0.75]	0.85 [0.79, 0.90]



B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; NM: non-meningitis; O: other reference standard not listed in protocol; TN: true negative; TP: true positive; VM: viral meningitis

Figure 4: Forest plot for sensitivity and specificity of white cell count (WCC) for diagnosis of bacterial meningitis in undefined age

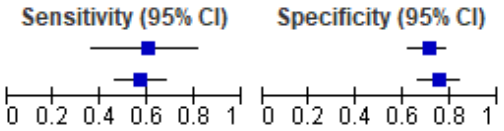
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Borchsenius 1991	47	17	6	13	BM VM NM	<4000 or 11000 cells/µl	CBO	0.89 [0.77, 0.96]	0.43 [0.25, 0.63]



B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; O: other reference standard not listed in protocol; NM: non-meningitis; TN: true negative; TP: true positive; VM: viral meningitis

Figure 5: **Forest plot for sensitivity and specificity of neutrophils for diagnosis of bacterial meningitis in babies and children**

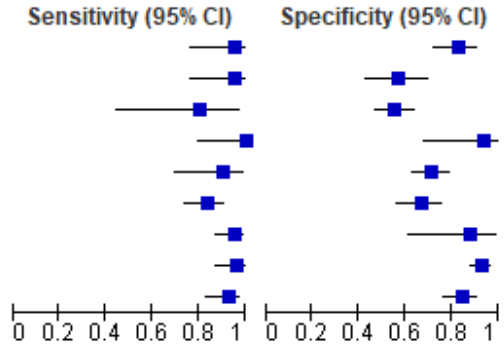
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2006	12	39	8	94	BM VM	10000 cells/µl	CAB	0.60 [0.36, 0.81]	0.71 [0.62, 0.78]
Dubos 2008	49	25	37	77	BM VM	10000 cells/µl	CAB	0.57 [0.46, 0.68]	0.75 [0.66, 0.83]



A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; VM: viral meningitis

Figure 6: **Forest plot for sensitivity and specificity of c-reactive protein (CRP) for diagnosis of bacterial meningitis in babies and children***

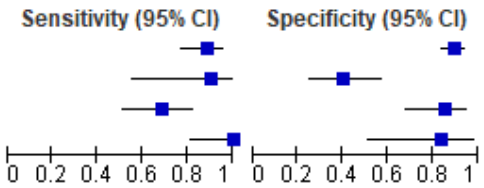
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
De Cauwer 2007	20	12	1	58	BM VM	02 mg/l	CBO	0.95 [0.76, 1.00]	0.83 [0.72, 0.91]
Benjamin 1984	20	25	1	33	BM VM NM	10 mg/l	C	0.95 [0.76, 1.00]	0.57 [0.43, 0.70]
Lembo 1991b	8	67	2	83	BM VM NM	10 mg/l	CAO	0.80 [0.44, 0.97]	0.55 [0.47, 0.63]
Peltola 1982	16	1	0	14	BM VM	10 mg/l	CB	1.00 [0.79, 1.00]	0.93 [0.68, 1.00]
Dubos 2006	19	42	2	104	BM VM	20 mg/l	CAB	0.90 [0.70, 0.99]	0.71 [0.63, 0.78]
Dubos 2008	79	34	16	68	BM VM	20 mg/l	CAB	0.83 [0.74, 0.90]	0.67 [0.57, 0.76]
Roine 1991	64	2	3	14	BM VM	20 mg/l	CB	0.96 [0.87, 0.99]	0.88 [0.62, 0.98]
Sormunen 1999	53	13	2	169	BM VM	20 mg/l	C	0.96 [0.87, 1.00]	0.93 [0.88, 0.96]
Tatara 2000	61	20	5	106	BM VM	20 mg/l	C	0.92 [0.83, 0.97]	0.84 [0.77, 0.90]



A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; NM: non-meningitis; O: other reference standard not listed in protocol; TN: true negative; TP: true positive; VM: viral meningitis
**arranged by threshold and then by study ID*

Figure 7: **Forest plot for sensitivity and specificity of c-reactive protein (CRP) for diagnosis of bacterial meningitis in children and adults**

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Hansson 1993	53	15	7	131	BM VM	50 mg/l	CA	0.88 [0.77, 0.95]	0.90 [0.84, 0.94]
Knudsen 2007	9	25	1	17	BM VM NM	40 mg/l	CAO	0.90 [0.55, 1.00]	0.40 [0.26, 0.57]
Morales-Cosado 2016	26	5	12	28	BM VM	90 mg/l	CA	0.68 [0.51, 0.82]	0.85 [0.68, 0.95]
Santotoribo 2018	18	2	0	10	BM VM	14 mg/l	CAO	1.00 [0.81, 1.00]	0.83 [0.52, 0.98]

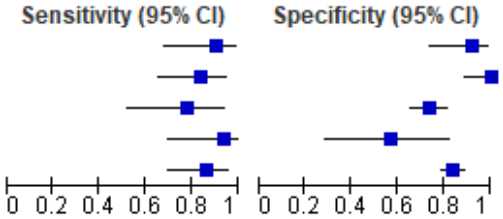


A: CSF antigen; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; NM: non-meningitis; O: other reference standard not listed in protocol; TN: true

negative; TP: true positive; VM: viral meningitis

Figure 8: **Forest plot for sensitivity and specificity of c-reactive protein (CRP) for diagnosis of bacterial meningitis in adults**

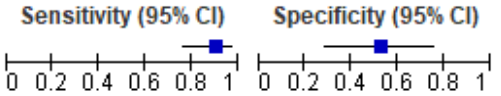
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Jereb 2001	18	2	2	23	BM VM	50 mg/l	CBO	0.90 [0.68, 0.99]	0.92 [0.74, 0.99]
Paradowski 1995	25	0	5	30	BM VM	40 mg/l	CAO	0.83 [0.65, 0.94]	1.00 [0.88, 1.00]
Ray 2007	14	35	4	98	BM VM	22 mg/l	CABO	0.78 [0.52, 0.94]	0.74 [0.65, 0.81]
Schwarz 2000	15	6	1	8	BM VM	08 mg/l	CBO	0.94 [0.70, 1.00]	0.57 [0.29, 0.82]
Viallon 2011	30	35	5	183	BM VM	37 mg/l	C	0.86 [0.70, 0.95]	0.84 [0.78, 0.89]



A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; O: other reference standard not listed in protocol; TN: true negative; TP: true positive; VM: viral meningitis

Figure 9: **Forest plot for sensitivity and specificity of c-reactive protein (CRP) for diagnosis of bacterial meningitis in undefined age**

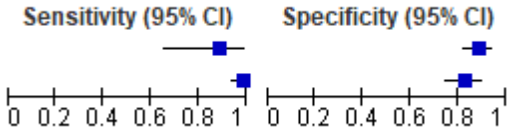
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Borchsenius 1991	36	9	4	10	BM VM NM	20 mg/l	CBO	0.90 [0.76, 0.97]	0.53 [0.29, 0.76]



B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; NM: non-meningitis; O: other reference standard not listed in protocol; TN: true negative; TP: true positive; VM: viral meningitis

Figure 10: **Forest plot for sensitivity and specificity of procalcitonin (PCT) for diagnosis of bacterial meningitis in babies and children**

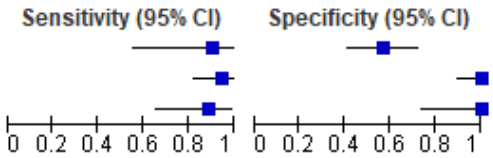
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2006	16	15	2	119	BM VM	0.5 ng/ml	CAB	0.89 [0.65, 0.99]	0.89 [0.82, 0.94]
Dubos 2008	89	17	1	83	BM VM	0.5 ng/ml	CAB	0.99 [0.94, 1.00]	0.83 [0.74, 0.90]



A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; VM: viral meningitis

Figure 11: **Forest plot for sensitivity and specificity of procalcitonin (PCT) for diagnosis of bacterial meningitis in children and adults**

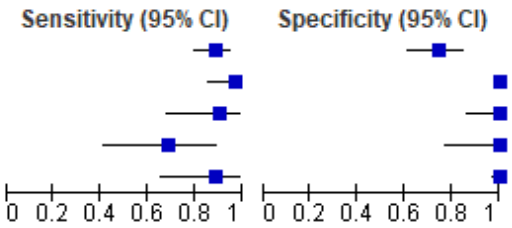
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Knudsen 2007	9	18	1	24	BM VM NM	0.25 ng/ml	CAO	0.90 [0.55, 1.00]	0.57 [0.41, 0.72]
Morales-Cosado 2016	36	0	2	33	BM VM	0.74 ng/ml	CA	0.95 [0.82, 0.99]	1.00 [0.89, 1.00]
Santotoribo 2018	16	0	2	12	BM VM	0.18 ng/ml	CAO	0.89 [0.65, 0.99]	1.00 [0.74, 1.00]



A: CSF antigen; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; NM: non-meningitis; O: other reference standard not listed in protocol; TN: true negative; TP: true positive; VM: viral meningitis

Figure 12: Forest plot for sensitivity and specificity of procalcitonin (PCT) for diagnosis of bacterial meningitis in adults*

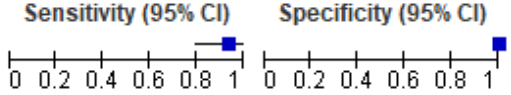
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Park 2017	71	15	9	43	BM VM	0.12 ng/ml	CAO	0.89 [0.80, 0.95]	0.74 [0.61, 0.85]
Viallon 2011	34	0	1	218	BM VM	0.28 ng/ml	C	0.97 [0.85, 1.00]	1.00 [0.98, 1.00]
Jereb 2001	18	0	2	25	BM VM	0.5 ng/ml	CBO	0.90 [0.68, 0.99]	1.00 [0.86, 1.00]
Schwarz 2000	11	0	5	14	BM VM	0.5 ng/ml	CBO	0.69 [0.41, 0.89]	1.00 [0.77, 1.00]
Ray 2007	16	0	2	133	BM VM	2.13 ng/ml	CABO	0.89 [0.65, 0.99]	1.00 [0.97, 1.00]



A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; O: other reference standard not listed in protocol; TN: true negative; TP: true positive; VM: viral meningitis
**arranged by threshold and then by study ID*

Figure 13: Forest plot for sensitivity and specificity of polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by N. meningitidis in undefined age

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Tzanakaki 2005	31	0	2	150	BM VM	undefined	CB	0.94 [0.80, 0.99]	1.00 [0.98, 1.00]



B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; VM: viral meningitis

Figure 14: Forest plot for sensitivity and specificity of polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by S. pneumoniae in babies and children

Study	TP	FP	FN	TN	Population	Threshold	Reference stand
Dagan 1998	4	71	0	206	BM NM HC	undefined	

B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; HC: healthy controls; NM: non-meningitis; TN: true negative; TP: true positive

Figure 15: Forest plot for sensitivity and specificity of polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by S. pneumoniae in undefined age

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Tzanakaki 2005	24	0	2	150	BM VM	undefined	CB	0.92 [0.75, 0.99]	1.00 [0.98, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; VM: viral meningitis

Figure 16: Forest plot for sensitivity and specificity of polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by group B streptococcus in babies

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Morrisey 2017	5	17	0	805	BM U	undefined	C	1.00 [0.48, 1.00]	0.98 [0.97, 0.99]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; U: undefined population

Figure 17: Forest plot for sensitivity and specificity of polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by H. influenzae in undefined age

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Tzanakaki 2005	7	0	1	150	BM VM	undefined	CB	0.88 [0.47, 1.00]	1.00 [0.98, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

B: blood culture; BM: bacterial meningitis; C: CSF culture; FN: false negative; FP: false positive; TN: true negative; TP: true positive; VM: viral meningitis

Appendix F GRADE tables

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

Table 5: White cell count (WCC) for diagnosis of bacterial meningitis in babies

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bonsu 2003)	Population: BM U Threshold: 15000 cells/µl Reference standard: C	5353	Sensitivity: 0.29 (0.11 to 0.52)	No serious	No serious	No serious	Serious[1]	MODERATE	0.005	0.996
			Specificity: 0.77 (0.76 to 0.78)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; C: CSF culture; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1]95% CI crosses 1 decision making threshold

Table 6: White cell count (WCC) for diagnosis of bacterial meningitis 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 (Dubos 2006)	Population: BM VM	165	Sensitivity: 0.62 (0.38 to 0.82)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.33	0.94

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 15000 cells/µl Reference standard: CAB		Specificity: 0.82 (0.75 to 0.88)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Dubos 2008)	Population: BM VM	198	Sensitivity: 0.48 (0.38 to 0.58)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.68	0.62
	Threshold: 15000 cells/µl Reference standard: CAB		Specificity: 0.78 (0.69 to 0.86)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Lembo 1991a)	Population: BM VM NM	232	Sensitivity: 0.22 (0.11 to 0.36)	Serious[1]	No serious	No serious	No serious	MODERATE	0.17	0.79
	Threshold: 15000 cells/µl Reference standard: CAO		Specificity: 0.73 (0.66 to 0.79)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Lembo 1991b)	Population: BM VM NM	160	Sensitivity: 0.40 (0.12 to 0.74)	No serious	No serious	No serious	Serious[2]	MODERATE	0.07	0.94

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 15000 cells/µl Reference standard: CAO		Specificity: 0.64 (0.56 to 0.72)	No serious	No serious	No serious	No serious	HIGH		
1 (Sormunen 1999)	Population: BM VM Threshold: 15000 cells/µl Reference standard: C	237	Sensitivity: 0.62 (0.48 to 0.75)	Serious[1]	No serious	No serious	Serious[1]	LOW	0.56	0.88
			Specificity: 0.85 (0.79 to 0.90)	Serious[1]	No serious	No serious	Serious[1]	LOW		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NM: non-meningitis; NPV: negative predictive value; O: other reference standard not listed in 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 7: White cell count (WCC) for diagnosis of bacterial meningitis in 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: BM VM NM	83	Sensitivity: 0.89 (0.77 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.73	0.68

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: <4000 or ≥11000 cells/µl Reference standard: CBO		Specificity: 0.43 (0.25 to 0.63)	Serious[1]	No serious	No serious	Serious[2]	LOW		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NM: non-meningitis; NPV: negative predictive value; O: other reference standard not listed in 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 8: Neutrophils for diagnosis of bacterial meningitis 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 (Dubos 2006)	Population: BM VM Threshold: 10000 cells/µl Reference standard: CAB	153	Sensitivity: 0.60 (0.36 to 0.81)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.24	0.92
			Specificity: 0.71 (0.62 to 0.78)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Dubos 2008)	Population: BM VM	188	Sensitivity: 0.57 (0.46 to 0.68)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.66	0.68

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 10000 cells/µl Reference standard: CAB		Specificity: 0.75 (0.66 to 0.83)	Serious[1]	No serious	No serious	No serious	MODERATE		

A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; 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 9: C-reactive protein (CRP) for diagnosis of bacterial meningitis 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 (De Cauwer 2007)	Population: BM VM Threshold: 2 mg/l Reference standard: CBO	91	Sensitivity: 0.95 (0.76 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.63	0.98
			Specificity: 0.83 (0.72 to 0.91)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Benjamin 1984)	Population: BM VM NM	79	Sensitivity: 0.95 (0.76 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE	0.44	0.97

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 10 mg/l Reference standard: C		Specificity: 0.57 (0.43 to 0.70)	No serious	No serious	No serious	Serious[2]	MODERATE		
1 (Lembo 1991b)	Population: BM VM NM	160	Sensitivity: 0.80 (0.44 to 0.97)	No serious	No serious	No serious	Very serious[3]	LOW	0.11	0.98
	Threshold: 10 mg/l Reference standard: CAO		Specificity: 0.55 (0.47 to 0.63)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Peltola 1982)	Population: BM VM	31	Sensitivity: 1.00 (0.79 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.94	1.00
	Threshold: 10 mg/l Reference standard: CB		Specificity: 0.93 (0.68 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Dubos 2006)	Population: BM VM	167	Sensitivity: 0.90 (0.70 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.31	0.98

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 20 mg/l Reference standard: CAB		Specificity: 0.71 (0.63 to 0.78)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Dubos 2008)	Population: BM VM Threshold: 20 mg/l Reference standard: CAB	197	Sensitivity: 0.83 (0.74 to 0.90)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.70	0.81
			Specificity: 0.67 (0.57 to 0.76)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Roine 1999)	Population: BM VM Threshold: 20 mg/l Reference standard: CB	83	Sensitivity: 0.96 (0.87 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.97	0.82
			Specificity: 0.88 (0.62 to 0.98)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.96 (0.87 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.80	0.99

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 20 mg/l Reference standard: C		Specificity: 0.93 (0.88 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Tatara 2000)	Population: BM VM	192	Sensitivity: 0.92 (0.83 to 0.97)	No serious	No serious	No serious	Serious[2]	MODERATE	0.75	0.96
	Threshold: 20 mg/l Reference standard: C		Specificity: 0.84 (0.77 to 0.90)	No serious	No serious	No serious	Serious[2]	MODERATE		

A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NM: non-meningitis; NPV: negative predictive value; O: other reference standard not listed in protocol; PPV: positive predictive value; VM: viral meningitis
**arranged by threshold and then by study ID*
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold
[3]95% CI crosses 2 decision making thresholds

Table 10: C-reactive protein (CRP) for diagnosis of bacterial meningitis in children and 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 (Hansson 1993)	Population: BM VM	206	Sensitivity: 0.88 (0.77 to 0.95)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.78	0.95

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 50 mg/l Reference standard: CA		Specificity: 0.90 (0.84 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Knudsen 2007)	Population: BM VM NM Threshold: 40 mg/l Reference standard: CAO	52	Sensitivity: 0.90 (0.55 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE	0.26	0.94
			Specificity: 0.40 (0.26 to 0.57)	No serious	No serious	No serious	Serious[2]	MODERATE		
1 (Morales-Cosado 2016	Population: BM VM Threshold: 90 mg/l Reference standard: CA	71	Sensitivity: 0.68 (0.51 to 0.82)	No serious	No serious	No serious	No serious	HIGH	0.84	0.70
			Sensitivity: 0.85 (0.68 to 0.95)	No serious	No serious	No serious	Serious[2]	MODERATE		
			AUC: 0.92 (0.84 to 0.99)	No serious	No serious	No serious	No serious	HIGH		
1 (Santotoribo 2018)	Population: BM VM	30	Sensitivity: 1.00 (0.81 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.90	1.00

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 14 mg/l Reference standard: CAO		Specificity: 0.83 (0.52 to 0.98)	Serious[1]	No serious	No serious	Serious[2]	LOW		

A: CSF antigen; AUC: area under the curve; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NM: non-meningitis; NPV: negative predictive value; O: other reference standard not listed in 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 11: C-reactive protein (CRP) for diagnosis of bacterial meningitis in 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 (Jereb 2001)	Population: BM VM Threshold: 50 mg/l Reference standard: CBO	45	Sensitivity: 0.90 (0.68 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.90	0.92
			Specificity: 0.92 (0.74 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Paradowski 1995)	Population: BM VM	60	Sensitivity: 0.83 (0.65 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.86

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 40 mg/l Reference standard: CAO		Specificity: 1.00 (0.88 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Ray 2007)	Population: BM VM Threshold: 22 mg/l Reference standard: CABO	151	Sensitivity: 0.78 (0.52 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.29	0.96
			Specificity: 0.74 (0.65 to 0.81)	Serious[1]	No serious	No serious	No serious	MODERATE		
			AUC 0.81 (0.58 to 0.92)	Serious[1]	No serious	No serious	Very serious[3]	VERY LOW		
1 (Schwarz 2000)	Population: BM VM Threshold: 8 mg/l Reference standard: CBO	30	Sensitivity: 0.94 (0.70 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.71	0.89
			Specificity: 0.57 (0.29 to 0.82)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Viallon 2011)	Population: BM VM Threshold: 37 mg/l	253	Sensitivity: 0.86 (0.70 to 0.95)	No serious	No serious	No serious	Serious[2]	MODERATE	0.46	0.97
			Specificity: 0.84 (0.78 to 0.89)	No serious	No serious	No serious	No serious	HIGH		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Reference standard: C		AUC: 0.92 (0.92 to 0.98)	No serious	No serious	No serious	No serious	HIGH		

A: CSF antigen; AUC: area under the curve: B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; O: other reference standard not listed in 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
[3] 95% CI crosses 2 decision making thresholds

Table 12: C-reactive protein (CRP) for diagnosis of bacterial meningitis in undefined age

No 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: BM VM NM Threshold: 20 mg/l Reference standard: CBO	59	Sensitivity: 0.90 (0.76 to 0.97)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.80	0.71
			Specificity: 0.53 (0.29 to 0.76)	Serious[1]	No serious	No serious	Serious[2]	LOW		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NM: non-meningitis; NPV: negative predictive value; O: other reference standard not listed in 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 13: Procalcitonin (PCT) for diagnosis of bacterial meningitis 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

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Dubos 2006)	Population: BM VM Threshold: 0.5 ng/ml Reference standard: CAB	152	Sensitivity: 0.89 (0.65 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.52	0.98
			Specificity: 0.89 (0.82 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Dubos 2008)	Population: BM VM Threshold: 0.5 ng/ml Reference standard: CAB	190	Sensitivity: 0.99 (0.94 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE	0.84	0.99
			Specificity: 0.83 (0.74 to 0.90)	Serious[1]	No serious	No serious	Serious[2]	LOW		

A: CSF antigen; B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; 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 14: Procalcitonin (PCT) for diagnosis of bacterial meningitis in children and 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 (Knudsen 2007)	Population: BM VM NM	52	Sensitivity: 0.90 (0.55 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.33	0.96

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 0.25 ng/ml Reference standard: CAO		Specificity: 0.57 (0.41 to 0.72)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Morales-Cosado 2016)	Population: BM VM	71	Sensitivity: 0.95 (0.82 to 0.99)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	0.94
	Threshold: 0.74 ng/ml		Specificity: 1.00 (0.89 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE		
	Reference standard: CA		AUC: 0.996 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Santotoribo 2018)	Population: BM VM	30	Sensitivity: 0.89 (0.65 to 0.99)	Serious[2]	No serious	No serious	Serious[1]	LOW	1.00	0.86
	Threshold: 0.18 ng/ml Reference standard: CAO		Specificity: 1.00 (0.74 to 1.00)	Serious[2]	No serious	No serious	Serious[1]	LOW		

A: CSF antigen; AUC: area under the curve; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NM: non-meningitis; NPV: negative predictive value; O: other reference standard not listed in protocol; PPV: positive predictive value; 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 15: Procalcitonin (PCT) for diagnosis of bacterial meningitis in 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 (Park 2017)	Population: BM VM Threshold: 0.12 ng/ml Reference standard: CAO	138	Sensitivity: 0.89 (0.80 to 0.95)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.83	0.83
			Specificity: 0.74 (0.61 to 0.85)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Viallon 2011)	Population: BM VM Threshold: 0.28 ng/ml Reference standard: C	253	Sensitivity: 0.97 (0.85 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE	1.00	0.995
			Specificity: 1.00 (0.98 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
			AUC 0.99 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Jereb 2001)	Population: BM VM Threshold: 0.5 ng/ml Reference standard: CBO	45	Sensitivity: 0.90 (0.68 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.93
			Specificity: 1.00 (0.86 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Schwarz 2000)	Population: BM VM	30	Sensitivity: 0.69 (0.41 to 0.89)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.74

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: 0.5 ng/ml Reference standard: CBO		Specificity: 1.00 (0.77 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Ray 2007)	Population: BM VM Threshold: 2.13 ng/ml Reference standard: CABO	151	Sensitivity: 0.89 (0.65 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.99
			Specificity: 1.00 (0.97 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
			AUC 0.98 (0.83 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

A: CSF antigen; AUC: area under the curve; B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; O: other reference standard not listed in 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 16: Polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by N. meningitidis in 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 (Tzanakaki 2005)	Population: BM VM	183	Sensitivity: 0.94 (0.80 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.99

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	Threshold: Undefined Reference standard: CB		Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; 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 17: Polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by S. pneumoniae 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 (Dagan 1998)	Population: BM NM HC Threshold: Undefined Reference standard: CB	281	Sensitivity: 1.00 (0.40 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.05	1.00
			Specificity: 0.74 (0.69 to 0.79)	Serious[1]	No serious	No serious	No serious	MODERATE		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; HC: healthy controls; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds

Table 18: Polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by S. pneumoniae in 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 (Tzanakaki 2005)	Population: BM VM Threshold: Undefined Reference standard: CB	176	Sensitivity: 0.92 (0.75 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.99
			Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; 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 19: Polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by group B streptococcus in babies

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Morrissey 2017)	Population: BM U Threshold: Undefined Reference standard: C	827	Sensitivity: 1.00 (0.48 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.23	1.00
			Specificity: 0.98 (0.97 to 0.99)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; GBS: group B streptococcus; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds

Table 20: Polymerase chain reaction (PCR) for diagnosis of bacterial meningitis caused by H. influenzae in undefined age

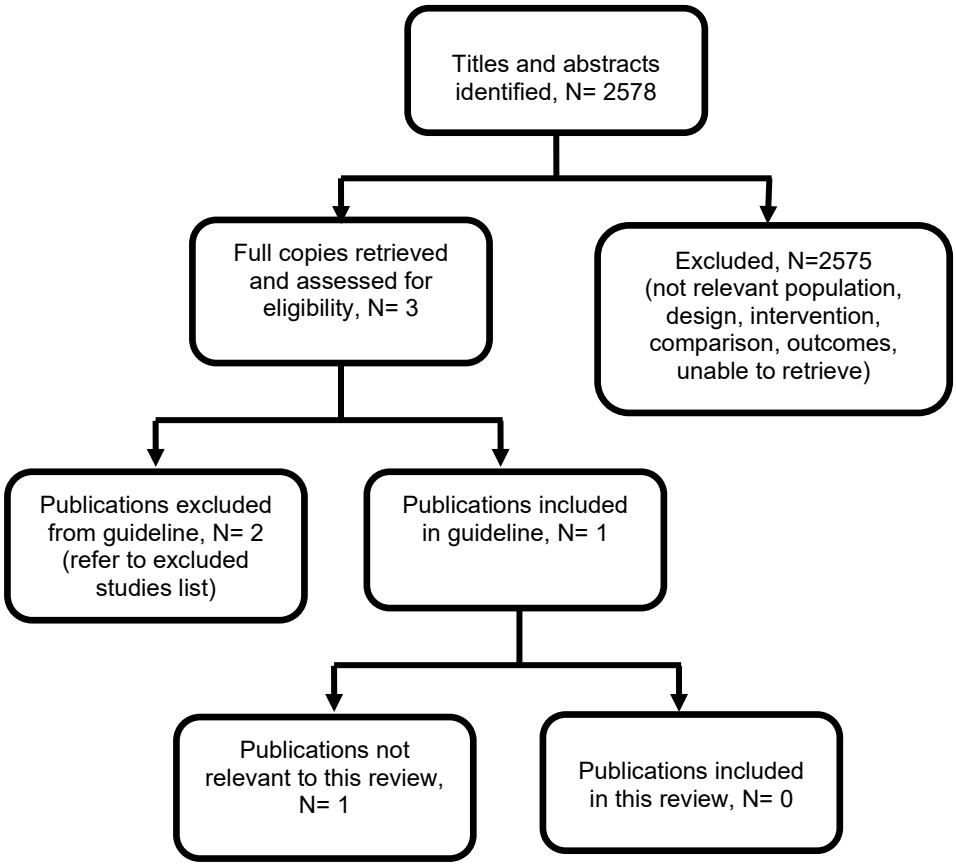
No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Tzanakaki 2005)	Population: BM VM Threshold: Undefined Reference standard: CB	158	Sensitivity: 0.88 (0.47 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	0.99
			Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

B: blood culture; BM: bacterial meningitis; C: CSF culture; CI: confidence interval; NPV: negative predictive value; 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 2 decision making thresholds

Appendix G Economic evidence study selection

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

Figure15: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 bacterial meningitis?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

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

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 bacterial meningitis?

Although there was a combined search to cover both this review (evidence review B1) and evidence review B2, the excluded studies list only reflects those excluded from the current review (B1).

Diagnostic studies

Table 21: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Abdeldaim, G. M. K, Stralin, K, Korsgaard, J et al. (2010) Multiplex quantitative PCR for detection of lower respiratory tract infection and meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis. BMC Microbiology 10 (no pagination)	- Index test not of interest for review *PCR on CSF*
Abelian, A and Pritchard, I. (2011) Neonatal bacterial meningitis: Has time come for polymerase chain reaction?. Journal of Pediatric Infectious Diseases 6(3): 227-229	- Index test not of interest for review *Only CSF samples tested*
Aksoy, F, Yilmaz, G, Nur Aydin, N et al. (2017) Are new biomarkers useful in the diagnosis of meningitis in adults?. Open Forum Infectious Diseases 4 (Supplement 1): 303	- Study design not of interest for review *Conference abstract*
Albuquerque, R. C, Moreno, A. C. R, Dos Santos, S. R et al. (2019) Multiplex-PCR for diagnosis of bacterial meningitis. Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology] 50(2): 435-443	- Index test not of interest for review *Only CSF samples tested*
Alkholi, U. M, Abd Al-Monem, N, Abd El-Azim, A. A et al. (2011) Serum procalcitonin in viral and bacterial meningitis. Journal of Global Infectious Diseases 3(1): 14-18	- Country not of interest for review *Not a high-income OECD country*
Alons, I. M, Verheul, R. J, Kuipers, I et al. (2016) Procalcitonin in cerebrospinal fluid in meningitis: a prospective diagnostic study. Brain and Behavior 6(11): e00545	- Insufficient presentation of results *Cannot calculate 2x2 table for plasma PCT (data reported for CSF PCT only)*
Altun, O, Athlin, S, Almuhayawi, M et al. (2016) Rapid identification of Streptococcus pneumoniae in blood	- Population does not meet inclusion criteria *Streptococcus pneumoniae in blood culture (diagnosis*

cultures by using the ImmuLex, Slidex and Wellcogen latex agglutination tests and the BinaxNOW antigen test. European Journal of Clinical Microbiology and Infectious Diseases 35(4): 579-585	*not reported)*
Ansong, A. K, Smith, P. B, Benjamin, D. K et al. (2009) Group B streptococcal meningitis: cerebrospinal fluid parameters in the era of intrapartum antibiotic prophylaxis. Early human development 85(10suppl): S5-7	- Population does not meet inclusion criteria *Neonates*
Anttila, M and Peltola, H. (1992) Serum C-reactive protein in the course of Haemophilus influenzae type b meningitis. Journal of infectious diseases 165(suppl1): S36-S37	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Ao, D, Wei, L, Hui-Hui, G et al. (2014) Rapid diagnosis and discrimination of bacterial meningitis in children using gram probe real-time polymerase chain reaction. Clinical pediatrics 53(9): 839-844	- Index test not of interest for review *Only CSF samples tested*
Ascher, D. P; Wilson, S; Fischer, G. W. (1991) Comparison of commercially available group B streptococcal latex agglutination assays. Journal of clinical microbiology 29(12): 2895-6	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Athlin, S, Altun, O, Eriksen, H. B et al. (2015) The Uni-GoldTM Streptococcus pneumoniae urinary antigen test: an interassay comparison with the BinaxNOW Streptococcus pneumoniae test on consecutive urine samples and evaluation on patients with bacteremia. European Journal of Clinical Microbiology and Infectious Diseases 34(8): 1583-1588	- Population does not meet inclusion criteria *Streptococcus pneumoniae positive bacteraemia (diagnosis not reported)*
Athlin, S; Iversen, A; Ozenci, V. (2017) Comparison of the ImmuView and the BinaxNOW antigen tests in detection of Streptococcus pneumoniae and Legionella pneumophila in urine. European journal of clinical microbiology & infectious diseases 36(10): 1933-1938	- Population does not meet inclusion criteria *Streptococcus pneumoniae positive bacteraemia (diagnosis not reported)*
Avni, T, Mansur, N, Leibovici, L et al. (2010) PCR using blood for diagnosis of invasive pneumococcal disease: systematic review and meta-analysis. Journal of clinical microbiology 48(2): 489-496	- Population does not meet inclusion criteria *Checked included studies for inclusion.*
Aygun, F, Durak, C, Varol, F et al. (2020) Evaluation of complete blood count parameters for diagnosis in children with	- Population does not meet inclusion criteria *Sepsis (only 11% were CNS in origin)*

sepsis in the pediatric intensive care unit. Cocuk Enfeksiyon Dergisi 14(2): e55-e62	
Azzari, C, Moriondo, M, Indolfi, G et al. (2008) Molecular detection methods and serotyping performed directly on clinical samples improve diagnostic sensitivity and reveal increased incidence of invasive disease by Streptococcus pneumoniae in Italian children. Journal of Medical Microbiology 57(10): 1205-1212	- Index test not of interest for review *PCR and culture used as reference standard*
Backman, A, Lantz, P. G, Radstrom, P et al. Evaluation of an extended diagnostic PCR assay for detection and verification of the common causes of bacterial meningitis in CSF and other biological samples. Molecular and Cellular Probes 13(1): 49-60	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Baker, C. J and Rench, M. A. (1983) Commercial latex agglutination for detection of group B streptococcal antigen in body fluids. Journal of pediatrics 102(3): 393-395	- Index test not of interest for review *Latex agglutination*
Ballard, T. L; Roe, M. H; Wheeler, R. C. (1987) Comparison of three latex agglutination kits and counterimmunoelectrophoresis for the detection of bacterial antigens in a pediatric population. Pediatric infectious disease journal 6(7): 630-634	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Ben, R. J, Kung, S, Chang, F. Y et al. (2008) Rapid diagnosis of bacterial meningitis using a microarray. Journal of the Formosan Medical Association 107(6): 448-453	- Reference standard not of interest for review *CSF pleocytosis (> 5 leukocytes/µL of CSF)*
Bilavsky, E, Yarden-Bilavsky, H, Ashkenazi, S et al. (2009) C-reactive protein as a marker of serious bacterial infections in hospitalized febrile infants. Acta Paediatrica 98(11): 1776-1780	- Population does not meet inclusion criteria *10% with bacterial meningitis*
Borrow, R, Claus, H, Chaudhry, U et al. (1998) siaD PCR ELISA for confirmation and identification of serogroup Y and W135 meningococcal infections. FEMS Microbiology Letters 159(2): 209-14	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Borschsenius, F, Bruun, J. N, Michaelsen, T. E et al. (1986) Serum C-reactive protein in systemic infections due to Neisseria meningitidis. NIPH annals 9(1): 15-21	- Insufficient presentation of results *Same data as reported in Borschsenius 1991*
Boudet, A, Pantel, A, Carles, M. J et al. (2019) A review of a 13-month period of	- Index test not of interest for review *Only CSF samples tested*

FilmArray Meningitis/Encephalitis panel implementation as a first-line diagnosis tool at a university hospital. 14(10): e0223887	
Brouwer, M. C; Tunkel, A. R; Van De Beek, D. (2010) Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clinical Microbiology Reviews 23(3): 467-492	- Study design not of interest for review *Discussion paper*
Bryant, P. A, Li, H. Y, Zaia, A et al. (2004) Prospective study of a real-time PCR that is highly sensitive, specific, and clinically useful for diagnosis of meningococcal disease in children. Journal of clinical microbiology 42(7): 2919-2925	- Index test/reference standard not of interest for review *Index tests: blood culture and lab-based PCR; reference standard includes clinical criteria*
Carrol, E. D, Newland, P, Thomson, A. P. J et al. (2005) Prognostic value of procalcitonin in children with meningococcal sepsis. Critical care medicine 33(1): 224-225	- Study design and outcomes not of interest for review *PCT as a prognostic marker in people with meningococcal sepsis*
Carrol, E.D, Newland, P, Riordan, F.A.I et al. (2002) Procalcitonin as a diagnostic marker of meningococcal disease in children presenting with fever and a rash. Archives of Disease in Childhood 86(4): 282-285	- Population not of interest for review *Meningococcal disease*
Carrol, E.D, Thomson, A.P.J, Shears, P et al. (2000) Performance characteristics of the polymerase chain reaction assay to confirm clinical meningococcal disease. Archives of Disease in Childhood 83(3): 271-273	- Index test not of interest for review *Lab-based PCR (meningococcal disease)*
Clarke, D and Cost, K. (1983) Use of serum C-reactive protein in differentiating septic from aseptic meningitis in children. Journal of pediatrics 102(5): 718-720	- Insufficient presentation of results *Insufficient information to calculate 2x2 tables*
Coant, P.N, Kornberg, A.E, Duffy, L.C et al. (1992) Blood culture results as determinants in the organism identification of bacterial meningitis. Pediatric Emergency Care 8(4): 200-205	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Cocquerelle, V, Fossard, C, Souply, L et al. (2009) Evaluation of three diagnosis models for differentiating bacterial from viral meningitis. Clinical Microbiology and Infection 15 (S4): S224-S225	- Study design not of interest for review *Conference Abstract*
Drakopoulou, Z, Kesanopoulos, K, Sioumala, M et al. (2008) Simultaneous single-tube PCR-based assay for the direct identification of the five most	- Population does not meet inclusion criteria *All patients confirmed as having meningococcal serogroups, diagnostic accuracy data on identification of individual serogroups in confirmed meningococcal*

common meningococcal serogroups from clinical samples. FEMS Immunology and Medical Microbiology 53(2): 178-182	*isolates*
Drew, R. J, O. Maoldomhnaigh C, Gavin, P. J, O' Sullivan N, Butler, K. M et al. (2012) The impact of meningococcal polymerase chain reaction testing on laboratory confirmation of invasive meningococcal disease. Pediatric infectious disease journal 31(3): 316-8	- Reference standard not of interest for review *Unclear if culture of CSF done for comparator group of BSI*
Dubos, F, Korczowski, B, Aygun, D.A et al. (2010) Distinguishing between bacterial and aseptic meningitis in children: European comparison of two clinical decision rules. Archives of Disease in Childhood 95(12): 963-967	- Index test not of interest for review *Combination of index tests not of interest (includes clinical presentation and CSF parameters)*
Edelstein, P. H; Jorgensen, C. S; Wolf, L. A. (2020) Performance of the ImmuView and BinaxNOW assays for the detection of urine and cerebrospinal fluid Streptococcus pneumoniae and Legionella pneumophila serogroup 1 antigen in patients with Legionnaires' disease or pneumococcal pneumonia and meningitis. PloS one 15 (8 August)	- Population does not meet inclusion criteria *Legionnaires disease or pneumonia*
El Bashir, H; Laundy, M; Booy, R. (2003) Diagnosis and treatment of bacterial meningitis. Archives of Disease in Childhood 88(7): 615-620	- Study design not of interest for review *Discussion paper*
El shorbagy, H. H, Barseem, N. F, Abdelghani, W. E et al. (2018) The value of serum procalcitonin in acute meningitis in children. Journal of Clinical Neuroscience 56: 28-33	- Country not of interest for review *Not a high-income OECD country*
Emiroglu, M; Kesli, R; Kilicaslan, M. (2020) Diagnostic Value of Clinical and Laboratory Findings in Childhood Meningitis. Journal of Pediatric Infectious Diseases 15(2): 79-85	- Population does not meet inclusion criteria *Meningitis (predominantly viral meningitis)*
Failace, L, Wagner, M, Chesky, M et al. (2005) Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae and Streptococcus sp. by polymerase chain reaction for the diagnosis of bacterial meningitis. Arquivos de neuro-psiquiatria 63(4): 920-924	- Country not of interest for review *Not a high-income OECD country*
Fan, S. J, Tan, H. K, Xu, Y. C et al. (2020) A pooled analysis of the LAMP assay for the detection of Neisseria meningitidis. BMC Infectious Diseases 20 (1)	- Study design not of interest for review *All studies in the meta-analysis don't meet the inclusion criteria for the review. Studies that meet the inclusion criteria (McKenna 2011; Bourke 2015; Higgins 2018) extracted from primary paper*

Farahani, H, Ghaznavi-Rad, E, Mondanizadeh, M et al. (2016) Specific detection of common pathogens of acute bacterial meningitis using an internally controlled tetraplex-PCR assay. Molecular & Cellular ProbesMol Cell Probes 30(4): 261-265	- Country not of interest for review *Not a high-income OECD country*
Favaro, M, Savini, V, Favalli, C et al. (2013) A multi-target real-time PCR assay for rapid identification of meningitis-associated microorganisms. Molecular BiotechnologyMol Biotechnol 53(1): 74-9	- Index test not of interest for review *Only CSF samples tested*
Feigin, R. D, Wong, M, Shackelford, P. G et al. (1976) Countercurrent immunoelectrophoresis of urine as well as of CSF and blood for diagnosis of bacterial meningitis. Journal of pediatrics 89(5): 773-775	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Fraisier, C, Stor, R, Tenebray, B et al. (2009) Use of a new single multiplex PCR-based assay for direct simultaneous characterization of six Neisseria meningitidis serogroups. Journal of Clinical MicrobiologyJ Clin Microbiol 47(8): 2662-6	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Gendrel, D, Raymond, J, Coste, J et al. (1999) Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. Pediatric Infectious Disease Journal 18(10): 875-881	- Insufficient presentation of results *Not enough data to construct 2 x 2 tables for review*
Gerdes, L. U, Jorgensen, P. E, Nexo, E et al. (1998) C-reactive protein and bacterial meningitis: a meta-analysis. Scandinavian Journal of Clinical & Laboratory InvestigationScand J Clin Lab Invest 58(5): 383-93	- Insufficient presentation of results *Insufficient info to construct 2 x 2 tables. Reference list checked for studies*
Guiducci, S, Moriondo, M, Nieddu, F et al. (2019) Culture and Real-time Polymerase Chain reaction sensitivity in the diagnosis of invasive meningococcal disease: Does culture miss less severe cases?. PLoS ONE [Electronic Resource] 14(3): e0212922	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Hackett, S. J, Carrol, E. D, Guiver, M et al. (2002) Improved case confirmation in meningococcal disease with whole blood Taqman PCR. Archives of disease in childhood 86(6): 449-452	- Index test not of interest for review *Lab-based PCR (meningococcal disease)*
Henry, B. M, Roy, J, Ramakrishnan, P. K et al. (2016) Procalcitonin as a Serum	- Study design not of interest for review *All studies in the meta-analysis don't meet the inclusion*

Biomarker for Differentiation of Bacterial Meningitis from Viral Meningitis in Children:Evidence from a Meta-Analysis. Clinical pediatrics 55(8): 749-764	*criteria for the review (includes studies that are not from a high-income OECD country). Studies that meet the inclusion criteria extracted from primary papers*
Higa, F. T, Fukasawa, L. O, Goncalves, M. G et al. (2013) Use of sodC versus ctrA for real-time polymerase chain reaction-based detection of Neisseria meningitidis in sterile body fluids. Memorias do Instituto Oswaldo Cruz 108(2): 246-247	- Country not of interest for review *Not a high-income OECD country*
Higgins, O, Clancy, E, Cormican, M et al. (2018) Evaluation of an Internally Controlled Multiplex Tth Endonuclease Cleavage Loop-Mediated Isothermal Amplification (TEC-LAMP) Assay for the Detection of Bacterial Meningitis Pathogens. International Journal of Molecular SciencesInt 19(2): 9	- Index test not of interest for review *PCR in various clinical samples (blood, CSF, pleural fluid, knee fluid)*
Higgins, O, Clancy, E, Forrest, M. S et al. (2018) Duplex recombinase polymerase amplification assays incorporating competitive internal controls for bacterial meningitis detection. Analytical Biochemistry 546: Oct-16	- Index test not of interest for review *PCR in various clinical samples (blood, CSF, pleural fluid, knee fluid)*
Hu, R; Gong, Y; Wang, Y. (2015) Relationship of serum procalcitonin levels to severity and prognosis in pediatric bacterial meningitis. Clinical pediatrics 54(12): 1141-1144	- Country not of interest for review *Not a high-income OECD country*
Huy, N. T, Hang le, T. T, Boamah, D et al. Development of a single-tube loop-mediated isothermal amplification assay for detection of four pathogens of bacterial meningitis. FEMS Microbiology Letters 337(1): 25-30	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Jenkins, P; Barnes, R. A; Coakley, W. T. (1997) Detection of meningitis antigens in buffer and body fluids by ultrasound-enhanced particle agglutination. Journal of Immunological Methods 205(2): 191-200	- Study design not of interest for review *Not enough data to construct 2 x 2 tables for review*
Jing-Zi, P, Zheng-Xin, H, Wei-Jun, C et al. (2018) Detection of bacterial meningitis pathogens by PCR-mass spectrometry in cerebrospinal fluid. Clinical Laboratory 64(6): 1013-1019	- Country not of interest for review *Not a high-income OECD country*
Julian-Jimenez, A and Morales-Casado, M. I. (2019) Usefulness of blood and cerebrospinal fluid laboratory testing to predict bacterial meningitis in the emergency department. NeurologiaNeurologia 34(2): 105-113	- Non-English language article *Article in Spanish*

Kaldor, J; Asznowicz, R; Buist, D. G. P. (1977) Latex agglutination in diagnosis of bacterial infections, with special reference to patients with meningitis and septicemia. American Journal of Clinical Pathology 68(2): 284-289	- Population does not meet inclusion criteria *Purulent meningitis or septicaemia (no proportions reported)*
Kesanopoulos, K, Tzanakaki, G, Levidiotou, S et al. (2005) Evaluation of touch-down real-time PCR based on SYBR Green I fluorescent dye for the detection of Neisseria meningitidis in clinical samples. FEMS Immunology and Medical Microbiology 43(3): 419-424	- Index test not of interest for review *Lab-based PCR*
Korczowski, B; Bijoś, A; Rybak, A. (2000) Procalcitonin in diagnosis of purulent and aseptic meningitis in children. Polski merkuriusz lekarski 9(53): 755-757	- Non-English language article *Article in Polish*
La Scolea Jr, L. J and Dryja, D. (1984) Quantitation of bacteria in cerebrospinal fluid and blood of children with meningitis and its diagnostic significance. Journal of clinical microbiology 19(2): 187-190	- Index test not of interest for review *Only CSF samples tested*
Lansac, N, Picard, F. J, Menard, C et al. (2000) Novel genus-specific PCR-based assays for rapid identification of Neisseria species and Neisseria meningitidis. European journal of clinical microbiology & infectious diseases 19(6): 443-51	- Study design/index test not of interest for review *Development of PCR assays for neisseria species*
Lee, C. T, Hsiao, K. M, Chen, J. C et al. (2015) Multiplex polymerase chain reaction assay developed to diagnose adult bacterial meningitis in Taiwan. Apmis 123(11): 945-50	- Country not of interest for review *Not a high-income OECD country*
Leitner, E, Hoenigl, M, Wagner, B et al. (2016) Performance of the FilmArray Blood culture identification panel in positive blood culture bottles and cerebrospinal fluid for the diagnosis of sepsis and meningitis. GMS Infectious DiseasesGMS Infect Dis 4: doc06	- Study design not of interest for review *PCR applied to positive cultures only*
Mace, S. E. (2008) Acute Bacterial Meningitis. Emergency Medicine Clinics of North America 26(2): 281-317	- Study design not of interest for review *Discussion paper*
Makoo, Z. B, Soltani, H. R, Hasani, A et al. (2010) Diagnostic value of serum and Cerebrospinal fluid procalcitonin in differentiation bacterial from Aseptic meningitis. American Journal of Infectious Diseases 6(4): 93-97	- Country not of interest for review *Not a high-income OECD country*
Manzano, S, Bailey, B, Gervaix, A et al.	- Insufficient presentation of results

(2011) Markers for bacterial infection in children with fever without source. Archives of Disease in Childhood 96(5): 440-446	*Outcome is detection of serious bacterial infection and results not presented separately for meningitis or meningococcal disease*
Maor, Y, Avnon, T, Schindler, Y et al. (2012) The significance of PCR in the diagnosis of post surgical meningitis. Clinical Microbiology and Infection 3: 356	- Study design not of interest for review *Conference Abstract*
Metrou, M and Crain, E. F. (1991) The complete blood count differential ratio in the assessment of febrile infants with meningitis. Pediatric infectious disease journal 10(4): 334-335	- Study design not of interest for review *Not diagnostic accuracy study*
Michael, B. D, Sidhu, M, Stoeter, D et al. (2010) Acute central nervous system infections in adults-a retrospective cohort study in the NHS North West region. Qjm 103(10): 749-758	- Index test not of interest for review *Only CSF samples tested*
Moayedi, A. R, Nejatizadeh, A, Mohammadian, M et al. (2015) Accuracy of universal polymerase chain reaction (PCR) for detection of bacterial meningitis among suspected patients. Electronic Physician [Electronic Resource]Electron Physician 7(8): 1609-12	- Country not of interest for review *Not a high-income OECD country*
Mohamed, H. B, Alif, H. A, Awadalla, A. A et al. (2012) Detection and significance of blood neutrophil CD64 expression as a diagnostic marker in bacterial meningitis in children. The Egyptian journal of immunology / Egyptian Association of Immunologists 19(2): 35-40	- Country not of interest for review *Not a high-income OECD country*
Mohammadi, S. F, Patil, A. B, Nadagir, S. D et al. (2013) Diagnostic value of latex agglutination test in diagnosis of acute bacterial meningitis. Annals of Indian Academy of Neurology 16(4): 645-649	- Country not of interest for review *Not a high-income OECD country*
Nacro, B, Konate, S, Gaudreault, S et al. (2008) Use of polymerase chain reaction in the diagnosis of acute bacterial meningitis in children. Journal of Pediatric Infectious Diseases 3(2): 119-124	- Country not of interest for review *Not a high-income OECD country*
Nolte, F. S, Rogers, B. B, Tang, Y. W et al. (2011) Evaluation of a rapid and completely automated real-time reverse transcriptase PCR assay for diagnosis of enteroviral meningitis. Journal of Clinical MicrobiologyJ Clin Microbiol 49(2): 528-33	- Index test not of interest for review *Only CSF samples tested*
Onal, H, Onal, Z, Ozdil, M et al. (2008) A new parameter in the differential diagnosis	- Country not of interest for review *Not a high-income OECD country*

of bacterial and viral meningitis. Neurosciences 13(1): 91-92	
Orvelid, P; Backman, A; Olcen, P. (1999) PCR identification of the group A Neisseria meningitidis gene in cerebrospinal fluid. Scandinavian Journal of Infectious Diseases 31(5): 481-483	- Index test not of interest for review *Only CSF samples tested*
Papavasileiou, K, Papavasileiou, E, Tzanakaki, G et al. (2011) Acute bacterial meningitis cases diagnosed by culture and PCR in a children's hospital throughout a 9-year period (2000-2008) in Athens, Greece. Molecular Diagnosis and Therapy 15(2): 109-113	- Study design not of interest for review *Descriptive study (no DTA data)*
Poplin, V; Boulware, D. R; Bahr, N. C. (2020) Methods for rapid diagnosis of meningitis etiology in adults. Biomarkers in MedicineBiomark 14(6): 459-479	- Study design not of interest for review *Discussion paper*
Poppert, S, Essig, A, Stoehr, B et al. (2005) Rapid diagnosis of bacterial meningitis by real-time PCR and fluorescence in situ hybridization. Journal of clinical microbiology 43(7): 3390-7	- Index test not of interest for review *Only CSF samples tested*
Porritt, R. J; Mercer, J. L; Munro, R. (2000) Detection and serogroup determination of Neisseria meningitidis in CSF by polymerase chain reaction (PCR). Pathology 32(1): 42-45	- Index test not of interest for review *Only CSF samples tested*
Porritt, R. J; Mercer, J. L; Munro, R. (2003) Ultrasound-enhanced latex immunoagglutination test (USELAT) for detection of capsular polysaccharide antigen of Neisseria meningitidis from CSF and plasma. Pathology 35(1): 61-4	- Index test not of interest for review *Latex agglutination*
Prasad, P. L; Nair, M. N. G; Kalghatgi, A. T. (2005) Childhood bacterial meningitis and usefulness of C-reactive protein. Medical Journal Armed Forces India 61(1): 13-15	- Country not of interest for review *Not a high-income OECD country*
Prat, C, Dominguez, J, Rodrigo, C et al. (2004) Use of quantitative and semiquantitative procalcitonin measurements to identify children with sepsis and meningitis. European Journal of Clinical Microbiology and Infectious Diseases 23(2): 136-138	- Population not of interest for review *Groups those with sepsis and/or meningitis*
Requejo, H. I; Nascimento, C. M; Fahrat, C. K. (1992) Comparison of counterimmunoelectrophoresis, latex agglutination and bacterial culture for the	- Country not of interest for review *Not a high-income OECD country*

diagnosis of bacterial meningitis using urine, serum and cerebrospinal fluid samples. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica .. etal25(4): 357-367	
Sakushima, K, Hayashino, Y, Kawaguchi, T et al. (2011) Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. Journal of InfectionJ Infect 62(4): 255-62	- Index test not of interest for review *Only CSF samples tested*
Saravolatz, L. D, Manzor, O, VanderVelde, N et al. (2003) Broad-range bacterial polymerase chain reaction for early detection of bacterial meningitis. Clinical infectious diseases 36(1): 40-5	- Index test not of interest for review *Only CSF samples tested*
Schaad, U.B. (1997) Diagnosis and treatment of bacterial meningitis. Annales Nestle 55(3): 103-110	- Study design not of interest for review *Discussion paper*
Seward, R. J and Towner, K. J. (2000) Evaluation of a PCR-immunoassay technique for detection of Neisseria meningitidis in cerebrospinal fluid and peripheral blood. Journal of Medical Microbiology 49(5): 451-456	- Index test not of interest for review *No index test of interest*
Sippel, J. E, Girgis, N. I, Kilpatrick, M. E et al. (1991) Laboratory diagnosis of bacterial meningitis. Transactions of the royal society of tropical medicine and hygiene 85(suppl1): 06-Aug	- Study design not of interest for review *Discussion paper*
Soetiono, S; Sunartini, Machfudz, S; Setyawati, P. S. (1989) Cerebrospinal fluid C-reactive protein in the diagnosis of meningitis in children. Paediatrica Indonesiana 29(01feb): 20-27	- Country not of interest for review *Not a high-income OECD country*
Srifuengfung, S and Chokephaibulkit, K. (2010) Detection of bacterial antigen in cerebrospinal fluid in patients with bacterial meningitis: a literature review. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 93suppl5: S71-75	- Study design not of interest for review *Discussion paper*
Srinivasan, L, Pisapia, J. M, Shah, S. S et al. (2012) Can broad-range 16S ribosomal ribonucleic acid gene polymerase chain reactions improve the diagnosis of bacterial meningitis? A systematic review and meta-analysis. Annals of Emergency MedicineAnn Emerg Med 60(5): 609-	- Index test not of interest for review *PCR tested in CSF*

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Taveras, J and Villalobos-Fry, T. (2018) The use of multiplex PCR panel in the diagnosis of meningitis in children. Open Forum Infectious Diseases 5 (Supplement 1): 135	- Study design not of interest for review *Conference Abstract*
Ure, R, Lindsay, D, Edwards, G et al. (2012) Evaluation of the FTD bacterial meninigitis kit in comparison to in-house assays for the direct detection of N. meningitidis, S. pneumoniae and H. influenzae in clinical specimens. Clinical Microbiology and Infection 3: 403	- Study design not of interest for review *Conference Abstract*
Van Gastel, E, Bruynseels, P, Verstrepen, W et al. (2007) Evaluation of a real-time polymerase chain reaction assay for the diagnosis of pneumococcal and meningococcal meningitis in a tertiary care hospital. European Journal of Clinical Microbiology and Infectious Diseases 26(9): 651-653	- Insufficient presentation of results *Data cannot be extracted as control group includes those with other types of bacterial meningitis*
Velissaris, D, Pintea, M, Pantzaris, N et al. (2018) The Role of Procalcitonin in the Diagnosis of Meningitis: A Literature Review. Journal of Clinical MedicineJ 7(6): 11	- Study design not of interest for review *Non-systematic review*
Viallon, A, Zeni, F, Lambert, C et al. (1999) High sensitivity and specificity of serum procalcitonin levels in adults with bacterial meningitis. Clinical infectious diseases 28(6): 1313-1316	- Insufficient presentation of results *Insufficient information to calculate 2x2 table or precision around the estimates*
Vikse, J, Henry, B. M, Roy, J et al. (2015) The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis. International Journal of Infectious DiseasesInt J Infect Dis 38: 68-76	- Reference standard not of interest for review *No comparator of interest*
Vuong, J, Collard, J. M, Whaley, M. J et al. (2016) Development of real-time PCR methods for the detection of bacterial meningitis pathogens without DNA extraction. PloS one 11 (2)	- Index test not of interest for review *PCR on CSF*
Wang, X, Theodore, M. J, Mair, R et al. (2012) Clinical validation of multiplex real-time PCR assays for detection of bacterial meningitis pathogens. Journal of Clinical MicrobiologyJ Clin Microbiol 50(3): 702-8	- Index test/country not of interest for review *PCR on nasal washes and/or throat swabs for Lakeland (USA) cohort and other cohorts not from a high-income OECD country*
Wei, T. T, Hu, Z. D, Qin, B. D et al. (2016) Diagnostic Accuracy of Procalcitonin in Bacterial Meningitis Versus Nonbacterial	- Study design not of interest for review *Studies that meet inclusion criteria for review extracted from primary papers*

Meningitis: A Systematic Review and Meta-Analysis. MedicineMedicine (Baltimore) 95(11): e3079	
Zhang, L, Ma, L, Zhou, X et al. (2019) Diagnostic Value of Procalcitonin for Bacterial Meningitis in Children: A Comparison Analysis Between Serum and Cerebrospinal Fluid Procalcitonin Levels. Clinical pediatrics 58(2): 159-165	- Country not of interest for review *Not a high-income OECD country*

CSF: cerebrospinal fluid; LAMP: Loop-mediated isothermal amplification; PCR: polymerase chain reaction; PCT: procalcitonin; OECD: Organisation for Economic Co-operation and Development; RCT: randomised controlled trial

Excluded economic studies

Table 22: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Duff, S., Hasbun, R., Balada-Llasat, J. M., Zimmer, L., Bozzette, S. A., Ginocchio, C. C., Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in adult patients, Infection, 20, 20, 2019	Excluded as rated not applicable. US resource use and costs and judged unlikely to be applicable to current UK NHS context.
Duff, S., Hasbun, R., Ginocchio, C. C., Balada-Llasat, J. M., Zimmer, L., Bozzette, S. A., Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in pediatric patients, Future Microbiology, 13, 617-629, 2018	Excluded as rated not applicable. US resource use and costs and judged unlikely to be applicable to current UK NHS context.

Appendix K Research recommendations – full details

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

No research recommendation was made for this review.