National Institute for Health and Care Excellence

Final

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

[B3] Evidence review for investigating and diagnosing suspected bacterial meningitis with cerebrospinal fluid parameters

NICE guideline NG240

Evidence reviews underpinning recommendations 1.4.9 to 1.4.19 and the recommendation for research on novel diagnostic techniques applied to blood or cerebrospinal fluid

March 2024

Final

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-5757-6

Contents

Investigating and diagnosing suspected bacterial meningitis with cerebrospinal fluid parameters

Review question

What is the accuracy and effectiveness of cerebrospinal fluid 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.

Cerebrospinal fluid (CSF) investigations are crucial for the diagnosis of bacterial meningitis, and obtaining CSF samples for urgent investigation should be prioritised whenever a diagnosis of bacterial meningitis is being considered.

It is therefore important to determine which CSF investigations are the most accurate and cost-effective for use in clinical practice. The aim of this review is to evaluate the available CSF tests and determine the utility of these tests in diagnosing 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	**Inclusion:** All adults, young people, children and babies (including neonates defined as aged 28 days old and younger) with suspected bacterial meningitis
Index test	The use of the following Cerebrospinal fluid (CSF) investigations, individually or in combination: • white cell count • neutrophil count • microscopy for bacteria • glucose concentration (absolute or relative to simultaneously estimated blood glucose) • protein concentration • molecular diagnosis for bacterial pathogens
Reference standard	CSF bacterial culture with or without molecular diagnosis in the CSF for bacterial pathogens
Target condition	Bacterial meningitis (including meningococcal meningitis alone)

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

Seventy studies were included in this review, 66 single-gate, cross-sectional diagnostic accuracy (DTA) (Abdeldaim 2010, Agueda 2013, Alqayoudhi 2017, Ansong 2009, Arora 2017, Balamuth 2021, BenGershom 1986, Benjamin 1984, Bonadio 1989, Bonsu 2003, Bonsu 2008, Bortolussi 1982, Boudet 2019, Boving 2009, Brizzi 2012, Bryant 2004, Buch 2018, Chiba 2009, Corrall 1981, D'Inzeo 2020, Dastych 2015, De Cauwer 2007, Deutch 2006, Deutch 2008, Dubos 2006, Dubos 2008, Dunbar 1998, Ena 2021, Esparcia 2011, Favaro 2013, Freedman 2001, Garges 2006, Giulieri 2015, Jorgensen 1978, Kennedy 2007, Khurana 1987, Kim 2012, Kleine 2003, Kotilainen 1998, La Scolea Jr 1984, Leber 2016, Lee 2015, Leitner 2016, Leli 2019, Lindquist 1988, Morrissey 2017, Nabower 2019, Negrini 2000, Nelson 1986, Neuman 2008, Pfefferle 2020, Piccirilli 2018, Poppert 2005, Porritt 2000, Ray 2007, Richardson 2003, Rothman 2010, Schuurman 2004, Seward 2000a, Seward 2000b, Viallon 2011, Vincent 2020, Wagner 2018, Welinder-Olsson 2007, White 2012, Xirogianni 2009), and 4 two-gate, cross-sectional DTA studies (Bonsu 2005, Meyer 2014, Ni 1992, Sormunen 1999). No eligible test-and-treat RCTs were identified.

The included studies are summarised in Table 2.

Twenty studies looked at the DTA of white cell count (WCC; Agueda 2013, Ansong 2009, BenGershom 1986, Bonsu 2003, Bonsu 2008, Boudet 2019, Buch 2018, Corrall 1981, D'Inzeo 2020, Dubos 2006, Dubos 2008, Freedman 2001, Garges 2006, Giulieri 2015, Kleine 2003, Lindquist 1988, Nelson 1986, Ray 2007, Sormunen 1999, White 2012), 12 studies looked at the DTA for neutrophil count (Benjamin 1984, Bonsu 2005, Bonsu 2008, Buch 2018, Corrall 1981, Dastych 2015, De Cauwer 2007, Dubos 2006, Dubos 2008, Giulieri 2015, Negrini 2000, Viallon 2011), 17 studies looked at the DTA of microscopy for bacteria (Balamuth 2021, Bonadio 1989, Bortolussi 1982, Boudet 2019, Brizzi 2012, Corrall 1981, D'Inzeo 2020, Deutch 2006, Dunbar 1998, Ena 2021, Jorgensen 1978, Khurana 1987, Kim 2012, Kotilainen 1998, La Scolea Jr 1984, Meyer 2014, Neuman 2008), 19 studies looked at the DTA of glucose concentration (Ansong 2009, BenGershom 1986, Bonadio 1989, Bonsu 2005, Bonsu 2008, Buch 2018, Corrall 1981, D'Inzeo 2020, Dastych 2015, De Cauwer 2007, Dubos 2006, Dubos 2008, Garges 2006, Giulieri 2015, Lindquist 1988, Nelson 1986, Ray 2007, Sormunen 1999, Viallon 2011), 21 studies looked at the DTA of protein concentration (Ansong 2009, BenGershom 1986, Benjamin 1984, Bonadio 1989, Bonsu 2005, Bonsu 2008, Buch 2018, Corrall 1981, D'Inzeo 2020, Dastych 2015, De Cauwer 2007, Dubos 2006, Dubos 2008, Garges 2006, Giulieri 2015, Kleine 2003, Lindquist 1988, Ray 2007, Sormunen 1999, Viallon 2011, White 2012), and 37 studies investigated the DTA of molecular diagnosis for bacterial pathogens (Abdeldaim 2010, Alqayoudhi 2017, Arora 2017, Boudet 2019, Boving 2009, Bryant 2004, Chiba 2009, D'Inzeo 2020, Deutch 2006, Deutch 2008, Ena 2021, Esparcia 2011, Favaro 2013, Kennedy 2007, Kim 2012, Kotilainen 1998, Leber 2016, Lee 2015, Leitner 2016, Leli 2019, Meyer 2014, Morrissey 2017, Nabower 2019, Ni 1992, Pfefferle 2020, Piccirilli 2018, Poppert 2005, Porritt 2000, Richardson 2003, Rothman 2010, Schuurman 2004, Seward 2000a, Seward 2000b, Vincent 2020, Wagner 2018, Welinder-Olsson 2007, Xirogianni 2009).

Fifty studies used CSF bacterial culture alone as a reference standard (Alqayoudhi 2017, Ansong 2009, Arora 2017, Balamuth 2021, BenGershom 1986, Benjamin 1984, Bonsu 2003, Bonsu 2008, Bortolussi 1982, Boudet 2019, Brizzi 2012, Bryant 2004, Chiba 2009, Corrall 1981, D'Inzeo 2020, Deutch 2006, Deutch 2008, Dunbar 1998, Ena 2021, Esparcia 2011, Favaro 2013, Garges 2006, Jorgensen 1978, Kennedy 2007, Khurana 1987, Kim 2012, Kotilainen 1998, La Scolea Jr 1984, Leber 2016, Lee 2015, Leitner 2016, Leli 2019, Meyer 2014, Morrissey 2017, Nabower 2019, Nelson 1986, Neuman 2008, Piccirilli 2018, Poppert 2005, Porritt 2000, Richardson 2003, Rothman 2010, Schuurman 2004, Seward 2000a, Seward 2000b, Sormunen 1999, Viallon 2011, Wagner 2018, Welinder-Olsson 2007, Xirogianni 2009). One study used CSF culture and molecular diagnosis (Pfefferle 2020). Two studies used CSF culture, microscopy and molecular diagnosis (Vincent 2020, White 2012). Three studies used CSF culture and/or microscopy (Abdeldaim 2010, Agueda 2013, Ni 1992). Two studies used CSF culture and/or blood culture and/or microscopy (Bonsu 2005, Kleine 2003). Two studies used CSF culture and/or blood culture, microscopy and/or molecular diagnosis (Buch 2018, Boving 2009, Giuleri 2015). Two studies used CSF culture and/or CSF pleocystosis and blood culture (De Cauwer 2007, Negrini 2000). Three studies used CSF culture and/or other CSF findings (including serology, pleocytosis, latex agglutination and/or counter immunoelectophoresis; Bonadio 1989, Dastych 2015, Lindquist 1988). Four studies used CSF culture and/or blood culture and/or other CSF findings and clinical criteria (such as diagnosis of meningitis or rapid improvement after antibacterial therapy; Dubos 2006, Dubos 2008, Freedman 2001, Ray 2007).

Three studies included neonates only (defined as ≤28 days; Ansong 2009, Bonadio 1989, Garges 2006), and 4 included neonates and younger babies (defined as ≤3 months; Arora 2017, Balamuth 2021, Bonsu 2003, Morrissey 2017). Seven studies included neonates, babies and children (defined as <18 years; Alqayoudhi 2017, De Cauwer 2007, Kennedy 2007, Kim 2012, Lee 2015, Nabower 2019, Nelson 1986). One study (Benjamin 1984) did not report age as part of the inclusion or exclusion criteria, but has been classified as including neonates, babies and children based on the age range of included participants (1 week-18 years). None of the studies including neonates presented separate results for pre-term and term neonates. Eleven studies included babies and children (defined as >28 days to <18 years; Agueda 2013, BenGershom 1986, Bonsu 2005, Bonsu 2008, Brizzi 2012, Bryant 2004, Corrall 1981, Dubos 2006, Freedman 2001, Negrini 2000, Sormunen 1999). One study (Neuman 2008) defined children as ≤21 years but has been classified as including babies and children based on the reported age range of recruited participants (median 74 days, inter-quartile range 38-562 days). Two studies did not report age ranges, but both were conducted in a paediatric setting and have been classified as including babies and children (Khurana 1987, La Scolea Jr 1984). One study (Dubos 2008) included children only (defined as ≥1 to <18 years). No studies were identified that included only younger babies (defined as 28 days to 3 months) or older babies (defined as 3 months to 1 year).

Five studies enrolled adults only (defined as ≥18 years; Buch 2018, Dastych 2015, Kleine 2003, Ray 2007, Viallon 2011), 1 study included adults only but defined adults as ≥17 years (Favaro 2013), 1 study included adults only but defined adults as ≥16 years (Giulieri 2015), and 1 study included adults but provided no further details on lower age limits (Dunbar 1998). Two studies did not report age as part of the inclusion or exclusion criteria but have been classified as including adults only based on the ages of recruited participants (Leli 2019 [median 60 years, inter-quartile range 41.5-71 years]; Piccirilli 2018 [92% adults]).

Thirteen studies did not include age as part of the eligibility criteria but have reported patient age ranges crossing all categories (Abdeldaim 2010, Boudet 2019, D'Inzeo 2020, Deutch 2006, Deutch 2008, Ena 2021, Leber 2016, Ni 1992, Richardson 2003, Schuurman 2004, Vincent 2020, Welinder-Olsson 2007, White 2012). One study did not report the ages of participants, but as the inclusion criteria states participants should be ≥2 months, it has also been classified as all ages (Lindquist 1988). Sixteen studies did not describe age as part of the inclusion or exclusion criteria and did not report the ages of recruited participants (Bortolussi 1982, Boving 2009, Chiba 2009, Esparcia 2011, Jorgensen 1978, Kotilainen

1998, Leitner 2016, Meyer 2014, Pfefferle 2020, Poppert 2005, Porritt 2000, Rothman 2010, Seward 2000a, Seward 2000b, Wagner 2018, Xirogianni 2009).

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
Abdeldaim 2010 Single-gate, cross-sectional DTA study Denmark	N=87 CSF samples sent for culture at study laboratory with CSF white blood cell count was ≥10 cells/µL. Age (median [range]): 34 years (1 day-91 years) Positive for bacterial meningitis: 8% (Population: BM U)	Molecular diagnosis Specific PCR • for N. meningitidis • for S. pneumoniae	CSF bacterial culture and/or microscopy	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: 100% Causative organisms: n=5 S. pneumoniae, n=2 N. meningitidis
Agueda 2013 Single-gate, cross-sectional DTA study Portugal	N=295 Children aged 29 days-17 years with CSF pleocytosis (defined as white blood count ≥7 cells/µL). Age in years for bacterial meningitis group (medium [SD]): 3.6 (5.0) Positive for bacterial meningitis: 11% (Population: BM VM AM)	CSF white cell count Threshold 321 cells/µL.	CSF bacterial culture and/or CSF Gram stain	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=15 N. meningitidis, n=10 S. pneumoniae, n=3 other Streptococcus spp., n=3 other organisms
Alqayoudhi 2017 Single-gate, cross	N=2025 Children <16 years old with suspected	Molecular diagnosis Specific PCR for S. pneumoniae	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=16 S. pneumoniae

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
sectional DTA study Ireland	meningitis, and with a CSF sample tested for S. pneumoniae DNA by PCR. Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 0.8% (Population: PM U)				
Ansong 2009 Single-gate, cross-sectional DTA study USA	N=13,495 Babies discharged from study NICUs with results of first lumbar puncture available. Gestational age in weeks for bacterial meningitis group (median [IQR]): 38 (36-39) Positive for bacterial meningitis: 0.3% (Population: GBM GBS U)	<u>CSF white cell count</u> Threshold >26 cells/mm^3 for premature neonates (<37 weeks) and >23 cells/mm^3 for term neonates (≥37 weeks) (converted to cells/μL for consistency with other studies). <u>CSF glucose concentration</u> Threshold <23 mg/dL for premature neonates (<37 weeks) and <33 mg/dL for term neonates (≥37 weeks) (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Threshold >151 mg/dL for premature neonates (<37 weeks) and >171 mg/dL for term neonates (≥37 weeks).	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=46 group B Streptococcus
Arora 2017 Single-gate, cross-sectional DTA study USA	N=62 Babies undergoing lumbar puncture for suspected meningitis. Age range: 0-3	<u>Molecular diagnosis</u> Multiplex PCR (FA-M/E panel) for group B streptococcus and E. coli	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=5 group B Streptococcus or E. coli

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	months Positive for bacterial meningitis: 8% (Population: BM U)				
Balamuth 2021 Single-gate, cross-sectional DTA study USA	N=20,947 Babies aged ≤60 days with CSF culture obtained within 24 hours of emergency department presentation. Age in days (median [IQR]): 28 (15-41) Positive for bacterial meningitis: 1% (Population: BM U)	Microscopy Gram staining	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=63 group B Streptococcus, n=39 E. coli, n=26 S. aureus, n=17 Enterococcus spp., n=15 Klebsiella spp., n=7 Enterobacter spp., n=7 S. pneumoniae, n=5 L. monocytogenes, n=5 N. meningitidis, n=3 C. cloacae, n=2 P. mirabilis, n=1 group A Streptococcus, n=1 Haemophilus, n=1 P. aeruginosa, n=12 other pathogens
BenGershom 1986 Single-gate, cross-sectional DTA study Netherlands	N=45 All babies and children referred to hospital with suspected meningitis and sufficient CSF remaining after routine testing. Age (range): 1 month-13 years Positive for bacterial meningitis: 38%* (Population: BM VM NM) *44% were considered to have bacterial meningitis but this was only culture confirmed in 38%.	CSF white cell count Threshold >500 cells/µL. CSF glucose concentration Threshold <2.2 mmol/L. CSF protein concentration Threshold >100 mg/dL.	CSF bacterial culture and/or other undefined reference standard	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: 85%, but results reported are based on culture-confirmed cases. Causative organisms: Exact numbers not reported but included H. influenzae, N. meningitidis., S. pneumoniae, group B Streptococcus, E. coli, Pseudomonas spp.
Benjamin 1984 Single-gate,	N=119 CSF samples submitted to	CSF neutrophil count Threshold >50 cells/cm (could not	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=14 H. influenzae type b, n=2 S.

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
cross-sectional DTA study USA	laboratory, including all cases of bacterial and aseptic meningitis. Age (range): 1 week-18 years Positive for bacterial meningitis: 18% (Population: BM AM NM)	convert for consistency with other studies due to uncertainty regarding unit of measurement). <u>CSF protein concentration</u> Threshold > 40 mg/dL.			pneumoniae, n=3 N. meningitidis, n=1 M. tuberculosis, n=1 Salmonella spp.
Bonadio 1989 Single-gate, cross-sectional DTA study USA	N=72 Previously healthy neonates born at term, under 4 weeks old, receiving diagnostic lumbar puncture showing CSF pleocytosis or culture-positive for pathogenic organisms. Age in weeks (n [%]): 0-2: 36 (50%); 2-4: 36 (50%) Positive for bacterial meningitis: 25% (Population: BM VM AM)	<u>Microscopy</u> Gram staining <u>CSF glucose concentration</u> Threshold <34mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Threshold >170 mg/dL.	CSF bacterial culture and/or CSF pleocytosis with CSF latex agglutination	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: 89% Causative organisms: n=9 group B Streptococcus, n=5 E. coli, n=2 L. monocytogenes, n=2 H. influenzae
Bonsu 2003 Single-gate, cross-sectional DTA study USA	N=5353 Babies undergoing routine sepsis evaluation for suspected serious bacterial infection in the emergency department of study hospital. Age in days (range): 3-89 Positive for bacterial meningitis: 0.4% (Population: BM U)	<u>CSF white cell count</u> Thresholds ≥8 cells/mm^3, ≥10 cells/ mm^3, ≥100 cells/ mm^3, and ≥1,000 cells/ mm^3 (converted to cells/μL for consistency with other studies).	CSF bacterial culture	• Sensitivity • Specificity • AUC	Causative organisms: n= 11 E. coli, n=9 group B streptococcus, n=1 S. pneumoniae, n=1 C. koseri
Bonsu 2005 Two-gate, cross-	N=7,712 January 1993-July 1999: Children	<u>CSF neutrophil count</u> (reported as percentage neutrophils)	CSF bacterial culture and/or blood bacterial culture with confirmatory	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: not

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
sectional DTA study* USA *Although the initial study design was a single-gate study, this has been classified as a two-gate study because the latter cohort was selected based on culture results	aged >29 days-18 years old with low CSF white blood cell counts (defined as <30 cells/mm^3). January 1984-December 1992: Children aged 1 month-3 years old with low CSF white blood cell counts and confirmed bacterial meningitis. Age in years (median [IQR]): 0.5 (0.27-1.33) in bacterial meningitis group and 0.3 (0.15-1.76) in non-bacterial meningitis group. Positive for bacterial meningitis: 0.3% (Population: BM U)	Thresholds ≥1%, ≥25%, ≥50% and ≥75%. <u>CSF glucose concentration</u> Thresholds <20 mg/dL, <40 mg/dL, <60 mg/dL and <120 mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Thresholds ≥40 mg/dL, ≥80 mg/dL, ≥120 mg/dL and ≥200 mg/dL.	CSF Gram stain		reported Causative organisms: n=9 S. pneumoniae, n=6 N. meningitidis, n=4 E. coli, n=3 group B Streptococcus
Bonsu 2008 Single-gate, cross-sectional DTA study USA	N=78 Children presenting at emergency department with signs of acute meningitis. Age in years for bacterial meningitis group (median [IQR]): 1.0 (0.4-2.2) Positive for bacterial meningitis: 24% (Population: BM VM)	<u>CSF white cell count</u> Threshold >597 cells/µL. <u>CSF neutrophil count</u> (reported as percentage neutrophils) Threshold >74%. <u>CSF glucose concentration</u> Threshold <38mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Threshold >97 mg/dL.	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n = 12 S. pneumoniae, n = 6 N. meningitidis, n = 1 group B Streptococcus
Bortolussi 1982 Single-gate, cross-sectional	N=208 People with suspected bacterial meningitis based	<u>Microscopy</u> Gram staining • for all bacteria • for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=29 H. influenzae type b, n=2 N. meningitidis group A, n=3 N.

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
study Canada	on clinical and CSF findings. Age of participants not reported. Positive for bacterial meningitis: 24% (Population: BM U)	• for S. pneumoniae • for H. influenzae • for group B Streptococcus • for Gram-negative bacilli (E. coli)			meningitidis group B, n=6 N. meningitidis group C, n=3 E. coli K1, n=4 S. pneumoniae, n=3 group B Streptococcus
Boudet 2019 Single-gate cross-sectional DTA study France	N=734 CSF samples from 708 people CSF samples taken through lumbar puncture and tested by FA-M/E panel per physician or microbiologist order. Age (mean [range]): 44 years (1 day-98 years) Positive for bacterial meningitis: 2% (Population: BM VM NM)	<u>CSF white cell count</u> Thresholds ≥10 cells/mm^3 for neonates and ≥5 cells/mm^3 for all other age groups (converted to cells/µL for consistency with other studies). <u>Microscopy</u> Gram staining: • for all bacteria • for N. meningitidis • for S. pneumoniae • for Group B streptococcus <u>Molecular diagnosis</u> Multiplex PCR (FA-ME panel): • for N. meningitidis • for S. pneumoniae • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli)	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=4 group B Streptococcus, n=4 N. meningitidis, n=2 S. pneumoniae, n=1 H. influenzae, n=1 E. coli
Boving 2009 Single-gate, cross-sectional DTA study Denmark	N=1187 CSF samples sent to study centre for analysis. Ages of participants not reported Positive for bacterial	<u>Molecular diagnosis</u> Multiplex PCR (PCR-Luminex assay): • for N. meningitidis • for S. pneumoniae • for Gram-negative bacilli (E. coli)	CSF microscopy, CSF bacterial culture, PCR, or blood culture	• Sensitivity • Sensitivity	Positive CSF cultures in population with bacterial meningitis: 82%, but results reported are based on culture-confirmed cases. Causative organisms: n=16 S. pneumoniae,

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	meningitis: 2%* (Population: BM U) *3% were considered to have bacterial meningitis but this was only culture confirmed in 2%.	• for L. monocytogenes			n=5 N. meningitidis, n=4 S. aureus, n-1 E. coli, n=1 L. monocytogenes
Brizzi 2012 Single-gate, cross-sectional study USA	N=1,938 Children <18 years old with lumbar puncture performed in emergency department and had CSF clinical data available. Age (median [IQR]): 1.6 years (1.4 months- 9.9 years) Positive for bacterial meningitis: 0.9% (Population: BM U)	Microscopy Gram staining	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=10 S. pneumoniae, n=5 group B Streptococcus, n=2 N. meningitidis
Bryant 2004 Single-gate, cross-sectional DTA study Australia	N=118 Inclusion criteria: • July 2000 and October 2000: Admitted with clinical suspicion of meningitis or septicaemia. • August 2000 - January 2001: Admitted with clinical suspicion of meningococcal septicaemia and/or meningitis. Age in years (median [range]): 2.6 (0.1-15.4) in suspected meningococcal disease group Positive for bacterial meningitis: 1.7%* (Population: MM	Molecular diagnosis Specific PCR for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n= 4 N. meningitidis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	UM US) *14% were considered to have bacterial meningitis but this was only culture confirmed in 2%.				
Buch 2018 Single-gate, cross-sectional DTA study Denmark	N=176 People aged 15 years and older, clinically and/or microbiologically diagnosed acute meningitis, plus available CSF lactate values Age in years (median [IQR]): 64 (52-74) Positive for bacterial meningitis: 29% (Population: BM AME)	CSF white cell count Threshold $15x10^6$ cells/L (converted to cells/µL for consistency with other studies). CSF neutrophil count (reported as CSF neutrophil fraction) Threshold 67%. CSF glucose concentration (reported as CSF/blood glucose ratio) Threshold 0.4. CSF protein concentration Threshold >0.45 g/L (converted to mg/dL for consistency with other studies).	CSF bacterial culture and/or bacterial blood culture and/or CSF PCR and/or CSF microscopy and/or Spanos criteria.	• Sensitivity • Specificity • AUC	Positive CSF cultures in population with bacterial meningitis: 61% Causative organisms: n = 30 S. pneumoniae, n=6 other Streptococcus spp., n=2 E. coli, n=4 S. aureus, n=1 Coagulase-negative Staphylococcus spp., n=2 L. monocytogenes, n=1 H. influenzae, n = 3 N. meningitidis and n=2 unknown aetiology
Chiba 2009 Single-gate cross-sectional DTA study Japan	N=168 People with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing. Ages of participants not reported. Positive for bacterial meningitis: 48% (Population: BM U)	Molecular diagnosis Multiplex PCR: • for all included bacteria • for S. pneumoniae • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli) • for L. monocytogenes	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=48 H. influenzae, n=27 S. pneumoniae, n=3 E. coli, n=2 group B Streptococcus, n=1 L. monocytogenes
Corrall 1981 Single-gate, cross-	N=56 Children aged 1 month-16 years,	CSF white cell count Threshold >500 cells/mm^3	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=12 H. influenzae type b, n=5 S. pneumoniae, n=4

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
sectional DTA study USA	with clinical symptoms suggestive of meningitis and CSF pleocytosis (defined as >10 white blood cells/mm^3). Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 43% (Population: BM VM NM)	(converted to cells/µL for consistency with other studies). <u>CSF neutrophil count</u> (reported as polymorphonuclear concentration) Threshold >200 cells/mm^3 (converted to cells/µL for consistency with other studies). <u>Microscopy</u> Gram staining <u>CSF glucose concentration</u> Threshold <40 mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Threshold >100 mg/dL.			N. meningitidis, n=1 group B streptococcus, n=1 group C Streptococcus, n=1 E. Coli Polymorphonuclear count: As only a proportion of these cells are neutrophils, index test has been marked down for applicability in QUADAS-2 assessment.
D'Inzeo 2020 Single-gate, cross-sectional DTA study Italy	N=135 CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis. Age in years (median [IQR]): 51.5 (8-64.5) in bacterial meningitis group only Positive for bacterial meningitis: 24%* (Population: BM U) *33% were considered to have bacterial meningitis but this was only culture confirmed in 24%.	<u>CSF white cell count</u> Threshold >5 cells/mm^3 (converted to cells/µL for consistency with other studies). <u>Microscopy: Gram staining</u>: • for all bacteria • for N. meningitidis • for S. pneumoniae • for group B streptococcus • for Gram-negative bacilli (E.coli and C. koseri) • for L. monocytogenes <u>CSF glucose concentration</u> (reported as glucose CSF/blood ratio)	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=21 S. pneumoniae, n=10 N. meningitidis, n=6 L. monocytogenes, n=3 E. coli, n=2 S. pyogenes, n=1 group B Streptococcus, n=1 C. koseri

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
		Threshold <0.66. CSF protein concentration Threshold >40 mg/dl. Molecular diagnosis Multiplex LAMP (easyplex® CSF panel): • for all included bacteria • for N. meningitidis • for S. pneumoniae • for group B streptococcus • for Gram-negative bacilli (E. coli) • for L. monocytogenes Gram stain plus multiplex LAMP As above.			
Dastych 2015 Single-gate, cross-sectional DTA study Czech Republic	N=73 Adults with suspected inflammatory disease of the CNS. Age in years (range): 21-70 Positive for bacterial meningitis: 32% (Population: BM AM)	CSF neutrophil count (reported as polynuclear count) Threshold >37 cells/µL. CSF glucose concentration Threshold <2.7 mmol/L. CSF protein concentration Threshold >1.01 g/L (converted to mg/dL for consistency with other studies).	CSF bacterial culture and/or positive serology (including PCR)	• Sensitivity • Specificity • AUC	Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=8 S. aureus, n=8 Pneumococcus spp., n=4 N. meningitidis, n=4 P. aeruginosa, n=3 E. coli, n=2 Meningococcus spp. Polynuclear count: As only a proportion of these cells are neutrophils, index test has been marked down for applicability in QUADAS-2 assessment.
De Cauwer 2007 Single-gate,	N= 92 Children (aged 0–15 years)	CSF neutrophil count (reported as percentage neutrophils)	CSF bacterial culture and /or blood bacterial culture with CSF	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
cross-sectional DTA study Belgium	admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of viral or bacterial meningitis. Age in years (median [range]): 5.6 (0-15) Positive for bacterial meningitis: 23% (Population: BM VM)	Threshold >80%. <u>CSF glucose concentration</u> Threshold <53 mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Threshold ≥100 mg/dL.	pleocytosis		meningitis: 67% Causative organisms: n=16 N. meningitidis, n=5 S. pneumoniae, n=1 H. influenzae
Deutch 2006 Single-gate, cross-sectional DTA study Denmark	N=206 specimens from 203 people CSF specimens submitted to study laboratory during study period. Age (range): 6 days-86 years old Positive for bacterial meningitis: 8% (Population: BM U)	<u>Microscopy</u> Gram staining <u>Molecular diagnosis</u> • Broad-range (16S) conventional PCR • Broad-range (16S) real-time PCR with DNA sequencing	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=7 N. meningitidis, n=3 S. pneumoniae, n=3 E. coli, n=2 group B Streptococcus, n=1 H. influenzae, n=1 other bacterial pathogens
Deutch 2008 Single-gate, cross-sectional DTA study Denmark	N=1015 samples from 994 people CSF specimens submitted to study laboratory during study period. Age in years (mean [range]): 40 (0-97) Positive for bacterial meningitis: 2%* samples (Population: BM U) *3% of samples were considered to have bacterial meningitis but this was only culture confirmed in 2%.	<u>Molecular diagnosis</u> Multiplex PCR: • for N. meningitidis • for S. pneumoniae	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=16 S. pneumoniae, n=5 N. meningitidis
Dubos 2006	N=167	<u>CSF white cell count</u>	Acute onset of meningitis and	• Sensitivity • Specificity	Positive CSF cultures in

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
Single-gate, cross-sectional DTA study France	Children aged 28 days-16 years and admitted during the study period with a diagnosis of acute meningitis. Age in years (median [range]): 4.6 (0.2-14.9) Positive for bacterial meningitis: 13% (Population: BM AM)	Threshold >200 cells/mm^3 (converted to cells/µL for consistency with other studies). <u>CSF neutrophil count</u> Threshold >100 cells/mm^3 (converted to cells/µL for consistency with other studies). <u>CSF glucose concentration</u> Threshold <2.5 mmol/L. <u>CSF protein concentration</u> Threshold >0.5 g/L (converted to mg/dL for consistency with other studies).	documented bacterial infection in CSF (direct examination and/or bacterial culture and/or latex agglutination) and/or blood bacterial culture.	• AUC	population with bacterial meningitis: not reported Causative organisms: n=10 S. pneumoniae, n=9 N. meningitidis, n=1 H. influenzae type b, n=1 group B Streptococcus
Dubos 2008 Secondary analysis of single-gate, cross-sectional DTA study France (data collected from 5 European countries [France, Poland, Spain, Switzerland, Turkey])	N=198 Children aged 29 days to 18 years admitted to hospital for bacterial or aseptic meningitis and had measurements of the main CSF and blood inflammatory markers in the Emergency Department. Age in years (mean [SD]): 3.2 (1.7) Positive for bacterial meningitis: 48% (Population: BM AM)	<u>CSF white cell count</u> Threshold >200 cells/µL. <u>CSF neutrophil count</u> Threshold >100 cells/µL. <u>CSF glucose concentration</u> Threshold <45 mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Threshold >0.5 g/L (converted to mg/dL for consistency with other studies).	Acute onset of meningitis and documented bacterial infection in CSF (direct examination and/or bacterial culture and/or latex agglutination and/or PCR) and/or blood bacterial culture.	• Sensitivity • Specificity • AUC	Positive CSF cultures in population with bacterial meningitis: 79% Causative organisms: n=45 N. meningitidis, n=32 S. pneumoniae, n=7 H. influenzae, n=4 group B Streptococcus
Dunbar 1998 Single-gate, cross-sectional DTA study	N=2635 CSF specimens submitted to study laboratory during study period. Ages: not reported	<u>Microscopy</u> Gram staining: • for all bacteria • for S. pneumoniae • for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=6 S. pneumoniae, n=2 N. meningitidis, n=1 L. monocytogenes, n=1 S. aureus,

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
USA	beyond all adults Positive for bacterial meningitis: 0.5% (Population: BMU)				n=1 M. morganii, n=1 S. sanguis II, n=1 S. bovis
Ena 2021 Single-gate, cross-sectional DTA study Spain	N=46 People with suspected meningitis, encephalitis or meningoencephalitis, with abnormal CSF results. Age in years (median [IQR]): bacterial or fungal aetiology 57 (20-77), unknown aetiology 45 (13-73), viral aetiology 13 (0.06-69) Positive for bacterial meningitis: 15%* (Population: BMENBME) *26% were considered to have bacterial meningitis but this was only culture confirmed in 15%.	<u>Microscopy</u> Gram staining: • for all bacteria • for N. meningitidis • for S. pneumoniae • for H. influenzae • for L. monocytogenes <u>Molecular diagnosis</u> Multiplex PCR (FA-ME panel): • for all included bacteria • for N. meningitidis • for S. pneumoniae • for H. influenzae • for L. monocytogenes	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=4 S. pneumoniae, n=1 N. meningitidis, n=1 H. influenzae, n=1 L. monocytogenes
Esparcia 2011 Single-gate, cross-sectional DTA study Spain	N=101 CSF samples from 108 people People with clinical suspicion of bacterial meningitis (defined as CSF white cell count ≥ 10 cells/μL, with or without positive cultures, antigen detections, or Gram stain of CSF). Ages of participants not reported. Positive for bacterial	<u>Molecular diagnosis</u> Broad-range (16S) PCR: • for all bacteria • for N. meningitidis • for S. pneumoniae • for L. monocytogenes	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=39 S. pneumoniae, n=12 N. meningitidis, n=8 L. monocytogenes

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	meningitis: 66%* (Population: BM U) *89% were considered to have bacterial meningitis but this was only culture confirmed in 66%.				
Favaro 2013 Single-gate, cross-sectional DTA study Italy	N=296 People with suspected meningitis. Age in years (range): 17-79 Positive for bacterial meningitis: 11%* (Population: BM U) *15% were considered to have bacterial meningitis but this was only culture confirmed in 11%.	<u>Molecular diagnosis</u> Combined (specific and broad-rage (16S)) PCR: • for all bacteria • for S. pneumoniae • for N. meningitidis • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli) • for L. monocytogenes	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=9 L. monocytogenes, n=6 N. meningitidis, n=2 S. pneumoniae, n=2 E. coli, n=1 group B Streptococcus, n=12 other bacterial pathogens not specified in protocol (L. innocua, E. faecalis, C. amycolatum, S. aureus, C. neoformans)
Freedman 2001 Single-gate, cross-sectional DTA study Canada	N=1617 Children aged 2 months to 17 years who underwent a lumbar puncture in 4 wards of study hospital, to assess the possibility of community-acquired bacterial meningitis. Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 3% (Population: BM U)	<u>CSF white cell count</u> Thresholds >3 cells/μL and >30 cells/μL.	• Definite: CSF bacterial culture and/or CSF latex agglutination • Presumed: Not definitely proven (as defined above) but receiving clinical diagnosis and treatment for bacterial meningitis.	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: 64% Causative organisms: n=18 S. pneumoniae, n=4 N. meningitidis, n=3 H. influenzae type b, n=2 M. tuberculosis, n=2 Enterococcus spp., n=1 E. coli, n=1 S. aureus, n=1 P. vesicularis, n=1 group B Streptococcus
Garges 2006 Single-gate, cross-sectional DTA study	N=9111 Neonates ≥ 34 weeks estimated gestational age, discharged from	<u>CSF white cell count</u> Thresholds >0 cells/mm^3, >8 cells/ mm^3, >21 cells/ mm^3, and >100 cells/ mm^3	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: • Gram-positive organisms 62 (65.3%): n=6 Enterococcus spp., n=37

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
USA	study NICUs and had a lumbar puncture performed. Estimated gestational age in weeks (mean [range]): 38 (34-44) Positive for bacterial meningitis: 1% (Population: BM U)	(converted to cells/µL for consistency with other studies). <u>CSF glucose concentration</u> Thresholds <20 mg/dL and <60 mg/dL (converted to mmol/L for consistency with other studies). <u>CSF protein concentration</u> Thresholds >40 mg/dL, >90 mg/dL, and >120 mg/dL.			group B streptococcus, n=1 L. monocytogenes, n=4 S. aureus, n=2 S. pneumoniae, n=12 Gram-positive coccuss (not further specified). • Gram-negative organisms 31 (32.6%): n=3 Acinetobacter spp., n=1 Citrobacter spp., n=12 E. coli, n=4 Enterobacter spp., n=2 Haemophilus influenzae, n=1 Proteus spp., n=3 Pseudomonas spp., n=1 Salmonella spp., n=2 Serratia spp., n=2 Neisseria spp., n=2 Gram-negative rod (not further specified).
Giulieri 2015 Single-gate, cross-sectional DTA study Switzerland	N=45 People ≥16 years old with microbiologically documented acute meningitis, a clinical presentation that includes fever, headache, neck stiffness or impaired level of consciousness and CSF pleocytosis (defined as >4 white blood cells/mm³). Age in years (median [range]): 53 (17–86) in bacterial meningitis group only Positive for	<u>CSF white cell count</u> Threshold >388 cells/mm^3 (converted to cells/µL for consistency with other studies). <u>CSF neutrophil count</u> Threshold >260 cells/mm^3 (converted to cells/µL for consistency with other studies). <u>CSF glucose concentration</u> (reported as CSF/blood glucose ratio). Threshold <0.35. <u>CSF protein concentration</u>	CSF bacterial culture and/or CSF Gram stain and/or CSF PCR and/or blood bacterial culture	• Sensitivity • Specificity • AUC	Positive CSF cultures in population with bacterial meningitis: 55% Causative organisms: n=11 S. pneumoniae, n=5 N. meningitidis, n=1 H. influenzae, n=1 group B Streptococcus

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	bacterial meningitis: 40% (Population: BM VM)	Threshold >1934 mg/L (converted to mg/dL for consistency with other studies).			
Jorgensen 1978 Single-gate, cross-sectional DTA study USA	N=305 People with suspected meningitis and with a lumbar puncture performed. Ages of participants not reported. Positive for bacterial meningitis: 24% (Population: BM UM NM)	<u>Microscopy</u> Gram staining • for all bacteria • for N. meningitidis • for S. pneumoniae • for H. influenzae • for group B Streptococcus • for Gram-negative bacilli (E. coli, P. aeruginosa, K. pneumoniae)	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=38 H. influenzae, n=6 N. meningitidis, n=6 E. coli, n=2 K. pneumoniae, n=1 A. faecalis, n=4 P. aeruginosa, n=1 F. meningosepticum, n=1 A. calcoaceticus var. anitratus, n=1 A. calcoaceticus var. lwoffi, n=1 C. diversus, n=4 group B Streptococcus, n=6 S. pneumoniae, n=3 S. aureus
Kennedy 2007 Single-gate, cross-sectional DTA study South Korea, Vietnam and People's Republic of China* *Samples came from South Korea, Vietnam, and People's Republic of China. The latter 2 countries do not meet inclusion criteria but the study was not considered indirect as testing was performed in South Korea	N=577 tested for S. pneumoniae • 1% with bacterial meningitis caused by S. pneumoniae N=1063 tested for H. influenzae • 2% with bacterial meningitis caused by H. influenzae meningitis Children <5 years old with suspected meningitis. Ages not reported beyond inclusion criteria. Population: BM U	<u>Molecular diagnosis</u> Specific PCR: • for S. pneumoniae • for H. influenzae	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=23 H. influenzae, n=8 S. pneumoniae
Khurana 1987 Single-gate, cross-sectional DTA	N=138 Children either admitted to or born at study	<u>Microscopy</u> Gram staining	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=6 H. influenzae, n=2 N. meningitidis, n=3 S. pneumoniae,

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
study USA	centre with suspected meningitis and lumbar puncture performed. Ages of participants not reported, although study conducted in paediatric setting. Positive for bacterial meningitis: 9% (Population: BM AM NM)				n=1 group B Streptococcus, n=1 group D Streptococcus
Kim 2012 Single-gate, cross-sectional DTA study South Korea, People's Republic of China and Vietnam* *Samples came from South Korea, Vietnam, and People's Republic of China. The latter 2 countries do not meet inclusion criteria but the study was not considered indirect as testing was performed in South Korea	N=106 Children <5 years old with suspected meningitis. Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 10%* (Population: BM U) *17% were considered to have bacterial meningitis but this was only culture confirmed in 10%.	<u>Microscopy</u> Gram staining for S. pneumoniae <u>Molecular diagnosis</u> Specific LAMP for S. pneumoniae <u>Molecular diagnosis</u> Specific PCR for S. pneumoniae	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=11 S. pneumoniae
Kleine 2003 Single-gate, cross-sectional DTA study* Germany *Although full study used a two-gate design, the	N=86 People with paired CSF and serum samples, with different forms of meningitis. • Study population also included people with multiple sclerosis, and various non-inflammatory	<u>CSF white cell count</u> Threshold ≥450 M/L (could not convert for consistency with other studies due to uncertainty regarding unit of measurement). <u>CSF protein concentration</u> Threshold ≥1.3g/L	CSF bacterial culture and/or direct microscopy and/or blood bacterial culture	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: Not reported.

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
data of interest for this review has been classified as a single-gate study because there was a single set of criteria for this group (not selected based on final diagnosis)	diseases. These have not been included in this analysis as not of interest for current review. Age in years (mean [range]) 49.5 (38.8-64.2) Positive for bacterial meningitis: 47% (Population: BM VM AM)	(converted to mg/dL for consistency with other studies).			
Kotilainen 1998 Single-gate, cross-sectional DTA study Finland	N=56 samples from 46 people People with a clinical diagnosis or suspicion of CNS infection, clinical microbiological testing and broad-range bacterial PCR assay testing. Ages of participants not reported Positive for bacterial meningitis: 7%* samples (Population: BM UM NM) *11% were considered to have bacterial meningitis but this was only culture confirmed in 7%.	Microscopy Gram staining (no details reported) Molecular diagnosis Broad-range (16S and/or 23S) bacterial PCR for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=5 N. meningitidis, n=1 L. monocytogenes
La Scolea Jr 1984 Single-gate cross-sectional DTA study USA	N=2031 Paediatric inpatient and outpatient patients. No further details reported. Ages of participants not reported, although study conducted in paediatric setting.	Microscopy Gram and methylene blue staining: • for all bacteria • for N. meningitidis • for S. pneumoniae • for H. influenza • for group B streptococcus	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=36 H. influenzae type b, n=9 group B Streptococcus, n=9 S. pneumoniae, n=7 N. meningitidis, n=2 E. coli

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Positive for bacterial meningitis: 3% (Population: BM U)				
Leber 2016 Single-gate cross-sectional DTA study USA	N=1560 CSF specimens collected by lumbar puncture and submitted to study laboratory during study period. Age in years (n): 921 adults ≥18 years, 639 children <18 years Positive for bacterial meningitis: 0.5% (Population: BM VM FM NM)	Molecular diagnosis Multiplex PCR (FA-ME panel): • for all included bacteria • S. pneumoniae • for H. influenzae • for Gram-negative bacilli (E. coli)	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=4 S. pneumoniae, n=2 E. coli, n=1 H. influenzae, n=1 group B Streptococcus
Lee 2015 Single-gate cross-sectional DTA study Vietnam, Peopl''s Republic of China, and South Korea* *Samples came from South Korea, Vietnam, and People's Republic of China. The latter 2 countries do not meet inclusion criteria but the study was not considered indirect as testing was performed in South Korea	N=1574 Children <5 years old with suspected meningitis. Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 0.2% (Population: MM U)	Molecular diagnosis • Specific LAMP for N. meningitidis • Specific PCR for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=3 N. meningitidis
Leitner 2016 Single-gate cross-sectional DTA	N=20 People with clinically suspected	Molecular diagnosis Multiplex PCR (FA-M/E panel) for all included bacteria	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=2 L. monocytogenes, n=2 N. meningitidis, n=2

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
study Austria	community acquired or drainage associated meningitis. Ages of participants not reported. Positive for bacterial meningitis: 40%* (Population: BM U) *45% were considered to have bacterial meningitis but this was only culture confirmed in 40%.				S. epidermidis, n=1 S. haemolyticus, n=1 S. hominis, n=1 S. pneumoniae Population has been marked down for applicability in QUADAS-2 assessment due to inclusion of 'drainage associated' meningitis (number in this group not reported).
Leli 2019 Single-gate cross-sectional DTA study Italy	N=109 People with CSF samples collected by lumbar puncture, and with results for bacterial culture and multiplex PCR. Age in years (median [IQR]): 60 (41.5-71) Positive for bacterial meningitis: 12%* (Population: BM VM NM) *13% were considered to have bacterial meningitis but this was only culture confirmed in 12%.	Molecular diagnosis Multiplex PCR (FA-ME panel): • for all included bacteria • for N. meningitidis for S. pneumoniae • for group B streptococcus • for L. monocytogenes	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=3 S. pneumoniae, n=1 group B Streptococcus, n=2 S. aureus, n=1 L. monocytogenes, n=2 N. meningitidis, n=1 P. aeruginosa, n=1 S. schleiferi, n=1 M. tuberculosis complex, n=1 T. otitidis, n=1 Kingella spp.
Lindquist 1988 Single-gate, cross-sectional DTA study Sweden	N=710 People ≥2 months old receiving lumbar puncture due to suspected CNS infection. Ages not reported beyond inclusion criteria.	CSF white cell count Thresholds >500x10^6 cells/L, >1000x10^6 cells/L, and >1500x10^6 cells/L (converted to cells/µL for consistency with other studies). CSF glucose concentration	CSF bacterial culture and/or CSF latex agglutination and/or CSF counter immune-electrophoresis	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: 86% Causative organisms: n=22 H. influenzae, n=19 N. meningitidis, n=14 S. pneumoniae, n=3

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Positive for bacterial meningitis: 11% (Population: BMU)	Threshold <2.2 mmol/L. CSF glucose concentration (reported as CSF/blood glucose ratio). Thresholds <0.4 and <0.5. CSF protein concentration Thresholds >0.5 g/L, >1.0 g/L, and >1.5 g/L (converted to mg/dL for consistency with other studies).			L. monocytogenes, n = 3 S. aureus, n = 3 streptococci of groups A and B, n=1 P. mirabilis, n=1 H. parainfluenzae, n=1 Brucella spp., n=1 M. tuberculosis, n=11 without proven bacterial aetiology
Meyer 2014 Two-gate, cross-sectional DTA study Germany	N=40 CSF samples from people with clinical symptoms of CNS infection who were and were not suspected to have a bacterial infection (based on white cell counts > or <500µL, respectively). Ages of participants not reported Positive for bacterial meningitis: 15% (Population: BMBIUI)	Microscopy Gram staining Molecular diagnosis Broad-range (16S) bacterial PCR	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: Not reported.
Morrissey 2017 Single gate, cross-sectional DTA study Ireland	N=827 Babies (aged 7–90 days) with a blood or CSF sample tested by group B Streptococcus PCR. Age in days (median [IQR]): 35 (20.75-57) Positive for bacterial meningitis: 0.6% (Population: GBM	Molecular diagnosis Specific PCR for group B streptococcus	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=5 group B Streptococcus

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	U)				
Nabower 2019 Single-gate, cross-sectional DTA study USA	N=223 Children 0-18 years old who had a CSF culture or FA-M/E panel obtained within 48 hours of admission, to evaluate potential infectious aetiology. Age in days (n [%]): 67 (30.0) <30 days, 100 (44.8) 30-90, >90 57 (25.6) Positive for bacterial meningitis: 2% (Population: BM U)	Molecular diagnosis Multiplex PCR (FA-M/E panel) for all included bacteria	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: Not reported.
Negrini 2000 Single-gate, cross-sectional DTA study USA	N=158 All paediatric patients aged ≥30 days hospitalised with a diagnosis of meningitis. Age (range): 30 days-18 years Positive for bacterial meningitis: 13% (Population: BM AM)	CSF neutrophil count (reported as polymorphonuclear cells). Threshold 50%.	CSF bacterial culture and/or CSF pleocytosis with blood bacterial culture	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: 85% Causative organisms: n=13 S. pneumoniae, n=6 H. influenza, n=1 E. coli Polymorphonuclear count: As only a proportion of these cells are neutrophils, index test has been marked down for applicability in QUADAS-2 assessment.
Nelson 1986 Single-gate, cross-sectional DTA study Sweden	N=133 Children with suspected meningitis admitted to study paediatric department with suspected meningitis. Age (range): 11 days-16 years Positive for	CSF white cell count Threshold >8 cells/μL. CSF glucose concentration (reported as CSF/blood glucose ratio). Threshold <0.40.	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=12 H. influenzae type B, n=2 E. coli, n=1 group B Streptococcus, n=1 N. meningitidis, n=1 S. pneumoniae, n=1 S. epidermidis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	bacterial meningitis: 14% (Population: BM AM NM)				
Neuman 2008 Single-gate, cross-sectional DTA study USA	N=17,569 samples from 16,036 children Children ≤21 years of age admitted to emergency department and lumbar puncture performed within 24 hours. Age in days (median [IQR]): 74 (38-562) Positive for bacterial meningitis: 0.4% samples (Population: BM U)	Microscopy Gram staining	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=19 S. pneumoniae, n=15 E. coli, n=9 group B Streptococcus, n=8 N. meningitidis, n=2 Citrobacter spp., n=2 H. influenzae type b, n=2 S. bovis, n=1 L. monocytogenes, n=1 Salmonella group B, n=1 S. aureus, n=1 S. pyogenes, n=1 S. MG-intermedius, n=1 non-enteric Gram-negative rods
Ni 1992 Two-gate, cross-sectional DTA study UK	N=54 People with suspected meningococcal disease and control group (no further details reported) undergoing lumbar puncture. Age in years (range): 1-61 in bacterial meningitis group Positive for bacterial meningitis: 33% (Population: BM MD VM NM)	Molecular diagnosis Specific PCR for N. meningitidis	CSF bacterial culture and/or Gram stain	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=11 N. meningitidis, n=6 H. influenzae type b and n=1 S. pneumoniae
Pfefferle 2020 Single-gate, cross-sectional DTA study Germany	N=171 CSF samples of people with suspected CNS infection (defined as abnormality in Gram-stain results (for example, leucocytes and/or bacteria visible) or communicated by clinicians.	Molecular diagnosis Multiplex PCR (FA-M/E panel) for all included bacteria	CSF bacterial culture and PCR	• Sensitivity • Specificity	Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=16 S. pneumoniae, n=5 N.meningitidis, n=3 L.

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Ages of participants not reported. Positive for bacterial meningitis: 16% (Population: BM VM FM NM)				monocytogenes, n=2 H. influenzae, n=1 group B Streptococcus
Piccirilli 2018 Single-gate, cross-sectional DTA study Italy	N=25 People with suspected meningitis or encephalitis. Age (n [%]): 5 (8) paediatric; 58 (92) adults in total retrospective study population Positive for bacterial meningitis: 32%* (Population: BM U) *64% were considered to have bacterial meningitis but this was only culture confirmed in 32%.	Molecular diagnosis Multiplex PCR (FA-ME panel) for all included bacteria	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=6 N. meningitidis, n=3 H. influenzae, n=1 L. monocytogenes, n=3 group B Streptococcus, n=3 S. pneumoniae
Poppert 2005 Single-gate, cross-sectional DTA study Germany	N=151 CSF samples from people with suspected meningitis, which had been sent for routine diagnosis. Ages of participants not reported. Positive for bacterial meningitis: 23% (Population: BM U)	Molecular diagnosis Multiplex PCR for all included bacteria	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: Not reported.
Porritt 2000 Single-gate, cross-sectional DTA study Australia	N=85 CSF samples from people with suspected meningococcal disease.	Molecular diagnosis Specific PCR for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=14 N. meningitidis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Ages of participants not reported. Positive for bacterial meningitis: 16%* (Population: MM U) *45% were considered to have bacterial meningitis but this was only culture confirmed in 16%.				
Ray 2007 Single-gate, cross-sectional DTA study France	N=151 People over 16 years old who attended the emergency department and received a diagnosis of meningitis based on compatible clinical features and pleocytosis (CSF > 5 white blood cells/mm³). Age in years (mean [SD]): 52 (20) in bacterial meningitis group only. Positive for bacterial meningitis: 12% (Population: BM UM)	<u>CSF white cell count</u> Threshold ≥300 cells/mm³ (converted to cells/µL for consistency with other studies). <u>CSF glucose concentration</u> (reported as CSF/blood glucose ratio). Threshold ≤0.15. <u>CSF protein concentration</u> Threshold ≥1.31 g/L (converted to mg/dL for consistency with other studies).	CSF bacterial culture and/or CSF antigen test and/or blood bacterial culture and/or CSF pleocytosis with a neutrophil count >500/mm³ and rapid improvement after antibacterial therapy	• Sensitivity • Specificity • AUC	Positive CSF cultures in population with bacterial meningitis: 61% Causative organisms: n=4 Streptococcus spp. other than pneumonia, n=2 S. pneumoniae, n=2 N. meningitidis, n=1 Fusobacterium, n=1 K. pneumoniae, n=1 M. tuberculosis, n=7 unknown
Richardson 2003 Single-gate, cross-sectional DTA study Canada	N=281 People with suspected bacterial meningitis. Age (median [range]): 16 years (6 weeks-63 years) in meningococcal meningitis group Positive for bacterial meningitis caused by N. meningitidis: 7%* (Population:	<u>Molecular diagnosis</u> Specific PCR for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=45 S. pneumoniae, n=21 N. meningitidis, n=5 H. influenzae, n=4 S. aureus, n=3 group B streptococcus, n=1 C. albicans, n=1 group G streptococcus, n=1 P. aeruginosa, n=1 K. oxytoca, n=1 E. cloacae, n=1 A. baumannii

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	MM BM UM) *14% were considered to have bacterial meningitis caused by N. meningitidis but this was only culture confirmed in 7%.				
Rothman 2010 Single-gate, cross-sectional DTA study USA	N=108 Excess CSF specimens submitted to study laboratory during study period. Ages of participants not reported. Positive for bacterial meningitis: 17% (Population: BM U)	Molecular diagnosis Multiplex PCR (Uniprobe PCR) for all included bacteria	CSF bacterial culture	• Sensitivity • Specificity	Causative organism: Not reported.
Schuurman 2004 Single-gate, cross-sectional DTA study The Netherlands	N=227 samples from 222 people CSF samples collected at participating laboratories during study period, from people with meningitis (of any type) as part of their differential diagnosis. Age in years (mean [range]): 24.5 (0-87.9) Positive for bacterial meningitis: 12% (Population: BM U)	Molecular diagnosis Broad-range (16S) PCR	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=12 N. meningitidis, n=8 S. pneumoniae, n=2 E. coli, n=2 H. influenzae, n=1 L. monocytogenes, and n=1 S. salivarius
Seward 2000a Single-gate, cross-sectional DTA study UK	N=74 CSF samples from people with suspected meningococcal meningitis. Ages of participants not	Molecular diagnosis Specific PCR for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=19 N. meningitidis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	reported. Positive for bacterial meningitis: 26% (Population: MMU)				
Seward 2000b Single-gate, cross-sectional DTA study UK	N=294 People with suspected meningitis. Ages of participants not reported. Psoitive for bacterial meningitis: 9% (Population: BMU)	Molecular diagnosis Multiplex PCR: • for all included bacteria • for N. meningitidis	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=11 N. meningitidis, n=4 S. pneumoniae, n=4 S. epidermidis, n=2 S. aureus, n=2 group B Streptococcus, n=1 P. aeruginosa, n=1 K. aerogenes
Sormunen 1999 Two-gate, cross-sectional DTA study Finland	N=237 Bacterial meningitis group: People with positive bacterial CSF culture and negative initial CSF Gram stain. Viral meningitis group: People with a diagnosis of viral meningitis at the time of hospital discharge. Age (range): 3 months-15 years in bacterial meningitis group only. Positive for bacterial meningitis: 23% (Population: BMVM)	CSF white cell count Thresholds >100x10^6 cells/L, >500x10^6 cells/L, >1000x10^6 cells/L, and >2000x10^6 cells/L (converted to cells/µL for consistency with other studies). CSF glucose concentration Thresholds <2.0 mmol/L, <2.5 mmol/L and <3.0 mmol/L. CSF protein concentration Thresholds >0.5 g/L, >1.0 g/L, and >1.5 g/L (converted to mg/dL for consistency with other studies).	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=26 N. meningitidis, n=23 H. influenzae type b, n=3 S. pneumoniae, n=1 L. monocytogenes, n=1 E. coli, n=1 group B Streptococcus
Viallon 2011 Single-gate, cross-sectional DTA study France	N=253 Adults admitted to the emergency unit with meningitis (defined by leukocyte count >5 cells/mm^3 in the CSF) and negative direct CSF examination.	CSF neutrophil count Threshold >118 cells/mm^3 (converted to cells/µL for consistency with other studies). CSF glucose concentration	CSF bacterial culture	• Sensitivity • Specificity • AUC	Causative organisms: n=14 S. pneumoniae, n=6 L. monocytogenes, n=5 N. meningitidis, n=4 Streptococcus spp., n=2 H. influenzae, n=2 S. aureus, n=2 other species

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Age in years (mean [SD]): 55 (20) in bacterial meningitis group only Positive for bacterial meningitis: 14% (Population: BM VM VME)	Threshold <2.2 mmol/L. <u>CSF glucose concentration</u> (reported as CSF/serum glucose ratio). Threshold <0.48. <u>CSF protein concentration</u> Threshold >1.88 g/L (converted to mg/dL for consistency with other studies).			
Vincent 2020 Single-gate, cross-sectional DTA study France	N=1124 CSF samples submitted for the diagnosis of infectious meningitis at study laboratory. Age (n): n=815 adults (>18 years old), n=309 children (≤18 years old) Positive for bacterial meningitis: 1% (Population: BM U)	<u>Molecular diagnosis</u> Multiplex PCR (FA-ME panel): • for N. meningitidis for S. pneumoniae • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli)	CSF bacterial culture, Gram stain and PCR	• Specificity • Sensitivity	Positive CSF cultures in population with bacterial meningitis: 100% Causative organisms: n=8 S. pneumoniae, n=3 N. meningitidis, n=2 group B Streptococcus, n=1 H. influenzae
Wagner 2018 Single-gate, cross-sectional DTA study Switzerland	N=220 CSF samples from people with meningitis symptoms collected in secondary and tertiary care hospitals in study area. Ages of participants not reported. Positive for bacterial meningitis: 7%* (Population: BM U) *9% were considered to	<u>Molecular diagnosis</u> Multiplex LightMix RT-PCR: • for all included bacteria • for S. pneumoniae	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: n=8 S. pneumoniae, n=4 S. epidermidis, n=2 E. coli., n=2 S. hominus, n=1 N. meningitidis, n=1 group B Streptococcus, n=1 K. pneumoniae, n=1 S. marcescens

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	have bacterial meningitis but this was only culture confirmed in 7%.				
Welinder-Olsson 2007 Single-gate, cross-sectional DTA study Sweden	N=345 People with suspected meningitis (defined as CSF white blood cell count ≥10 cells/μL). Age (median [range]): 34 years (1 day-91 years) Positive fotr bacterial meningitis: 21% (Population: BM VM UM NM)	Molecular diagnosis Broad-range (16S) PCR	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: Numbers not reported but included N. meningitidis, S. pneumoniae, H. influenzae, Listeria spp., Gram-negative bacilli, streptococci or staphylococci.
White 2012 Single-gate, cross-sectional DTA study Australia	N=2290 People over 5 years of age receiving lumbar puncture (without repeat lumbar puncture samples within 6 months). Age in years (median [IQR]): 38 (15-51) for males, 20 (18-54) for females in bacterial meningitis group only. Positive for bacterial meningitis: 1% (Population: BM VM CM NM)	CSF white cell count Threshold >90x10^6 cells/L (converted to cells/μL for consistency with other studies). CSF protein concentration Threshold >600 mg/L (converted to mg/dL for consistency with other studies).	Traditional methods (including CSF culture and Gram stain) and or NAAT	• Sensitivity • Specificity • AUC	Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=12 S. pneumoniae, n=8 N. meningitidis, n=2 H. influenzae, n=1 B. pseudomallei
Xirogianni 2009 Single-gate, cross-sectional DTA study Greece	N=262 CSF samples sent to National Meningitis Reference Laboratory. Ages of participants not reported. Positive for bacterial	Molecular diagnosis Multiplex PCR: • for H. influenzae • for Gram-negative bacilli (P. aeruginosa)	CSF bacterial culture	• Sensitivity • Specificity	Causative organisms: Numbers not reported but included H. influenzae, P. aeruginosa, S. aureus, or Streptococcus spp.

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	meningitis: 8% (Population: BM VM NM)				

AM: aseptic meningitis; AME: aseptic meningitis/encephalitis; AUC: area under the curve; A. baumannii: Acinetobacter baumannii; A. faecalis: Alcaligenes faecalis; A. calcoaceticus: Acinetobacter calcoaceticus; BI: bacterial CNS infection; BM: bacterial meningitis; BME: bacterial meningitis/encephalitis; B. pseudomallei: Burkholderia pseudomallei; CM: cryptococcal meningitis; CNS: central nervous system; CSF: cerebrospinal fluid; C. albicans: Candida albicans; C. amycolatum: Corynebacterium amycolatum; C. cloacae: Citrobacter cloacae; C. diversus: Citrobacter diversus; C. koseri: Citrobacter koseri; C. neoformans: Cryptococcus neoformans; DTA: diagnostic test accuracy; E. coli; Escherichia coli; E. cloacae: Enterobacter cloacae; E. faecalis: FA-M/E: FilmArray® Meningitis/Encephalitis; FM: fungal meningitis; F. meningosepticum: Flavobacterium meningosepticum; GBM: group B Streptococcus meningitis; GBS: group B streptococcus septicaemia; H. influenzae: Haemophilus influenzae; IQR: interquartile range; K. aerogenes: Klebisella aerogenes; K. oxytoca: Klebsiella oxytoca; K. pneumoniae: Klebsiella pneumoniae; L. innocua: Listeria innocua; L. monocytogenes; Listeria monocytogenes; MD: meningococcal disease; MM: meningococcal meningitis; M. morganii: Morganella morganii; M. tuberculosis: Mycobacterium tuberculosis; N/n: number; NBME: non-bacterial meningitis/encephalitis; NAAT: nucleic acid amplifications testing; NICU: neonatal intensive care unit; NM: non-meningitis; N. meningitidis; Neisseria meningitidis; PCR: polymerase chain reaction; P. aeruginosa: Pseudomonas aeruginosa; PM: pneumococcal meningitis; P. mirabilis: Proteus mirabilis; P. vesicularis: Pseudomonas vesicularis; RT-PCR: real-time polymerase chain reaction; SD: standard deviation; spp.: species; S. aureus: Staphylococcus aureus; S. bovis: Streptococcus bovis; S. epidermidis: Staphylococcus epidermidis; S. haemolyticus: Staphylococcus haemolyticus; S. hominis: Staphylococcus hominis; S. marcescens: Serratia marcescens; S. pneumoniae: Streptococcus pneumoniae; S. pyogenes: Streptococcus pyogenes; S. sanguis: Streptococcus sanguinis; S. salivarius: Streptococcus salivarius; S. schleiferi: Staphylococcus schleiferi; T. otitidis: Turicella otitidis; U: undefined population; UI: undefined CNS infection; UM: undefined meningitis; US: undefined septicaemia; var.: variety; VM: viral meningitis; VME: viral meningoencephalitis

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

Summary of the evidence

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

The evidence was assessed as being high to very low quality. Any downgrading was due to serious or very serious risk of bias according to the QUADAS-2 checklist and 95% confidence intervals crossing decision-making thresholds. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

No meta-analyses were conducted for any of the index tests due insufficient evidence to conduct meta-analyses after stratifying for age, index test threshold, bacterial pathogen and reference standard used. Where there was sufficient evidence to pool studies, a high level of heterogeneity remained between studies in terms of study design, population and prevalence of bacterial meningitis.

White cell count (WCC)

Neonates

The evidence for WCC in neonates was high to low quality. WCC was very sensitive but not specific for diagnosis of any bacterial meningitis in neonates at a threshold of more than 0 cells/µl, moderately sensitive and specific at thresholds of more than 8-21 cells/µl, and moderately sensitive and very specific at a threshold of more than 100 cells/µl. One study investigated the accuracy of WCC for diagnosing bacterial meningitis caused by group B Streptococcus. At a threshold of more than 26 cells/µL for premature and 23 cells/µL for term neonates, sensitivity and specificity were both moderate. Most of the sensitivity evidence (apart from at thresholds of more than 21 and 100 cells/µL) was seriously imprecise so should not be taken as definitive evidence of the sensitivity.

Neonates and babies combined

The evidence for WCC in neonates and babies combined was high to moderate quality. WCC was moderately sensitive and specific for diagnosis of any bacterial meningitis in neonates and babies at thresholds of more than 8-10 cells/μL. At thresholds of more than 100-1000 cells/μL, it was not sensitive but very specific. At thresholds of more than 8 and 100 cells/μL, the sensitivity evidence was seriously imprecise (due to 95% confidence intervals crossing decision making thresholds) so should not be taken as definitive evidence of the sensitivity. One study calculated an area under the curve (AUC) for WCC, which also indicated WCC was a very useful test. However, the AUC value was also seriously imprecise so shouldn't be taken as definitive evidence of diagnostic accuracy.

Neonates, babies and children combined

One study reported the diagnostic accuracy of WCC in a population of neonates, babies and children at a threshold of more than 8 cells/μL. The evidence was moderate to high quality and showed that WCC was very sensitive and moderately specific for diagnosis of any bacterial meningitis at this threshold in this population. However, the sensitivity data was seriously imprecise so should not be taken as definitive evidence of the sensitivity.

Babies and children combined

The evidence for WCC in babies and children combined was high to very low quality. WCC was moderately sensitive and specific for diagnosis of any bacterial meningitis at thresholds of more than 3 cells/μL, more than 200 cells/μL and more than 321 cells/μL. At thresholds of more than 30 cells/μL, more than 597 cells/μL, more than 1000 cells/μL and more than 2000 cells/μL, accuracy was moderately sensitive and very specific. At a threshold of more than 100 cells/μL, WCC was moderately sensitive but not specific. Three studies investigated the accuracy of WCC at a threshold of more than 500 cells/μL. All reported moderate sensitivity; two reported moderate specificity and the other reported the test to be very specific at this threshold. Most of the sensitivity evidence (apart from at thresholds of more than 30, 1000 and 2000 cells/μL) was seriously imprecise so should not be taken as definitive evidence of the sensitivity. Similarly, the specificity evidence was seriously imprecise at thresholds of more than 500 and 597 cells/μL.

Children

One study reported the diagnostic accuracy of WCC in children at a threshold of more than 200 cells/μL. The evidence was moderate quality and WCC was moderately sensitive and specific for diagnosis of any bacterial meningitis at this threshold.

Adults

The evidence for WCC in adults was high to very low quality. WCC was very sensitive but not specific for the diagnosis of any bacterial meningitis at thresholds of more than 15 and more than 90 cells/μL; apart from when differentiating between bacterial meningitis and cryptococcal meningitis, where the index test was moderately specific. At thresholds of more than 300-388 cells/μL, WCC was reported to be moderately sensitive and very specific, and moderately sensitive and specific at a threshold of more than 5.1 M/L. However, most of the estimates were seriously imprecise for both sensitivity and specificity, so should not be taken as definitive evidence of diagnostic accuracy. Three studies calculated an area under the curve for WCC in this population. The AUC value from 2 studies (comparator population aseptic meningoencephalitis/viral meningitis) indicated WCC was a very useful test, but the AUC value from the remaining study (comparator population undefined meningitis) indicated that it was not a useful test. All 3 estimated AUC values were at least seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

All ages combined

In a population of mixed ages, the evidence for WCC was moderate to very low quality. WCC was very sensitive and moderately specific for the diagnosis of any bacterial meningitis at a threshold of more than 5 cells/μL. At thresholds of more than 500–1500 cells/μL, WCC was moderately sensitive and very specific. At a threshold of more than or equal to 10 cells/μL for neonates and 5 cells/μL for adults, index test accuracy was reported to be very sensitive and very specific. The estimated values for sensitivity were seriously imprecise at all thresholds apart from more than 500 cells/μL, so should not be taken as definitive evidence of the sensitivity. The estimate for specificity was also imprecise at a threshold of more than 5 cells/μL.

Neutrophil count

Neonates, babies and children combined

Evidence for neutrophil count in combined populations of neonates, babies and children was moderate to low quality. Neutrophil count was very sensitive and specific for diagnosis of any bacterial meningitis in this population at a threshold of more than 50 cells/cm (note this threshold could not be converted for consistency with other studies due to uncertainty regarding the unit of measurement), and moderately sensitive and specific at a threshold of more than 80%. At both thresholds, the sensitivity estimates were seriously imprecise, so should not be taken as definitive evidence of sensitivity.

Babies and children combined

The evidence for neutrophil count was high to very low quality in babies and children combined. Neutrophil count was moderately sensitive and specific for the diagnosis of any bacterial meningitis in babies and children at thresholds of more than 1%, more than 74%, and more than 100 cells/μL. Two studies investigated the accuracy of neutrophil count at a threshold of more than 50%. It was reported to be very sensitive but not specific by 1 study (comparator population aseptic meningitis), while the other reported neutrophil count to be a moderately sensitive and very specific (comparator population was undefined). Neutrophil count was reported to be moderately sensitive and very specific at thresholds of more than 25% and more than 75%, and very sensitive and moderately specific at a threshold of more than 200 cells/μL. All the sensitivity estimates were at least seriously imprecise, so shouldn't be taken as definitive evidence of sensitivity. Similarly, specificity estimates were imprecise at threshold of more than 50% more than 74% and more than 200 cells/μL.

Children

The evidence for neutrophil count in children was moderate to low quality. Neutrophil count was moderately sensitive and specific for the diagnosis of any bacterial meningitis in this population at a threshold of more than 100 cells/μL and the AUC value indicated it was a very useful test. However, the estimated AUC value was seriously imprecise so should not be taken as definitive evidence of diagnostic accuracy.

Adults

The evidence for neutrophil count in adults was moderate to very low quality. Neutrophil count was very sensitive and specific for the diagnosis of any bacterial meningitis in adults, at thresholds of more than 37 cells/μL and more than 260 cells/μL. It was calculated to be moderately sensitive and specific at thresholds of more than 118 cells/μL and more than 67%. However, all these estimates, apart from specificity at a threshold of more tha 188 cells/μL, were seriously imprecise so should not be taken as definitive evidence of diagnostic accuracy. Four studies calculated AUC values for neutrophil count in this population, with all reporting that it is a very useful test.

Microscopy for bacteria: Gram staining

Neonates

The evidence for gram staining in neonates was moderate to low quality. Gram staining was not sensitive but very specific for the diagnosis of any bacterial meningitis in neonates. However, the estimate for sensitivity was seriously imprecise so should not be taken as definitive evidence of the sensitivity.

Neonates and younger babies combined

The evidence for gram staining in a combined population of neonates and younger babies was high quality. Gram staining was not sensitive but very specific for the diagnosis of any bacterial meningitis in this population.

Neonates, babies and children combined

One study investigated the accuracy of Gram staining for diagnosing bacterial meningitis caused by Streptococcus pneumoniae (S. pneumoniae) in neonates, babies and children. The evidence was moderate quality and it showed gram staining was very sensitive and specific in this combined population. However, the estimates for both sensitivity and specificity were imprecise so should not be taken as definitive evidence of diagnostic accuracy.

Babies and children combined

The evidence for gram staining in combined populations of babies and children was high to low quality. Three studies reported gram staining as moderately sensitive, with the remaining study reporting it as very sensitive. All studies reported this index test to be very sensitive. Apart from 1 study, all the sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity. For one study, the specificity estimate was also imprecise.

Adults

The evidence for gram staining in adults was moderate to very low quality. Gram staining was very sensitive and specific for the diagnosis of any bacterial meningitis, bacterial meningitis caused by Neisseria meningitidis (N. meningitidis), and bacterial meningitis caused by S. pneumoniae in adults. However, all of the sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

All ages combined

The evidence for gram staining in mixed populations of all ages was high to low quality. Gram staining was moderately sensitive and very specific for the diagnosis of any bacterial meningitis, bacterial meningitis caused by N. meningitidis, and bacterial meningitis caused by S. pneumoniae in this population. It was very sensitive and specific for the diagnosis of bacterial meningitis caused by group B Streptococcus or Gram-negative bacilli, and not sensitive but very specific for the diagnosis of bacterial meningitis caused by Listeria monocytogenes (L. monocytogenes). However, apart from for the diagnosis of any bacterial meningitis, all of the sensitivity estimates were at least seriously imprecise, so should not be taken as definitive evidence of sensitivity. Similarly, the estimated specificity for any bacterial meningitis was also seriously imprecise.

Undefined age

The evidence for gram staining in studies with undefined ages was high to very low quality. The sensitivity of gram staining for the diagnosis of any bacterial meningitis varied. One study reported the test as not sensitive, and 3 reported it as moderately sensitive. All 4

studies reported gram staining to be very specific for diagnosing any bacterial meningitis in this population. However, most of the sensitivity estimates and 1 of the specificity estimates were at least seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

For the diagnosis of bacterial meningitis caused by N. meningitis in undefined ages, 1 study reported Gram staining to be moderately sensitive and very specific and another study reported it to be very sensitive and specific. Again, both sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity. Gram staining was found to be moderately sensitive and very specific for diagnosis of bacterial meningitis caused by S. pneumoniae, H. influenzae, or group B Streptococcus, but all the sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity. For the diagnosis of bacterial meningitis caused by Gram-negative bacilli, 1 study reported gram staining was not sensitive but very specific and another reported it to be very sensitive and specific. Again, both sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

Microscopy for bacteria: Gram and methylene blue staining

Babies and children combined

One study investigated the accuracy of Gram and methylene blue staining in babies and children and the evidence was high to low quality. For the diagnosis of any bacterial meningitis, this combined index test was moderately sensitive and very specific. It was not sensitive but very specific for the diagnosis of bacterial meningitis caused by N. meningitidis and moderately sensitive and very specific for the diagnosis of bacterial meningitis caused by S. pneumoniae, Haemophilus influenzae (H. influenzae), or group B Streptococcus. However, the sensitivity estimates for specific causes of bacterial meningitis were all at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

Absolute glucose concentration

Neonates

The evidence for glucose concentration in neonates was high to low quality. Glucose concentration was not sensitive but very specific for diagnosis of any bacterial meningitis in neonates at a threshold of less than 1.11 mmol/L, moderately sensitive and specific at a threshold of less than 1.89 mmol/L, and moderately sensitive but not specific at a threshold of less than 3.33 mmol/L. However, all of the sensitivity estimates were seriously imprecise so should not be taken as definitive evidence of sensitivity.

One study investigated the accuracy of glucose concentration for diagnosing bacterial meningitis caused by group B Streptococcus. At a threshold of less than 1.28 mmol/L for premature and 1.83 for term neonates, glucose concentration was reported to be moderately sensitive and very specific. However, the sensitivity estimate was seriously imprecise so should not be taken as definitive evidence of sensitivity.

Neonates, babies and children combined

The evidence for glucose concentration in a population of combined neonates, babies and children was low. Glucose concentration was moderately sensitive and specific for the diagnosis of any bacterial meningitis in this population at a threshold of less than 2.94 mmol/L but both estimates were seriously imprecise so should not be taken as definitive evidence of diagnostic accuracy.

Babies and children combined

The evidence for glucose concentration in babies and children combined was high to very low quality. Glucose concentration was not sensitive but very specific for diagnosis of any bacterial meningitis in this population at thresholds of less than 1.11 mmol/L, less than 2.0 mmol/L and less than 2.2 mmol/L. It was found to be moderately sensitive and very specific at a thresholds of less than 2.11 mmol/L. Two studies investigated the accuracy of glucose concentration at a threshold of less than 2.22 mmol/L. One study reported the index test as not sensitive (comparator population was undefined), the other moderately sensitive (comparator population included viral meningitis and non-meningitis). Both studies reported specificity as very sensitive. Two studies investigated the accuracy of glucose concentration at a threshold of less than 2.5 mmol/L. One study reported the index test as moderately sensitive and specific, the other as not sensitive but very specific. Glucose concentration was not sensitive and moderately specific at a threshold of less than 3.0 mmol/L, not sensitive or specific at a threshold of less than 3.33 mmol/L and very sensitive but not specific at a threshold of 6.66 mmol/L. However, several of both the sensitivity and specificity estimates were imprecise, so these should not be taken as definitive evidence of diagnostic accuracy.

Children

The evidence for glucose concentration in children was moderate quality. Glucose concentration was moderately sensitive and specific for the diagnosis of any bacterial meningitis in this population at a threshold of less than 2.5 mmol/L.

Adults

The evidence for glucose concentration in adults was low quality. Glucose concentration was very sensitive but not specific for the diagnosis of any bacterial meningitis in this population at a threshold of less than 2.2 mmol/L, and moderately sensitive and very specific at a threshold of less than 2.7 mmol/L. Two studies calculated an AUC value; one indicated glucose concentration to be a very useful index test, but the other indicated it was not a useful test. All the estimates were imprecise so should not be taken as definitive evidence of diagnostic accuracy.

All ages combined

Evidence for glucose concentration in a mixed population of all ages combined was moderate to low quality. Glucose concentration was moderately sensitive and very specific for the diagnosis of any bacterial meningitis in this population at a threshold of less than 2.2 mmol/L. However, the estimate for sensitivity was seriously imprecise so should not be taken as definitive evidence of sensitivity.

CSF:serum glucose

Neonates, babies and children combined

The evidence for CSF:serum glucose in a combined population of neonates, babies and children was moderate to low quality. CSF:serum glucose was moderately sensitive and very specific for the diagnosis of any bacterial meningitis in this population at a threshold of less than 0.40. However, the sensitivity estimate was seriously imprecise so should not be taken as definitive evidence of sensitivity.

Adults

The evidence for CSF:serum glucose in adults was moderate to very low quality. CSF:serum glucose was not sensitive or specific for the diagnosis of any bacterial meningitis in adults at a threshold of less than 0.15, very sensitive and specific at a threshold of less than 0.35, and moderately sensitive and specific at thresholds of less than 0.40 and0.48. However, all the estimates for both sensitivity and specificity were seriously imprecise so should not be taken

as definitive evidence of diagnostic accuracy. Four studies calculated an AUC value. One indicated it was not a useful test, the other 3 indicated that it was a very useful test.

All ages combined

The evidence for CSF:serum glucose in mixed populations of all ages was moderate to low quality. CSF:serum glucose was moderately sensitive and specific at a threshold of less than 0.40, moderately sensitive and very specific at a threshold of less than 0.50, and very sensitive but moderately specific at a threshold of less than 0.66. However, both estimates at a threshold of less than 0.66 and the sensitivity estimate at a threshold of 0.40 were seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

Protein concentration

Neonates

The evidence for protein concentration in neonates was moderate to low quality. Protein concentration was very sensitive but not specific for the diagnosis of any bacterial meningitis in neonates at a threshold of more than 40 mg/dL, and moderately sensitive but not specific at a threshold of more than 90 mg/dL. At a threshold of less than 120 mg/dL, protein concentration was moderately sensitive and specific, and moderately sensitive and very specific at a threshold of more than 120 mg/dL. The sensitivity estimates at thresholds of more than 90mg/dL and 170mg/dL were seriously imprecise, so should not be taken as definitive evidence of sensitivity.

One study investigated the accuracy of protein concentration for diagnosing bacterial meningitis caused by group B Streptococcus. At a threshold of more than 151 mg/dL for premature and 171 mg/dL for term neonates, protein concentration was reported to be very sensitive and moderately specific. However, the sensitivity estimate was seriously imprecise so should not be taken as definitive evidence of sensitivity.

Neonates, babies and children combined

In populations of neonates, babies and children combined, the quality of the evidence was moderate to low. Protein concentration was moderately sensitive and very specific for diagnosis of any meningitis in this population at thresholds of more than 40mg/dL and more than 100 mg/dL. However, both estimates at a threshold of more than 40mg/dL and the sensitivity estimate at a threshold of 100mg/dL were seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

Babies and children combined

The evidence for protein concentration in populations of babies and children combined was moderate to very low quality. Protein concentration was not sensitive and moderately specific for the diagnosis of any bacterial meningitis in this population at a threshold of more than 40 mg/dL. It was not sensitive but very specific at thresholds of more than 80 mg/dL, more than 120 mg/dL and more than 200 mg/dL. Protein concentration was moderately sensitive and specific at a threshold of more than 50 mg/dL, and moderately sensitive but very specific at a threshold of more than 97 mg/dL. Three studies investigated the accuracy of protein concentration at a threshold of more than 100 mg/dL. Two studies found it to be moderately sensitive, and 1 study found it to be very sensitive. All 3 studies reported it being a very specific index text. However, most of the estimates were seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

Children

The evidence for protein concentration in children was moderate to low quality. Protein concentration was moderately sensitive and specific for the diagnosis of any bacterial meningitis in this population at a threshold of more than 50 mg/dL, but the estimate for

sensitivity was seriously imprecise so should not be taken as definitive evidence of sensitivity. The AUC value for protein concentration in this population indicated that it was a very useful test, but again the estimate was seriously imprecise.

Adults

In adult populations, the evidence quality for protein concentration was moderate to very low. Protein concentration was very sensitive but not specific for the diagnosis of any bacterial meningitis in this population at a threshold of more than 45 mg/dL. At a threshold of more than 60 mg/dL, protein concentration was reported to be moderately to very sensitive, and not specific to moderately specific, across 3 different estimates depending on the comparator population, with the lowest specificity being for distinguishing between bacterial meningitis and cryptococcal meningitis. Protein concentration was moderately sensitive and specific at thresholds of more than 101mg/dL and 130 mg/dL, and moderately sensitive but very specific at thresholds of more than 131, 188 and 93.4 mg/dL. However, most of the estimates for both sensitivity and specificity were at least seriously imprecise so should not be taken as definitive evidence of diagnostic accuracy. Five studies calculated AUC values. Two of these indicated protein concentration was a moderately useful index test and the remaining 3 indicated it was a very useful test. However, the two estimates that indicated it was a moderately useful test were very seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

All ages combined

The evidence for protein concentration in mixed populations of all ages was moderate to low quality. Protein concentration was very sensitive and moderately specific for the diagnosis of any bacterial meningitis in this population at a threshold of more than 40 mg/dL. It was moderately sensitive and specific at a threshold of more than 50 mg/dL, and moderately sensitive but very specific at thresholds of more than 100mg/dL and 150 mg/dL. However, all the sensitivity estimates, apart from at a threshold of more than 100mg/dL were seriously imprecise so should not be taken as definitive evidence of sensitivity. Similarly, the specificity estimate at thresholds of more than 40mg/dL and 100mg/dL was also seriously imprecise.

Molecular diagnosis for bacterial pathogens: PCR

Neonates and younger babies combined

The evidence for PCR in combined populations of neonates and younger babies was high to low quality. PCR was very sensitive and specific for the diagnosis of bacterial meningitis caused by group B Streptococcus and group B Streptococcus and Gram-negative bacilli (Escherichia coli). However, both the sensitivity estimates were very seriously imprecise so should not be taken as definitive evidence of sensitivity. Similarly, the specificity estimate for the diagnosis of bacterial meningitis caused by group B streptococcus or Gram-negative bacilli was also imprecise.

Neonates, babies and children combined

In combined populations of neonates babies and children, the evidence quality for PCR was high to very low. PCR was moderately sensitive and very specific for diagnosis of any bacterial meningitis in neonates, babies and children. It was very sensitive and specific for diagnosis of bacterial meningitis caused by N. meningitis, S. pneumoniae or H. influenzae. However, all the sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

Babies and children combined

The evidence for PCR in a combined population of babies and children was very low quality, PCR was very sensitive and specific for the diagnosis of bacterial meningitis caused by N.

meningitidis in this population but both estimates were at least seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

Adults

The evidence for PCR in adults was high to low quality. For the diagnosis of any bacterial meningitis, diagnostic accuracy varied. One study reported PCR as being very sensitive and specific, 1 reported it as being very sensitivity and moderately specific, and the remaining study reported it as not sensitive but very specific. However, all the sensitivity estimates were seriously imprecise so should not be taken as definitive evidence of sensitivity. Similarly, the specificity estimate was imprecise for one of the studies.

PCR was very sensitive and specific for the diagnosis of bacterial meningitis caused by N. meningitidis, S. pneumoniae, H. influenzae, group B Streptococcus, Gram-negative bacilli, or L. monocytogenes. However, all the sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

All ages combined

In mixed populations of all ages, the evidence for PCR was high to very low quality. For the diagnosis of any bacterial meningitis, 1 study reported PCR as being very sensitive and specific, 1 study as moderately specific and sensitive and the remaining studies reported PCR to be moderately sensitive and very specific. However, all the sensitivity estimates were at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

For the diagnosis of bacterial meningitis caused by N. meningitidis, all studies apart from 1. For bacterial meningitis caused by S. pneumoniae, most studies reported that PCR was very sensitive and specific, but 1 study reported it to be very sensitive and moderately specific and 1 reported it to be moderately sensitive and very specific. The PCR results for bacterial meningitis caused by group B Streptococcus was mixed, with 1 study reporting it to be very sensitive and specific and another reporting it to be moderately sensitive and very specific. PCR was very sensitive and specific for diagnosis of bacterial meningitis caused by H. influenzae, Gram-negative bacilli, or L. monocytogenes. PCR was moderately sensitive and very specific in diagnosis of bacterial meningitis caused by N. meningitidis and S. pneumoniae in mixed ages. However, all the sensitivity estimates (across all causative organisms) were at least seriously imprecise so should not be taken as definitive evidence of sensitivity.

Undefined age

The evidence for PCR in populations with undefined age ranges was high to very low quality. For the diagnosis of any bacterial meningitis, 4 studies reported PCR to be very sensitive and specific, 2 as very sensitive and moderately specific, 1 as very sensitive and not specific, 3 as moderately sensitive and very specific, and 1 as moderately sensitive and specific. However, most of the estimates were at least seriously imprecise, so should not be taken as definitive evidence of diagnostic accuracy.

for the diagnosis of bacterial meningitis caused by N. meningitidis, all studies apart from 1 reported it to be very sensitive and specific, with the remaining concluding it to be very sensitive and moderately specific. However, all the sensitivity estimates were at least seriously imprecise, so should not be taken as definitive evidence of sensitivity. For the diagnosis of bacterial meningitis caused by S. pneumoniae, again, all studies apart from 1 reported it to be very sensitive and specific, with the remaining concluding it to be very sensitive and moderately specific. All the sensitivity estimates apart from 1 were seriously imprecise and 1 of the specificity estimates was seriously imprecise, so again these should not be taken as definitive evidence of diagnostic accuracy. For the diagnosis of bacterial meningitis caused by H. influenzae, 1 study reported PCR as being very sensitive and specific and another study reported it as very sensitive but moderately specific. One of the

sensitivity estimates was very seriously imprecise, but there was no imprecision in the remaining estimates. PCR was very sensitive and specific in the diagnosis of bacterial meningitis cause by group B Streptococcus, or bacterial meningitis caused by Gram-negative bacilli, but all the sensitivity estimates were very seriously imprecise so should not be taken as definitive evidence of the sensitivity. Three studies investigated the accuracy of PCR for diagnosis of bacterial meningitis caused by L. monocytogenes; 2 of these studies reported PCR as being very sensitive and specific, and the remaining study reported it to be moderately sensitive and very specific, but again all the sensitivity estimates were very seriously imprecise.

Molecular diagnosis for bacterial pathogens: LAMP

Neonates, babies and children combined

In mixed populations of neonates, babies and children, the evidence quality for LAMP was high to low quality. LAMP was very sensitive and specific for the diagnosis of bacterial meningitis caused by N. meningitidis in this population, and very sensitive but moderately specific for the diagnosis of bacterial meningitis caused by S. pneumoniae. However, the sensitivity estimates were at least seriously imprecise, so should not be taken as definitive evidence of sensitivity.

All ages combined

The evidence for LAMP in mixed populations of all ages was high to low quality. For the diagnosis of bacterial meningitis caused by all bacteria, LAMP was very sensitivity and moderately specific but both estimates were seriously imprecise so should not be taken as definitive evidence of diagnostic accuracy. For bacterial meningitis caused by N. meningitidis, S. pneumoniae, group B streptococcus, or Listeria monocytogenes, PCR was both very sensitive and very specific. However, all the sensitivity estimates were at least seriously imprecise, so should not be taken as definitive evidence of sensitivity. For bacterial meningitis caused by Gram-negative bacilli, PCR was found to be moderately sensitive and very specific, but again the sensitivity estimate was very seriously imprecise so should not be taken as definitive evidence of sensitivity.

Combined index tests

WCC, glucose concentration and protein concentration in neonates

WCC plus glucose concentration plus protein concentration was moderately sensitive and very specific for diagnosis of any bacterial meningitis in neonates, based on high to moderate quality evidence. However, the sensitivity estimate was seriously imprecise so should not be taken as definitive evidence of sensitivity. Thresholds were as follows: WCC of more than 26 cells/μL for premature neonates and <23 cells/μL for term neonates; protein concentration of more than 151 mg/dL for premature neonates and 171 mg/dL for term neonates; and glucose concentration less than 23 mg/dL for premature neonates and 33 mg/dL for term neonates.

Gram staining and LAMP in all ages combined

The evidence for the combination of gram staining and LAMP in a mixed age population was moderate quality. This combined index test was very sensitive and moderately specific in this population, but both estimates were seriously imprecise so should not be taken as definitive evidence of diagnostic accuracy.

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.

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 adults and parents of babies and children that they do not have bacterial meningitis), false positives (potentially promoting definitive interventions that are unnecessary) and false negatives (failing to identify adults, children, and babies that require further interventions and intensive management) and noted that false negatives could be particularly impactful – 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 ranged from high to very low. Generally, evidence was downgraded for issues relating to imprecision of effect estimates and risk of bias (for example, applicability of population or studies using a mixture of reference standards).

Despite there being a significant body of evidence, meta-analyses couldn't be conducted either due to stratification decreasing available evidence for pooling, or the heterogeneity between studies (for example different comparator populations).

Benefits and harms

The committee emphasised that CSF investigations including microscopy, biochemical analysis and PCR analysis are the only techniques currently available that allow direct confirmation of a diagnosis of bacterial meningitis, and lumbar puncture is required to obtain the CSF sample.

The committee emphasised the importance of obtaining a CSF sample for microbial culture and other diagnostic tests before starting antibiotics. The committee were, however, wary of implying that there is no benefit to doing a lumbar puncture after antibiotics have started. Based on their clinical knowledge and experience, the committee recommended that if a lumbar puncture cannot be performed prior to antibiotic treatment, then it should be performed as soon as possible (if it is safe to perform) after starting antibiotics as the closer to the initiation of antibiotic treatment the increased likelihood of a reasonable yield.

The committee did not recommend a specific timeframe for performing lumbar puncture because they were concerned that it would be interpreted as a hard cutoff. The key timeframe is the 1-hour timeframe for giving antibiotics (Evidence report C1), but clinical

judgement is needed for decisions on how to fit lumbar puncture around this. For example, for some people it may be safe to delay the antibiotics by slightly longer than 1 hour, if this would allow a lumbar puncture to be performed first.

The committee used their clinical experience to highlight situations that need treating or stabilising before performing a lumbar puncture (including an unprotected airway, respiratory compromise, shock, uncontrolled seizures, and bleeding risk) in people with suspected bacterial meningitis, because they present a greater risk than delayed meningitis treatment. Based on their clinical knowledge the committee also included contraindications to performing a lumbar puncture. The committee recommended that a lumbar puncture should not be performed in people with suspected bacterial meningitis if there is extensive or rapidly spreading purpura as this could be an indicator of sepsis or septicaemia where blood investigations would be the appropriate diagnostic tool. The committee recommended that lumbar puncture should not be performed where there is infection at the lumbar puncture site, because there is a risk of carrying the infection into the CSF with the lumbar puncture needle. The committee also included risk factors for an evolving space occupying lesion or any of the features of brain herniation as contraindications to lumbar puncture (Evidence reports B4 and B5).

The committee considered the evidence for the accuracy of CSF investigations in diagnosing bacterial meningitis and although a number of investigations were at least moderately sensitive and moderately specific, there was no single CSF variable that would allow bacterial meningitis to be ruled in or out.

The committee considered the evidence for the accuracy of the ratio between CSF glucose and serum glucose to diagnose bacterial meningitis. Although there were a limited number of studies that examined this, overall the evidence suggested that the CSF:serum ratio for glucose concentration was predominantly at least moderately sensitive and moderately specific, the one exception was at a very low threshold relative to other studies. The committee considered the evidence for the CSF:serum glucose ratio in the context of the evidence for the accuracy of CSF glucose concentration. Overall, the data was quite mixed regarding the accuracy of CSF glucose concentration for diagnosing bacterial meningitis. There were not many thresholds or populations in which glucose concentration was at least moderately sensitive and specific and none where it was very sensitive and specific. The committee also looked at the AUC values for glucose concentration, which were only available for adults, and the evidence was inconsistent with one study indicating that glucose concentration was not a useful test, and the other study showing glucose concentration to be a very useful test. Based on the evidence for both glucose concentration, and CSF:serum glucose the committee agreed that the ratio measure was likely to be a better index test than the absolute values for CSF glucose, and recommended that CSF to blood glucose level ratio should be included in the CSF investigations for bacterial meningitis.

The committee agreed, based on their clinical knowledge and experience, that it was important to measure blood glucose (to enable calculation of CSF to blood glucose ratio) immediately prior to the lumbar puncture. This was based on practical considerations as the stress of a lumbar puncture will make the blood test difficult, especially in children.

The evidence showed white cell count was at least moderately sensitive and specific at most thresholds and there was some evidence that it can be very specific and sensitive, but this was very low quality and only in studies that included all ages (rather than stratifications of interest). The AUC values for white cell count also indicated that it is a very useful test, except for one study in adults. Neutrophil count was also shown to be at least moderately sensitive and moderately specific at nearly all thresholds reported, the only exception being at >50% neutrophils for distinguishing between bacterial and aseptic meningitis. The AUC values for neutrophil count all indicated that this is a very useful test and some of the evidence was moderate quality. Based on this evidence, the committee recommended that

cell count and cell type (including differential white cell count) should be one of the CSF investigations for diagnosing bacterial meningitis.

The committee considered the evidence for CSF protein concentration for diagnosing bacterial meningitis. Although there were some thresholds where protein concentration was either not sensitive or not specific, and one threshold (in babies and children) where it was very sensitive and specific, most studies indicated that protein concentration was at least moderately sensitive and specific, and on this basis the committee agreed that total protein should be included in the CSF investigations for bacterial meningitis.

Overall, all the data showed that gram staining was very specific for diagnosing bacterial meningitis by any cause and for all the specific causes of interest. There was more variation in the estimates of sensitivity across studies, however, the weight of the evidence suggested at least moderate sensitivity. The committee considered the only study that investigated the combination of gram and methylene blue staining in a population of babies and children. For any cause, and most of the specific causes, the evidence showed that the combination of gram and methylene blue staining was moderately sensitive and very specific. For bacterial meningitis caused by N. meningitidis, the combination of gram and methylene blue staining was not sensitive but was very specific. The committee agreed that CSF investigations should include microscopy for bacteria (using gram stain) and microbiological culture and sensitivities. The committee discussed that for other causes that are outside the scope of this review other types of microscopy may be used but for bacterial meningitis all evidence was for gram stain.

The committee discussed the evidence for molecular diagnosis for biological pathogens and agreed that PCR should be included in the recommended CSF investigations based on a fairly large and consistent body of evidence showing it to be at least moderately sensitive and very specific for bacterial meningitis with specific causes. The only exception in terms of specific causes, was 1 study for S. pneumoniae, but this showed moderate specificity. The evidence showed slightly less accuracy when PCR was used for diagnosing bacterial meningitis with any cause, however with 1 exception it was at least moderately sensitive and moderately specific.

The committee considered the accuracy of loop-mediated isothermal amplification (LAMP) assays for CSF analysis in bacterial meningitis. The evidence base was small but showed at least moderate sensitivity and moderate specificity. However, the committee did not consider it appropriate to include LAMP in the recommendations because it is not routinely available outside of the research setting in the UK, and the committee did not find the evidence sufficiently compelling to recommend a change to current clinical practice.

The committee discussed that sometimes additional investigations may be required if the results of initial tests are inconclusive or if there is a change in an individual's presentation. Therefore, the committee agreed that residual CSF from the initial sample should be retained, to minimise the impact of antibiotic treatment on the accuracy of results and to avoid an additional procedure for the individual.

The committee highlighted that CSF cell counts, total protein and glucose concentrations are important for clinical decision making, and thus there should not be a delay in getting these test results and agreed that the results of these tests should be available within 4 hours of lumbar puncture.

The committee agreed, based on their clinical knowledge and experience, that a number of factors need to be taken into account when interpreting the results of the CSF investigations, including: difficulties in interpreting CSF samples containing red cells which may indicate blood contamination (traumatic lumbar puncture) or a diagnosis other than meningitis; whether earlier antibiotic therapy may have sterilised the CSF (thus reducing the diagnostic reliability of these investigations); and the need to be aware that the normal white cell count

and protein level may be higher in young babies and to use age-appropriate threshold values.

The committee agreed that it was important to take into account the whole clinical picture and not rely on CSF values alone. The need to take a good clinical history, including maternal history for babies aged 28 days or under, was particularly emphasised. This is because there are factors that may reduce the reliability of CSF investigations. Based on their knowledge and expertise the committee highlighted the most important of these factors (earlier antibiotic use or suspected immunodeficiency).

The committee recommended that healthcare professionals should routinely consider alternative viral, mycobacterial, fungal, or non-infectious causes of an abnormal CSF result. Although this is a good clinical practice point, the committee considered it important to include in the recommendations based on the seriousness of the consequences if a potentially treatable alternative cause is missed.

The committee noted that there are novel diagnostic techniques currently in development, for example host biomarker or metagenomic techniques, that have the potential to address some of the problems with the current gold standards for diagnosing bacterial meningitis, including the time taken to receive results (and the imperative to start antibiotic treatment in the meantime) and the difficulties with differential diagnoses. Novel host biomarker or metagenomic techniques have been largely restricted to use in the research setting and have not been sufficiently validated for clinical use. However, the committee agreed that research on the diagnostic accuracy of the clinical application of these techniques was important and included this as a research recommendation (see Appendix K).

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 noted that collecting CSF samples was low cost as were the investigations they recommended. Therefore, they considered that their recommendations were likely to be cost-effective for the on-going management of babies (including newborn babies), children, young people, and adults with suspected bacterial meningitis. The committee noted that their recommendations were in line with current NHS practice and therefore, no significant resource impact was anticipated.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.9 to 1.4.19 and the recommendation for research on novel diagnostic techniques applied to blood or cerebrospinal fluid.

References – included studies

Diagnostic

Abdeldaim 2010

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)

Agueda 2013

Agueda, S; Campos, T; Maia, A. (2013) Prediction of bacterial meningitis based on cerebrospinal fluid pleocytosis in children. Brazilian Journal of Infectious Diseases 17: 401-404

Alqayoudhi 2017

Alqayoudhi, A, Nielsen, M, O'Sullivan, N et al. (2017) Clinical Utility of Polymerase Chain Reaction Testing for Streptococcus pneumoniae in Pediatric Cerebrospinal Fluid Samples: A Diagnostic Accuracy Study of More Than 2000 Samples from 2004 to 2015. Pediatric infectious disease journal 36: 833-836

Ansong 2009

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: S5-7

Arora 2017

Arora, H. S, Asmar, B. I, Salimnia, H et al. (2017) Enhanced Identification of Group B Streptococcus and Escherichia Coli in Young Infants with Meningitis Using the Biofire Filmarray Meningitis/Encephalitis Panel. Pediatric infectious disease journal 36: 685-687

Balamuth 2021

Balamuth, F, Cruz, A. T, Freedman, S. B et al. (2021) Test Characteristics of Cerebrospinal Fluid Gram Stain to Identify Bacterial Meningitis in Infants Younger Than 60 Days. Pediatric Emergency Care 37: E227-E229

BenGershom 1986

BenGershom, E; Briggeman-Mol, G. J; de Zegher, F. (1986) Cerebrospinal fluid C-reactive protein in meningitis: diagnostic value and pathophysiology. European Journal of Pediatrics 145: 246-9

Benjamin 1984

Benjamin, D. R; Opheim, K. E; Brewer, L. (1984) Is C-reactive protein useful in the management of children with suspected bacterial meningitis?. American Journal of Clinical Pathology 81: 779-782

Bonadio 1989

Bonadio, W. A and Smith, D. S. (1989) CBC differential profile in distinguishing etiology of neonatal meningitis. Pediatric Emergency Care 5: 94-96

Bonsu 2003

Bonsu, B. K and Harper, M. B. (2003) Utility of the peripheral blood white blood cell count for identifying sick young infants who need lumbar puncture. Annals of emergency medicine 41: 206-214

Bonsu 2005

Bonsu, B. K and Harper, M. B. (2005) Accuracy and test characteristics of ancillary tests of cerebrospinal fluid for predicting acute bacterial meningitis in children with low white blood cell counts in cerebrospinal fluid. Academic emergency medicine 12: 303-309

Bonsu 2008

Bonsu, B. K, Ortega, H. W, Marcon, M. J et al. (2008) A decision rule for predicting bacterial meningitis in children with cerebrospinal fluid pleocytosis when gram stain is negative or unavailable. Academic emergency medicine 15: 437-444

Bortolussi 1982

Bortolussi, R; Wort, A. J; Casey, S. (1982) The latex agglutination test versus counterimmunoelectrophoresis for rapid diagnosis of bacterial meningitis. Canadian medical association journal 127: 489-493

Boudet 2019

Boudet, A, Pantel, A, Carles, M. J et al. (2019) A review of a 13-month period of FilmArray Meningitis/Encephalitis panel implementation as a first-line diagnosis tool at a university hospital. 14: e0223887

Boving 2009

Boving, M. K; Pedersen, L. N; Moller, J. K. (2009) Eight-plex PCR and liquid-array detection of bacterial and viral pathogens in cerebrospinal fluid from patients with suspected meningitis. Journal of clinical microbiology 47: 908-13

Brizzi 2012

Brizzi, K, Hines, E. M, McGowan, K. L et al. (2012) Diagnostic accuracy of cerebrospinal fluid gram stain in children with suspected bacterial meningitis. Pediatric infectious disease journal 31: 195-7

Bryant 2004

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: 2919-2925

Buch 2018

Buch, K, Bodilsen, J, Knudsen, A et al. (2018) Cerebrospinal fluid lactate as a marker to differentiate between community-acquired acute bacterial meningitis and aseptic

meningitis/encephalitis in adults: a Danish prospective observational cohort study. Infectious Diseases 50: 514-521

Chiba 2009

Chiba, N, Murayama, S. Y, Morozumi, M et al. (2009) Rapid detection of eight causative pathogens for the diagnosis of bacterial meningitis by real-time PCR. Journal of Infection and Chemotherapy 15: 92-98

Corrall 1981

Corrall, C. J, Pepple, J. M, Moxon, E. R et al. (1981) C-reactive protein in spinal fluid of children with meningitis. Journal of pediatrics 99: 365-9

D'Inzeo 2020

D'Inzeo, T, Menchinelli, G, De Angelis, G et al. (2020) Implementation of the eazyplex® CSF direct panel assay for rapid laboratory diagnosis of bacterial meningitis: 32-month experience at a tertiary care university hospital. European journal of clinical microbiology & infectious diseases 39: 1845-1853

Dastych 2015

Dastych, M; Gottwaldova, J; Cermakova, Z. (2015) Calprotectin and lactoferrin in the cerebrospinal fluid; Biomarkers utilisable for differential diagnostics of bacterial and aseptic meningitis?. Clinical Chemistry and Laboratory Medicine 53: 599-603

De Cauwer 2007

De Cauwer, H. G, Eykens, L, Hellinckx, J et al. (2007) Differential diagnosis between viral and bacterial meningitis in children. European Journal of Emergency Medicine 14: 343-347

Deutch 2006

Deutch, S, Pedersen, L. N, Podenphant, L et al. (2006) Broad-range real time PCR and DNA sequencing for the diagnosis of bacterial meningitis. Scandinavian journal of infectious diseases 38: 27-35

Deutch 2008

Deutch, S; Moller, J. K; Ostergaard, L. (2008) Combined assay for two-hour identification of Streptococcus pneumoniae and Neisseria meningitidis and concomitant detection of 16S ribosomal DNA in cerebrospinal fluid by real-time PCR. Scandinavian Journal of Infectious Diseases 40: 607-14

Dubos 2006

Dubos, F, Moulin, F, Gajdos, V et al. (2006) Serum procalcitonin and other biologic markers to distinguish between bacterial and aseptic meningitis. Journal of pediatrics 149: 72-76

Dubos 2008

Dubos, F, Korczowski, B, Aygun, D.A et al. (2008) 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 162: 1157-1163

Dunbar 1998

Dunbar, S. A, Eason, R. A, Musher, D. M et al. (1998) Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis. Journal of Clinical Microbiology 36: 1617-1620

Ena 2021

Ena, J, Afonso-Carrillo, R. G, Bou-Collado, M et al. (2021) Evaluation of FilmArray ME panel for the rapid diagnosis of meningitis-encephalitis in emergency departments. Internal & Emergency MedicineIntern 5: 5

Esparcia 2011

Esparcia, O, Montemayor, M, Ginovart, G et al. (2011) Diagnostic accuracy of a 16S ribosomal DNA gene-based molecular technique (RT-PCR, microarray, and sequencing) for bacterial meningitis, early-onset neonatal sepsis, and spontaneous bacterial peritonitis. Diagnostic microbiology and infectious disease 69: 153-160

Favaro 2013

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: 74-9

Freedman 2001

Freedman, S. B, Marrocco, A, Pirie, J et al. (2001) Predictors of bacterial meningitis in the era after Haemophilus influenzae. Archives of Pediatrics & Adolescent MedicineArch Pediatr Adolesc Med 155: 1301-6

Garges 2006

Garges, H. P, Anthony Moody, M, Cotten, C. M et al. (2006) Neonatal meningitis: What is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters?. Pediatrics 117: 1094-1100

Giulieri 2015

Giulieri, S, Chapuis-Taillard, C, Jaton, K et al. (2015) CSF lactate for accurate diagnosis of community-acquired bacterial meningitis. European Journal of Clinical Microbiology and Infectious Diseases 34: 2049-2055

Jorgensen 1978

Jorgensen, J. H and Lee, J. C. (1978) Rapid diagnosis of gram-negative bacterial meningitis by the Limulus endotoxin assay. Journal of Clinical Microbiology 7: 12-Jul

Kennedy 2007

Kennedy, W. A, Chang, S. J, Purdy, K et al. (2007) Incidence of bacterial meningitis in Asia using enhanced CSF testing: Polymerase chain reaction, latex agglutination and culture. Epidemiology and Infection 135: 1217-1226

Khurana 1987

Khurana, C. M and Deddish, P. A. (1987) Comparison of results of limulus amebocyte lysate, counterimmunoelectrophoresis, and gram stain on spinal fluids of patients with suspected meningitis. Current Therapeutic Research - Clinical and Experimental 41: 604-608

Kim 2012

Kim, D. W, Kilgore, P. E, Kim, E. J et al. (2012) The enhanced pneumococcal LAMP assay: a clinical tool for the diagnosis of meningitis due to Streptococcus pneumoniae. PloS ONE [Electronic Resource]PloS ONE 7: e42954

Kleine 2003

Kleine, T.O, Zwerenz, P, Zofel, P et al. (2003) New and old diagnostic markers of meningitis in cerebrospinal fluid (CSF). Brain Research Bulletin 61: 287-297

Kotilainen 1998

Kotilainen, P, Jalava, J, Meurman, O et al. (1998) Diagnosis of meningococcal meningitis by broad-range bacterial PCR with cerebrospinal fluid. Journal of clinical microbiology 36: 2205-2209

La Scolea Jr 1984

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: 187-190

Leber 2016

Leber, A. L, Everhart, K, Balada-Llasat, J. M et al. (2016) Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens. Journal of Clinical Microbiology 54: 2251-61

Lee 2015

Lee, D, Kim, E. J, Kilgore, P. E et al. (2015) Clinical evaluation of a loop-mediated isothermal amplification (LAMP) assay for rapid detection of Neisseria meningitidis in cerebrospinal fluid. PloS ONE [Electronic Resource]PloS ONE 10: e0122922

Leitner 2016

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

Leli 2019

Leli, C, Gotta, F, Vay, D et al. (2019) Diagnostic accuracy of a commercial multiplex pcr for the diagnosis of meningitis and encephalitis in an italian general hospital. Infezioni in Medicina 27: 141-148

Lindquist 1988

Lindquist, L, Linne, T, Hansson, L. O et al. (1988) Value of cerebrospinal fluid analysis in the differential diagnosis of meningitis: A study in 710 patients with suspected central nervous

system infection. European Journal of Clinical Microbiology and Infectious Diseases 7: 374-380

Meyer 2014

Meyer, T, Franke, G, Polywka, S. K et al. (2014) Improved detection of bacterial central nervous system infections by use of a broad-range PCR assay. Journal of Clinical Microbiology 52: 1751-3

Morrissey 2017

Morrissey, S. M, Nielsen, M, Ryan, L et al. (2017) 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 & Infectious DiseasesEur J Clin Microbiol Infect Dis 36: 1317-1324

Nabower 2019

Nabower, A. M, Miller, S, Biewen, B et al. (2019) Association of the FilmArray Meningitis/Encephalitis Panel With Clinical Management. Hospital Pediatrics 9: 763-769

Negrini 2000

Negrini, B; Kelleher, K. J; Wald, E. R. (2000) Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics 105: 316-319

Nelson 1986

Nelson, N, Eeg-Olofsson, O, Larsson, L et al. (1986) The diagnostic and predictive value of cerebrospinal fluid lactate in children with meningitis. Acta Paediatrica Scandinavica 75: 52-57

Neuman 2008

Neuman, M. I; Tolford, S; Harper, M. B. (2008) Test characteristics and interpretation of cerebrospinal fluid gram stain in children. Pediatric infectious disease journal 27: 309-13

Ni 1992

Ni, H, Knight, A. I, Cartwright, K et al. (1992) Polymerase chain reaction for diagnosis of meningococcal meningitis. Lancet 340: 1432-4

Pfefferle 2020

Pfefferle, S, Christner, M, Aepfelbacher, M et al. (2020) Implementation of the FilmArray ME panel in laboratory routine using a simple sample selection strategy for diagnosis of meningitis and encephalitis. BMC Infectious Diseases 20 (1)

Piccirilli 2018

Piccirilli, G, Chiereghin, A, Gabrielli, L et al. (2018) Infectious meningitis/encephalitis: evaluation of a rapid and fully automated multiplex PCR in the microbiological diagnostic workup. The new microbiologica 41: 118-125

Poppert 2005

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: 3390-7

Porritt 2000

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: 42-45

Ray 2007

Ray, P, Badarou-Acossi, G, Viallon, A et al. (2007) 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 25: 179-184

Richardson 2003

Richardson, D. C, Louie, L, Louie, M et al. (2003) Evaluation of a rapid PCR assay for diagnosis of meningococcal meningitis. Journal of clinical microbiology 41: 3851-3853

Rothman 2010

Rothman, R, Ramachandran, P, Yang, S et al. (2010) Use of quantitative broad-based polymerase chain reaction for detection and identification of common bacterial pathogens in cerebrospinal fluid. Academic emergency medicine 17: 741-7

Schuurman 2004

Schuurman, T, De Boer, R. F, Kooistra-Smid, A. M. D et al. (2004) Prospective Study of Use of PCR Amplification and Sequencing of 16S Ribosomal DNA from Cerebrospinal Fluid for Diagnosis of Bacterial Meningitis in a Clinical Setting. Journal of clinical microbiology 42: 734-740

Seward 2000a

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: 451-456

Seward 2000b

Seward, R. J and Towner, K. J. (2000) Use of an automated DNA analysis system (DARAS) for sequence-specific recognition of Neisseria meningitidis DNA. Clinical Microbiology & InfectionClin Microbiol Infect 6: 29-33

Sormunen 1999

Sormunen, P, Kallio, M. J. T, Kilpi, T et al. (1999) C-reactive protein is useful in distinguishing Gram stain-negative bacterial meningitis from viral meningitis in children. Journal of pediatrics 134: 725-729

Viallon 2011

Viallon, A, Desseigne, N, Marjollet, O et al. (2011) Meningitis in adult patients with a negative direct cerebrospinal fluid examination: Value of cytochemical markers for differential diagnosis. Critical Care 15 (3)

Vincent 2020

Vincent, J. J, Zandotti, C, Baron, S et al. (2020) Point-of-care multiplexed diagnosis of meningitis using the FilmArray R ME panel technology. European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis 39: 1573-1580

Wagner 2018

Wagner, K, Springer, B, Pires, V. P et al. (2018) Pathogen Identification by Multiplex LightMix Real-Time PCR Assay in Patients with Meningitis and Culture-Negative Cerebrospinal Fluid Specimens. Journal of clinical microbiology 56

Welinder-Olsson 2007

Welinder-Olsson, C, Dotevall, L, Hogevik, H et al. (2007) Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis. Clinical Microbiology and Infection 13: 879-886

White 2012

White, K, Ostrowski, K, Maloney, S et al. (2012) The utility of cerebrospinal fluid parameters in the early microbiological assessment of meningitis. Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis 73: 27-30

Xirogianni 2009

Xirogianni, A, Tzanakaki, G, Karagianni, E et al. (2009) Development of a single-tube polymerase chain reaction assay for the simultaneous detection of Haemophilus influenzae, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus spp. directly in clinical samples. Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis 63: 121-6

Economic

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

Appendices

Appendix A Review protocols

Review protocol for review question: What is the accuracy and effectiveness of cerebrospinal fluid investigations in diagnosing bacterial meningitis?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42021267938
1.	Review title	Investigating and diagnosing suspected bacterial meningitis with cerebrospinal fluid parameters
2.	Review question	What is the accuracy and effectiveness of cerebrospinal fluid investigations in diagnosing bacterial meningitis?
3.	Objective	To determine the accuracy and effectiveness of cerebrospinal fluid parameters in diagnosing bacterial meningitis
4.	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

ID	Field	Content
		of the PRESS 2015 Guideline Evidence-Based Checklist.
5.	Condition or domain being studied	Bacterial meningitis
6.	Population	**Inclusion:** All adults, young people, children and babies (including neonates defined as aged 28 days old and younger) with suspected bacterial meningitis. **Exclusion:** People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
7.	Test	The use of the following CSF investigations, individually or in combination: • white cell count • neutrophil count • microscopy for bacteria • glucose concentration (absolute or relative to simultaneously estimated blood glucose) • protein concentration • Molecular diagnosis for bacterial pathogens
8.	Comparator/Reference standard/Confounding factors	Reference standard: • Cerebrospinal fluid (CSF) bacterial culture with or without molecular diagnosis in the CSF for bacterial pathogens
9.	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

ID	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.
10.	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
11.	Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
12.	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

ID	Field	Content
		discharge) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayley's 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
13.	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) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or

ID	Field	Content
		that are life threatening or otherwise considered medically significant **2. Cross-sectional diagnostic test accuracy studies** • Area under the curve
14.	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.
15.	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.
16.	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

ID	Field	Content
		adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/" **Minimally important differences:** **Test and Treat RCTs:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Length of hospitalisation: 1 day • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs **Decision making thresholds:** **Diagnostic accuracy studies:** • Sensitivity: o Very useful test: ≥90% o Moderately useful test: ≥50% o Not a useful test <50% • Specificity: o Very useful test: ≥90% o Moderately useful test: ≥50% o Not a useful test <50% • AUC: o Very useful test: >0.80 o Moderately useful test: >0.70 o Not a useful test: ≤0.70
17.	Analysis of sub-groups	Evidence will be stratified by: Age: • Neonates: Birth to ≤29 days for term babies; birth to ≤28 days after due date for preterm babies

ID	Field	Content
		○ Extremely or very preterm: <32 weeks ○ Preterm: ≥32 weeks to <37 weeks ○ Term: ≥37 weeks • Younger Infants: >28 days to ≤3 months of age • Older infants: >3 months to <1 year of age • Children: ≥1 year of age to <18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children. Different thresholds for the index test Infective organism diagnosed as a result of testing: • Neisseria meningitidis • Streptococcus pneumoniae • Haemophilus influenza • group B streptococcus • Gram-negative bacilli • Listeria monocytogenes Reference standard used: • Cerebrospinal fluid (CSF) bacterial culture • CSF bacterial culture and molecular diagnosis for bacterial pathogens Evidence will be sub grouped by the following only in the event that there is significant heterogeneity in outcomes:

ID	Field	Content	
		Age: • Young and middle aged adults • Older adults* Molecular diagnosis technique: • Specific PCR, particularly for Streptococcus pneumoniae and Neisseria meningitidis. • Multiplex PCR platforms: single test using PCR to detect multiple relevant bacterial pathogens that cause meningitis. For example, Biofire Filmarray ME panel (PCR bacterial targets are: E. coli, H. influenzae, L. monocytogenes, N. meningitidis, Group B streptococcus – also known as Streptococcus agalactiae, and Streptococcus pneumoniae). • 16S PCR - a generic PCR used to detect ANY bacterial organism. *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or sub grouped 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.	
18.	Type and method of review	☒	Intervention
		☒	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

ID	Field	Content		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	11/03/2021		
22.	Anticipated completion date	07/12/2023		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	**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		
25.	Review team members	National Guideline Alliance		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting		

ID	Field	Content	
		will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
29.	Other registration details	None	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021267938	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Bacterial meningitis, diagnosis, sensitivity, specificity, cerebrospinal fluid, mortality, impairments	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	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 cerebrospinal fluid investigations in diagnosing bacterial meningitis?

Clinical Search

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 07, **Ovid MEDLINE(R) ALL** 1946 to November 07, 2022
Date of last search: 08 November 2022
Multifile database codes: emczd = Embase Classic+Embase; medall= MEDLINE(R) ALL

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/ or exp Neisseria Meningitidis/
2	1 use medall
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/ or neisseria meningitidis/
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* or mening* encephalitis*).ti,ab.
9	(Neisseria* mening* or n mening*).ti,ab.
10	or/2,4-9
11	*Cerebrospinal Fluid/ use medall
12	*cerebrospinal fluid/ or *cerebrospinal fluid cytology/ or *cerebrospinal fluid analysis/
13	12 use emczd
14	((cerebrospinal* or cerebro-spinal*) adj3 fluid*).ti.
15	((CSF or (cerebrospinal* adj3 fluid*) or (cerebro-spinal* adj3 fluid*)) adj5 (white cell* or WBC or WBCC or WCC or CBC or ALC or leukocyte* or neutrophil* or lymphocyte* or glucose* or protein* or procalcitonin* or pro calcitonin* or calcitonin* or lactate* or lactic* or bacteria* or paramet* or culture* or PCR or CRP)).ti,ab.
16	or/11,13-15
17	Cerebrospinal Fluid/ use medall
18	cerebrospinal fluid/ or cerebrospinal fluid cytology/ or cerebrospinal fluid analysis/
19	18 use emczd
20	((cerebrospinal* or cerebro-spinal*) adj3 fluid*).ti,ab.
21	CSF.ti,ab.
22	cf.fs.
23	or/17,19-22
24	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 Bacterial Proteins/ or Cerebrospinal Fluid Proteins/ or Protein Precursors/ or Glucose/ or Blood Glucose/
25	24 use medall
26	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 protein/ or protein blood level/ or protein cerebrospinal fluid level/ or glucose/ or glucose blood level/
27	26 use emczd
28	neutrophil?.ti,ab.
29	((c-reactiv* or reactiv*) adj3 protein*).ti,ab.
30	CRP.ti,ab.
31	(protein* adj2 (level* or concentration*)).ti,ab.
32	(procalcitonin* or pro calcitonin* or calcitonin*).ti,ab.
33	(white adj3 Cell? adj3 (count* or number*)).ti,ab.
34	((white or WBC* or WBCC* or WCC* or CBC* or ALC*) adj2 count*).ti,ab.
35	(complete* adj3 (blood* and count*)).ti,ab.
36	(WBC or WBCC or WCC or CBC or ALC).ti,ab.
37	(leukocytosis or lymphocytosis).ti,ab.

#	Searches
38	((leukocyt* or lymphocyt*) adj3 (count* or number*)).ti,ab.
39	(polymer* adj3 chain* adj3 reaction*).ti,ab.
40	PCR.ti,ab.
41	(loop* adj3 isotherm* adj3 amplif*).ti,ab.
42	LAMP.ti,ab.
43	(direct* adj3 sequenc*).ti,ab.
44	(latex* adj3 agglutinat*).mp.
45	((latex or agglutinat*) adj3 (test* or immunoassay* or assay* or method* or slide or kit or kits or typing)).ti,ab.
46	(platelet* adj count*).ti,ab.
47	lactate* dehydrogenase*.mp.
48	((lactate* or lactic*) adj3 (level* or value* or count* or concentration* or distribution* or serum)).ti,ab.
49	(molecul* adj diagnos*).mp.
50	((pathogen or antigen) adj detect*).ti,ab.
51	(bacteria* adj culture*).ti,ab.
52	microscop*.mp.
53	glucose*.mp.
54	or/25,27-53
55	10 and 23 and 54
56	10 and 16
57	55 or 56
58	exp "SENSITIVITY AND SPECIFICITY"/ or LIKELIHOOD FUNCTIONS/ or DIAGNOSIS, DIFFERENTIAL/
59	58 use medall
60	"SENSITIVITY AND SPECIFICITY"/ or STATISTICAL MODEL/ or *DIAGNOSTIC ACCURACY/ or DIAGNOSTIC TEST ACCURACY STUDY/ or DIFFERENTIAL DIAGNOSIS/
61	60 use emczd
62	(sensitivity or specificity).ti,ab.
63	((pre test or pretest or post test or posttest) adj probability).ti,ab.
64	(predictive value* or PPV or NPV).ti,ab.
65	likelihood ratio*.ti,ab.
66	(ROC curve* or AUC).ti,ab.
67	diagnos*.ti.
68	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
69	gold standard.ab.
70	di.fs.
71	or/59,61-70
72	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
73	72 use medall
74	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
75	74 use emczd
76	meta-analysis/
77	meta-analysis as topic/
78	systematic review/
79	meta-analysis/
80	(meta analy* or metanaly* or metaanaly*).ti,ab.
81	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
82	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
83	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
84	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
85	(search* adj4 literature).ab.
86	(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.
87	cochrane.jw.
88	((pool* or combined) adj2 (data or trials or studies or results)).ab.
89	(or/76-77,80,82-87) use medall
90	(or/78-81,83-88) use emczd
91	or/71,73,75,89-90
92	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or (animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
93	92 use medall
94	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
95	94 use emczd
96	93 or 95
97	57 and 91
98	97 not 96
99	limit 98 to English language

#	Searches
100	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 or exp Neisseria Meningitidis/di or *Bacterial Infections/di
101	100 use medall
102	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 or neisseria meningitidis/di or *bacterial infection/di
103	102 use emczd
104	101 or 103
105	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 *Bacterial Proteins/ or *Cerebrospinal Fluid Proteins/ or *Protein Precursors/ or *Glucose/ or *Blood Glucose/
106	105 use medall
107	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 *protein/ or *protein blood level/ or *protein cerebrospinal fluid level/ or *glucose/ or *glucose blood level/
108	107 use emczd
109	106 or 108
110	104 and 109
111	or/59,61-69,73,75,89-90
112	110 and 111
113	112 not 96
114	limit 113 to English language
115	99 or 114
116	limit 115 to yr="1960 -Current"

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 11 of 12, November 2022, **Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2022
Date of last search: 08 November 2022

#	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	MeSH descriptor: [Neisseria meningitidis] explode all trees
#10	((bacter* or infect*) near/3 (mening* or leptomening* or subarachnoid space*)):ti,ab,kw
#11	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or (h next influenz*) or listeria* or pneumococc* or (gram next negativ* next bacill*) or streptococc* or GBS or (s next pneumon*)) near/3 (septic* or sepsis* or bacteraemi* or bacteremi* or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or (mening* next encephalitis*)).:ti,ab,kw
#13	((neisseria* next mening*) or (n next mening*)):ti,ab,kw
#14	MeSH descriptor: [Meningococcal Infections] this term only
#15	meningococc*:ti,ab,kw
#16	{or #1-#15}
#17	MeSH descriptor: [Cerebrospinal Fluid] this term only
#18	(((cerebrospinal* or "cerebro spinal*") NEAR/3 fluid*)):ti
#19	(((CSF or (cerebrospinal* NEAR/3 fluid*) or ("cerebro spinal"* NEAR/3 fluid*)) NEAR/5 ("white cell*" or WBC or WBCC or WCC or CBC or ALC or leukocyte* or neutrophil* or lymphocyte* or glucose* or protein* or procalcitonin* or calcitonin* or lactate* or lactic* or bacteria* or paramet* or culture* or PCR or CRP))):ti,ab,kw
#20	{or #17-#19}
#21	MeSH descriptor: [Cerebrospinal Fluid] this term only
#22	(((cerebrospinal* or cerebro-spinal*) NEAR/3 fluid*)):ti,ab,kw
#23	(CSF):ti,ab,kw
#24	MeSH descriptor: [] explode all trees and with qualifier(s): [cerebrospinal fluid - CF]
#25	{or #21-#24}
#26	MeSH descriptor: [Blood Cell Count] explode all trees
#27	MeSH descriptor: [Leukocytes] explode all trees
#28	MeSH descriptor: [Lymphocytes] this term only
#29	MeSH descriptor: [Neutrophils] this term only
#30	MeSH descriptor: [C-Reactive Protein] this term only
#31	MeSH descriptor: [Calcitonin] this term only

#	Searches
#32	MeSH descriptor: [Procalcitonin] this term only
#33	MeSH descriptor: [Molecular Diagnostic Techniques] this term only
#34	MeSH descriptor: [Polymerase Chain Reaction] this term only
#35	MeSH descriptor: [Latex Fixation Tests] this term only
#36	MeSH descriptor: [Agglutination Tests] this term only
#37	MeSH descriptor: [Blood Culture] this term only
#38	MeSH descriptor: [Platelet Count] this term only
#39	MeSH descriptor: [L-Lactate Dehydrogenase] this term only
#40	MeSH descriptor: [Lactic Acid] this term only
#41	MeSH descriptor: [Lactates] this term only
#42	MeSH descriptor: [Antigens, Bacterial] this term only
#43	MeSH descriptor: [Bacterial Proteins] this term only
#44	MeSH descriptor: [Cerebrospinal Fluid Proteins] this term only
#45	MeSH descriptor: [Protein Precursors] this term only
#46	MeSH descriptor: [Glucose] this term only
#47	MeSH descriptor: [Blood Glucose] this term only
#48	(neutrophil?):ti,ab,kw
#49	(((c-reactiv* or reactiv*) NEAR/3 protein*)):ti,ab,kw
#50	(CRP):ti,ab,kw
#51	((protein* NEAR/2 (level* or concentration*))):ti,ab,kw
#52	((procalcitonin* or calcitonin*)):ti,ab,kw
#53	((white NEAR/3 cell? NEAR/3 (count* or number*))):ti,ab,kw
#54	(((white or WBC* or WBCC* or WCC* or CBC* or ALC*) NEAR/2 count*)):ti,ab,kw
#55	((complete* NEAR/3 (blood* and count*))):ti,ab,kw
#56	((WBC or WBCC or WCC or CBC or ALC)):ti,ab,kw
#57	((leukocytosis or lymphocytosis)):ti,ab,kw
#58	(((leukocyt* or lymphocyt*) NEAR/3 (count* or number*))):ti,ab,kw
#59	((polymer* NEAR/3 chain* NEAR/3 reaction*)):ti,ab,kw
#60	(PCR):ti,ab,kw
#61	((loop* NEAR/3 isotherm* NEAR/3 amplif*)):ti,ab,kw
#62	(LAMP):ti,ab,kw
#63	((direct* NEAR/3 sequenc*)):ti,ab,kw
#64	((latex* NEAR/3 agglutinat*)):ti,ab,kw
#65	(((latex or agglutinat*) NEAR/3 (test* or immunoassay* or assay* or method* or slide or kit or kits or typing))):ti,ab,kw
#66	((platelet* NEXT count*)):ti,ab,kw
#67	(lactate* NEXT dehydrogenase*):ti,ab,kw
#68	(((lactate* or lactic*) NEAR/3 (level* or value* or count* or concentration* or distribution* or serum))):ti,ab,kw
#69	((molecul* NEXT diagnos*)):ti,ab,kw
#70	(((pathogen or antigen) NEXT detect*)):ti,ab,kw
#71	((bacteria* NEXT culture*)):ti,ab,kw
#72	(microscop*):ti,ab,kw
#73	(glucose*):ti,ab,kw
#74	{or #26-#73}
#75	#15 AND #20
#76	#15 AND #25 AND #73
#77	#75 OR #76
#78	"conference":pt or (clinicaltrials or trialsearch):so
#79	#77 NOT #78

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

Date of last search: 17 June 2021

Line	Search
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 Neisseria meningitidis IN DARE,HTA
12	((Neisseria* NEXT mening*)) IN DARE, HTA
13	MeSH DESCRIPTOR Cerebrospinal Fluid IN DARE,HTA
14	(((cerebrospinal* or cerebro-spinal*) NEAR3 fluid*)) IN DARE, HTA

Line	Search
15	(CSF) 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
17	#13 OR #14 OR #15
18	#16 AND #17

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
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 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022

Date of last search: 10 November 2022

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.

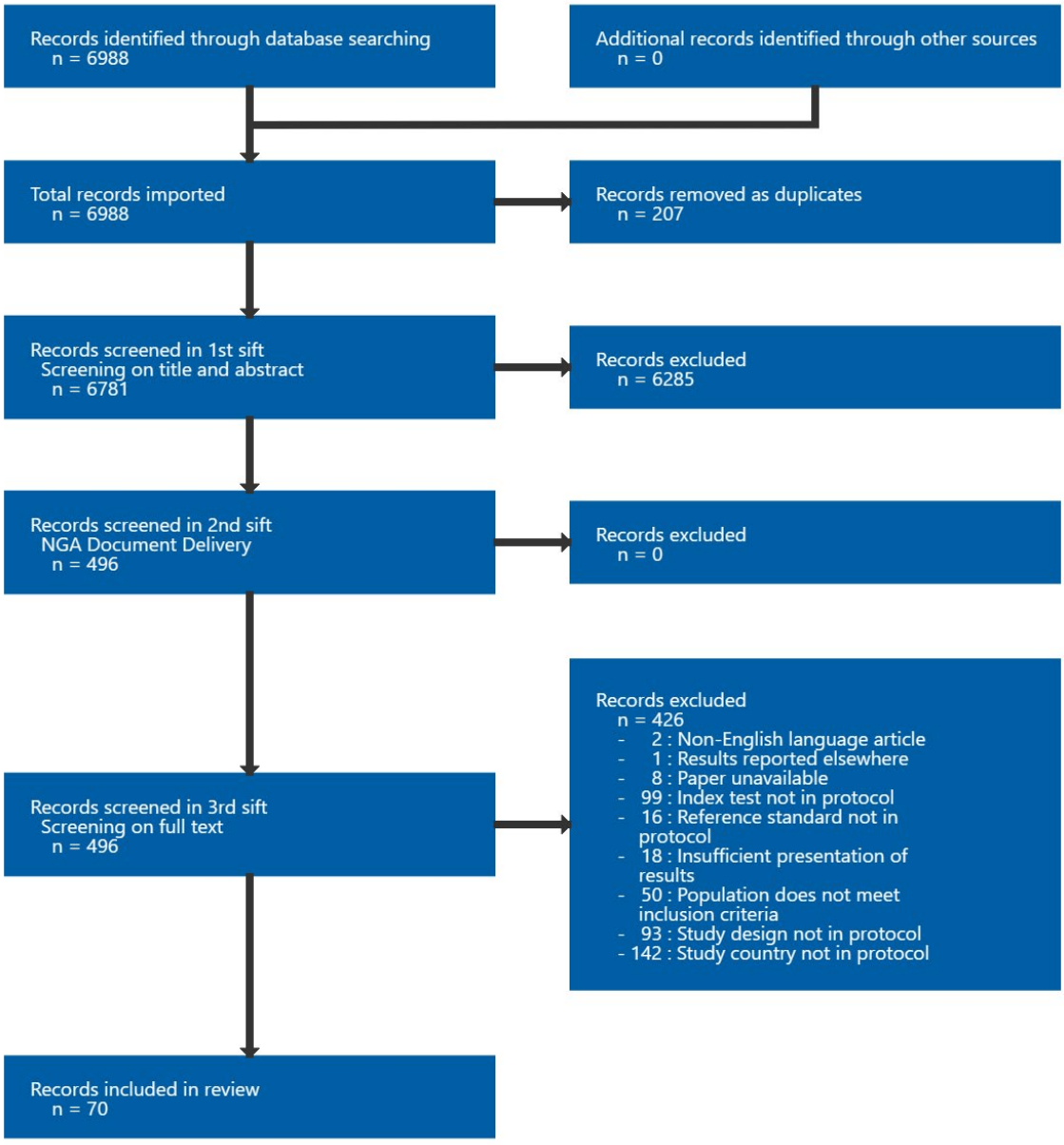
#	Searches
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	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 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/

#	Searches
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 cerebrospinal fluid 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 cerebrospinal fluid investigations in diagnosing bacterial meningitis?

Table 4: Evidence tables

Abdeldaim, 2010

Bibliographic Reference Abdeldaim, G. M. K; Stralin, K; Korsgaard, J; Blomberg, J; Welinder-Olsson, C; Herrmann, B.; Multiplex quantitative PCR for detection of lower respiratory tract infection and meningitis caused by Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis; BMC Microbiology; 2010; vol. 10 (no. no pagination)

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective single-gate cross-sectional DTA study
Study dates	1997-2000
Inclusion criteria	CSF samples with total CSF white blood cell count ≥10×10(6) cells/L sent for at study centre
Exclusion criteria	Subsequent CSF samples from patients already included in study
Patient characteristics	N=87 Age (median [range]): 34 years (1 day-91 years) Positive for bacterial meningitis: 8% (Population: BM U) Positive CSF cultures in population with bacterial meningitis: 100% Causative organisms: n=5 S. pneumoniae, n=2 N. meningitidis
Index test(s)	Molecular diagnosis Specific PCR: • for N. meningitidis • for S. pneumoniae
Reference standard(s)	CSF bacterial culture and/or microscopy

Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR for N. meningitidis (n=87): TP 2; FP 8; FN 0; TN 77 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=87): TP 5; FP 9; FN 0; TN 73 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; 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 *(Poorly detailed exclusion criteria and patient characteristics not thoroughly reported. Also, inclusion of people based on WCC may restrict the population of interest and potentially inflate diagnostic accuracy)*
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 *(CSF culture and/or microscopic examination. No details on proportion of population diagnosed with 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)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies; WCC: white cell count

Agueda, 2013

Bibliographic Reference	Agueda, S; Campos, T; Maia, A.; Prediction of bacterial meningitis based on cerebrospinal fluid pleocytosis in children; Brazilian Journal of Infectious Diseases; 2013; vol. 17; 401-404

Study details

Country/ies where study was carried out	Portugal
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 2005 to December 2009
Inclusion criteria	Children aged 29 days to 17 years with CSF pleocytosis (defined as white blood count ≥7 cells/µl).
Exclusion criteria	Cases of traumatic lumbar puncture (LP) and of antibiotic treatment before LP were excluded.
Patient characteristics	N=295 Age in years for bacterial meningitis group (medium [SD]): 3.6 (5.0) Male (%) in bacterial meningitis: 12 (38.7%) Positive for bacterial meningitis: 11% (Population: BM VM AM) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=15 N. meningitidis, n=10 S. pneumoniae, n=3 other Streptococcus spp., n=3 other organisms
Index test(s)	CSF white cell count Threshold 321 cells/µL.
Reference standard(s)	CSF bacterial culture and/or CSF Gram stain
Sources of funding	No sources of funding reported.
Results	CSF white cell count, threshold >321 cells/µl (n=295): TP 25; FP 49; FN 6; TN 215 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; SD: standard deviation; spp.: species; S. pneumoniae: Streptococcus pneumoniae; 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 *(Not clear if consecutive sample was enrolled; children with antibiotic use prior to lumbar puncture were excluded. While this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting. Also, inclusion of people based on WCC may restrict the population of interest and potentially inflate diagnostic accuracy)*
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?	High *(Optimal threshold was calculated from ROC curves.)*
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 defined as positive CSF culture and/or Gram staining. Exact proportions of the tests are not given)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards.)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve: receiver operating characteristic curve

Alqayoudhi, 2017

Bibliographic Reference Alqayoudhi, A; Nielsen, M; O'Sullivan, N; Corcoran, M; Gavin, P. J; Butler, K. M; Cunney, R; Drew, R. J.; Clinical Utility of Polymerase Chain Reaction Testing for Streptococcus pneumoniae in Pediatric Cerebrospinal Fluid Samples: A Diagnostic Accuracy Study of More Than 2000 Samples from 2004 to 2015; Pediatric infectious disease journal; 2017; vol. 36; 833-836

Study details

Country/ies where study was carried out	Ireland
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	2004-2015
Inclusion criteria	Children <16 years old with suspected meningitis, and with a CSF sample tested for S. pneumoniae DNA by PCR
Exclusion criteria	Samples with insufficient quantity of material for testing Subsequent CSF samples from patients already included in study PCR samples without a matching culture on the same sample
Patient characteristics	N=2025 n=16 culture-positive S. pneumoniae bacterial meningitis n=1990 without culture-positive S. pneumoniae bacterial meningitis n=19 not reported No patient characteristics reported beyond inclusion criteria Positive for bacterial meningitis: 0.8% (Population: PM U) Causative organisms: n=16 S. pneumoniae
Index test(s)	Molecular diagnosis Specific PCR for S. pneumoniae
Reference standard(s)	CSF bacterial culture
Sources of funding	Non-industry funded
Results	Molecular diagnosis: PCR for S. pneumoniae (n=2025): TP 16; FP 28; FN 0; TN 1962 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection:	Could the selection of patients have introduced	Low

Section	Question	Answer
risk of bias	bias?	
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 *(Index test was interpreted with full knowledge of the reference standard results; however, test is objective so decreases the likelihood of 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?	Unclear *(Reference standard was interpreted with full knowledge of the index test results; however, test is objective so decreases the likelihood of 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; 19/2025 not included in the analysis with 12/2025 due to no CSF culture; small percentage (0.6%) but all in PCR test negative group so possibility of impacting FN)*

CSF: cerebrospinal fluid; FN: false negative; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Ansong, 2009

Bibliographic Reference Ansong, A. K; Smith, P. B; Benjamin, D. K; Clark, R. H; Li, J. S; Cotten, C. M; Mangum, B; Garges, H. P; Benjamin Jr, D. K.; Group B streptococcal meningitis: cerebrospinal fluid parameters in the era of intrapartum antibiotic prophylaxis; Early human development; 2009; vol. 85; S5-7

Study details

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

Study dates	1997 to 2004
Inclusion criteria	Infants discharged from study NICUs with results of first lumbar puncture available.
Exclusion criteria	Excluded neonates with CSF reservoirs/shunts, and infants who with positive CSF results for viral pathogens and bacterial species other than Group B streptococcus (GBS).
Patient characteristics	N=13,495 n=46 GBS meningitis n=133 GBS bacteremia, culture negative CSF n=13,316 negative blood and CSF culture Gestational age in weeks for bacterial meningitis group (median [IQR]): 38 (36-39) Male (%) in GBS meningitis: 20 (43%) Positive for bacterial meningitis: 0.3% (Population: GBM GBS U) Causative organisms: n=46 group B Streptococcus
Index test(s)	CSF white cell count Threshold >26 cells/mm3 for premature neonates (<37 weeks) and >23 cells/mm3 for term neonates (≥37 weeks) (converted to cells/µL for consistency with other studies). CSF glucose concentration Threshold <23 mg/dL for premature neonates (<37 weeks) and <33 mg/dL for term neonates (≥37 weeks) (converted to mmol/L for consistency with other studies). CSF protein concentration Threshold >151 mg/dL for premature neonates (<37 weeks) and >171 mg/dL for term neonates (≥37 weeks).
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	Elevated CSF white cell count, threshold as above (n=13495): TP 41; FP 2461; FN 5; TN 10988 Low CSF glucose concentration, threshold as above (n=13495): TP 28; FP 578; FN 18; TN 12871 Elevated CSF protein concentration, threshold as above (n=13495): TP 43; FP 3268; FN 3; TN 10181

	White cell count, protein and glucose in neonates, threshold 'abnormal' values as above (n=13495): TP 27; FP 242; FN 19; TN 13207 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: CSF white cell count – cells/μL. Equivalent to cells/mm3; CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; IQR: interquartile range; N/n: number; 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 *(Excluded infants with positive CSF results for viral pathogens and bacterial species other than group B Streptococcus. Likely that these infants will have had suspected bacterial meningitis at time of testing and therefore may be inflating diagnostic accuracy)*
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.)*
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.)*

QUADAS: quality assessment of diagnostic accuracy studies

Arora, 2017

Bibliographic Reference Arora, H. S; Asmar, B. I; Salimnia, H; Agarwal, P; Chawla, S; Abdel-Haq, N.; Enhanced Identification of Group B Streptococcus and Escherichia Coli in Young Infants with Meningitis Using the Biofire Filmarray Meningitis/Encephalitis Panel; Pediatric infectious disease journal; 2017; vol. 36; 685-687

Study details

Country/ies where study was carried out	USA
Study type	Prospective single-gate cross-sectional DTA study
Study dates	August 2014-May 2015
Inclusion criteria	Infants with suspected meningitis (defined as those who underwent spinal tap for suspected sepsis and had 1 or more of the following criteria: bacteremia; fever (>38.5°C) with or without documented seizures; leukocytosis [WBC>30000 cells/mm3]; leukopenia (WBC <5000 cells/mm3); or abnormal CSF analysis (CSF WBC >22 cells/mm3 for infants <28 days old or WBC >15 cells/mm3 for infants >28 days old or CSF protein >120 mg/dL or CSF glucose <20 mg/dL or CSF glucose <50% of concomitant serum glucose level))
Exclusion criteria	Not reported
Patient characteristics	N=62 (n=12 bacteraemia (n=9 GBS, n=3 E. coli) with or without abnormal CSF analysis, n=8 leukocytosis with or without abnormal CSF analysis, n=4 leukopenia with or without abnormal CSF analysis, n=33 had abnormal CSF analysis only, n=5 fever with or without seizures) Age range: 0-3 months Positive for bacterial meningitis: 8% (Population: BM U) Causative organisms: n=5 group B Streptococcus or E. coli
Index test(s)	Molecular diagnosis Multiplex PCR (FA-M/E panel) for group B streptococcus and E. coli
Reference standard(s)	CSF bacterial culture
Sources of funding	Partially industry funded (grant from BioFire Diagnostics)
Results	Molecular diagnosis: Multiplex PCR for group B streptococcus and E. coli (n=62): TP 5; FP 4; FN 0; TN 53 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae; Haemophilus influenzae; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; 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?	Unclear *(Infants undergoing lumbar puncture for suspected sepsis; similar symptoms to bacterial meningitis and additional inclusion criteria limit included samples to suspected bacterial meningitis; however some cases may have been missed)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

QUADAS: quality assessment of diagnostic accuracy studies

Balamuth, 2021

Bibliographic Reference Balamuth, F; Cruz, A. T; Freedman, S. B; Ishimine, P. T; Garro, A; Curtis, S; Grether-Jones, K. L; Miller, A. S; Uspal, N. G; Schmidt, S. M; Shah, S. S; Nigrovic, L. E.; Test Characteristics of Cerebrospinal Fluid Gram Stain to Identify Bacterial Meningitis in Infants Younger Than 60 Days; Pediatric Emergency Care; 2021; vol. 37; E227-E229

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study Secondary analysis of Pediatric Emergency Medicine Collaborative Research Committee Herpes Simplex Virus study.
Study dates	2005-2013
Inclusion criteria	Infants aged ≤60 days with CSF culture obtained within 24 hours of emergency department presentation.
Exclusion criteria	Infants without CSF Gram stain results.
Patient characteristics	N=20947 n=204 bacterial meningitis n=20743 without bacterial meningitis Age in days (range [IQR]): 28 (15-41) Sex (n): 11,633 male:9,314 female Positive for bacterial meningitis: 1% (Population: BM U) Causative organisms: n=63 group B Streptococcus, n=39 E. coli, n=26 S. aureus, n=17 Enterococcus spp., n=15 Klebsiella spp., n=7 Enterobacter spp., n=7 S. pneumoniae, n=5 L. monocytogenes, n=5 N. meningitidis, n=3 C. cloacae, n=2 P. mirabilis, n=1 group A Streptococcus, n=1 Haemophilus, n=1 P. aeruginosa, n=12 other pathogens
Index test(s)	Microscopy Gram staining
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported.
Results	Direct microscopy: Gram staining (n=20947): TP 70; FP 44; FN 134; TN 20699 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

A&E: accident and emergency; CSF: cerebrospinal fluid; C. cloacae: Citrobacter cloacae; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; IQR: interquartile range; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; P. aeruginosa: Pseudomonas aeruginosa; P. mirabilis: Proteus mirabilis; spp: species; S. aureus: Staphylococcus aureus; S. pneumoniae: Streptococcus pneumoniae; 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 *(Secondary analysis of Pediatric Emergency Medicine Collaborative Research Committee Herpes Simplex Virus study; unclear whether parent study enrolled consecutive samples or what exclusion criteria was applied)*
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 index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias; 454/658 (69%) positive cultures determined to be contaminants but these were defined a priori)*
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)*

QUADAS: quality assessment of diagnostic accuracy studies

BenGershom, 1986

Bibliographic Reference BenGershom, E; Briggeman-Mol, G. J; de Zegher, F.; Cerebrospinal fluid C-reactive protein in meningitis: diagnostic value and pathophysiology; European Journal of Pediatrics; 1986; vol. 145; 246-9

Study details

Country/ies where study was carried out	Netherlands

Study type	Prospective single-gate cross-sectional DTA study
Study dates	Data was collected during one year period. Exact dates are not reported.
Inclusion criteria	All infants and children referred to hospital with suspected meningitis and sufficient CSF remaining after routine testing.
Exclusion criteria	Patients who had pre-existent hydrocephalus or atraumatic lumbar puncture.
Patient characteristics	N=126 n=30 neonates n=96 infants and children N=45 infants and children considered for analysis n=20 bacterial meningitis n=25 viral meningitis (21 cases were culture-proven with Mumps virus, Epstein-Barr virus or Entero virus) Age (range): 1 month-13 years Positive for bacterial meningitis: 38%* (Population: BM VM NM) *44% were considered to have bacterial meningitis but this was only culture confirmed in 38%. Positive CSF cultures in population with bacterial meningitis: 85%, but results reported are based on culture-confirmed cases. Causative organisms: Exact numbers not reported but included H. influenzae, N. meningitidis., S. pneumoniae, group B Streptococcus, E. coli, Pseudomonas spp.
Index test(s)	CSF white cell count Threshold >500 cells/µL. CSF glucose concentration Threshold <2.2 mmol/L. CSF protein concentration Threshold >100 mg/dL.
Reference standard(s)	CSF bacterial culture and/or other undefined reference standard

Sources of funding	No sources of funding reported
Results	CSF white cell count, threshold >500 cells/µL (n=42): TP 15; FP 7; FN 2; TN 18 CSF glucose concentration, threshold <2.2 mmol/L (n=40): TP 8; FP 1; FN 9; TN 22 CSF protein concentration, threshold >100 mg/dL (n=42): TP 16; FP 2; FN 1; TN 23 Those classified as bacterial meningitis but who did not have a positive culture were not included in the analysis. N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; H. influenzae; Haemophilus influenzae; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; spp.: species; S. pneumoniae: Streptococcus pneumoniae; 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 *(Consecutive sample enrolled but only children diagnosed with bacterial meningitis or viral meningitis were included; neonates were excluded from the analyses (n=3 (7%)) in bacterial meningitis group. Biological reason for exclusion given but this was only in relation to CRP levels and no information given whether this reasoning can be applied for WCC, glucose concentration and protein concentration. Additional 2 excluded from glucose concentration results due to failed measurement)*
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	Is there concern that the target	Low

Section	Question	Answer
standard: applicability	condition as defined by the reference standard does not match the review question?	*(Only 85% of those with bacterial meningitis were confirmed based on culture (other reference standard undefined); however, enough data presented to calculate 2x2 tables using only culture as reference standard)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

CRP: C-reactive protein; N/n: number; QUADAS: quality assessment of diagnostic accuracy studies; WCC: white cell count

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; 779-782

Study details

Country/ies where study was carried out	USA
Study type	Prospective single-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	CSF samples submitted to laboratory during study period, including all cases of bacterial and aseptic meningitis
Exclusion criteria	Not reported
Patient characteristics	N=119 n=21 bacterial meningitis n=8 aseptic meningitis n=90 no meningitis Age (range): 1 week-18 years Positive for bacterial meningitis: 18% (Population: BM AM NM) Causative organisms: n=14 H. influenzae type b, n=2 S. pneumoniae, n=3 N. meningitidis, n=1 M. tuberculosis, n=1 Salmonella spp.
Index test(s)	CSF neutrophil count

	Threshold >50 cells/cm (could not convert for consistency with other studies due to uncertainty regarding unit of measurement). CSF protein concentration Threshold > 40 mg/dL.
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	CSF neutrophil count, threshold >50 neutrophils/cm (n=119): TP 19; FP 2; FN 2; TN 96 CSF protein concentration, threshold >40 mg/dL (n=119): TP 18; FP 9; FN 3; TN 89 N.B. 2x2 tables and relevant outcomes calculated in RevMan

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; M. Tuberculosis: Mycobacterium tuberculosis; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae; Streptococcus pneumoniae; 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 *(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?	High *(Participants included n=40 with leukaemia who had CSF samples taken as part the routine protocol or assessment of leukaemia)*
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*

Section	Question	Answer
		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

CSF: cerebrospinal fluid; N/n: number; QUADAS: quality assessment of diagnostic accuracy studies

Bonadio, 1989

Bibliographic Reference Bonadio, W. A; Smith, D. S.; CBC differential profile in distinguishing etiology of neonatal meningitis; Pediatric Emergency Care; 1989; vol. 5; 94-96

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 1985 - September 1988
Inclusion criteria	Previously healthy neonates born at term, under 4 weeks old, receiving diagnostic lumbar puncture showing CSF pleocytosis or culture-positive for pathogenic organisms.
Exclusion criteria	Immunodeficient infants; received antibiotic therapy within 72 hours of evaluation (unless CSF positive for bacterial pathogen); traumatic lumbar puncture (>1000 red blood cells/mm3) (unless CSF positive for bacterial pathogen)
Patient characteristics	N=72 n=18 bacterial meningitis n=13 viral meningitis n=41 aseptic Age 0-2 weeks: n=36 (n=8 bacterial meningitis, n=4 viral meningitis, n=24 aseptic meningitis) Age 2-4 weeks: n=36 (n=10 bacterial meningitis, n=9 viral meningitis, n=17 aseptic meningitis) Male (%): 40 (55.6%)

	Positive for bacterial meningitis: 25% (Population: BM VM AM) Positive CSF cultures in population with bacterial meningitis: 89% Causative organisms: n=9 group B Streptococcus, n=5 E. coli, n=2 L. monocytogenes, n=2 H. influenzae
Index test(s)	Microscopy Gram staining CSF glucose concentration Threshold <34mg/dL (converted to mmol/L for consistency with other studies). CSF protein concentration Threshold >170 mg/dL.
Reference standard(s)	CSF bacterial culture and/or CSF pleocytosis with CSF latex agglutination
Sources of funding	No sources of funding reported.
Results	Microscopy: Gram staining (n=72): TP 8; FP 0; FN 10; TN 54 CSF glucose concentration, threshold <34 mg/dL (n=72): TP 11; FP 14; FN 7; TN 40 CSF protein concentration, threshold >170 mg/dL (n=72): TP 10; FP 0; FN 8; TN 54 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: CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus Influenzae; L. monocytogenes: Listeria monocytogenes; N/n: number; 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 *(Children with antibiotic use within 72 hours of lumbar puncture were excluded unless CSF was found to be positive for bacterial pathogen. While this is not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting. Also, inclusion of people based on pleocytosis and culture results may restrict the population of interest and*

Section	Question	Answer
		potentially inflate diagnostic accuracy)
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 for glucose and protein concentration were pre-specified using published threshold and no threshold needed for Gram stain; No information about whether reference standards were interpreted without knowledge of the index tests; 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 *(Only 16/18 (89%) neonates with bacterial meningitis diagnosed using CSF bacterial culture. Remaining diagnosed using latex agglutination)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

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; 206-214

Study details

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

Study dates	January 1992 - July 1999
Inclusion criteria	Infants undergoing routine sepsis evaluation for suspected serious bacterial infection in the emergency department of study hospital (presenting with a temperature of 38°C or greater [physician referred or self-referred by reliable caretakers] or who are noted to have a temperature at triage of 38°C).
Exclusion criteria	All cerebrospinal fluid samples that were blood contaminated, as defined by an RBC count of 10000 cells/mm3 or greater, or that were obtained from infants given a diagnosis of leukaemia were excluded.
Patient characteristics	N=5353 n=22 bacterial meningitis Age in days (range): 3-89 Positive for bacterial meningitis: 0.4% (Population: BM U) Causative organisms: n= 11 E. coli, n=9 group B streptococcus, n=1 S. pneumoniae, n=1 C. koseri
Index test(s)	CSF white cell count Thresholds ≥8 cells/mm3, ≥10 cells/ mm3, ≥100 cells/ mm3, and ≥1,000 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
Results	CSF white cell count, threshold ≥8 cells/mm³ (n=5353): TP 17; FP 1130; FN 5; TN 4201 CSF white cell count, threshold ≥10 cells/mm³ (n=5353): TP 16; FP 880; FN 6; TN 4451 CSF white cell count, threshold ≥100 cells/mm³ (n=5353): TP 9; FP 203; FN 13; TN 5128 CSF white cell count, threshold ≥1,000 cells/mm³ (n=5353): TP 5; FP 37; FN 17; TN 5294 CSF white cell count AUC (95% CI): 0.82 (0.71- 0.94) 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: CSF white cell count – cells/μL. Equivalent to cells/mm3.

AUC: area under the curve; CSF: cerebrospinal fluid; C. koseri: Citrobacter koseri; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; N/n: number; S. pneumoniae; Streptococcus pneumoniae; 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 *(Children with a subsequent diagnosis of leukaemia were excluded, as this will affect CSF white cell counts. May lead to differences in diagnostic accuracy than might be seen in a clinical setting)*
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)*
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

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Bonsu, 2005

Bibliographic Reference Bonsu, B. K; Harper, M. B.; Accuracy and test characteristics of ancillary tests of cerebrospinal fluid for predicting acute bacterial meningitis in children with low white blood cell counts in cerebrospinal fluid; Academic emergency medicine; 2005; vol. 12; 303-309

Study details

Country/ies where	USA

study was carried out	
Study type	Retrospective two-gate cross-sectional DTA study Although the initial study design was a single-gate study, this has been classified as a two-gate study because the latter cohort was selected based on culture results
Study dates	January 1984 - July 1999
Inclusion criteria	January 1993-July 1999: Primary population. Children aged >29 days-18 years old, seen at the study centre who had low CSF white blood cell counts (defined as <30 cells/mm3). January 1984-December 1992. Secondary population. Children aged 1 month-3 years old who had low CSF white blood cell counts (defined as <30 cells/mm3) and confirmed bacterial meningitis.
Exclusion criteria	Subsequent CSF samples from same patient after initial sample, CSF samples contaminated with blood (defined as ≥10000 cells/mm3). All children diagnosed with acute bacterial meningitis caused by Haemophilus influenzae type b, CSF samples with culture or stain suggestive of tuberculous meningitis as well as subjects with a coded International Classification of Diseases, version 9 (ICD-9) diagnosis of leukaemia, immunodeficiency (including human immunodeficiency virus infection), congenital heart disease, and ventriculoperitoneal or ventriculoarterial device at that visit. Removed children with bacteraemia who had no associated evidence of CSF infection (negative Gram stain and culture).
Patient characteristics	N=7,712 n=21 bacterial meningitis (n=10 1992-1999, n=11 1984-1992) n=7,691 without bacterial meningitis Age in years (median [IQR]): 0.5 (0.27-1.33) in bacterial meningitis group, 0.3 (0.15-1.76) in those without bacterial meninigits Positive for bacterial meningitis: 0.3% (Population: BM U) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=9 S. pneumoniae, n=6 N. meningitidis, n=4 E. coli, n=3 group B Streptococcus
Index test(s)	CSF neutrophil count (reported as percentage neutrophils) Thresholds ≥1%, ≥25%, ≥50% and ≥75%. CSF glucose concentration Thresholds <20 mg/dL, <40 mg/dL, <60 mg/dL and <120 mg/dL (converted to mmol/L for consistency with other studies).

	CSF protein concentration Thresholds ≥40 mg/dL, ≥80 mg/dL, ≥120 mg/dL and ≥200 mg/dL.
Reference standard(s)	CSF bacterial culture and/or blood bacterial culture with confirmatory CSF Gram stain
Sources of funding	No sources of funding reported.
Results	CSF neutrophil count (reported as percentage neutrophils), threshold ≥1% (n=7707): TP: 16; FP: 3034; FN: 2; TN: 4655 CSF neutrophil count (reported as percentage neutrophils), threshold ≥25% (n=7707): TP: 13; FP: 549; FN: 5; TN: 7140 CSF neutrophil count (reported as percentage neutrophils), threshold ≥50% (n=7707): TP: 11; FP: 221; FN: 7; TN: 7468 CSF neutrophil count (reported as percentage neutrophils), threshold ≥75% (n=7707): TP: 9; FP: 66; FN: 9; TN: 7623 CSF glucose concentration, threshold <20 mg/dL (n=7710): TP: 3; FP: 71; FN: 18; TN: 7618 CSF glucose concentration, threshold <40 mg/dL (n=7710): TP: 4; FP: 186; FN: 17; TN: 7503 CSF glucose concentration, threshold <60 mg/dL (n=7710): TP: 8; FP: 3947; FN: 13; TN: 3742 CSF glucose concentration, threshold <120 mg/dL (n=7710): TP: 19; FP: 7652; FN: 2; TN: 37 CSF protein concentration, threshold ≥40 mg/dL (n=7710): TP: 8; FP: 1827; FN: 13; TN: 5862 CSF protein concentration, threshold ≥80 mg/dL (n=7710): TP: 6; FP: 230; FN:15; TN: 7459 CSF protein concentration, threshold ≥120 mg/dL (n=7710): TP: 6; FP: 89; FN: 15; TN 7600 CSF protein concentration, threshold ≥200 mg/dL (n=7710): TP: 2; FP: 33; FN: 19; TN 7658 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: CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; GRADE: Grading of Recommendations Assessment, Development and Evaluation; FN: false negative; FP: false positive; IQR: interquartile range; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae: Streptococcus pneumoniae; 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 *(Not a true two-gate study but bacterial meningitis group was supplemented with data from n=11 confirmed cases of bacterial meningitis from another time period; Only includes children with a low white cell count (defined as <30 cells/mm3; Children with a culture or stain suggestive of tuberculous meningitis, children diagnosed with acute bacterial meningitis caused by Haemophilus influenzae type b and children with bacteraemia but negative Gram stain and culture were excluded. These inclusion and exclusion criteria may restrict the population of interest and potentially inflate diagnostic accuracy)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Study has excluded children with acute bacterial meningitis caused by Haemophilus influenzae type b as pathogen is no longer a common cause of bacterial meningitis in North America. However, this is a pathogen of interest in this review)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(Thresholds pre-specified; Index test 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 *(For glucose and protein concentration.)* Unclear *(For neutrophil count: Reported as percentage neutrophil count.)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(Reference standard interpreted without knowledge of the index tests)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	High *(Mixed reference standard of CSF bacterial culture and/or CSF Gram stain with confirmatory blood bacterial culture. Proportions of participants diagnosed using each method not reported)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(For neutrophil count: No information about interval between index tests and reference standards. 3/21 (14.3%) children with bacterial meningitis did not have a record of the percentage of neutrophils in CSF)* Unclear *(For protein and glucose: No information about interval between index tests and reference standards)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Bonsu, 2008

Bibliographic Reference Bonsu, B. K; Ortega, H. W; Marcon, M. J; Harper, M. B.; A decision rule for predicting bacterial meningitis in children with cerebrospinal fluid pleocytosis when gram stain is negative or unavailable; Academic emergency medicine; 2008; vol. 15; 437-444

Study details

Country/ies where	USA

study was carried out	
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	June 1998-June 2004
Inclusion criteria	Children presenting at emergency department with signs of acute meningitis.
Exclusion criteria	Children who did not have CSF pleocytosis (CSF leukocyte count <8 cells/μL) or with blood-contaminated CSF (>10000 erythrocytes/μL), or, for some analyses, missing results of selected tests were excluded.
Patient characteristics	N=78 n=19 bacterial meningitis n=59 enteroviral meningitis Age in years for bacterial meningitis group (median [IQR]): 1.0 (0.4-2.2) Positive for bacterial meningitis: 24% (Population: BM VM) Causative organisms: n = 12 S. pneumoniae, n = 6 N. meningitidis, n = 1 group B Streptococcus
Index test(s)	CSF white cell count Threshold >597 cells/μL. CSF neutrophil count (reported as percentage neutrophils) Threshold >74%. CSF glucose concentration Threshold <38mg/dL (converted to mmol/L for consistency with other studies). CSF protein concentration Threshold >97 mg/dL.
Reference standard(s)	CSF bacterial culture
Sources of funding	No source of funding reported.

Results	CSF white cell count, threshold >597 cells/µL (n=78): TP 12; FP 4; FN 7; TN 55 CSF neutrophil count, threshold >74% (n=78): TP 14; FP 10; FN 5; TN 49 CSF glucose concentration, threshold <38 mg/dL (n=78): TP 14; FP 0; FN 5; TN 59 CSF protein concentration, threshold >97 mg/dL (n=78): TP 16; FP 4; FN 3; TN 55 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: CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18.

A&E: accident and emergency; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; GRADE: Grading of Recommendations Assessment, Development and Evaluation; FN: false negative; FP: false positive; IQR: interquartile range; N/n: number; N. meningitidis: Neisseria meningitidis; spp: species; S. pneumoniae: Streptococcus pneumoniae; 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 *(Consecutive sample enrolled but only children diagnosed with bacterial meningitis or viral meningitis were included. Also, excluded children who did not have CSF pleocytosis. These inclusion and exclusion criteria may restrict the population of interest and potentially inflate diagnostic accuracy)*
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?	High *(Threshold was derived from the index test ROC curves through recursive partitioning)*
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 *(No information about interval between index tests and reference standards; however both performed on the same frozen CSF specimen)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve: receiver operating characteristic curve

Bortolussi, 1982

Bibliographic Reference Bortolussi, R; Wort, A. J; Casey, S.; The latex agglutination test versus counterimmunoelectrophoresis for rapid diagnosis of bacterial meningitis; Canadian medical association journal; 1982; vol. 127; 489-493

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	People with suspected bacterial meningitis based on clinical and CSF findings.
Exclusion criteria	Not reported
Patient characteristics	N=207 n=50 bacterial meningitis n=157 non-bacterial meningitis Age of participants not reported. Positive for bacterial meningitis: 24% (Population: BM U) Causative organisms: n=29 H. influenzae type b, n=2 N. meningitidis group A, n=3 N. meningitidis group B, n=6 N. meningitidis group C, n=3 E. coli K1, n=4 S. pneumoniae, n=3 group B Streptococcus ≈30% patients had received antibiotics orally before the CSF sample was obtained.
Index test(s)	Microscopy Gram staining

	• for all bacteria • for N. meningitidis • for S. pneumoniae • for H. influenzae • for group B Streptococcus • for Gram-negative bacilli (E. coli)
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	Microscopy: Gram staining for all bacteria (n=202): TP 36; FP 1; FN 9; TN 156 Microscopy: Gram staining for N. meningitidis (n=202): TP 10; FP 0; FN 1; TN 191 Microscopy: Gram staining for S. pneumoniae (n=202): TP 3; FP 0; FN 1; TN 198 Microscopy: Gram staining for H. influenzae (n=202): TP 19; FP 0; FN 6; TN 177 Microscopy: Gram staining for group B Streptococcus (n=202): TP 2; FP 0; FN 1; TN 199 Microscopy: Gram staining for Gram-negative bacilli (E. coli) (n=202): TP 2; FP 1; FN 0; TN 199 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae; Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae: Streptococcus pneumoniae; 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 *(Consecutive sample not obtained. No information provided on exclusion criteria.)*
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

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(5 (2.4%) people with bacterial meningitis excluded from the analyses. Reason for exclusion not given)*

QUADAS: quality assessment of diagnostic accuracy studies

Boudet, 2019

Bibliographic Reference Boudet, A; Pantel, A; Carles, M. J; Bocle, H; Charachon, S; Enault, C; Stephan, R; Cadot, L; Lavigne, J. P; Marchandin, H.; A review of a 13-month period of FilmArray Meningitis/Encephalitis panel implementation as a first-line diagnosis tool at a university hospital; 2019; vol. 14; e0223887

Study details

Country/ies where study was carried out	France
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	April 2017-April 2018
Inclusion criteria	CSF samples taken through lumbar puncture and tested by FA-M/E panel per physician or microbiologist order
Exclusion criteria	Not reported
Patient characteristics	N=734 CSF samples from 708 patients Age (mean[range]): 44 years (1 day-98 years) (n=556 adult [mean 52.9 years, range 18-98 years], n=152 children [mean 3.3 years, range 1 day-17 years]) Sex (%): 53.4 male: 46.6 female

	Positive for bacterial meningitis: 2% (Population: BM VM NM) Causative organisms: n=4 group B Streptococcus, n=4 N. meningitidis, n=2 S. pneumoniae, n=1 H. influenzae, n=1 E. coli
Index test(s)	SF white cell count Thresholds ≥10 cells/mm3 for neonates and ≥5 cells/mm3 for all other age groups (converted to cells/μL for consistency with other studies). Microscopy Gram staining: • for all bacteria • for N. meningitidis • for S. pneumoniae • for Group B streptococcus Molecular diagnosis Multiplex PCR (FA-ME panel): • for N. meningitidis • for S. pneumoniae • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli)
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	CSF white cell count (reported as positive cytology). Thresholds ≥10 cells/mm3 in neonates and ≥5 cells/mm3 in other patients (n=706): TP 12; FP 4; FN 0; TN 690 Molecular diagnosis: Multiplex PCR for all included bacteria (n=708): TP 12; FP 6*; FN 0**; TN 690 Molecular diagnosis: Multiplex PCR for N. meningitidis (n=708): TP 4; FP 0; FN 0; TN 704 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=708): TP 2; FP 2; FN 0; TN 704 Molecular diagnosis: Multiplex PCR for H. influenzae (n=708): TP 1; FP 2; FN 0; TN 705 Molecular diagnosis: Multiplex PCR for group B streptococcus (n=708): TP 4; FP 1; FN 0; TN 703 Molecular diagnosis: Multiplex PCR for Gram-negative bacilli (E. coli) (n=708): TP 1; FP 1; FN 0; TN 706

	N.B. 2x2 tables and relevant outcomes calculated in RevMan * Paper reports 5 of these as true positives as all patients had been pre-treated with antibiotics and had abnormal cytology consistent with bacterial meningitis. ** Culture also identified 2 additional pathogens not included in the panel, in people at high-risk of non-panel target (Staphylococcus aureus in healthcare-associated infection and Streptococcus salivarius in a carcinomatous meningitis). For consistency across studies, results have been reported as follows in forest plots and GRADE tables: CSF white cell count – cells/µL. Equivalent to cells/mm3.

A&E: accident and emergency; CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; HSV: herpes simplex virus; ICU: intensive care unit; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis; Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(Exclusion criteria not reported; only patients from certain departments (A&E, ICU, infectious disease units, paediatrics and neonatology) received systematic testing with index test (consecutive sample tested); 18% were from other units and tested only if clinical data suggested high probability of meningitis or encephalitis)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Sample includes 80/708 (11%) patients from neurology; suggests previous neurosurgical procedures which are excluded)*
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, tests are objective so unlikely that knowledge of results would introduce bias; Thresholds for white cell count not explicitly stated as pre-specified but have utilised normal ranges so have assumed they 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)*

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?	High *(No information about interval between index tests and reference standards; 27 people received multiple tests for clinical reasons (time period 0-47 days); assuming everyone received bacterial culture (even those with fungal and viral meningitis) but not explicitly stated; 2x2 results only reported by patient so unsure which PCR and/or culture result was selected to report)*

A&E: accident and emergency; ICU: intensive care unit; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Boving, 2009

Bibliographic Reference Boving, M. K; Pedersen, L. N; Moller, J. K.; Eight-plex PCR and liquid-array detection of bacterial and viral pathogens in cerebrospinal fluid from patients with suspected meningitis; Journal of clinical microbiology; 2009; vol. 47; 908-13

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective single-gate cross-sectional DTA study
Study dates	November 2004-November 2005
Inclusion criteria	CSF samples sent to study centre for analysis
Exclusion criteria	Doublet CSF samples (1 sample sent for bacterial analysis and 1 for viral analysis on the same day), samples sent from the forensic medical department, samples with insufficient volumes, samples that were not collected for this project
Patient characteristics	N=1187 n=1031 suspected bacterial meningitis n=156 suspected viral meningitis Ages of participants not reported Positive for bacterial meningitis: 2%* (Population: BM U)

	*3% were considered to have bacterial meningitis but this was only culture confirmed in 2%. Positive CSF cultures in population with bacterial meningitis: 82%, but results reported are based on culture-confirmed cases. Causative organisms: n=16 S. pneumoniae, n=5 N. meningitidis, n=4 S. aureus, n-1 E. coli, n=1 L. monocytogenes
Index test(s)	Molecular diagnosis Multiplex PCR (PCR-Luminex assay): • for N. meningitidis • for S. pneumoniae • for Gram-negative bacilli (E. coli) • for L. monocytogenes
Reference standard(s)	CSF microscopy, CSF bacterial culture, PCR, or blood culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (Luminex PCR) (n=1187): TP 24; FP 31; FN 3; TN 1129 Molecular diagnosis: Multiplex PCR for N. meningitidis (Luminex PCR) (n=1187): TP 5; FP 3; FN 0; TN 1179 Molecular diagnosis: Multiplex PCR for S. pneumoniae (Luminex PCR) (n=1187): TP 15; FP 13; FN 1; TN 1158 Molecular diagnosis: Multiplex PCR for Gram-negative bacilli (E. coli) (Luminex PCR) (n=1187): TP 1; FP 6; FN 0; TN 1180 Molecular diagnosis: Multiplex PCR for L. monocytogenes (Luminex PCR) (n=1187): TP 1; FP 0; FN 0; TN 1186 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; 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 *(Not clear if consecutive sample was enrolled. Study excluded samples sent for bacterial and viral analysis on the same day to prevent double counting; however, presumably the people who such samples came from were suspected as having either bacterial or viral aetiologies so their exclusion may inflate diagnostic accuracy by excluding those with a less clear suspected diagnosis)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Samples sent for bacterial or viral analysis at study centre; participant characteristics not reported and only brief description of exclusion criteria)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(Reference standard of study is microscopy and/or culture or PCR detecting same microorganism found in blood culture within 7 days. All samples received all reference standard tests which minimises impact on bias and enough data presented to calculate 2x2 tables using only culture as reference standard for bacterial samples)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(There were differences in the reference standards used for samples sent for bacterial and viral analysis)*

CSF: cerebrospinal fluid; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Brizzi, 2012

Bibliographic Reference Brizzi, K; Hines, E. M; McGowan, K. L; Shah, S. S.; Diagnostic accuracy of cerebrospinal fluid gram stain in children with suspected bacterial meningitis; Pediatric infectious disease journal; 2012; vol. 31; 195-7

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 2002 - August 2010

Inclusion criteria	Children <18 years old with lumbar puncture performed in emergency department and had CSF clinical data available.
Exclusion criteria	Patients, who underwent neurosurgery within the past month or had a ventricular shunt, or with LPs performed before transfer.
Patient characteristics	N=1938 n=21 bacterial meningitis: n=17 definite, defined as known pathogen growth on CSF culture; n=4 probable, defined as other than a known pathogen growth on CSF culture and if the CSF WBC count was >500 cells/mm3 without an alternate explanation, and at least one of the following was present: positive peripheral blood culture results, a CSF glucose level <20 mg/dL, or an elevated CSF protein. Age (median [IQR]): 1.6 years (1.4 months- 9.9 years) Male (%): 1027 (53%) Positive for bacterial meningitis: 0.9% (Population: BM U) Causative organisms: n=10 S. pneumoniae, n=5 group B Streptococcus, n=2 N. meningitidis Patients pretreated with antibiotics: n=6 in definite meningitis group, n=4 probable meningitis group
Index test(s)	Microscopy Gram staining
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	Microscopy: Gram staining in definite meningitis (n=1938): TP 16; FP 18; FN 1; TN 1903 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

A&E: accident and emergency; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled)*
Patient selection:	Are there concerns that included patients do not	Low

Section	Question	Answer
applicability	match the review question?	
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

QUADAS: quality assessment of diagnostic accuracy studies

Bryant, 2004

Bibliographic Reference Bryant, P. A; Li, H. Y; Zaia, A; Griffith, J; Hogg, G; Curtis, N; Carapetis, J. R.; 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; 2004; vol. 42; 2919-2925

Study details

Country/ies where study was carried out	Australia
Study type	Prospective single-gate cross-sectional DTA study
Study dates	Group 1: July 200 and October 2000 Group 2: August 2000-January 2001
Inclusion criteria	Group 1: All consecutive patients admitted to study centre during each of the 2 months studied, with a clinical suspicion of meningitis or

	septicaemia (defined as admission diagnosis of acute (bacterial, viral or unknown cause), meningoencephalitis, fever or pyrexia of unknown origin, or septicaemia or septic shock). Group 2: All patients admitted to study centre during 6 month period, with an admission diagnosis of probable meningococcal septicaemia and/or meningitis. NB. Every participant (both group 1 and 2) had an acute febrile illness and therefore a possible diagnosis of meningococcal meningitis and/or septicaemia.
Exclusion criteria	Not reported
Patient characteristics	N=118 n=24 meningococcal disease n=8 septicaemia n=11 septicaemia with signs of meningits n=5 meningitis n=54 with suspected meningococcal septicaemia or meningitis on admission (n=29 suspected septicaemia, n=25 suspected meningitis) Age in years (median [range]): 2.6 (0.1-15.4) in suspected meningococcal disease group Male/female ratio: 1.4:1 Positive for bacterial meningitis: 1.7%* (Population: MM UM US) *14% were considered to have bacterial meningitis but this was only culture confirmed in 2%. Causative organisms: n= 4 N. meningitidis
Index test(s)	Molecular diagnosis Specific PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported.
Results	Molecular diagnosis: Specific PCR for N. meningitidis (n=48): TP 2; FP 2; FN 0; TN 44 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis; Neisseria meningitidis; 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 *(No information provided on exclusion criteria.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Population is indirect. Children with suspicion of meningitis and/or meningococcal septicaemia were enrolled)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(Index tests 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 *(Reference standard interpreted without knowledge of the index tests)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(No information about interval between index tests and reference standards. Only 55/118 (46.6%) received lumbar puncture to perform CSF bacterial culture. Of these, only 48/55 (87.3%) were tested with PCR. No information given on the missing data)*

CSF: cerebrospinal fluid; N/n: number; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Buch, 2018

Bibliographic Reference Buch, K; Bodilsen, J; Knudsen, A; Larsen, L; Helweg-Larsen, J; Storgaard, M; Brandt, C; Wiese, L; Ostergaard, C; Nielsen, H; Lebech, A. M.; Cerebrospinal fluid lactate as a marker to differentiate between community-acquired acute bacterial meningitis and aseptic meningitis/encephalitis in adults: a Danish prospective observational cohort study; Infectious Diseases; 2018; vol. 50; 514-521

Study details

Country/ies where study was carried out	Denmark

Study type	Prospective single-gate cross-sectional DTA study
Study dates	January 2015-September 2016
Inclusion criteria	People aged 15 years and older, clinically and/or microbiologically diagnosed acute meningitis, plus available CSF lactate values
Exclusion criteria	DASGIB cohort: Patients with hospital-acquired CNS infections, as defined by the Centre of Disease Control and Prevention, or an implanted neurosurgical device. This study: Patients with missing data, not fulfilling Spanos criteria, verified of suspected autoimmune encephalitis, neurosyphilis or neuroborreliosis
Patient characteristics	N=176 n=51 acute bacterial meningitis (ABM) (n=49 microbiologically verified) n=125 aseptic meningitis/encephalitis (AME) Age in years (median [IQR]): 64 (52-74) Female (%): 25 (49.0) Positive for bacterial meningitis: 29% (Population: BM AME) Positive CSF cultures in population with bacterial meningitis: 61% Causative organisms: n = 30 S. pneumoniae, n=6 other Streptococcus spp., n=2 E. coli, n=4 S. aureus, n=1 Coagulase-negative Staphylococcus spp., n=2 L. monocytogenes, n=1 H. influenzae, n = 3 N. meningitidis and n=2 unknown aetiology Immunosuppressed (%): 15 (29.4). Patients were defined as immunosuppressed if having one or more of the following conditions: Diabetes mellitus, solid/haematological cancer, active alcohol abuse, HIV, congenital immunodeficiency or immunosuppressive drug therapy including prednisolone ≥7.5mg per day. Antibiotics before CSF (%): 8 (15.7)
Index test(s)	CSF white cell count Threshold 15x106 cells/L (converted to cells/μL for consistency with other studies). CSF neutrophil count (reported as CSF neutrophil fraction) Threshold 67%.

	CSF glucose concentration (reported as CSF/blood glucose ratio) Threshold 0.4. CSF protein concentration Threshold >0.45 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture and/or bacterial blood culture and/or CSF PCR and/or CSF microscopy and/or Spanos criteria.
Sources of funding	Not industry funded
Results	CSF white cell (reported as leukocyte) count, threshold >15x106 cells/L (n=176): TP 50; FP 111; FN 1; TN 14; AUC (95% CI): 0.80 (0.72-0.88) CSF neutrophil count (reported as CSF neutrophil fraction), threshold >0.67 (n=176): TP 41; FP 19; FN 10; TN 106; AUC (95% CI): 0.89 (0.84-0.94) CSF glucose concentration (reported as CSF/blood glucose ratio), threshold <0.4 (n=176): TP 45; FP 16; FN 6; TN 109; AUC (95% CI): 0.91 (0.87-0.96) CSF protein concentration, threshold >0.45g/L (n=176): TP 51; FP 96; FN 0; TN 29; AUC (95% CI): 0.91 (0.87-0.96) 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: CSF white cell count – cells/μL. Calculated by diving by 106; CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100.

AUC: area under the curve; CI: confidence interval; CNS: central nervous system; CSF: cerebrospinal fluid; DASGIB: Danish study group for infections in the brain; DTA: diagnostic test accuracy; E. coli: Escherichia coli; H. influenzae; Haemophilus influenzae; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IQR: interquartile range; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; spp.: species; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; 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 *(Consecutive sample enrolled but only people diagnosed with bacterial meningitis or aseptic meningitis/encephalitis were included (selected on the basis of CSF leucocytes); n=438 participants excluded due to missing CSF lactate data; however, participants with and without CSF lactate data not significantly different, and CSF lactate not an index test of interest for review. These inclusion and exclusion criteria may restrict the population of interest and potentially inflate diagnostic accuracy. Population includes people who are immunosuppressed (n=15 (29.4%) in bacterial meningitis group which is not in protocol)*

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 31/51 (61%) participants with bacterial meningitis used CSF culture reference standard. Remaining participants used a mixture of blood culture (13/51), CSF PCR (4/51) and Spanos criteria (2/51). For AME group, 64/151 (42%) used CSF PCR as reference standard with remaining participants not specified)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards; Use of clinical symptoms in diagnosis of bacterial meningitis could have affected timing of CSF samples)*

AME: aseptic meningitis/encephalitis; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Chiba, 2009

Bibliographic Reference Chiba, N; Murayama, S. Y; Morozumi, M; Nakayama, E; Okada, T; Iwata, S; Sunakawa, K; Ubukata, K.; Rapid detection of eight causative pathogens for the diagnosis of bacterial meningitis by real-time PCR; Journal of Infection and Chemotherapy; 2009; vol. 15; 92-98

Study details

Country/ies where study was carried out	Japan
Study type	Prospective single-gate cross-sectional DTA study

Study dates	January 2005-December 2007
Inclusion criteria	People with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing.
Exclusion criteria	Not reported
Patient characteristics	N=168 Ages of participants not reported Positive for bacterial meningitis: 48% (Population: BM U) Causative organisms: n=48 H. influenzae, n=27 S. pneumoniae, n=3 E. coli, n=2 group B Streptococcus, n=1 L. monocytogenes
Index test(s)	Molecular diagnosis Multiplex PCR: • for all included bacteria • for S. pneumoniae • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli) • for L. monocytogenes
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=168): TP 81; FP 40; FN 0; TN 47 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=168): TP 27; FP 9; FN 0; TN 132 Molecular diagnosis: Multiplex PCR for H. influenzae (n=168): TP 48; FP 28; FN 0; TN 92 Molecular diagnosis: Multiplex PCR for group B Streptococcus (n=168): TP 2; FP 2; FN 0; TN 164 Molecular diagnosis: Multiplex PCR for Gram-negative bacilli (E. coli) (n=168): TP 3; FP 0; FN 0; TN 165 Molecular diagnosis: Multiplex PCR for L. monocytogenes (n=168): TP 1; FP 0; FN 0; TN 167 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; L. monocytogenes; Listeria monocytogenes; N/n: number; S. agalactia; Streptococcus agalactia; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; 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 *(Not clear if consecutive sample was enrolled; exclusion criteria not reported; only people with suspected bacterial meningitis included (based on CSF findings, which may inflate diagnostic accuracy))*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Diagnosed rather than suspected bacterial meningitis)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(Index test performed before reference standard so without knowledge of reference standard results)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	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)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Corrall, 1981

Bibliographic Reference Corrall, C. J; Pepple, J. M; Moxon, E. R; Hughes, W. T.; C-reactive protein in spinal fluid of children with meningitis; Journal of pediatrics; 1981; vol. 99; 365-9

Study details

Country/ies where study was carried out	USA
Study type	Prospective single-gate cross-sectional DTA study
Study dates	August 1978-November 1980
Inclusion criteria	Children aged 1 month-16 years, with clinical symptoms suggestive of meningitis and CSF pleocytosis (defined as >10 white blood cells/mm3).
Exclusion criteria	Not reported
Patient characteristics	N=56 n=24 bacterial meningitis n=8 viral meningitis n=24 no meningitis Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 43% (Population: BM VM NM) Causative organisms: n=12 H. influenzae type b, n=5 S. pneumoniae, n=4 N. meningitidis, n=1 group B streptococcus, n=1 group C Streptococcus, n=1 E. Coli
Index test(s)	SF white cell count Threshold >500 cells/mm3 (converted to cells/μL for consistency with other studies). CSF neutrophil count (reported as polymorphonuclear concentration) Threshold >200 cells/mm3 (converted to cells/μL for consistency with other studies). Microscopy Gram staining CSF glucose concentration Threshold <40 mg/dL (converted to mmol/L for consistency with other studies). CSF protein concentration

	Threshold >100 mg/dL.
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	CSF white cell count, cut off >500 cell/mm3 (n=55): TP 17; FP 2; FN 6; TN 30 CSF neutrophil count (reported as polymorphonuclear concentration), cut off >200 cell/mm3 (n=55): TP 21; FP 5; FN 2; TN 27 Microscopy: Gram staining (n=55): TP 17; FP 0; FN 6; TN 32 CSF glucose concentration, cut off <40 mg/dL (n=55): TP 18; FP 0; FN 5; TN 32 CSF protein concentration, cut off >100 mg/dL (n=55): TP 17; FP 2; FN 6; TN 30 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: CSF white cell and neutrophil count – cells/µL. Equivalent to cells/mm3; CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae; Streptococcus pneumoniae; 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 *(People were selected based on CSF pleocytosis, which may inflate diagnostic accuracy)*
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 thresholds were pre-specified. Index test results interpreted without knowledge of the reference standard results)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low *(For CSF white blood cell concentration, Gram staining, protein concentration and glucose concentration)* High *(For neutrophil count. Reported as polymorphonuclear leukocytes, of which only a proportion are neutrophils)*

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(CSF samples tested within 1-12 hours of lumbar puncture)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

D'Inzeo, 2020

Bibliographic Reference D'Inzeo, T; Menchinelli, G; De Angelis, G; Fiori, B; Liotti, F. M; Morandotti, G. A; Sanguinetti, M; Posteraro, B; Spanu, T.; Implementation of the eazyplex® CSF direct panel assay for rapid laboratory diagnosis of bacterial meningitis: 32-month experience at a tertiary care university hospital; European journal of clinical microbiology & infectious diseases; 2020; vol. 39; 1845-1853

Study details

Country/ies where study was carried out	Italy
Study type	Prospective single-gate cross-sectional DTA study
Study dates	May 2016-December 2018
Inclusion criteria	CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis (defined as a combination of headache, irritability, vomiting, lethargy, neck stiffness, or altered mental status and 1 or more of the following: temperature > 38 °C, white blood cell count > 10000 cells/mm3, CRP serum level >5 mg/l, blood glucose level > 110 mg/dl, and a petechial or purpuric rash)
Exclusion criteria	Post-surgical meningitis cases.
Patient characteristics	N=135 n=44 with bacterial meningitis n=91 without bacterial meningitis

	Age in years (median [IQR]): 51.5 (8-64.5) in bacterial meningitis group only (n=30 adults; n=10 children; n=4 neonates) 22 males (50%) in bacterial meningitis group only Positive for bacterial meningitis: 24%* (Population: BM U) *33% were considered to have bacterial meningitis but this was only culture confirmed in 24%. Causative organisms: n=21 S. pneumoniae, n=10 N. meningitidis, n=6 L. monocytogenes, n=3 E. coli, n=2 S. pyogenes, n=1 group B Streptococcus, n=1 C. koseri 15/44 patients with bacterial meningitis received antibiotic therapy prior to CSF collection.
Index test(s)	CSF white cell count Threshold >5 cells/mm3 (converted to cells/μL for consistency with other studies). Microscopy: Gram staining: • for all bacteria • for N. meningitidis • for S. pneumoniae • for group B streptococcus • for Gram-negative bacilli (E.coli and C. koseri) • for L. monocytogenes CSF glucose concentration (reported as glucose CSF/blood ratio) Threshold <0.66. CSF protein concentration Threshold >40 mg/dl. Molecular diagnosis Multiplex LAMP (easyplex® CSF panel): • for all included bacteria • for N. meningitidis • for S. pneumoniae

	• for group B streptococcus • for Gram-negative bacilli (E. coli) • for L. monocytogenes Gram stain plus multiplex LAMP As above.
Reference standard(s)	CSF bacterial culture
Sources of funding	Sources of funding not reported.
Results	CSF white cell count, threshold >5 cells/mm3 (n=135): TP 32; FP 12; FN 0; TN 91 Glucose CSF/blood ratio, threshold <0.66 (n=135): TP 32; FP 11; FN 0; TN 92 CSF protein concentration, threshold >40 mg/dl (n=135): TP 30; FP 12; FN 2; TN 91 Microscopy: Gram staining for all bacteria (n=135): TP: 22; FP: 6; FN: 10; TN: 97 Microscopy: Gram staining for N. meningitidis (n=135): TP: 2; FP: 2; FN: 2; TN: 129 Microscopy: Gram staining for S. pneumoniae (n=135): TP: 11; FP: 4; FN: 4; TN: 116 Microscopy: Gram staining for group B Streptococcus (n=135): TP: 1; FP: 0; FN: 0; TN: 134 Microscopy: Gram staining for Gram-negative bacilli (E. coli and C. koseri) (n=135): TP: 4; FP: 0; FN: 0; TN: 131 Microscopy: Gram staining for L. monocytogenes (n=135): TP: 2; FP: 0; FN: 4; TN: 129 Molecular diagnosis: Multiplex LAMP for all included bacteria (n=135): TP: 28; FP: 12; FN: 1*; TN: 94 Molecular diagnosis: Multiplex LAMP for N. meningitidis (n=135): TP: 4; FP: 6**; FN: 0; TN: 125 Molecular diagnosis: Multiplex LAMP for S. pneumoniae (n=135): TP: 15; FP: 6**; FN: 0; TN: 114 Molecular diagnosis: Multiplex LAMP for group B streptococcus (n=135): TP: 1; FP: 0; FN: 0; TN: 134 Molecular diagnosis: Multiplex LAMP for Gram-negative bacilli (E. coli) (n=135): TP: 2; FP: 0; FN: 1***; TN: 132 Molecular diagnosis: Multiplex LAMP for L. monocytogenes (n=135): TP: 6; FP: 0; FN: 0; TN: 129 Gram staining plus multiplex LAMP for all included bacteria (n=135): TP 32; FP 12; FN 0; TN 91 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: CSF white cell count – cells/µL. Equivalent to cells/mm3. *Culture also detected n=2 S. pyogenes and n=1 C. koseri, which were all LAMP-negative. However, these primers were not included in the multiplex LAMP panel and therefore have not been included as FN in this analysis. **Paper reported these results as probably true positives according to confirmatory 16S/broad range PCR testing. *** Culture also detected n=1 C. koseri, which was LAMP-negative. However, this primer was not included in the multiplex LAMP panel

	and therefore have not been included as FN in this analysis.

CRP: C-reactive protein; CSF: cerebrospinal fluid; C. koseri: Citrobacter koseri; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; LAMP: loop-mediated isothermal amplification; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; S. pyogenes: Streptococcus pyogenes; 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 *(People were selected based on laboratory tests such as WCC, which may inflate diagnostic accuracy)*
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 *(For white cell count, glucose concentration and protein concentration: Thresholds used have been previously reported and published. For Gram stain and LAMP: Not applicable; Index tests 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 *(For multiplex PCR testing: Broad-range (16S) PCR confirmatory testing applied to all samples. However, enough data presented to calculate 2x2 tables using only culture as reference standard)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies; WCC: white cell count

Dastych, 2015

Bibliographic Reference	Dastych, M; Gottwaldova, J; Cermakova, Z.; Calprotectin and lactoferrin in the cerebrospinal fluid; Biomarkers utilisable for differential diagnostics of bacterial and aseptic meningitis?; Clinical Chemistry and Laboratory Medicine; 2015; vol. 53; 599-603

Study details

Country/ies where study was carried out	Czech Republic
Study type	Prospective single-gate cross-sectional DTA study
Study dates	2013-2014
Inclusion criteria	Adults with suspected inflammatory disease of the CNS.
Exclusion criteria	Not reported
Patient characteristics	N=73 n=23 bacterial meningitis n=50 aseptic meningitis Age in years (range): 21-70 Sex (n): 15 male:8 female Positive for bacterial meningitis: 32% (Population: BM AM) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=8 S. aureus, n=8 Pneumococcus spp., n=4 N. meningitidis, n=4 P. aeruginosa, n=3 E. coli, n=2 Meningococcus spp.
Index test(s)	CSF neutrophil count (reported as polynuclear count) Threshold >37 cells/µL. CSF glucose concentration Threshold <2.7 mmol/L. CSF protein concentration

	Threshold >1.01 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture and/or positive serology (including PCR)
Sources of funding	No sources of funding declared
Results	CSF neutrophil count (reported as polynuclear count), threshold >37 cells/µL (n=73): TP 21; FP 5; FN 2; TN 45; AUC (95% CI): 0.93 (0.85-0.98) CSF glucose concentration, threshold <2.7 mmol/L (n=73): TP 16; FP 5; FN 7; TN 45; AUC (95% CI): 0.81 (0.70-0.89) CSF protein concentration, threshold >1.01 g/L (n=73): TP 16; FP 12; FN 7; TN 38; AUC (95% CI) 0.74 (0.63-0.83) 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: CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100.

AUC: area under the curve; CI: confidence interval; CNS: central nervous system; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; P. aeruginosa: Pseudomonas aeruginosa; PCR: polymerase chain reaction; spp.: species; S. aureus: Staphylococcus aureus; 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 *(No information on whether consecutive sample was enrolled. Only adults 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?	High *(Threshold was derived from the index test ROC curves)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low *(For glucose and protein concentration)* High *(For neutrophil count. Reported as CSF polynuclear cells, of which only a proportion are neutrophils)*
Reference standard: risk of	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*

Section	Question	Answer
bias		*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 positive serology, including PCR methods. Proportions not reported)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

CSF: cerebrospinal fluid; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve; receiver operating characteristic curve

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; 343-347

Study details

Country/ies where study was carried out	Belgium
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	1997-September 2005
Inclusion criteria	Children (age 0–15 years) admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of viral or bacterial meningitis.
Exclusion criteria	Not reported
Patient characteristics	N= 92 n= 21 bacterial meningitis n= 71 viral meningitis Age in years (median [range]): 5.6 (0-15) Male: 63% (Viral meningitis: 65%; bacterial meningitis: 57%) Positive for bacterial meningitis: 23% (Population: BM VM) Positive CSF cultures in population with bacterial meningitis: 67%

	Causative organisms: n=16 N. meningitidis, n=5 S. pneumoniae, n=1 H. influenzae
Index test(s)	CSF neutrophil count (reported as percentage neutrophils) Threshold >80%. CSF glucose concentration Threshold <53 mg/dL (converted to mmol/L for consistency with other studies). CSF protein concentration Threshold ≥100 mg/dL.
Reference standard(s)	CSF bacterial culture and /or blood bacterial culture with CSF pleocytosis
Sources of funding	No sources of funding reported.
Results	CSF neutrophil count, threshold >80% (n=72): TP 14; FP 13; FN 3; TN 42 CSF glucose concentration, threshold <53 mg/dL (n=92): TP 12; FP 9; FN 9; TN 62 CSF protein concentration, threshold ≥100 mg/dL (n=92): TP 12; FP 0; FN 9; TN 71 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: CSF glucose concentration – mmol/L. Calculated by dividing mg by 18.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae: Streptococcus pneumoniae; 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 children 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?	High *(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;*

Section	Question	Answer
		Thresholds were not pre-specified and were chosen based on which was best in differentiating bacterial from viral meningitis)
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 defined as positive CSF culture and/or CSF pleocytosis and a positive blood culture (only 14/21 in bacterial meningitis group had positive CSF culture)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(For neutrophil count. 20/91 (23%) missing data. No information given on missing data)* Unclear *(For glucose and protein concentration. No information about interval between index tests and reference standards; no information on when relevant clinical samples (CSF and blood) were taken with respect to each other)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Deutch, 2006

Bibliographic Reference Deutch, S; Pedersen, L. N; Podenphant, L; Olesen, R; Schmidt, M. B; Moller, J. K; Ostergaard, L.; Broad-range real time PCR and DNA sequencing for the diagnosis of bacterial meningitis; Scandinavian journal of infectious diseases; 2006; vol. 38; 27-35

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective single-gate cross-sectional DTA study
Study dates	May-November 2004
Inclusion criteria	CSF specimens submitted to study laboratory during study period.

Exclusion criteria	Not reported
Patient characteristics	N=206 specimens from 203 patients Age (range): 6 days-86 years old Sex: 107 male:96 female Positive for bacterial meningitis: 8% (Population: BM U) Causative organisms: n=7 N. meningitidis, n=3 S. pneumoniae, n=3 E. coli, n=2 group B Streptococcus, n=1 H. influenzae, n=1 other bacterial pathogens
Index test(s)	Microscopy Gram staining Molecular diagnosis • Broad-range (16S) conventional PCR • Broad-range (16S) real-time PCR with DNA sequencing
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Microscopy: Gram staining (n=196*): TP 9; FP 1; FN 5; TN 181 Molecular diagnosis: broad-range (16S) conventional PCR (n=196*): TP 9; FP 3; FN 5; TN 179 Molecular diagnosis: broad-range (16S) real time PCR with DNA sequencing (n=196*): TP 11; FP 3; FN 3; TN 179 N.B. 2x2 tables and relevant outcomes calculated in RevMan. *Assuming 196 specimens for all 2x2 tables. Only specifically mentioned in RT-PCR, not microscopy or conventional PCR results.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; H. influenzae; Haemophilus influenzae; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; RT-PCR: real-time polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection:	Could the selection of patients have introduced bias?	Unclear

Section	Question	Answer
risk of bias		*(No information provided on exclusion criteria.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(CSF specimens collected from people with suspected bacterial meningitis from multiple clinical department; no inclusion or exclusion criteria reported)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(For PCR methods. Technician blinded to reference standard result)* Unclear *(For Gram staining. Performed at same time as culture. Unclear whether technician had knowledge of reference standard result)*
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 *(For PCR methods. Culture performed before index test so without knowledge of index test results)* Unclear *(For Gram staining. Performed at same time as culture. Unclear whether technician had knowledge of index test result)*
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 *(Only 196/206 (95%) CSF specimens reported for RT-PCR. Assuming this is true for microscopy or conventional PCR results, although not specifically reported)*

CSF: cerebrospinal fluid; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies; RT-PCR: real-time polymerase chain reaction

Deutch, 2008

Bibliographic Reference Deutch, S; Moller, J. K; Ostergaard, L.; Combined assay for two-hour identification of Streptococcus pneumoniae and Neisseria meningitidis and concomitant detection of 16S ribosomal DNA in cerebrospinal fluid by real-time PCR; Scandinavian Journal of Infectious Diseases; 2008; vol. 40; 607-14

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective single-gate cross-sectional DTA study
Study dates	November 2004-November 2005
Inclusion criteria	CSF specimens submitted to study laboratory during study period.
Exclusion criteria	Not reported
Patient characteristics	N=1015 samples from 994 patients n=35 bacterial meningitis Age in years (mean [range]): 40 (0-97) Positive for bacterial meningitis: 2%* samples (Population: BM U) *3% of samples were considered to have bacterial meningitis but this was only culture confirmed in 2%. Causative organisms: n=16 S. pneumoniae, n=5 N. meningitidis
Index test(s)	Molecular diagnosis Multiplex PCR: • for N. meningitidis • for S. pneumoniae
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: PCR for N. meningitidis and S. pneumoniae (n=1015): TP 17; FP 10; FN 7; TN 981 Molecular diagnosis: PCR for N. meningitidis (n=1015): TP 5; FP 3; FN 0; TN 1007 Molecular diagnosis: PCR for S. pneumoniae (n=1015): TP 12; FP 7; FN 4; TN 992 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(No information provided on exclusion criteria)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Poorly defined inclusion criteria; little information reported on participant characteristics)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(Index test was interpreted with no knowledge of the reference standard results)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(Culture performed before index test so without knowledge of index test results)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(Reference standard of study is culture or combined PCR or ICD-10 diagnosis code; however, enough data presented to calculate 2x2 tables with bacterial culture as reference standard)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

PCR: polymerase chain reaction; ICD-10: International Classification of Diseases, version 10; QUADAS: quality assessment of diagnostic accuracy studies

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; 72-76

Study details

Country/ies where study was carried out	France
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 1995-October 2004 for bacterial meningitis

	January 2000-October 2004 for aseptic meningitis
Inclusion criteria	Children aged 28 days-16 years and admitted during the study period with a diagnosis of acute meningitis.
Exclusion criteria	Known neurosurgical disease or known immunodepression, traumatic lumbar puncture (defined as CSF red blood cells >10000/mm³), pre-treated meningitis (antibiotics given within the 48 hours preceding lumbar puncture), or referral from another hospital after diagnosis. Patients whose files were incomplete were also excluded secondarily.
Patient characteristics	N=167 n=21 bacterial meningitis n=146 aseptic meningitis Age in years (median [range]): 4.6 (0.2-14.9) Sex: 70% male Positive for bacterial meningitis: 13% (Population: BM AM) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=10 S. pneumoniae, n=9 N. meningitidis, n=1 H. influenzae type b, n=1 group B Streptococcus
Index test(s)	CSF white cell count Threshold >200 cells/mm3 (converted to cells/μL for consistency with other studies). CSF neutrophil count Threshold >100 cells/mm3 (converted to cells/μL for consistency with other studies). CSF glucose concentration Threshold <2.5 mmol/L. CSF protein concentration Threshold >0.5 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	Acute onset of meningitis and documented bacterial infection in CSF (direct examination and/or bacterial culture and/or latex agglutination) and/or blood bacterial culture
Sources of funding	No sources of funding reported.

Results	CSF white cell count, threshold ≥200 cells/mm³ (n=167): TP 16; FP 37; FN 5; TN 109* CSF neutrophil count, threshold ≥100 cells/mm³ (n=164): TP 17; FP 27; FN 4; TN 116* CSF glucose concentration, threshold ≤2.5 mmol/L (n=164): TP 13; FP 32; FN 8; TN 111 CSF protein concentration, threshold ≥0.5 g/L (n=164): TP 18; FP 31; FN 3; TN 112* AUC also reported in study but without 95% CI so unable to extract and analyse. 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: CSF white cell and neutrophil count – cells/μL. Equivalent to cells/mm3.

AUC: area under the curve; CI: confidence interval; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae: Streptococcus pneumoniae; 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 *(Consecutive sample enrolled but only children with acute meningitis included (based on CSF WCC) which may inflate diagnostic accuracy. Different recruitment periods for bacterial and aseptic meningitis (bacterial meningitis was extended to increase the number of cases). Children with antibiotic use prior to lumbar puncture were excluded; while this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting)*
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 *(Index test was interpreted with full knowledge of the reference standard results; however, test is objective so decreases the likelihood of bias; thresholds pre-specified using Hanley and McNeil methodology)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of	Could the reference standard, its conduct, or its interpretation have	Low *(No information about whether reference standards were interpreted without knowledge of the index*

Section	Question	Answer
bias	introduced bias?	*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, other CSF findings or blood culture. No details on proportion of population diagnosed with CSF culture)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

AM: aseptic meningitis; BM; bacterial meningitis; CSF: CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies; WCC: white cell count

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; 1157-1163

Study details

Country/ies where study was carried out	France (data collected from 5 European countries [France, Poland, Spain, Switzerland, Turkey])
Study type	Retrospective single-gate cross-sectional DTA study Secondary analysis of retrospective multicentre hospital-based cohort studies.
Study dates	1993-2005
Inclusion criteria	Children aged 29 days to 18 years admitted to hospital for bacterial or aseptic meningitis and had measurements of the main CSF and blood inflammatory markers in the Emergency Department.
Exclusion criteria	Any known neurosurgical disease or known immunosuppression, traumatic lumbar puncture (defined as CSF red blood cell count >10000/µL), previously treated meningitis or were referred from another hospital because of a diagnosis of meningitis, or data essential to the ascertainment of bacterial or aseptic meningitis was missing.
Patient characteristics	N=198 n=96 bacterial meningitis Age in years (mean [SD]): 3.2 (1.7) for bacterial meningitis group

	Sex (male to female ratio): 0.9 for bacterial meningitis group Positive for bacterial meningitis: 48% (Population: BM AM) Positive CSF cultures in population with bacterial meningitis: 79% Causative organisms: n=45 N. meningitidis, n=32 S. pneumoniae, n=7 H. influenzae, n=4 group B Streptococcus
Index test(s)	CSF white cell count Threshold >200 cells/μL. CSF neutrophil count Threshold >100 cells/μL. CSF glucose concentration Threshold <45 mg/dL (converted to mmol/L for consistency with other studies). CSF protein concentration Threshold >0.5 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	Acute onset of meningitis and documented bacterial infection in CSF (direct examination and/or bacterial culture and/or latex agglutination and/or PCR) and/or blood bacterial culture
Sources of funding	Not industry funded.
Results	CSF white cell count, threshold ≥200 cells/μL (n=198): TP 76; FP 32; FN 20; TN 70 CSF neutrophil count, threshold ≥100cells/μL (n=184): TP 78; FP 24; FN 17; TN 65; AUC (95% CI): 0.87 (0–80- 0.93) CSF glucose concentration, threshold ≤45.0 mg/dL (n=194): TP 64; FP 18; FN 31; TN 81 CSF protein concentration, threshold ≥0.5 g/L (n=195): TP 84; FP 35; FN 11; TN 65; AUC (95% CI): 0.86 (0.79- 0.94) 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: CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18; CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100.

A&E: accident and emergency; AUC: area under the curve; CI: confidence interval; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae; Streptococcus pneumoniae; 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 *(Consecutive sample enrolled but only children diagnosed with bacterial meningitis or viral meningitis were included. Children with antibiotic use prior to lumbar puncture were excluded; while this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting)*
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 *(Index test was interpreted with full knowledge of the reference standard results; however, test is objective so decreases the likelihood of bias; thresholds pre-specified using Hanley and McNeil methodology)*
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 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?	High *(Initially collected data for n=232 but subsequently excluded information for n=34 (15%), mainly because of missing data. This was uneven between 2 groups - 27/34 had (or were presumed to have) bacterial meningitis, 7/37 had aseptic meningitis)*

CSF: cerebrospinal fluid; N/n: number; QUADAS: quality assessment of diagnostic accuracy studies

Dunbar, 1998

Bibliographic Reference Dunbar, S. A; Eason, R. A; Musher, D. M; Clarridge, Iii J. E.; Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis; Journal of Clinical Microbiology; 1998; vol. 36; 1617-1620

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 1993-July 1997
Inclusion criteria	CSF specimens submitted to study laboratory during study period.
Exclusion criteria	Not reported.
Patient characteristics	N=2635 n=13 bacterial meningitis n=2622 non-bacterial meningitis n=220 contaminants Ages: not reported beyond all adults Positive for bacterial meningitis: 0.5% (Population: BM U) Causative organisms: n=6 S. pneumoniae, n=2 N. meningitidis, n=1 L. monocytogenes, n=1 S. aureus, n=1 M. morganii, n=1 S. sanguis II, n=1 S. bovis
Index test(s)	Microscopy Gram staining: • for all bacteria • for S. pneumoniae • for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	Microscopy: Gram staining in all bacteria excluding contaminants* (n=2415): TP: 12; FP: 0; FN: 1; TN: 2402 Microscopy: Gram staining for N. meningitidis (n=2415): TP: 2; FP: 0; FN: 0; TN: 2413 Microscopy: Gram staining for S. pneumoniae (n=2415): TP: 6; FP: 0; FN: 0; TN: 2409

	N.B. 2x2 tables and relevant outcomes calculated in RevMan. *S. pneumoniae and N. meningitidis results plus (n=1 L. monocytogenes, n=1 S. aureus, n=1 M. morganii, n=1 S. sanguis II, n=1 S. bovis).

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; L. monocytogenes: Listeria monocytogenes; M. morganii: Morganella morganii; N/n: number; N. meningitidis: Neisseria meningitidis; S. aureus: Staphylococcus aureus; S. bovis: Streptococcus bovis; S. pneumoniae; Streptococcus pneumoniae; S. sanguis: Streptococcus sanguis; 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 *(No information provided on exclusion criteria.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Population is indirect. Adults with central nervous system infections, including shunt-associated meningitis, enrolled n=16 (28.6% of confirmed meningitis population))*
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 and positive Gram stains results were reviewed by senior staff 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?	Unclear *(n=220 (8.4%) culture-positive samples were judged to be contaminants. No definition of contaminants given but full list of organisms grown provided in paper. None were organisms of interest for this review)*
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.)*

CSF: cerebrospinal fluid; N/n: number; QUADAS: quality assessment of diagnostic accuracy studies

Ena, 2021

Bibliographic Reference	Ena, J; Afonso-Carrillo, R. G; Bou-Collado, M; Reyes-Jara, M. D; Navarro-Soler, R; de Haedo-Sanchez, D; Martinez-Peinado, C; Gomez-Alonso, B; Arjona-Zaragozi, F.; Evaluation of FilmArray ME panel for the rapid diagnosis of meningitis-encephalitis in emergency departments; Internal & Emergency MedicineIntern; 2021; vol. 5; 5

Study details

Country/ies where study was carried out	Spain
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	November 2016-June 2019
Inclusion criteria	People with suspected meningitis (defined as a combination of fever, headache, neck stiffness, followed by altered mental status with or without a petechial rash), or encephalitis (defined as focal neurological signs, seizures, fever, altered levels of consciousness, and/or changes in personality or behaviour), or meningoencephalitis (defined as a mixed presentation affecting both the brain parenchyma and the meninges); with abnormal CSF results (as defined by study laboratory reference values)
Exclusion criteria	Not reported
Patient characteristics	N=46 n=12 meningitis/encephalitis of bacterial aetiology n=11 meningitis/encephalitis of viral aetiology n=1 meningitis/encephalitis of fungal aetiology n=22 meningitis/encephalitis of unknown aetiology Age in years (median [IQR]): bacterial or fungal aetiology 57 (20-77), unknown aetiology 45 (13-73), viral aetiology 13 (0.06-69) Sex (n) : bacterial or fungal aetiology 7 male:6 female, unknown aetiology 15 male:7 female, viral aetiology 4 male:7 female Positive for bacterial meningitis: 15%* (Population: BME NBME) *26% were considered to have bacterial meningitis but this was only culture confirmed in 15%. Causative organisms: n=4 S. pneumoniae, n=1 N. meningitidis, n=1 H. influenzae, n=1 L. monocytogenes
Index test(s)	Microscopy Gram staining: • for all bacteria • for N. meningitidis

	• for S. pneumoniae • for H. influenzae • for L. monocytogenes <u>Molecular diagnosis</u> Multiplex PCR (FA-ME panel): • for all included bacteria • for N. meningitidis • for S. pneumoniae • for H. influenzae • for L. monocytogenes
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Microscopy: Gram staining for all bacteria (n=46): TP 4; FP 0; FN 3; TN 39 Microscopy: Gram staining for N. meningitidis (n=46): TP 0; FP 0; FN 1; TN 45 Microscopy: Gram staining for S. pneumoniae (n=46): TP 4; FP 0; FN 0; TN 42 Microscopy: Gram staining for H. influenzae (n=46): TP 0; FP 0; FN 1; TN 45 Microscopy: Gram staining for L. monocytogenes (n=46): TP 0; FP 0; FN 1; TN 45 Molecular diagnosis: Multiplex PCR for all included bacteria (n=46): TP 6; FP 5; FN 1; TN 34 Molecular diagnosis: Multiplex PCR for N. meningitidis (n=46): TP 1; FP 0; FN 0; TN 45 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=46): TP 4; FP 3; FN 0; TN 39 Molecular diagnosis: Multiplex PCR for H. influenzae (n=46): TP 0; FP 0; FN 1; TN 45 Molecular diagnosis: Multiplex PCR for L. monocytogenes (n=46): TP 1; FP 2; FN 0; TN 43 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae: Haemophilus influenzae; IQR: interquartile range; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(Exclusion criteria not reported. Also, people were included on the basis of abnormal CSF results, which may inflate diagnostic accuracy)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Only people diagnosed with meningitis and/or encephalitis included; at least 3/46 were immunocompromised (noted as having HIV infection) which is outside the scope of this guideline)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index test was interpreted with full knowledge of the reference standard results; however, test is objective so decreases the likelihood of 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 *(Retrospective study so culture performed first without knowledge of index test results)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(Index tests and reference standard both conducted on admission)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Esparcia, 2011

Bibliographic Reference Esparcia, O; Montemayor, M; Ginovart, G; Pomar, V; Soriano, G; Pericas, R; Gurgui, M; Sulleiro, E; Prats, G; Navarro, F; Coll, P.; Diagnostic accuracy of a 16S ribosomal DNA gene-based molecular technique (RT-PCR, microarray, and sequencing) for bacterial meningitis, early-onset neonatal sepsis, and spontaneous bacterial peritonitis; Diagnostic microbiology and infectious disease; 2011; vol. 69; 153-160

Study details

Country/ies where study was carried out	Spain

Study type	Prospective single-gate cross-sectional DTA study
Study dates	November 2005-January 2007
Inclusion criteria	People with clinical suspicion of bacterial meningitis (defined as CSF white cell count ≥ 10 cells/μL, with or without positive cultures, antigen detections, or Gram stain of CSF).
Exclusion criteria	Suspected viral meningitis (virologically documented or not)
Patient characteristics	N=101 CSF samples from 108 patients Note that the study included 181 total samples. However, 42 of these were sera and 38 were whole blood samples and therefore not included in this review Ages of participants not reported. Positive for bacterial meningitis: 66%* (Population: BM U) *89% were considered to have bacterial meningitis but this was only culture confirmed in 66%. Causative organisms: n=39 S. pneumoniae, n=12 N. meningitidis, n=8 L. monocytogenes
Index test(s)	Molecular diagnosis Broad-range (16S) PCR: • for all bacteria • for N. meningitidis • for S. pneumoniae • for L. monocytogenes
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Broad-range (16S) PCR for all included bacteria (n=101): TP 60; FP 23; FN 7; TN 11 Molecular diagnosis: Broad-range (16S) PCR for N. meningitidis (n=101): TP 11; FP 9; FN 1; TN 80 Molecular diagnosis: Broad-range (16S) PCR for S. pneumoniae (n=101): TP 36; FP 9; FN 0; TN 56 Molecular diagnosis: Broad-range (16S) PCR for L. monocytogenes (n=101): TP 7; FP 4; FN 1; TN 89

	N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(Not clear if consecutive sample was enrolled; only samples positive by study gold standard were tested by PCR and culture but gold standard is not defined. Also, people were selected based on CSF pleocytosis, which may inflate diagnostic accuracy)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(Reference standard of study is bacterial culture and/or PCR; however, enough data presented to calculate 2x2 tables with bacterial culture as reference standard. All samples received all reference standards tests which minimises impact on bias)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(No information about interval between index tests and reference standards; only 101 CSF samples included from 108 with no information given on missing data)*

CSF: cerebrospinal fluid; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Favaro, 2013

Bibliographic Reference	Favaro, M; Savini, V; Favalli, C; Fontana, C.; A multi-target real-time PCR assay for rapid identification of meningitis-associated microorganisms; Molecular BiotechnologyMol Biotechnol; 2013; vol. 53; 74-9

Study details

Country/ies where study was carried out	Italy
Study type	Prospective single-gate cross-sectional DTA study
Study dates	June 2010-June 2011
Inclusion criteria	People with suspected meningitis admitted to study hospitals
Exclusion criteria	Not reported
Patient characteristics	N=296 n=45 bacterial meningitis n=251 without bacterial meningitis Age in years (range): 17-79 Positive for bacterial meningitis: 11%* (Population: BM U) *15% were considered to have bacterial meningitis but this was only culture confirmed in 11%. Causative organisms: n=9 L. monocytogenes, n=6 N. meningitidis, n=2 S. pneumoniae, n=2 E. coli, n=1 group B Streptococcus, n=12 other bacterial pathogens not specified in protocol (L. innocua, E. faecalis, C. amycolatum, S. aureus, C. neoformans) At least 23 patients treated with antimicrobials before CSF sampling
Index test(s)	Molecular diagnosis Combined (specific and broad-rage (16S)) PCR: • for all bacteria • for S. pneumoniae • for N. meningitidis • for H. influenzae • for group B streptococcus

	• for Gram-negative bacilli (E. coli) • for L. monocytogenes
Reference standard(s)	CSF bacterial culture
Sources of funding	None reported
Results	Molecular diagnosis: Combined (specific and broad-range (16S)) PCR for all included bacteria* (n=296): TP: 30; FP 15; FN 2; TN 249 Molecular diagnosis: Combined (specific and broad-range (16S)) PCR for N. meningitidis (n=296): TP: 6; FP 5; FN 0; TN 285 Molecular diagnosis: Combined (specific and broad-range (16S)) PCR for S. pneumoniae (n=296): TP: 2; FP 6; FN 0; TN 288 Molecular diagnosis: Combined (specific and broad-range (16S)) PCR for group B Streptococcus (n=296): TP: 1; FP 0; FN 0; TN 295 Molecular diagnosis: Combined (specific and broad-range (16S)) PCR for Gram-negative bacilli (E. coli) (n=296): TP: 2**; FP 0; FN 0; TN 294 Molecular diagnosis: Combined (specific and broad-range (16S)) PCR for L. monocytogenes (n=296): TP: 9; FP 2; FN 0; TN 285 N.B. 2x2 tables and relevant outcomes calculated in RevMan. *Includes n=4 C. neoforms which is a fungus and therefore not included in the index test of interest for this review. ** Pathogens detected: E. coli

CSF: cerebrospinal fluid; C. amycolatum: Corynebacterium amycolatum; C. neoformans: Cryptococcus neoformans; DTA: diagnostic test accuracy; E. coli: Escherichia coli; E. faecalis: Enterococcus faecalis; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; L. innocua: Listeria innocua; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled)*
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:	Are there concerns that the index test, its conduct, or	Low

Section	Question	Answer
applicability	interpretation differ from the review question?	*(For specific pathogen PCR results.)* Unclear *(For all bacteria PCR results: Specific primers for Cryptococcus neoformans included in the index test, and fungal meningitis is not in scope for this review)*
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 *(Both tests performed immediately upon receipt at laboratory; No information given on if same samples used for both tests)*

PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Freedman, 2001

Bibliographic Reference Freedman, S. B; Marrocco, A; Pirie, J; Dick, P. T.; Predictors of bacterial meningitis in the era after Haemophilus influenzae; Archives of Pediatrics & Adolescent MedicineArch Pediatr Adolesc Med; 2001; vol. 155; 1301-6

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 1992 - October 1996
Inclusion criteria	Children aged 2 months to 17 years who underwent a lumbar puncture in 4 wards of study hospital, to assess the possibility of community-acquired bacterial meningitis.
Exclusion criteria	Exclusion criteria included: clotted samples; CSF red blood cell count greater than 10000/µl; identified ventriculoperitoneal shunt sample; second lumbar puncture within 14 days; any underlying medical condition that predisposed the child to bacterial meningitis or altered CSF findings, including preexisting conditions such as malignant neoplasms, immunodeficiency, trauma, prior neurosurgical procedure, or metabolic diseases.

Patient characteristics	N=1617 n=44 bacterial meningitis (n=33 definite bacterial meningitis; n=11 presumed bacterial meningitis) Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 3% (Population: BM U) Positive CSF cultures in population with bacterial meningitis: 64% Causative organisms: n=18 S. pneumoniae, n=4 N. meningitidis, n=3 H. influenzae type b, n=2 M. tuberculosis, n=2 Enterococcus spp., n=1 E. coli, n=1 S. aureus, n=1 P. vesicularis, n=1 group B Streptococcus n=636 (39.3%) antibiotics administered before the lumbar puncture was performed
Index test(s)	CSF white cell count Thresholds >3 cells/μL and >30 cells/μL. * CSF protein, glucose and Gram stain also reported but results were calculated using a 'computer-generated random subset of patients'. No details given regarding the sample size so unable to calculate 2x2 tables.
Reference standard(s)	Definite bacterial meningitis: CSF bacterial culture and/or CSF latex agglutination. Presumed bacterial meningitis: Not definitely proven (as defined above) but receiving clinical diagnosis and treatment for bacterial meningitis
Sources of funding	No sources of funding reported
Results	CSF white cell count, threshold >3 cells/μl (n=1617): TP 39; FP 477; FN 5; TN 1096 CSF white cell count, threshold >30 cells/μl (n=1617): TP 33; FP 115; FN 11; TN 1458 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

A&E: accident and emergency; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; H. influenzae; Haemophilus influenzae; FN: false negative; FP: false positive; M. tuberculosis: Mycobacterium tuberculosis; N/n: number; N. meningitidis: Neisseria meningitidis; P. vesicularis: Pseudomonas vesicularis; spp.: species; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient	Could the selection of patients have	Unclear

Section	Question	Answer
selection: risk of bias	introduced bias?	*(Exclusion criteria resulted in the exclusion of 9837 (86%) samples)*
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)*
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 latex agglutination for definite bacterial meningitis. 5 (11.4%) diagnoses of bacterial meningitis were based on positive CSF latex agglutination findings. 11 (25%) diagnoses of presumed bacterial meningitis were identified based on clinical symptoms of bacterial meningitis when CSF culture and latex agglutination results were negative)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Garges, 2006

Bibliographic Reference Garges, H. P; Anthony Moody, M; Cotten, C. M; Smith, P. B; Tiffany, K. F; Lenfestey, R; Li, J. S; Fowler Jr, V. G; Benjamin Jr, D. K.; Neonatal meningitis: What is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters?; Pediatrics; 2006; vol. 117; 1094-1100

Study details

Country/ies where study was carried out	USA

Study type	Retrospective single-gate cross-sectional DTA study
Study dates	1997 - 2004
Inclusion criteria	Neonates ≥ 34 weeks estimated gestational age, discharged from study NICUs and had a lumbar puncture performed.
Exclusion criteria	CSF cultures positive for coagulase-negative staphylococci and other probable contaminants, as well as fungal and viral pathogens, were excluded from analyses. Also, excluded patients in whom the culture was reported from a ventricular tap or shunt.
Patient characteristics	N=9111 n=95 bacterial meningitis (excluding contaminants) n=9016 not bacterial meningitis Estimated gestational age in weeks (mean [range]): 38 (34-44) Male (%) in all cohort: 5139 (56.4%) Majority of the LPs, 6988 (76.6%) of 9111, were performed in the first 3 days of life. Positive for bacterial meningitis: 1% (Population: BM U) Causative organisms: • Gram-positive organisms 62 (65.3%): n=6 Enterococcus spp., n=37 group B streptococcus, n=1 L. monocytogenes, n=4 S. aureus, n=2 S. pneumoniae, n=12 Gram-positive coccuss (not further specified). • Gram-negative organisms 31 (32.6%): n=3 Acinetobacter spp., n=1 Citrobacter spp., n=12 E. coli, n=4 Enterobacter spp., n=2 Haemophilus influenzae, n=1 Proteus spp., n=3 Pseudomonas spp., n=1 Salmonella spp., n=2 Serratia spp., n=2 Neisseria spp., n=2 Gram-negative rod (not further specified).
Index test(s)	CSF white cell count Thresholds >0 cells/mm3, >8 cells/ mm3, >21 cells/ mm3, and >100 cells/ mm3 (converted to cells/μL for consistency with other studies). CSF glucose concentration Thresholds <20 mg/dL and <60 mg/dL (converted to mmol/L for consistency with other studies). CSF protein concentration Thresholds >40 mg/dL, >90 mg/dL, and >120 mg/dL.
Reference standard(s)	CSF bacterial culture

Sources of funding	Not industry funded
Results	CSF white cell count, threshold >0 cellsmm3 (n=4624): TP 56; FP 4060; FN 2; TN 506 CSF white cell count, threshold >8 cells/mm3 (n=4624): TP 48; FP 1767; FN 10; TN 2799 CSF white cell count, threshold >21 cells/mm3 (n=4624): TP 46; FP 876; FN 12; TN 3690 CSF white cell count, threshold >100 cells/mm3 (n=4624): TP 38; FP 285; FN 20; TN 4281 CSF glucose concentration, threshold <20 mg/dL (n=4444): TP 24; FP 25; FN 31; TN 4364 CSF glucose concentration, threshold <60 mg/dL (n=4444): TP 49; FP 3529; FN 6; TN 860 CSF protein concentration, threshold >40 mg/dL (n=4451): TP 55; FP 4313; FN 0; TN 83 CSF protein concentration, threshold >90 mg/dL (n=4451): TP 46; FP 2697; FN 9; TN 1699 CSF protein concentration, threshold >120 mg/dL (n=4451): TP 42; FP 1624; FN 13; TN 2772 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: CSF white cell count – cells/μL. Equivalent to cells/mm3; CSF glucose concentration – mmol/L. Calculated by dividing mg/dL by 18.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; L. monocytogenes: Listeria monocytogenes; N/n: number; NICU: neonatal intensive care unit; spp.: species; S. aureus: Staphylococcus aureus; S. pneumoniae: Streptococcus pneumoniae; 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	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(No information about whether reference standards were interpreted without knowledge of*

Section	Question	Answer
bias		*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?	High *(In analyses included: 4624 (50.8%) for CSF white cell count, 4444 (48.78%) for CSF glucose concentration and 4451 (48.85%) for CSF protein concentration. No explanation given for missing data)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Giulieri, 2015

Bibliographic Reference Giulieri, S; Chapuis-Taillard, C; Jaton, K; Cometta, A; Chuard, C; Hugli, O; Du Pasquier, R; Bille, J; Meylan, P; Manuel, O; Marchetti, O.; CSF lactate for accurate diagnosis of community-acquired bacterial meningitis; European Journal of Clinical Microbiology and Infectious Diseases; 2015; vol. 34; 2049-2055

Study details

Country/ies where study was carried out	Switzerland
Study type	Prospective single-gate cross-sectional DTA study
Study dates	November 2005-October 2008
Inclusion criteria	People ≥16 years old with microbiologically documented acute meningitis, a clinical presentation that includes fever, headache, neck stiffness or impaired level of consciousness and CSF pleocytosis (defined as >4 white blood cells/mm³)
Exclusion criteria	Patients <16 years old, no lumbar puncture performed, patients with nosocomial meningitis according to CDC criteria, patients with neurosurgical shunt
Patient characteristics	N=45 n=18 bacterial meningitis n=27 viral meningitis Age (median[range]): 53 (17–86) years in bacterial meningitis group only

	Sex (n): 9 male:9 female in bacterial meningitis group only Age (median[range]): 35 (17–77) years in viral meningitis group only Sex (n): 15 male:12 female in viral meningitis group only Positive for bacterial meningitis: 40% (Population: BM VM) Positive CSF cultures in population with bacterial meningitis: 55% Causative organisms: n=11 S. pneumoniae, n=5 N. meningitidis, n=1 H. influenzae, n=1 group B Streptococcus
Index test(s)	CSF white cell count Threshold >388 cells/mm3 (converted to cells/μL for consistency with other studies). CSF neutrophil count Threshold >260 cells/mm3 (converted to cells/μL for consistency with other studies). CSF glucose concentration (reported as CSF/blood glucose ratio). Threshold <0.35. CSF protein concentration Threshold >1934 mg/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture and/or CSF Gram stain and/or CSF PCR and/or blood bacterial culture
Sources of funding	Not industry funded
Results	CSF white cell count, threshold >388 cells/mm3 (n=45): TP 15; FP 2; FN 3; TN 25; AUC (95% CI): 0.89 (0.76-1.00) CSF neutrophil count, threshold >260 cells/mm3 (n=45): TP 17; FP 0; FN 1; TN 27; AUC (95% CI): 0.97 (0.91-1.00) CSF/blood glucose ratio, threshold <0.35 (n=45): TP 17; FP 0; FN 1; TN 27; AUC (95% CI): 0.96 (0.88-1.00) CSF protein concentration, threshold >1934 mg/l (n=45): TP 16; FP 0; FN 2; TN 27; AUC (95% CI): 0.95 (0.88-1.00) 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: CSF white cell and neutrophil count – cells/μL. Equivalent to cells/mm3. CSF protein concentration – mg/dL. Calculated by diving mg/L by 10.

AUC: area under the curve; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(Unclear whether consecutive participants enrolled; only people diagnosed with microbiologically documented bacterial or viral meningitis included n=16 excluded due to missing data; however, analysis run with and without these people showed little difference. Also, included people based on CSF pleocytosis, which may inflate diagnostic accuracy)*
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?	High *(Thresholds derived from the index test ROC curves)*
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 defined as positive CSF culture, blood culture, or positive CSF PCR; Only 10/18 of those with bacterial meningitis 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; people with bacterial and viral meningitis received different reference standards)*

CSF: cerebrospinal fluid; N/n: number; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve: receiver operating characteristics curve

Jorgensen, 1978

Bibliographic Jorgensen, J. H; Lee, J. C.; Rapid diagnosis of gram-negative bacterial meningitis by the Limulus endotoxin assay; Journal

Reference of Clinical Microbiology; 1978; vol. 7; 12-Jul

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	People with suspected meningitis and with a lumbar puncture performed.
Exclusion criteria	Not reported
Patient characteristics	N=305 n=74 culture proven acute bacterial meningitis n=230 aseptic or non-meningitis n=1 tuberculous meningitis (Mycobacterium tuberculosis) Ages of participants not reported. Positive for bacterial meningitis: 24% (Population: BM UM NM) Causative organisms: n=38 H. influenzae, n=6 N. meningitidis, n=6 E. coli, n=2 K. pneumoniae, n=1 A. faecalis, n=4 P. aeruginosa, n=1 F. meningosepticum, n=1 A. calcoaceticus var. anitratus, n=1 A. calcoaceticus var. lwoffi, n=1 C. diversus, n=4 group B Streptococcus, n=6 S. pneumoniae, n=3 S. aureus
Index test(s)	Microscopy Gram staining • for all bacteria • for N. meningitidis • for S. pneumoniae • for H. influenzae • for group B Streptococcus • for Gram-negative bacilli (E. coli, P. aeruginosa, K. pneumoniae)
Reference standard(s)	CSF bacterial culture

Sources of funding	No sources of funding reported
Results	Microscopy: Gram staining for all bacteria (n=305): TP 50; FP 0; FN 24; TN 231 Microscopy: Gram staining for N. meningitidis (n=305): TP 5; FP 0; FN 1; TN 299 Microscopy: Gram staining for S. pneumoniae (n=305): TP 3; FP 0; FN 3; TN 300 Microscopy: Gram staining for H. influenzae (n=305): TP 30; FP 0; FN 8; TN 267 Microscopy: Gram staining for group B Streptococcus (n=305): TP 2; FP 0; FN 2; TN 301 Microscopy: Gram staining for Gram-negative bacilli* (n=305): TP 5; FP 0; FN 7; TN 293 N.B. 2x2 tables and relevant outcomes calculated in RevMan. *Included E. coli. pneumoniae and P. aeruginosa

A. calcoaceticus: Acinetobacter calcoaceticus; A. faecalis: Alcaligenes faecalis; CSF: cerebrospinal fluid; C. diversus: Citrobacter diversus; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; F. meningosepticum: Flavobacterium meningosepticum; H. influenzae: Haemophilus influenzae; K. pneumoniae: Klebsiella pneumoniae; N/n: number; N. meningitidis: Neisseria meningitidis; P. aeruginosa: Pseudomonas aeruginosa; PCR: polymerase chain reaction; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive; var. variety

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. No information provided on exclusion criteria.)*
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	Is there concern that the target condition as defined	Low

Section	Question	Answer
standard: applicability	by the reference standard does not match the review question?	
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

QUADAS: quality assessment of diagnostic accuracy studies

Kennedy, 2007

Bibliographic Reference Kennedy, W. A; Chang, S. J; Purdy, K; Le, T; Kilgore, P. E; Kim, J. S; Anh, D. D; Huong, P. L. T; Dong, B. Q; Tan, D. M; Clemens, J. D; Ward, J. I.; Incidence of bacterial meningitis in Asia using enhanced CSF testing: Polymerase chain reaction, latex agglutination and culture; Epidemiology and Infection; 2007; vol. 135; 1217-1226

Study details

Country/ies where study was carried out	South Korea, Vietnam and People's Republic of China* *Samples came from South Korea, Vietnam, and People's Republic of China. The latter 2 countries do not meet inclusion criteria but the study was not considered indirect as testing was performed in South Korea
Study type	Prospective single-gate cross-sectional DTA study
Study dates	September 1999-December 2002
Inclusion criteria	Children <5 years old with suspected meningitis (defined as signs and symptoms of meningitis [fever, mental status changes, headache, bulging anterior fontanelle, forceful vomiting or seizure] and an abnormal CSF)
Exclusion criteria	Not reported.
Patient characteristics	N=577 tested for S. pneumoniae • 1% with bacterial meningitis caused by S. pneumoniae N=1063 tested for H. influenzae • 2% with bacterial meningitis caused by H. influenzae meningitis Ages not reported beyond inclusion criteria. Population: BM U

	Causative organisms: n=23 H. influenzae, n=8 S. pneumoniae <50% of participants received previous antibiotics
Index test(s)	Molecular diagnosis Specific PCR: • for S. pneumoniae • for H. influenzae
Reference standard(s)	CSF bacterial culture
Sources of funding	Not reported.
Results	Molecular diagnosis: PCR for H. influenzae (n=1063): TP 23; FP 17*; FN: 0; TN 1023 Molecular diagnosis: PCR for S. pneumoniae (n=577): TP 8; FP 4*; FN: 0; TN: 565 *Nine of 21 (43%) culture-negative PCR-positive cases had prior antibiotic use based on parental interview. N.B. 2x2 tables and relevant outcomes calculated in RevMan.

AUC: area under the curve; CDC: Centers for Disease Control and Prevention; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenza; N/n: number; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(Enhanced active case finding employed so non-consecutive sample enrolled; Only CSF samples with abnormal cytological or biochemical parameters, or a positive bacterial culture and a sample of CSF with normal indices were included, which may inflate diagnostic accuracy. No information given as to how many children excluded or for what reasons)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(Populations includes children from South Korea (in protocol), and Vietnam and People's Republic of China (not in protocol). However, study testing performed in USA)*
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; CSF*

Section	Question	Answer
		samples for 'PCR were 'periodically' sent to USA for PCR testing. No information given on how long these samples were kept frozen)
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
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(Reference standard of study is a positive test in any of the three index tests; however, enough data presented to calculate 2x2 tables with bacterial CSF culture as reference standard. However, all samples received all reference standard tests which minimises impact on bias)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(No information on when culture was performed; Not all children received the same index tests. Study states that, whenever possible, abnormal CSF was tested for both H. influenzae and S. pneumoniae PCR but if there was insufficient CSF volume, prioritization of abnormal CSF testing occurred: H. influenzae PCR then S. pneumoniae PCR. Out of 4019 samples, only n=1063 tested for H. influenzae PCR and n=577 tested for S. pneumoniae PCR)*

CSF: cerebrospinal fluid; N/n: number; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Khurana, 1987

Bibliographic Reference Khurana, C. M; Deddish, P. A.; Comparison of results of limulus amebocyte lysate, counterimmunoelectrophoresis, and gram stain on spinal fluids of patients with suspected meningitis; Current Therapeutic–Research - Clinical and Experimental; 1987; vol. 41; 604-608

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	Children either admitted to or born at study centre with suspected meningitis and lumbar puncture performed.

Exclusion criteria	Not reported
Patient characteristics	N=138 n=13 bacterial meningitis n=2 aseptic meningitis n=123 non meningitis Ages of participants not reported, although study conducted in paediatric setting. Positive for bacterial meningitis: 9% (Population: BM AM NM) Causative organisms: n=6 H. influenzae, n=2 N. meningitidis, n=3 S. pneumoniae, n=1 group B Streptococcus, n=1 group D Streptococcus
Index test(s)	Microscopy Gram staining
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	Microscopy: Gram staining in all bacteria (n=138): TP 9; FP 2; FN 4; TN 123 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenzae; Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled. No information provided on exclusion criteria.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of	Could the conduct or interpretation of the index test	Low

Section	Question	Answer
bias	have introduced bias?	*(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards.)*

QUADAS: quality assessment of diagnostic accuracy studies

Kim, 2012

Bibliographic Reference Kim, D. W; Kilgore, P. E; Kim, E. J; Kim, S. A; Anh, D. D; Dong, B. Q; Kim, J. S; Seki, M.; The enhanced pneumococcal LAMP assay: a clinical tool for the diagnosis of meningitis due to Streptococcus pneumoniae; PLos ONE [Electronic resource]PLoS ONE; 2012; vol. 7; e42954

Study details

Country/ies where study was carried out	South Korea, People's Republic of China and Vietnam* *Samples came from South Korea, Vietnam, and People's Republic of China. The latter 2 countries do not meet inclusion criteria but the study was not considered indirect as testing was performed in South Korea
Study type	Prospective single-gate cross-sectional DTA study
Study dates	1998-2002
Inclusion criteria	Children <5 years old with suspected meningitis
Exclusion criteria	Not reported

Patient characteristics	N=106 Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 10%* (Population: BM U) *17% were considered to have bacterial meningitis but this was only culture confirmed in 10%. Causative organisms: n=11 S. pneumoniae
Index test(s)	Microscopy Gram staining for S. pneumoniae Molecular diagnosis Specific LAMP for S. pneumoniae Molecular diagnosis Specific PCR for S. pneumoniae
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Microscopy: Gram staining for S. pneumoniae (n=106): TP 10; FP 6; FN 1; TN 89 Molecular diagnosis: LAMP for S. pneumoniae (n=106): TP 11; FP 22; FN 0; TN 73 Molecular diagnosis: PCR for S. pneumoniae (n=106): TP 11; FP 7; FN 0; TN 88 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; LAMP: loop-mediated isothermal amplification; N/n: number; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; 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 *(Random CSF samples taken from previous prospective study; exclusion criteria and participant characteristics not reported)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(Populations includes children from South Korea (in protocol), and Vietnam and People's Republic of China (not in protocol). However, study testing performed in South Korea)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(Reference standard of study is LAMP; however, enough data presented to calculate 2x2 tables with bacterial culture as reference standard. All samples received all reference standard tests which minimises impact on bias)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

CSF: cerebrospinal fluid; LAMP: loop-mediated isothermal amplification; QUADAS: quality assessment of diagnostic accuracy studies

Kleine, 2003

Bibliographic Reference Kleine, T.O; Zwerenz, P; Zofel, P; Shiratori, K.; New and old diagnostic markers of meningitis in cerebrospinal fluid (CSF); Brain Research Bulletin; 2003; vol. 61; 287-297

Study details

Country/ies where study was carried out	Germany
Study type	Retrospective single-gate cross-sectional DTA study Although full study used a two-gate design, the data of interest for this review has been classified as a single-gate study because there was a single set of criteria for this group (not selected based on final diagnosis)

Study dates	Not reported
Inclusion criteria	People with paired CSF and serum samples, with different forms of meningitis. Study population also included people with multiple sclerosis, and various non-inflammatory diseases. These have not been included in this analysis as not of interest for current review.
Exclusion criteria	Not reported
Patient characteristics	N=111 N.B. Study population was N=196, including n=47 multiple sclerosis and n=22 non-neurological controls. However, these participants are outside of protocol so not extracted. Meningitis: -n= 40 acute bacterial meningitis (BM) with no antibiotics administered before sample collection -n= 25 bacterial meningitis treated with antibiotics for 1–4 days (TM) -n= 46 aseptic or viral meningitis (AM) Age in years (mean [range]) 49.5 (38.8-64.2) in BM group Male (%): 23 (57.5%) in BM group Age in years (mean [range]) 47.2 (26.7–64.8) in TM group Male (%): 18 (72%) in TM group Positive for bacterial meningitis: 47% (Population: BM VM AM) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: Not reported.
Index test(s)	CSF white cell count Threshold ≥450 M/L (could not convert for consistency with other studies due to uncertainty regarding unit of measurement). CSF protein concentration Threshold ≥1.3g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture and/or direct microscopy and/or blood bacterial culture

Sources of funding	Industry funded
Results	CSF white cell count, threshold ≥450 M/l (n=86): TP 29; FP 6; FN 11; TN 40 CSF protein concentration, threshold ≥1.3g/L (n=86): TP 33; FP 6; FN 7; TN 40 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: CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled; Only adults diagnosed with bacterial meningitis or viral/aseptic 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?	High *(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. Thresholds were calculated from the ROC curves.)*
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 *(Bacterial meningitis was identified by bacteria detected in stained CSF pellets and/or by positive bacterial CSF and blood cultures. Proportions are not reported.)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(People with bacterial meningitis treated with antibiotics (25/111 (22.5%)) were not included in the analysis. This was not pre-specified in the methodology.)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve: receiver operating characteristics curve

Kotilainen, 1998

Bibliographic Reference Kotilainen, P; Jalava, J; Meurman, O; Lehtonen, O. P; Rintala, E; Seppala, O. P; Eerola, E; Nikkari, S.; Diagnosis of meningococcal meningitis by broad-range bacterial PCR with cerebrospinal fluid; Journal of clinical microbiology; 1998; vol. 36; 2205-2209

Study details

Country/ies where study was carried out	Finland
Study type	Prospective single-gate cross-sectional DTA study
Study dates	1995
Inclusion criteria	People with a clinical diagnosis or suspicion of CNS infection, clinical microbiological testing and broad-range bacterial PCR assay testing.
Exclusion criteria	Not reported
Patient characteristics	N=56 CSF samples from 46 patients Ages of participants not reported Positive for bacterial meningitis: 7%* samples (Population: BM UM NM) *11% were considered to have bacterial meningitis but this was only culture confirmed in 7%. Causative organisms: n=5 N. meningitidis, n=1 L. monocytogenes
Index test(s)	Microscopy Gram staining (no details reported) Molecular diagnosis Broad-range (16S and/or 23S) bacterial PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	Not reported

Results	Microscopy: Gram staining (n=56): TP 2; FP 0; FN 2; TN 52 Molecular diagnosis: PCR for N. meningitidis (n=56): TP 4; FP 1*; FN 0; TN 51 N.B. 2x2 tables and relevant outcomes calculated in RevMan. * Paper reported this false positive result was likely to be a true positive as final diagnosis was recorded as meningococcal meningitis.

CNS: central nervous system; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; 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 *(No information provided on inclusion of exclusion criteria)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Population was people with clinical diagnosis or suspicion of central nervous system infection, not necessarily bacterial meningitis; only 7/46 (15%) presented with strong suspicion of bacterial meningitis. Remainder had moderate (20%), minor (54%) or no suspicion (11%))*
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. Threshold not applicable for Gram stain or PCR)*
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)*

QUADAS: quality assessment of diagnostic accuracy studies

La Scolea Jr, 1984

Bibliographic Reference	La Scolea Jr, L. J; Dryja, D.; Quantitation of bacteria in cerebrospinal fluid and blood of children with meningitis and its diagnostic significance; Journal of clinical microbiology; 1984; vol. 19; 187-190

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	CSF samples collected over a 16-month period. Exact dates are not reported.
Inclusion criteria	Paediatric inpatient and outpatient patients. No further details on inclusion criteria given.
Exclusion criteria	Not reported
Patient characteristics	N=2031 n=63 bacterial meningitis n=1968 without bacterial meningitis Ages of participants not reported, although study conducted in paediatric setting. Positive for bacterial meningitis: 3% (Population: BM U) Causative organisms: n=36 H. influenzae type b, n=9 group B Streptococcus, n=9 S. pneumoniae, n=7 N. meningitidis, n=2 E. coli
Index test(s)	Microscopy Gram and methylene blue staining: • for all bacteria • for N. meningitidis • for S. pneumoniae • for H. influenza • for group B streptococcus
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported

Results	Microscopy: Gram and methylene blue staining for all bacteria (n=2031): TP 48; FP 0; FN 15; TN 1968 Microscopy: Gram and methylene blue staining for N. meningitidis (n=2031): TP 3; FP 0; FN 4; TN 2024 Microscopy: Gram and methylene blue staining for S. pneumoniae (n=2031): TP 7; FP 0; FN 2; TN 2022 Microscopy: Gram and methylene blue staining for H. influenza type b (n=2031): TP 30; FP 0; FN 6; TN 1995 Microscopy: Gram and methylene blue staining for group B streptococcus (n=2031): TP 8; FP 0; FN 1; TN 2022 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae; Streptococcus pneumoniae; 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 *(No information provided on inclusion or exclusion criteria.)*
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 and results were reviewed by two separate technologists 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 *(Combination of two stains of direct microscopy: Gram and methylene blue)*
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

QUADAS: quality assessment of diagnostic accuracy studies

Leber, 2016

Bibliographic Reference	Leber, A. L; Everhart, K; Balada-Llasat, J. M; Cullison, J; Daly, J; Holt, S; Lephart, P; Salimnia, H; Schreckenberger, P. C; DesJarlais, S; Reed, S. L; Chapin, K. C; LeBlanc, L; Johnson, J. K; Soliven, N. L; Carroll, K. C; Miller, J. A; Dien Bard, J; Mestas, J; Bankowski, M; Enomoto, T; Hemmert, A. C; Bourzac, K. M.; Multicenter Evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for Detection of Bacteria, Viruses, and Yeast in Cerebrospinal Fluid Specimens; Journal of Clinical Microbiology; 2016; vol. 54; 2251-61

Study details

Country/ies where study was carried out	USA
Study type	Prospective single-gate cross-sectional DTA study
Study dates	February-September 2014
Inclusion criteria	CSF specimens collected by lumbar puncture and submitted to study laboratory during study period.
Exclusion criteria	Repeat samples from the same subject.
Patient characteristics	N=1560 n=8 bacterial meningitis n=95 viral meningitis n=1 fungal meningitis n=1,456 non-meningitis Age in years (n): 921 adults ≥18 years, 639 children <18 years Sex (n): 797 male:763 females Positive for bacterial meningitis: 0.5% (Population: BM VM FM NM) Causative organisms: n=4 S. pneumoniae, n=2 E. coli, n=1 H. influenzae, n=1 group B Streptococcus
Index test(s)	<u>Molecular diagnosis</u> Multiplex PCR (FA-ME panel): • for all included bacteria • for S. pneumoniae • for H. influenzae

	• for Gram-negative bacilli (E. coli)
Reference standard(s)	CSF bacterial culture
Sources of funding	Industry funded (designed and funded by BioFire Diagnostics).
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=1560): TP: 7; FP: 15; FN: 1; TN 1537 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=1560): TP: 4; FP: 12*; FN: 0; TN 1544 Molecular diagnosis: Multiplex PCR for H. influenzae (n=1560): TP: 1; FP: 1**; FN: 0; TN 1559 Molecular diagnosis: Multiplex PCR for Gram-negative bacilli (E. coli) (n=1560): TP: 2; FP: 1; FN: 0; TN 1557 N.B. 2x2 tables and relevant outcomes calculated in RevMan. *Paper reported that 5/12 results were likely to be true positive according to discrepancy testing (repeating FilmArray, comparator assay, or additional molecular testing when specimen volume was available) **Paper reported that this result was likely to be a true positive according to discrepancy testing (repeating FilmArray, comparator assay, or additional molecular testing when specimen volume was available)

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae: Haemophilus influenzae; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled; Lack of exclusion criteria reported.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Poor reporting of inclusion and exclusion criteria; Little information reported on participant characteristics)*
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	Could the reference standard, its conduct, or its	Low

Section	Question	Answer
standard: risk of bias	interpretation have introduced bias?	*(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 *(Same CSF sample used for both reference standard and index test; Specimen had to be able to be enrolled within 7 days of collection for testing (or frozen for later testing))*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Lee, 2015

Bibliographic Reference Lee, D; Kim, E. J; Kilgore, P. E; Kim, S. A; Takahashi, H; Ohnishi, M; Anh, D. D; Dong, B. Q; Kim, J. S; Tomono, J; Miyamoto, S; Notomi, T; Kim, D. W; Seki, M.; Clinical evaluation of a loop-mediated isothermal amplification (LAMP) assay for rapid detection of Neisseria meningitidis in cerebrospinal fluid; PloS ONE [Electronic Resource]PloS ONE; 2015; vol. 10; e0122922

Study details

Country/ies where study was carried out	Vietnam, People's Republic of China, and South Korea* *Samples came from South Korea, Vietnam, and People's Republic of China. The latter 2 countries do not meet inclusion criteria but the study was not considered indirect as testing was performed in South Korea
Study type	Prospective single-gate cross-sectional DTA study
Study dates	1999-2002
Inclusion criteria	Children <5 years old with suspected meningitis
Exclusion criteria	Not reported
Patient characteristics	N=1574 n=3 culture-confirmed meningitis caused by N. meningitidis n=1571 without culture-confirmed meningitis caused by N. meningitidis

	Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 0.2% (Population: MM U) Causative organisms: n=3 N. meningitidis
Index test(s)	Molecular diagnosis • Specific LAMP for N. meningitidis • Specific PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: LAMP for N. meningitidis (n=1574): TP 3; FP 28; FN 0; TN 1543 Molecular diagnosis: PCR for N. meningitidis (n=1574): TP 3; FP 22; FN 0; TN 1549 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; LAMP: loop-mediated isothermic amplification; N/n: number; N. meningitidis: Neisseria meningitidis; 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 *(Random CSF samples taken from previous prospective study; exclusion criteria and patient characteristics not reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(Populations includes children from South Korea (in protocol), and Vietnam and People's Republic of China (not in protocol). However, study testing performed in South Korea)*
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	Low

Section	Question	Answer
	question?	
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 *(Reference standard of study is LAMP; however, enough data presented to calculate 2x2 tables with bacterial culture as reference standard. All samples received all reference standard tests which minimises impact on bias)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

CSF: cerebrospinal fluid; LAMP: loop-mediated isothermic amplification; QUADAS: quality assessment of diagnostic accuracy studies

Leitner, 2016

Bibliographic Reference	Leitner, E; Hoenigl, M; Wagner, B; Krause, R; Feierl, G; Grisold, A. J.; 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; 2016; vol. 4; doc06

Study details

Country/ies where study was carried out	Austria
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	November 2013 - July 2014
Inclusion criteria	People with clinically suspected community acquired or drainage associated meningitis
Exclusion criteria	Not reported
Patient characteristics	N=20 n=9 bacterial meningitis n=11 non-bacterial meningitis Ages of participants not reported.

	Positive for bacterial meningitis: 40%* (Population: BM U) *45% were considered to have bacterial meningitis but this was only culture confirmed in 40%. Causative organisms: n=2 L. monocytogenes, n=2 N. meningitidis, n=2 S. epidermidis, n=1 S. haemolyticus, n=1 S. hominis, n=1 S. pneumoniae
Index test(s)	Molecular diagnosis Multiplex PCR (FA-M/E panel) for all included bacteria
Reference standard(s)	CSF bacterial culture
Sources of funding	Industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=20): TP 4; FP 1; FN 4; TN 11 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae; Haemophilus influenzae; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. epidermitis: Staphylococcus epidermitis; S. haemolyticus; Staphylococcus haemolyticus; S. hominis: Staphylococcus hominis; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled. No information provided on exclusion criteria.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Indirect population. People with drainage associated meningitis were enrolled to the study. Exact number is unknown)*
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:	Are there concerns that the index test, its conduct, or	Low

Section	Question	Answer
applicability	interpretation differ from the review question?	
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.)*

QUADAS: quality assessment of diagnostic accuracy studies

Leli, 2019

Bibliographic Reference Leli, C; Gotta, F; Vay, D; Calcagno, L; Callegari, T; Cassinari, M; Cattana, E; Ciriello, M. M; Copponi, V; Sacchi, M. C; Zambon, D; Guaschino, R; Rocchetti, A.; Diagnostic accuracy of a commercial multiplex pcr for the diagnosis of meningitis and encephalitis in an italian general hospital; Infezioni in Medicina; 2019; vol. 27; 141-148

Study details

Country/ies where study was carried out	Italy
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	February 2016 - December 2018
Inclusion criteria	Patients with CSF samples collected by lumbar puncture, and with results for bacterial culture and multiplex PCR.
Exclusion criteria	Excluded CSF samples drawn from shunts and lumbar puncture samples drawn at the same time without CSF indices or complete blood count, blood glucose and C-reactive protein.
Patient characteristics	N=109 n=14 bacterial meningitis n=9 viral meningitis n=86 non-meningitis

	Age in years (median [IQR]): 60 (41.5-71) Positive for bacterial meningitis: 12%* (Population: BM VM NM) *13% were considered to have bacterial meningitis but this was only culture confirmed in 12% Causative organisms: n=3 S. pneumoniae, n=1 group B Streptococcus, n=2 S. aureus, n=1 L. monocytogenes, n=2 N. meningitidis, n=1 P. aeruginosa, n=1 S. schleiferi, n=1 M. tuberculosis complex, n=1 T. otitidis, n=1 Kingella spp.
Index test(s)	Molecular diagnosis Multiplex PCR (FA-ME panel): • for all included bacteria • for N. meningitidis for S. pneumoniae • for group B streptococcus • for L. monocytogenes
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=109): TP 6; FP 1; FN 7; TN 95 Molecular diagnosis: Multiplex PCR for N. meningitidis (n=109): TP 1; FP 1; FN 0; TN 107 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=109): TP 3; FP 0; FN 0; TN 106 Molecular diagnosis: Multiplex PCR for group B streptococcus (n=109): TP 1; FP 0; FN 0; TN 108 Molecular diagnosis: Multiplex PCR for L. monocytogenes (n=109): TP 1; FP 0; FN 0; TN 108 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae; Haemophilus influenzae; IQR: interquartile range; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; spp. species; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

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

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

QUADAS: quality assessment of diagnostic accuracy studies

Lindquist, 1988

Bibliographic Reference Lindquist, L; Linne, T; Hansson, L. O; Kalin, M; Axelsson, G.; Value of cerebrospinal fluid analysis in the differential diagnosis of meningitis: A study in 710 patients with suspected central nervous system infection; European Journal of Clinical Microbiology and Infectious Diseases; 1988; vol. 7; 374-380

Study details

Country/ies where study was carried out	Sweden
Study type	Prospective single-gate cross-sectional DTA study
Study dates	August 1982 - December 1985
Inclusion criteria	People ≥2 months old receiving lumbar puncture due to suspected CNS infection.

Exclusion criteria	Excluded patients below two months of age and from June 1984 onward patients infected with human immunodeficiency virus. Patients with meningococcal septicaemia without laboratory evidence of meningitis were excluded from bacterial meningitis group.
Patient characteristics	N=710 n=79 acute or presumed bacterial meningitis n = 218 acute or presumed viral meningoencephalitis n = 6 acute unclassified meningitis n = 37 other infections of the central nervous system n = 76 non-infectious neurological diseases n = 294 control patients (patients with negative bacterial culture and did not meet the requirements for other groups) Ages not reported beyond inclusion criteria. Positive for bacterial meningitis: 11% (Population: BM U) Positive CSF cultures in population with bacterial meningitis: 86% Causative organisms: n=22 H. influenzae, n=19 N. meningitidis, n=14 S. pneumoniae, n=3 L. monocytogenes, n = 3 S. aureus, n = 3 streptococci of groups A and B, n=1 P. mirabilis, n=1 H. parainfluenzae, n=1 Brucella spp., n=1 M. tuberculosis, n=11 without proven bacterial aetiology
Index test(s)	<u>CSF white cell count</u> Thresholds >500x106 cells/L, >1000x106 cells/L, and >1500x106 cells/L (converted to cells/µL for consistency with other studies). <u>CSF glucose concentration</u> Threshold <2.2 mmol/L. <u>CSF glucose concentration</u> (reported as CSF/blood glucose ratio). Thresholds <0.4 and <0.5. <u>CSF protein concentration</u> Thresholds >0.5 g/L, >1.0 g/L, and >1.5 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture and/or CSF latex agglutination and/or CSF counter immune-electrophoresis

Sources of funding	Not industry funded
Results	CSF white cell count, threshold >500 cells × 106 cells/L (n=711*): TP 56; FP 30; FN 23; TN 602 CSF white cell count, threshold >1000 cells × 106 cells/L (n=711*): TP 48; FP 14; FN 31; TN 618 CSF white cell count, threshold >1500 cells × 106 cells/L (n=711*): TP 40; FP 5; FN 39; TN 627 CSF glucose concentration, threshold <2.2 mmol/L (n=671): TP 37; FP 14; FN 33; TN 587 CSF/blood glucose ratio, threshold <0.5 (n=663): TP 52; FP 94; FN 12; TN 505 CSF/blood glucose ratio, threshold <0.4 (n=663): TP 45; FP 24; FN 19; TN 575 CSF protein concentration, threshold >0.5 g/L (n=591): TP 57; FP 208; FN 8; TN 318 CSF protein concentration, threshold >1.0 g/L (n=591): TP 45; FP 54; FN 20; TN 472 CSF protein concentration, threshold >1.5 g/L (n=591): TP 36; FP 13; FN 29; TN 513 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: CSF white cell count – cells/μL. Calculated by diving by 106; CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100. *711 included in CSF white cell count analysis. Unexplained 1 additional person.

CNS: central nervous system; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; H. (para)influenzae; Haemophilus (para)influenzae; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; L. monocytogenes: Listeria monocytogenes; M. tuberculosis: Mycobacterium tuberculosis; N/n: number; N. meningitidis: Neisseria meningitidis; P. mirabilis: Proteus mirabilis; spp.: species; S. aureus: Staphylococcus aureus; S. pneumoniae: Streptococcus pneumoniae; 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

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	High *(Only 86% of population with bacterial meningitis diagnosed via positive CSF culture.)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(For protein concentration. No information about interval between index tests and reference standards. 120/710 (16.9%) excluded from CSF protein concentration analysis without explanation)* Unclear *(For glucose concentration and CSF/blood glucose ratio. No information about interval between index tests and reference standards. 39/710 (5.5%) for CSF glucose concentration and 47/710 (6.6%) for CSF/blood glucose ratio analyses without explanation, but small percentage unlikely to bias results)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Meyer, 2014

Bibliographic Reference Meyer, T; Franke, G; Polywka, S. K; Lutgehetmann, M; Gbadamosi, J; Magnus, T; Aepfelbacher, M.; Improved detection of bacterial central nervous system infections by use of a broad-range PCR assay; Journal of Clinical Microbiology; 2014; vol. 52; 1751-3

Study details

Country/ies where study was carried out	Germany
Study type	Prospective two-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	CSF samples from people with clinical symptoms of CNS infection who were and were not suspected to have a bacterial infection (based on white cell counts > or <500µL, respectively).
Exclusion criteria	Not reported

Patient characteristics	N=40 n=20 bacterial CNS infection (defined as white blood cell count >500/µl) n=20 non-bacterial CNS infection (defined as white blood cell count <500/µl) Ages of participants not reported Positive for bacterial meningitis: 15% (Population: BM BI UI) Causative organisms: Not reported.
Index test(s)	Microscopy Gram staining Molecular diagnosis Broad-range (16S) bacterial PCR
Reference standard(s)	CSF bacterial culture
Sources of funding	Not reported
Results	Microscopy: Gram staining (n=40): TP 2; FP 1; FN 4; TN 33 Molecular diagnosis: Broad-range (16S) PCR (n=40): TP 4; FP 9*; FN 2**; TN 25 N.B. 2x2 tables and relevant outcomes calculated in RevMan. * Paper reported these results were likely to be true positive results because (i) these samples had white cell counts of >500 cells/l, mainly consisting of neutrophils, (ii) these people presented with clinical features characteristic of CNS infection, and (iii) the PCR results represented typical CNS pathogens. 7/9 of these culture-negative, PCR-positive samples received antibiotics prior to lumbar puncture **Not common bacterial pathogens (S. epidermidis and K. pneumoniae) and found in people with ventriculoperitoneal shunts

CNS: central nervous system; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; K. pneumoniae: Klebsiella pneumoniae; N/n: number; PCR: polymerase chain reaction; S. epidermidis: Staphylococcus epidermidis; 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 *(Two-gate study design)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Exclusion criteria and participant characteristics not reported; at least 2 people with ventriculoperitoneal shunts indicating that they had previous neurological procedures which are excluded)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

QUADAS: quality assessment of diagnostic accuracy studies

Morrissey, 2017

Bibliographic Reference Morrissey, S. M; Nielsen, M; Ryan, L; Al Dhanhani, H; Meehan, M; McDermott, S; O'Sullivan, N; 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 & Infectious DiseasesEur J Clin Microbiol Infect Dis; 2017; vol. 36; 1317-1324

Study details

Country/ies where study was carried out	Ireland
Study type	Retrospective single-gate cross-sectional DTA study

Study dates	March 2010 - December 2014
Inclusion criteria	Infants (aged 7–90 days) with a blood or CSF sample tested by group B Streptococcus PCR
Exclusion criteria	Not reported
Patient characteristics	N=827 Age in days (median [IQR]): 35 (20.75-57) Sex (n): 478 male, 340 female, 9 unknown Positive for bacterial meningitis: 0.6% (Population: GBM U) Causative organisms: n=5 group B Streptococcus
Index test(s)	Molecular diagnosis Specific PCR for group B streptococcus
Reference standard(s)	CSF bacterial culture
Sources of funding	No funding received.
Results	Molecular diagnosis: Specific 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. *Of these false positives, n=1 was considered possible, n=4 were considered probable and n=6 were considered definite meningitis caused by group B Streptococcus (according to discrepancy analysis).

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; IQR: interquartile range; N/n: number; 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?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(Reference standard and index test conducted within 24 hours of each other)*

QUADAS: quality assessment of diagnostic accuracy studies

Nabower, 2019

Bibliographic Reference Nabower, A. M; Miller, S; Biewen, B; Lyden, E; Goodrich, N; Miller, A; Gollehon, N; Skar, G; Snowden, J.; Association of the FilmArray Meningitis/Encephalitis Panel With Clinical Management; Hospital Pediatrics; 2019; vol. 9; 763-769

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	June 2015-July 2017
Inclusion criteria	Children 0-18 years old who had a CSF culture or FA-M/E panel obtained within 48 hours of admission, to evaluate potential infectious aetiology
Exclusion criteria	Patients who died during hospitalization because of a non-infectious cause, who never received antibiotics, who had lumbar puncture to evaluate a non-infectious aetiology, who had a repeat LP in known meningitis, or who had a history of central nervous system surgery.

	Lumbar puncture to evaluate a non-infectious cause was determined through review of clinical notes. If no infectious aetiology was listed in the assessment in addition to no antimicrobial agents started, the patient was excluded. Excluded conditions included malignancy, pseudotumor cerebri, intractable epilepsy, maternal syphilis, autoimmune encephalitis, and Guillain Barré syndrome.
Patient characteristics	N=223* n=5 culture-confirmed bacterial meningitis n=218 without culture-confirmed bacterial meningitis *Total study included 571 patients. However, n=348 patients did not receive FA-ME panel (as PCR was only introduced in 2016) and therefore not included in the review. Age in days (n [%]): 67 (30.0) <30 days, 100 (44.8) 30-90, >90 57 (25.6) Sex (n): 113 male, 110 female Positive for bacterial meningitis: 2% (Population: BM U) Causative organisms: Not reported Immunosuppression (n [%]): 4 (1.8) Antibiotics before LP (n ([%]): 66 (29.6)
Index test(s)	Molecular diagnosis Multiplex PCR (FA-M/E panel) for all included bacteria
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded.
Results	Molecular diagnosis of bacterial pathogens: Multiplex PCR for all included bacteria (n=223): TP: 3; FP: 5*; FN: 2 TN: 213 N.B. 2x2 tables and relevant outcomes calculated in RevMan. *Clinically were thought to be true-positive results on the FA-M/E panel given antibiotic pre-treatment and the presence of pleocytosis.

CNS: central nervous system; CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae; Haemophilus influenzae; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive;

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled; children without previous antibiotic use were excluded. children with antibiotic use prior to lumbar puncture were excluded. While this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(n=348 not included in the analysis due to PCR only becoming available during 2016; unlikely to cause bias as it is a resource issue)*

N/n: number; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Negrini, 2000

Bibliographic Reference	Negrini, B; Kelleher, K. J; Wald, E. R.; Cerebrospinal fluid findings in aseptic versus bacterial meningitis; Pediatrics; 2000; vol. 105; 316-319

Study details

Country/ies where study was carried out	USA

Study type	Retrospective single-gate cross-sectional DTA study
Study dates	April-October for the years 1992-1997
Inclusion criteria	All paediatric patients aged ≥30 days hospitalised with a diagnosis of meningitis.
Exclusion criteria	Age <30 days, receiving antibiotics within 5 days of lumbar puncture, concurrent bacterial infection (including a parameningeal focus), neurosurgical procedure before the onset of meningitis, CNS shunt, known immunodeficiency
Patient characteristics	N=158 n=20 bacterial meningitis n=138 aseptic meningitis Age (range): 30 days-18 years (bacterial meningitis median: 11.0 months; aseptic meningitis 2.8 months) Sex: male % (bacterial meningitis: 45; aseptic meningitis: 64) Positive for bacterial meningitis: 13% (Population: BM AM) Positive CSF cultures in population with bacterial meningitis: 85% Causative organisms: n=13 S. pneumoniae, n=6 H. influenza, n=1 E. coli
Index test(s)	CSF neutrophil count (reported as polymorphonuclear cells). Threshold 50%.
Reference standard(s)	CSF bacterial culture and/or CSF pleocytosis with blood bacterial culture
Sources of funding	No sources of funding reported.
Results	CSF neutrophil count (reported as polymorphonuclear cells), threshold >50% (n=158): TP 18; FP 78; FN 2; TN 60 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CNS: central nervous system; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; N/n: number; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection:	Could the selection of patients have	Unclear

Section	Question	Answer
risk of bias	introduced bias?	*(Only children admitted and diagnosed with meningitis included; children with antibiotic use prior to lumbar puncture were excluded. While this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias. No information about whether threshold was pre-specified)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High *(Reported as CSF polymorphonuclear cells, of which only a proportion are neutrophils)*
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 defined as positive CSF culture or a CSF pleocytosis plus positive blood culture. Only 17/20 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; no information on when relevant clinical samples (CSF and blood) were taken with respect to each other)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Nelson, 1986

Bibliographic Reference Nelson, N; Eeg-Olofsson, O; Larsson, L; Ohman, S.; The diagnostic and predictive value of cerebrospinal fluid lactate in children with meningitis; Acta Paediatrica Scandinavica; 1986; vol. 75; 52-57

Study details

Country/ies where study was carried out	Sweden

Study type	Retrospective single-gate cross-sectional DTA study
Study dates	May 1980 - June 1983
Inclusion criteria	Children with suspected meningitis admitted to study paediatric department with suspected meningitis
Exclusion criteria	Excluded neonates in ages up to 10 days.
Patient characteristics	N=133 n=18 bacterial meningitis n=28 aseptic meningitis n=87 non-meningitis Age (range): 11 days-16 years Male (%): 79 (59%) Positive for bacterial meningitis: 14% (Population: BM AM NM) Causative organisms: n=12 H. influenzae type B, n=2 E. coli, n=1 group B Streptococcus, n=1 N. meningitidis, n=1 S. pneumoniae, n=1 S. epidermidis n=7/18 (38.9%) of bacterial meningitis group received antimicrobial medication before admission to hospital.
Index test(s)	CSF white cell count Threshold >8 cells/µL. CSF glucose concentration (reported as CSF/blood glucose ratio). Threshold <0.40
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	CSF white cell count (reported as leukocytes), threshold >8 cells/µL (n=130): TP 17; FP 28; FN 1; TN 84 CSF glucose concentration (reported as CSF/blood glucose ratio), threshold <0.40 (n=120): TP 10; FP 2; FN 7; TN 101 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae; Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; S. epidermidis: Staphylococcus epidermidis; S. pneumoniae: Streptococcus pneumoniae; 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 *(Excluded 3/133 (2.3%) from CSF leucocytes count and 13/133 (9.8%) from the CSF/blood glucose ratio analyses due to missing data. However, relatively small percentage so unlikely to bias results)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Neuman, 2008

Bibliographic Reference Neuman, M. I; Tolford, S; Harper, M. B.; Test characteristics and interpretation of cerebrospinal fluid gram stain in children; Pediatric infectious disease journal; 2008; vol. 27; 309-13

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	December 1992 - September 2005
Inclusion criteria	Children ≤21 years of age admitted to emergency department and lumbar puncture performed within 24 hours.
Exclusion criteria	Children who had ventricular shunts or those who received antibiotics 48 hours before CSF samples were obtained.
Patient characteristics	N=16036 (17569 specimens) n=63 bacterial meningitis Age in days (median [IQR]): 74 (38-562) Positive for bacterial meningitis: 0.4% samples (Population: BM U) Causative organisms: n=19 S. pneumoniae, n=15 E. coli, n=9 group B Streptococcus, n=8 N. meningitidis, n=2 Citrobacter spp., n=2 H. influenzae type b, n=2 S. bovis, n=1 L. monocytogenes, n=1 Salmonella group B, n=1 S. aureus, n=1 S. pyogenes, n=1 S. MG-intermedius, n=1 non-enteric Gram-negative rods
Index test(s)	Microscopy Gram staining
Reference standard(s)	CSF bacterial culture. The diagnosis of BM was defined if there was one of the following in the CSF culture: (1) growth of a pathogen (eg. S. pneumoniae, N. meningitidis) or (2) growth of a possible pathogen (eg. enterococci) and the patient had a treatment of parenteral antibiotics for 7 days or more without other indications.
Sources of funding	No sources of funding reported
Results	Microscopy: Gram staining in all bacteria (n=17569): TP 42; FP 28; FN 21; TN 17478 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae; Haemophilus influenzae; IQR: interquartile range; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; spp.: species; S. aureus: Staphylococcus aureus; S. bovis: Streptococcus bovis; S. MG- intermedius: Streptococcus MG-intermedius; S. pneumoniae; Streptococcus pneumoniae; S. pyogenes: Streptococcus pyogenes; 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?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

QUADAS: quality assessment of diagnostic accuracy studies

Ni, 1992

Bibliographic Reference Ni, H; Knight, A. I; Cartwright, K; Palmer, W. H; McFadden, J.; Polymerase chain reaction for diagnosis of meningococcal meningitis; Lancet; 1992; vol. 340; 1432-4

Study details

Country/ies where study was carried out	UK
Study type	Retrospective two-gate cross-sectional DTA study
Study dates	Not reported

Inclusion criteria	People with suspected meningococcal disease and control group (no further details reported) undergoing lumbar puncture
Exclusion criteria	Not reported
Patient characteristics	N=54 n=11 meningococcal meningitis (isolation of N. meningitidis) n=2 meningococcal septicaemia without meningitis n=2 probable bacterial meningitis n=7 proven bacterial meningitis n=14 other proven and probable infections (n=6 viral meningitis, n=6 febrile convulsions, n=1 otitis media 1 H influenzae type b cellulitis) n=18 other non-infectious neurological conditions (multiple sclerosis, subarachnoid haemorrhage, suspected spinal lesions). Age in years (range): 1-61 in bacterial meningitis group Positive for bacterial meningitis: 33% Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=11 N. meningitidis, n=6 H. influenzae type b and n=1 S. pneumoniae
Index test(s)	Molecular diagnosis Specific PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture and/or Gram stain
Sources of funding	Not industry funded
Results	Molecular diagnosis: Specific PCR for N. meningitidis (n=54): TP 10; FP 4; FN 1; TN 39 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection:	Could the selection of patients have introduced bias?	High

Section	Question	Answer
risk of bias		*(Two-gate study design)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Population is indirect as only people with suspected meningococcal disease and controls were enrolled in the study)*
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 *(Meningococcal meningitis defined by positive CSF culture or Gram-negative diplococci tests. Exact proportions of the tests are not given)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards.)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Pfefferle, 2020

Bibliographic Reference Pfefferle, S; Christner, M; Aepfelbacher, M; Lutgehetmann, M; Rohde, H.; Implementation of the FilmArray ME panel in laboratory routine using a simple sample selection strategy for diagnosis of meningitis and encephalitis; BMC Infectious Diseases; 2020; vol. 20 (no. 1)

Study details

Country/ies where study was carried out	Germany
Study type	Prospective single-gate cross-sectional DTA study

Study dates	September 2015 - February 2017
Inclusion criteria	CSF samples of people with suspected CNS infection (defined as abnormality in Gram-stain results (for example, leucocytes and/or bacteria visible) or communicated by clinicians.
Exclusion criteria	Not reported
Patient characteristics	N=171* n=15 bacterial meningitis n=24 viral meningitis n=1 fungal meningitis *Total study population=4623 CSF samples (from 1601 individuals). However, only 171 were selected for FA-ME panel testing and included in analysis. Ages of participants not reported. Positive for bacterial meningitis: 16% (Population: BM VM FM NM) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=16 S. pneumoniae, n=5 N.meningitidis, n=3 L. monocytogenes, n=2 H. influenzae, n=1 group B Streptococcus
Index test(s)	Molecular diagnosis Multiplex PCR (FA-M/E panel) for all included bacteria
Reference standard(s)	CSF bacterial culture and PCR
Sources of funding	No sources of funding reported
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=171): TP: 27 FP: 3; FN: 0*; TN: 141 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CNS: central nervous system; CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HSV: herpes simplex virus; H. influenzae; Haemophilus influenzae; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; 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 *(Not clear if consecutive sample was enrolled. No information provided on exclusion criteria. Also, people were selected on the basis of abnormal Gram stain results, which may inflate diagnostic accuracy)*
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; PCR was used as a reference standard, but was a different type of PCR (specific real-time PCR instead of multiplex FA-M/E) and therefore should not affect 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 bacterial culture and/or PCR. Culture only performed (n = 45), molecular analysis only (n = 20) or both methods (n = 106). Unclear what proportion of bacterial meningitis cases were confirmed by 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)*

PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Piccirilli, 2018

Bibliographic Reference Piccirilli, G; Chiereghin, A; Gabrielli, L; Giannella, M; Squarzoni, D; Turello, G; Felici, S; Vocale, C; Zuntini, R; Gibertoni, D; Maraolo, A. E; Ambretti, S; Lazzarotto, T.; Infectious meningitis/encephalitis: evaluation of a rapid and fully automated multiplex PCR in the microbiological diagnostic workup; The new microbiologica; 2018; vol. 41; 118-125

Study details

Country/ies where study was carried out	Italy
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	Not reported
Inclusion criteria	People with suspected meningitis or encephalitis
Exclusion criteria	Not reported
Patient characteristics	N=77 n=63 retrospective group n=14 prospective group Age (n [%]): 5 (8) paediatric; 58 (92) adults in total retrospective study population Positive for bacterial meningitis: 32%* (Population: BM U) *64% were considered to have bacterial meningitis but this was only culture confirmed in 32%. Causative organisms: n=6 N. meningitidis, n=3 H. influenzae, n=1 L. monocytogenes, n=3 group B Streptococcus, n=3 S. pneumoniae
Index test(s)	Molecular diagnosis Multiplex PCR (FA-ME panel) for all included bacteria
Reference standard(s)	CSF bacterial culture
Sources of funding	Industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=25): TP 8; FP 8*; FN 0; TN 9 * Paper reported these results as true positives based on results of real-time PCR.

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; HSV: herpes simplex virus; H. influenzae: Haemophilus influenzae; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection:	Could the selection of patients have	Unclear

Section	Question	Answer
risk of bias	introduced bias?	*(Not clear if consecutive sample was enrolled. No information provided on exclusion criteria.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(6 (7.8%) were immunocompromised; proportions not reported separately for bacterial meningitis group)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index test (FA/ME multiplex PCR) was interpreted with knowledge of the reference standard; however, test is objective which decreases probability of 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?	Unclear *(Reference standards (Real-time PCR) were interpreted with knowledge of the index tests; however, tests are objective which decreases probability of bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(Reference standard is bacterial culture and/or Gram stain and/or IC test and/or real-time PCR. Only 50% were diagnosed based on a positive culture result; however, enough data presented to calculate 2x2 tables using only culture as reference standard)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(No information about interval between index tests and reference standards. 38 (60.3%) were excluded from the analysis as conventional tests for bacterial pathogens were not performed)*

FA-M/E: FilmArray® Meningitis/Encephalitis; IC: immunochromatographic; PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Poppert, 2005

Bibliographic Reference Poppert, S; Essig, A; Stoehr, B; Steingruber, A; Wirths, B; Juretschko, S; Reischl, U; Wellinghausen, N.; Rapid diagnosis of bacterial meningitis by real-time PCR and fluorescence in situ hybridization; Journal of clinical microbiology; 2005; vol. 43; 3390-7

Study details

Country/ies where study was carried out	Germany
Study type	Prospective single-gate cross-sectional DTA study

Study dates	Not reported
Inclusion criteria	CSF samples from people with suspected meningitis, which had been sent for routine diagnosis
Exclusion criteria	Not reported
Patient characteristics	N=151 n=35 culture-confirmed bacterial meningitis n=116 without bacterial meningitis Ages of participants not reported. Positive for bacterial meningitis: 23% (Population: BM U) Causative organisms: Not reported
Index test(s)	Molecular diagnosis Multiplex PCR for all included bacteria
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=151): TP 35; FP 8; FN 0; TN 108

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; spp: species; S. aureus: Staphylococcus aureus; S. epidermidis: Staphylococcus epidermidis; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled. No information provided on study dates, exclusion criteria or patient characteristics)*
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*

Section	Question	Answer
		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 standard was interpreted without knowledge of the index test; however, test is 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 *(Study reference standard is microscopy and culture. However, enough data presented to calculate 2x2 tables using only culture as reference standard. All samples received all reference standard tests which minimises impact on bias)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index tests and reference standards)*

QUADAS: quality assessment of diagnostic accuracy studies

Porritt, 2000

Bibliographic Reference Porritt, R. J; Mercer, J. L; Munro, R.; Detection and serogroup determination of Neisseria meningitidis in CSF by polymerase chain reaction (PCR); Pathology; 2000; vol. 32; 42-45

Study details

Country/ies where study was carried out	Australia
Study type	Prospective single-gate cross-sectional DTA study CSF samples were submitted prospectively Retrospective single-gate cross-sectional DTA study 22 samples were collected prior to the evaluation
Study dates	Not reported
Inclusion criteria	CSF samples from people with suspected meningococcal disease

Exclusion criteria	Not reported
Patient characteristics	N=85 n=38 definite or probable bacterial meningitis caused by N. meningitidis n=47 without bacterial meningitis caused by N. meningitidis Ages of participants not reported. Positive for bacterial meningitis: 16%* (Population: MM U) *45% were considered to have bacterial meningitis but this was only culture confirmed in 16%. Causative organisms: n=14 N. meningitidis
Index test(s)	Molecular diagnosis Specific PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Specific PCR for N. meningitidis (n=85): TP 14; FP 20*; FN 0; TN 51** N.B. 2x2 tables and relevant outcomes calculated in RevMan. *All resolved to be probably cases of meningococcal meningitis. Paper reports 13/20 showed Gram-negative diplococci identified in CSF along with laboratory tests and clinical presentation of meningitis, Remaining 7/20 were clinically diagnosed with meningococcal meningitis and/or had CSF parameters consistent with meningitis. **4 were resolved to be probably cases of meningococcal meningitis based on elevated CSF leucocyte count and a positive blood culture or high CSF protein levels.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled. No information provided on study dates, exclusion criteria and patient characteristics)*

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

QUADAS: quality assessment of diagnostic accuracy studies

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; 179-184

Study details

Country/ies where study was carried out	France
Study type	Prospective single-gate cross-sectional DTA study
Study dates	January 2001 - December 2002
Inclusion criteria	People over 16 years old who attended the emergency department and received a diagnosis of meningitis based on compatible clinical

	features and pleocytosis (CSF > 5 white blood cells/mm³).
Exclusion criteria	Gram-stained smears showing presence of bacteria
Patient characteristics	N=151 n=18 bacterial meningitis n=133 non-bacterial meningitis Age in years (mean [SD]): 52 (20) in bacterial meningitis group only Female (%): 9 (51%) in bacterial meningitis group only Positive for bacterial meningitis: 12% (Population: BM UM) Positive CSF cultures in population with bacterial meningitis: 61% Causative organisms: n=4 Streptococcus spp. other than pneumonia, n=2 S. pneumoniae, n=2 N. meningitidis, n=1 Fusobacterium, n=1 K. pneumoniae, n=1 M. tuberculosis, n=7 unknown Previous antibiotics: 23% HIV positive n=2 (1.3 %), Daily steroid treatment n=2
Index test(s)	SF white cell count Threshold ≥300 cells/mm3 (converted to cells/μL for consistency with other studies). CSF glucose concentration (reported as CSF/blood glucose ratio). Threshold ≤0.15. CSF protein concentration Threshold ≥1.31 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture and/or CSF antigen test and/or blood bacterial culture and/or CSF pleocytosis with a neutrophil count >500/mm³ and rapid improvement after antibacterial therapy
Sources of funding	No sources of funding reported
Results	CSF white cell count, threshold >300 cells/mm³ (n=151): TP 9; FP 8; FN 9; TN 125; AUC (95% CI): 0.59 (0.21-0.82) CSF/blood glucose ratio, threshold <0.15 (n=151): TP 6; FP 77; FN 12; TN 56; AUC (95% CI): 0.11 (0.06-0.18)

	CSF protein concentration, threshold >1.31 g/L (n=151): TP 11; FP 8; FN 7; TN 125; AUC (95% CI): 0.70 (0.30-0.89) 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: CSF white cell count – cells/μL. Equivalent to cells/mm3; CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100.

A&E: accident and emergency; AUC: area under the curve; CI: confidence interval; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; K. pneumoniae: Klebisella pneumoniae; M. tuberculosis: Mycobacterium tuberculosis; N/n: number; N. meningitidis: Neisseria meningitidis; SD: standard deviation; spp.: species; S. pneumoniae: Streptococcus pneumoniae; 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 *(Study only included people with bacterial meningitis who had negative Gram-stained smears. Also, people were included based on CSF leukocyte count, which may inflate diagnostic accuracy)*
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?	High *(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. Cut-off values derived from ROC curves)*
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?	Low

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve: receiver operating characteristics curve

Richardson, 2003

Bibliographic Reference	Richardson, D. C; Louie, L; Louie, M; Simor, A. E.; Evaluation of a rapid PCR assay for diagnosis of meningococcal meningitis; Journal of clinical microbiology; 2003; vol. 41; 3851-3853

Study details

Country/ies where study was carried out	Canada
Study type	Prospective single-gate cross-sectional DTA study
Study dates	February 1998-June 2002
Inclusion criteria	People with suspected bacterial meningitis
Exclusion criteria	Not reported
Patient characteristics	N=281 n=103 bacterial meningitis n=178 non-bacterial meningitis Age (median [range]): 16 years (6 weeks-63 years) in meningococcal meningitis group [not reported for other participants] Sex (%): 3% male: 67% female in meningococcal meningitis group [not reported for other participants] Positive for bacterial meningitis caused by N. meningitidis: 7%* (Population: MM BM UM) *14% were considered to have bacterial meningitis caused by N. meningitidis but this was only culture confirmed in 7%. Causative organisms: n=45 S. pneumoniae, n=21 N. meningitidis, n=5 H. influenzae, n=4 S. aureus, n=3 group B streptococcus, n=1 C. albicans, n=1 group G streptococcus, n=1 P. aeruginosa, n=1 K. oxytoca, n=1 E. cloacae, n=1 A. baumannii
Index test(s)	Molecular diagnosis Specific PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded

Results	Molecular diagnosis: Specific PCR for N. meningitidis (n=281): TP 21; FP 16; FN 0; TN 244 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

A. baumannii: Acinetobacter baumannii; C. albicans: Candida albicans; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. cloacae: Enterobacter cloacae; FN: false negative; FP: false positive; K. oxytoca: Klebsiella oxytoca; N/n: number; N. meningitidis: Neisseria meningitidis; P. aeruginosa; Pseudomonas aeruginosa; PCR: polymerase chain reaction; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; 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 *(Unclear whether consecutive sample enrolled; no exclusion criteria reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	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 standard was interpreted without knowledge of the index test; 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 *(Study reference standard is broader than review reference standard. However, results presented separately for target index test versus CSF bacterial 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)*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Rothman, 2010

Bibliographic Reference	Rothman, R; Ramachandran, P; Yang, S; Hardick, A; Won, H; Kecojevic, A; Quianzon, C; Hsieh, Y. H; Gaydos, C.; Use of quantitative broad-based polymerase chain reaction for detection and identification of common bacterial pathogens in cerebrospinal fluid; Academic emergency medicine; 2010; vol. 17; 741-7

Study details

Country/ies where study was carried out	USA
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	July 2006-July 2007
Inclusion criteria	Excess CSF specimens submitted to study laboratory during study period
Exclusion criteria	Not reported
Patient characteristics	N=108 n=18 culture-confirmed bacterial meningitis n=90 without bacterial meningitis Ages of participants not reported. Positive for bacterial meningitis: 17% (Population: BM U) Causative organism: Not reported
Index test(s)	Molecular diagnosis Multiplex PCR (Uniprobe PCR) for all included bacteria
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR (Uniprobe PCR) for all included bacteria (n=108) adjusted analysis*: TP 16; FP 0; FN 2; TN 90 N.B. 2x2 tables and relevant outcomes calculated in RevMan. *Study reported adjusted 2x2 table after assigning the common microbiologic contaminants (M. luteus, R. dentocariosa, Corneybacterium spp.) to the culture-negative cell)

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; L. monocytogenes; Listeria monocytogenes; M. luteus: Micrococcus luteus; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; R. dentocariosa: Rothia dentocariosa; spp.: species; S. aureus: Staphylococcus aureus; S. epidermidis: Staphylococcus epidermidis; S. pneumoniae; Streptococcus pneumoniae; 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 *(No information provided on exclusion criteria and patient characteristics)*
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 standard was interpreted without knowledge of the index test; however, test is 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)*

QUADAS: quality assessment of diagnostic accuracy studies

Schuurman, 2004

Bibliographic Reference Schuurman, T; De Boer, R. F; Kooistra-Smid, A. M. D; Van Zwet, A. A.; Prospective Study of Use of PCR Amplification and Sequencing of 16S Ribosomal DNA from Cerebrospinal Fluid for Diagnosis of Bacterial Meningitis in a Clinical Setting; Journal of clinical microbiology; 2004; vol. 42; 734-740

Study details

Country/ies where study was carried out	The Netherlands
Study type	Prospective single-gate cross-sectional DTA study

Study dates	January 2002 and May 2003
Inclusion criteria	CSF samples collected at participating laboratories during study period, from people with meningitis (of any type) as part of their differential diagnosis
Exclusion criteria	Not reported
Patient characteristics	N=227 samples from 222 people Age in years (mean [range]): 24.5 (0-87.9) Male n(%): 125 (56.3) Positive for bacterial meningitis: 12% (Population: BM U) Causative organisms: n=12 N. meningitidis, n=8 S. pneumoniae, n=2 E. coli, n=2 H. influenzae, n=1 L. monocytogenes, and n=1 S. salivarius 5 CSF samples obtained after the start of antimicrobial therapy
Index test(s)	Molecular diagnosis Broad-range (16S) PCR
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Broad-range (16S) PCR (n=227 specimens): TP 22*; FP 6; FN 4**; TN 195 N.B. 2x2 tables and relevant outcomes calculated in RevMan. * Narrative summary reports only 22 TP results. However, table 1 (page 736) notes 24 TP. Reported as per text as numbers of pathogens add to 22. ** 9 other samples were culture-positive, PCR-negative. However, these were determined to be contaminants and therefore have not been included in the analysis

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; S. salivarius: Streptococcus salivarius; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled; exclusion criteria not reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	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 standard was interpreted without knowledge of the index test; however, test is 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)*

QUADAS: quality assessment of diagnostic accuracy studies

Seward, 2000

Bibliographic Reference Seward, R. J; Towner, K. J.; Use of an automated DNA analysis system (DARAS) for sequence-specific recognition of Neisseria meningitidis DNA; Clinical Microbiology & InfectionClin Microbiol Infect; 2000; vol. 6; 29-33

Study details

Country/ies where study was carried out	UK
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	Not reported

Inclusion criteria	CSF samples from people with suspected meningococcal meningitis
Exclusion criteria	Not reported
Patient characteristics	N=74 n=19 with bacterial meningitis n=55 without bacterial meningitis Ages of participants not reported. Positive for bacterial meningitis: 26% (Population: MM U) Causative organisms: n=19 N. meningitidis
Index test(s)	Molecular diagnosis Specific PCR for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: PCR for N. meningitidis (n=74): TP 19; FP 0; FN 0; TN 55 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; N/n: number; N. meningitidis: Neisseria meningitidis; 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 *(No information on whether consecutive sample was enrolled; no information provided on study dates, exclusion criteria or patient characteristics)*
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*

Section	Question	Answer
		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 standard was interpreted without knowledge of the index test; however, test is 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 test and reference standard)*

QUADAS: quality assessment of diagnostic accuracy studies

Seward, 2000b

Bibliographic Reference Seward, R. J; Towner, K. J.; Evaluation of a PCR-immunoassay technique for detection of Neisseria meningitidis in cerebrospinal fluid and peripheral blood; Journal of Medical Microbiology; 2000; vol. 49; 451-456

Study details

Country/ies where study was carried out	UK
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	No dates reported; reported that samples were collected over a period of 9 months
Inclusion criteria	People with suspected meningitis
Exclusion criteria	Not reported
Patient characteristics	N=294 n=25 bacterial meningitis n=269 without bacterial meningitis

	Ages of participants not reported. Positive for bacterial meningitis: 9% (Population: BM U) Causative organisms: n=11 N. meningitidis, n=4 S. pneumoniae, n=4 S. epidermidis, n=2 S. aureus, n=2 group B Streptococcus, n=1 P. aeruginosa, n=1 K. aerogenes
Index test(s)	Molecular diagnosis Multiplex PCR: • for all included bacteria • for N. meningitidis
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR* for all included bacteria (n=294): TP 25; FP 4; FN 0; TN 265 Molecular diagnosis: Multiplex PCR for N. meningitidis (n=294): TP 11; FP 4; FN 0; TN 279 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; false negative; FP: false positive; K. aerogenes: Klebisella aerogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; P. aeruginosa: Pseudomonas aeruginosa; S. aureus: Staphylococcus aureus; S. epidermidis: Staphylococcus epidermidis: S. pneumoniae: Streptococcus pneumoniae; 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 *(No information on whether consecutive sample was enrolled; no information provided on study dates, exclusion criteria or patient characteristics)*
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)*

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 standard was interpreted without knowledge of the index test; however, test is 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 test and reference standard)*

QUADAS: quality assessment of diagnostic accuracy studies

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; 725-729

Study details

Country/ies where study was carried out	Finland
Study type	Prospective two-gate cross-sectional DTA study
Study dates	1984 - 1991 for bacterial meningitis 1977 - 1992 for viral meningitis
Inclusion criteria	Bacterial meningitis group: People with positive bacterial CSF culture and negative initial CSF Gram stain. Viral meningitis group: People with a diagnosis of viral meningitis at the time of hospital discharge.
Exclusion criteria	Immunocompromised, prosthetic device (such as a ventriculo-peritoneal shunt), and received more than one dose of parenteral antimicrobial agents before the diagnosis (for bacterial meningitis group) or hospital charts included mention of oral antimicrobial treatment before or during hospitalization (for viral meningitis group).
Patient characteristics	N=237

	Age (range): 3 months-15 years in bacterial meningitis group only. Positive for bacterial meningitis: 23% (Population: BM VM) Causative organisms: n=26 N. meningitidis, n=23 H. influenzae type b, n=3 S. pneumoniae, n=1 L. monocytogenes, n=1 E. coli, n=1 group B Streptococcus
Index test(s)	CSF white cell count Thresholds >100x106 cells/L, >500x106 cells/L, >1000x106 cells/L, and >2000x106 cells/L (converted to cells/µL for consistency with other studies). CSF glucose concentration Thresholds <2.0 mmol/L, <2.5 mmol/L and <3.0 mmol/L. CSF protein concentration Thresholds >0.5 g/L, >1.0 g/L, and >1.5 g/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported
Results	CSF white cell count, threshold >100 x 106 cells/L (n=237): TP 49; FP 120; FN 6; TN 62 CSF white cell count, threshold >500 x 106 cells/L (n=237): TP 43; FP 20; FN 12; TN 162 CSF white cell count, threshold >1000 x 106 cells/L (n=237): TP 41; FP 5; FN 14; TN 177 CSF white cell count, threshold >2000 x 106 cells/L (n=237): TP 35; FP 2; FN 20; TN 180 CSF glucose concentration, threshold <2.0 mmol/L (n=237): TP 17; FP 0; FN 38; TN 182 CSF glucose concentration, threshold <2.5 mmol/L (n=237): TP 19; FP 7; FN 36; TN 175 CSF glucose concentration, threshold <3.0 mmol/L (n=237): TP 27; FP 58; FN 28; TN 124 CSF protein concentration, threshold >0.5 g/L (n=237): TP 43; FP 75; FN 12; TN 107 CSF protein concentration, threshold >1.0 g/L (n=237): TP 35; FP 7; FN 20; TN 175 CSF protein concentration, threshold >1.5 g/L (n=237): TP 28; FP 2; FN 27; TN 180 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: CSF white cell count – cells/µL. Equivalent to cells/mm3; CSF protein concentration – mg/dl. Calculated by multiplying g/L by 100.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae: Haemophilus influenzae; L. monocytogenes: Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; S. pneumoniae; Streptococcus pneumoniae; 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 *(Two-gate diagnostic study; children with antimicrobial use prior to lumbar puncture were excluded. While this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting; study only included people with bacterial meningitis who had negative Gram-stained smears and viral meningitis)*
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 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 *(CSF Gram stain results were not available for 21 (6.5%). No further explanation given)*

CSF: cerebrospinal fluid; N/n: number; QUADAS: quality assessment of diagnostic accuracy studies

Viallon, 2011

Bibliographic Viallon, A; Desseigne, N; Marjollet, O; Birynczyk, A; Belin, M; Guyomarch, S; Borg, J; Pozetto, B; Bertrand, J. C; Zeni, F.;

Reference 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	Prospective single-gate cross-sectional DTA study
Study dates	January 1997-December 2009
Inclusion criteria	Adults admitted to the emergency unit with meningitis (defined by leukocyte count >5 cells/mm3 in the CSF) and 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, >2 doses of antibiotic treatment before admission, presence of another focus of infection in addition to meningitis, and meningitis finally assumed to be of bacterial origin, despite the absence of microbiologic documentation, and treated with antibiotics during the patient's hospitalization
Patient characteristics	N=253 Age in years (mean [SD]): 55 (20) in bacterial meningitis group only Male (%): 45% in bacterial meningitis group only Positive for bacterial meningitis: 14% (Population: BM VM VME) Causative organisms: n=14 S. pneumoniae, n=6 L. monocytogenes, n=5 N. meningitidis, n=4 Streptococcus spp., n=2 H. influenzae, n=2 S. aureus, n=2 other species
Index test(s)	CSF neutrophil count Threshold >118 cells/mm3 (converted to cells/µL for consistency with other studies). CSF glucose concentration Threshold <2.2 mmol/L. CSF glucose concentration (reported as CSF/serum glucose ratio). Threshold <0.48. CSF protein concentration Threshold >1.88 g/L (converted to mg/dL for consistency with other studies).

Reference standard(s)	CSF bacterial culture
Sources of funding	No sources of funding reported.
Results	CSF neutrophil count, threshold >118 cells/mm3 (n=253): TP 28; FP 33; FN 7; TN 185; AUC (95% CI): 0.86 (0.86-0.94) CSF glucose concentration, threshold 2.2 mmol/L (n=253): TP 34; FP 111; FN 1; TN 107; AUC (95% CI): 0.69 (0.69-0.76) CSF/serum glucose ratio, threshold 0.48 (n=253): TP 29; FP 24; FN 6; TN 194; AUC (95% CI): 0.87 (0.86-0.91) CSF protein concentration, threshold 1.88 g/L (n=253): TP 31; FP 15; FN 4; TN 203; AUC (95% CI): 0.93 (0.92-0.98) 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: CSF neutrophil count – cells/μL. Equivalent to cells/mm3; CSF protein concentration – mg/dL. Calculated by multiplying g/L by 100.

AUC: area under the curve; CI: confidence interval; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; H. influenzae; Haemophilus influenzae; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; SD: standard deviation; spp.: species; S. aureus: Staphylococcus aureus; S. pneumoniae; Streptococcus pneumoniae; 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 *(Unclear if consecutive sample adopted; people with antibiotic use prior to lumbar puncture were excluded. While this in not inappropriate (as antibiotic usage will affect results) it may lead to an increased diagnostic accuracy than might be seen in a clinical setting; study only included adults with suspected meningitis and negative direct CSF examination. Also, included people based on CSK leukocyte count, which may inflate diagnostic accuracy)*
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

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Large percentage of adults with bacterial meningitis (62/97 (64%) excluded after enrolment))*

CSF: cerebrospinal fluid; QUADAS: quality assessment of diagnostic accuracy studies

Vincent, 2020

Bibliographic Reference Vincent, J. J; Zandotti, C; Baron, S; Kandil, C; Levy, P. Y; Drancourt, M; Raoult, D; Ninove, L.; Point-of-care multiplexed diagnosis of meningitis using the FilmArray R ME panel technology; European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis; 2020; vol. 39; 1573-1580

Study details

Country/ies where study was carried out	France
Study type	Prospective single-gate cross-sectional DTA study
Study dates	November 2017 to September 2018
Inclusion criteria	CSF samples submitted for the diagnosis of infectious meningitis at study laboratory
Exclusion criteria	Not reported
Patient characteristics	N=1124 n=14 culture-confirmed bacterial meningitis n=1110 without culture-confirmed bacterial meningitis Age (n): n=815 adults (>18 years old), n=309 children (≤18 years old) Positive for bacterial meningitis: 1% (Population: BM U)

	Positive CSF cultures in population with bacterial meningitis: 100% Causative organisms: n=8 S. pneumoniae, n=3 N. meningitidis, n=2 group B Streptococcus, n=1 H. influenzae
Index test(s)	Molecular diagnosis Multiplex PCR (FA-ME panel): • for N. meningitidis for S. pneumoniae • for H. influenzae • for group B streptococcus • for Gram-negative bacilli (E. coli)
Reference standard(s)	CSF bacterial culture, Gram stain and PCR
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=1124): TP 12; FP 4*; FN 2; TN 1106 Molecular diagnosis: Multiplex PCR for S. pneumoniae (n=1124): TP 8; FP 4*; FN 0; TN 1112 Molecular diagnosis: Multiplex PCR for N. meningitidis (n=1124): TP 2; FP 0; FN 1; TN 1121 Molecular diagnosis: Multiplex PCR for H. influenzae (n=1124): TP 1; FP 0; FN 0; TN 1123 Molecular diagnosis: Multiplex PCR for group B Streptococcus (n=1124) TP 1; FP 0; FN 1**; TN 1122 N.B. 2x2 tables and relevant outcomes calculated in RevMan. * Paper reported that 3/4 of these results were likely to be true positives as they were later confirmed to be meningitis caused by S. pneumoniae using clinical examination **Later determined to be meningitis caused by S. pneumoniae using clinical examination

CSF: cerebrospinal fluid; C. neoformans: Cryptococcus neoformans; C. gattii: Cryptococcus gatti; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FA-M/E: FilmArray® Meningitis/Encephalitis; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; HSV: herpes simplex virus; L. monocytogenes; Listeria monocytogenes; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled. No information provided on exclusion criteria)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index test was interpreted without knowledge of the reference standard; however, test is objective so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standard was interpreted without knowledge of the index test; however, test is 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 *(Although reference standard is reported as CSF bacterial culture and/or Gram stain and/or standard routine real-time PCR, it appears everyone had culture performed and was classified based on this)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index test and reference standard; real-time PCR was not done on all samples but bias as a result of this likely to be reduced as it appears people were classified based on culture alone)*

PCR: polymerase chain reaction; QUADAS: quality assessment of diagnostic accuracy studies

Wagner, 2018

Bibliographic Reference Wagner, K; Springer, B; Pires, V. P; Keller, P. M.; Pathogen Identification by Multiplex LightMix Real-Time PCR Assay in Patients with Meningitis and Culture-Negative Cerebrospinal Fluid Specimens; Journal of clinical microbiology; 2018; vol. 56

Study details

Country/ies where study was carried out	Switzerland
Study type	Prospective single-gate cross-sectional DTA study
Study dates	January 2017-July 2017

Inclusion criteria	CSF samples from people with meningitis symptoms collected in secondary and tertiary care hospitals in study area
Exclusion criteria	Not reported
Patient characteristics	N=220 n=20 bacterial meningitis n=200 without bacterial meningitis Ages of participants not reported. Positive for bacterial meningitis: 7%* (Population: BM U) *9% were considered to have bacterial meningitis but this was only culture confirmed in 7%. Causative organisms: n=8 S. pneumoniae, n=4 S. epidermidis, n=2 E. coli., n=2 S. hominus, n=1 N. meningitidis, n=1 group B Streptococcus, n=1 K. pneumoniae, n=1 S. marcescens
Index test(s)	Molecular diagnosis Multiplex LightMix RT-PCR: • for all included bacteria • for S. pneumoniae
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR for all included bacteria (n=220 samples): TP 6; FP 4*; FN 0**; TN 210 Molecular diagnosis: Multiplex for S. pneumoniae (n=220 samples): TP 6; FP 2*; FN 0; TN 212 N.B. 2x2 tables and relevant outcomes calculated in RevMan. * Paper reported these results were likely to be true positives as agreement with subsequent confirmatory testing by broad-range (16S) PCR and all people under antibiotic therapy at the time of lumbar puncture. **E. coli, K. pneumoniae, Serratia marcescens, Staphylococcus epidermidis, and Staphylococcus hominis detected by culture (n=10) but not included in multiplex LightMix RT-PCR and therefore not included in analysis.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; E. coli: Escherichia coli; FN: false negative; FP: false positive; K. pneumoniae: Klebsiella pneumoniae; N/n: number; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; RT-PCR: real-time polymerase chain reaction; S. epidermidis: Staphylococcus epidermidis; S. hominis: Staphylococcus hominis; S. marcescens: Serratia marcescens; S. pneumoniae; Streptococcus pneumoniae; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear (Not clear if consecutive sample was enrolled. No information provided on exclusion criteria and patient characteristics)
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 standard was interpreted without knowledge of the index test; however, test is 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 test and reference standard)

QUADAS: quality assessment of diagnostic accuracy studies

Welinder-Olsson, 2007

Bibliographic Reference Welinder-Olsson, C; Dotevall, L; Hogevik, H; Jungnelius, R; Trollfors, B; Wahl, M; Larsson, P.; Comparison of broad-range bacterial PCR and culture of cerebrospinal fluid for diagnosis of community-acquired bacterial meningitis; Clinical Microbiology and Infection; 2007; vol. 13; 879-886

Study details

Country/ies where study was carried out	Sweden
Study type	Prospective single-gate cross-sectional DTA study

Study dates	1999-2002
Inclusion criteria	People with suspected meningitis (defined as CSF white blood cell count ≥10 cells/μL)
Exclusion criteria	Samples from patients with nosocomial central nervous system (CNS) infections or inflammations, defined as an onset of symptoms >=3 days following hospitalisation (such as, shunt infections and post-operative CNS infections) were not included
Patient characteristics	N=345 n=74 bacterial meningitis n=102 viral meningitis n=91 other meningitis n= 78 non-meningitis Age (median [range]): 34 years (1 day-91 years) Female: 51% Positive for bacterial meningitis: 21% (Population: BM VM UM NM) Causative organisms: Numbers not reported but included N. meningitidis, S. pneumoniae, H. influenzae, Listeria spp., Gram-negative bacilli, streptococci or staphylococci. Severe underlying conditions (n=72): pre-term birth n=24; malignant disease n=16; diabetes mellitus n=13; alcohol abuse n=8; renal insufficiency n=3 n=22 patients received empirical antibiotic therapy before lumbar puncture
Index test(s)	Molecular diagnosis Broad-range (16S) PCR
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Broad-range (16S) PCR for all included bacteria (n=345): TP 25; FP 26; FN 14*; TN 280 *Includes n=7 with positive CSF culture results that did not receive a final diagnosis of bacterial meningitis

	N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; µL: microliter; N/n: number; 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 *(People were selected based on CSF WCC, which may inflate diagnostic accuracy)*
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 standard was interpreted without knowledge of the index test; however, test is 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)*

QUADAS: quality assessment of diagnostic accuracy studies; WCC: white cell count

White, 2012

Bibliographic Reference White, K; Ostrowski, K; Maloney, S; Norton, R.; The utility of cerebrospinal fluid parameters in the early microbiological assessment of meningitis; Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis; 2012; vol. 73; 27-30

Study details

Country/ies where study was carried out	Australia
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	CSF samples collected over a 13-year period. Exact dates are not reported.
Inclusion criteria	People over 5 years of age receiving lumbar puncture (without repeat lumbar puncture samples within 6 months)
Exclusion criteria	Not reported.
Patient characteristics	N=2290* n=23 bacterial meningitis n=45 viral meningitis n=17 cryptococcal meningitis n=2207 no meningitis *Total number do not equate to the sum of group of patients. In analysis we used N=2292 as total number. Age in years (median [IQR]): 38 (15-51) for males, 20 (18-54) for females in bacterial meningitis group only. Male (%): 11 (48%) in bacterial meningitis group only. Age in years (median [IQR]): 39 (34–58) for males, 38 (24–54) for females in whole cohort Male (%): 1189 (52%) in whole cohort Positive for bacterial meningitis: 1% (Population: BM VM CM NM) Positive CSF cultures in population with bacterial meningitis: not reported Causative organisms: n=12 S. pneumoniae, n=8 N. meningitidis, n=2 H. influenzae, n=1 B. pseudomallei
Index test(s)	CSF white cell count Threshold >90x106 cells/L (converted to cells/µL for consistency with other studies). CSF protein concentration Threshold >600 mg/L (converted to mg/dL for consistency with other studies).
Reference standard(s)	Traditional methods (including CSF culture and Gram stain) and or NAAT

Sources of funding	No sources of funding reported
Results	CSF white cell count, threshold 90 x 106 cells/L*: · Bacterial vs viral (n=68): TP 22; FP 31; FN 1; TN 14 · Bacterial vs cryptococcal (n=40): TP 22; FP 4; FN 1; TN 13 · Bacterial vs no meningitis (n=2230): TP 22; FP 1148; FN 1; TN 1059 CSF protein concentration, threshold 600 mg/L*: · Bacterial vs viral (n=68): TP 22; FP 20; FN 1; TN 25 · Bacterial vs cryptococcal (n=40): TP 22; FP 11; FN 1; TN 6 · Bacterial vs no meningitis (n=2230): TP 22; FP 362; FN 1; TN 1845 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: CSF white cell count – cells/μL. Equivalent to cells/mm3; CSF protein concentration – mg/dL. Calculated by diving mg/L by 10. *AUC also reported in study but without 95% CI so unable to extract and analyse.

AUC: area under the curve; B. pseudomallei: Burkholderia pseudomallei; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IQR: interquartile range; N/n: number; NAAT: nucleic acid amplification testing; 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?	High *(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. Optimal threshold values were calculated using ROC analysis for each group where a significant difference in medians was found. Cut-offs were chosen to preferentially optimise sensitivity)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	High *(n=14 (61%) bacteria were detected by traditional methods (which included culture, but number diagnosed based on this not reported) and in n=9 (39%) cases by NAAT (nucleic acid amplification testing) alone)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(No information about interval between index tests and reference standards. Not all CSF samples were tested for the same aetiological agents. Gram stain, culture, protein, WCC, and glucose were standard. NAAT, mycobacterial culture, and the cryptococcal antigen test were used selectively. Initial CSF parameters may have been used to guide further testing by the laboratory or clinician. The way the results have been presented (presumably due to differences in reference standards used) may inflate diagnostic accuracy as comparisons are between specific diagnoses rather than between all those with and without bacterial meningitis)*

CSF: cerebrospinal fluid; N/n: number; NAAT: nucleic acid amplification testing; QUADAS: quality assessment of diagnostic accuracy studies; ROC curve: receiver operating characteristics curve; WCC: white cell count

Xirogianni, 2009

Bibliographic Reference Xirogianni, A; Tzanakaki, G; Karagianni, E; Markoulatos, P; Kourea-Kremastinou, J.; Development of a single-tube polymerase chain reaction assay for the simultaneous detection of Haemophilus influenzae, Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus spp. directly in clinical samples; Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis; 2009; vol. 63; 121-6

Study details

Country/ies where study was carried out	Greece
Study type	Retrospective single-gate cross-sectional DTA study
Study dates	January 2003-February 2008
Inclusion criteria	CSF samples sent to National Meningitis Reference Laboratory
Exclusion criteria	Not reported

Patient characteristics	N=262* n=20 bacterial meningitis n=16 viral meningitis n=226 non-meningitis *The study included n=751 samples (from n=607 patients) isolated from blood, CSF, bronchial fluid, ear fluid or swabs, pus and wound swabs and other clinical samples. However, only CSF results extracted and reported in this review. Ages of participants not reported. Positive for bacterial meningitis: 8% (Population: BM VM NM) Causative organisms: Numbers not reported but included H. influenzae, P. aeruginosa, S. aureus, or Streptococcus spp.
Index test(s)	Molecular diagnosis Multiplex PCR: • for H. influenzae • for Gram-negative bacilli (P. aeruginosa)
Reference standard(s)	CSF bacterial culture
Sources of funding	Not industry funded
Results	Molecular diagnosis: Multiplex PCR in H. influenzae (n=262): TP 2; FP 3; FN 0; TN 257 Molecular diagnosis: Multiplex PCR in Gram-negative bacilli (P. aeruginosa) (n=262): TP 2; FP 2; FN 0; TN 258 N.B. 2x2 tables and relevant outcomes calculated in RevMan.

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; N/n: number; P. aeruginosa: Pseudomonas aeruginosa; PCr: polymerase chain reaction; spp. species; TN: true negative; TP: true positive

Critical appraisal – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Not clear if consecutive sample was enrolled. No information provided on exclusion criteria and patient characteristics)*
Patient selection:	Are there concerns that included patients do not	Low

Section	Question	Answer
applicability	match the review question?	
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 standard was interpreted without knowledge of the index test; however, test is 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 *(It appears that culture was performed on isolates that had already been identified by other methods, including Gram stain. However, diagnostic accuracy was calculated using culture as the reference standard)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(No information about interval between index test and reference standard)*

QUADAS: quality assessment of diagnostic accuracy studies

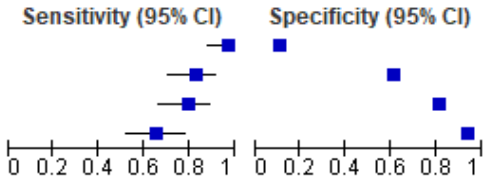
Appendix E Forest plots

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

White cell count

Figure 2: Forest plot for sensitivity and specificity of white cell count at all thresholds for diagnosis of bacterial meningitis in neonates

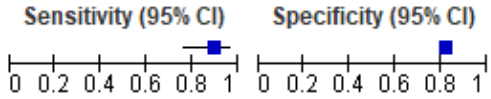
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Garges 2006a	56	4060	2	506	BM U	>0 cells/µL	C	0.97 [0.88, 1.00]	0.11 [0.10, 0.12]
Garges 2006b	48	1767	10	2799	BM U	>008 cells/µL	C	0.83 [0.71, 0.91]	0.61 [0.60, 0.63]
Garges 2006c	46	876	12	3690	BM U	>021 cells/µL	C	0.79 [0.67, 0.89]	0.81 [0.80, 0.82]
Garges 2006d	38	285	20	4281	BM U	>100 cells/µL	C	0.66 [0.52, 0.78]	0.94 [0.93, 0.94]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; 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 at 'elevated'* threshold for diagnosis of bacterial meningitis caused by group B streptococcus in neonates

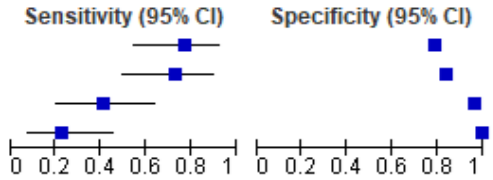
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Ansong 2009	41	2461	5	10988	GBM GBS U	Elevated	C	0.89 [0.76, 0.96]	0.82 [0.81, 0.82]



**Elevated thresholds defined as >26 cells/µL for premature neonates and >23 cells/µL for term neonates*
C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; GBM: group B Streptococcus meningitis; GBS: group B streptococcus septicaemia; TN: true negative; TP: true positive; U: undefined population

Figure 4: Forest plot for sensitivity and specificity of white cell count at all thresholds for diagnosis of bacterial meningitis in neonates and babies

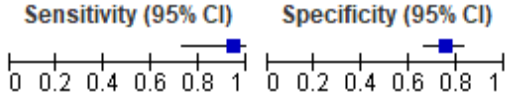
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2003a	17	1130	5	4201	BM U	>008 cells/µL	C	0.77 [0.55, 0.92]	0.79 [0.78, 0.80]
Bonsu 2003b	16	880	6	4451	BM U	>010 cells/µL	C	0.73 [0.50, 0.89]	0.83 [0.82, 0.84]
Bonsu 2003c	9	203	13	5128	BM U	>100 cells/µL	C	0.41 [0.21, 0.64]	0.96 [0.96, 0.97]
Bonsu 2003d	5	37	17	5294	BM U	>1000 cells/µL	C	0.23 [0.08, 0.45]	0.99 [0.99, 1.00]



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

Figure 5: Forest plot for sensitivity and specificity of white cell count at >8 cells/µL for diagnosis of bacterial meningitis in neonates, babies and children

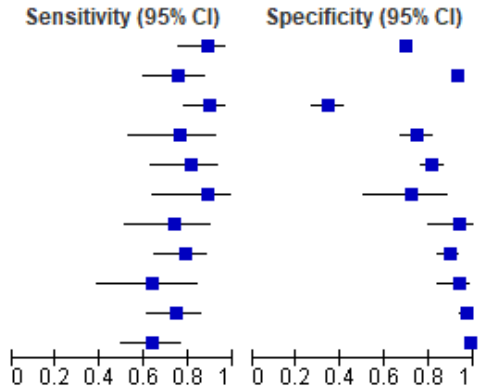
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Nelson 1986	17	28	1	84	BM AM NM	>08 cells/µL	C	0.94 [0.73, 1.00]	0.75 [0.66, 0.83]



AM: aseptic meningitis; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; TN: true negative; TP: true positive

Figure 6: Forest plot for sensitivity and specificity of white cell count at all thresholds for diagnosis of bacterial meningitis in babies and children

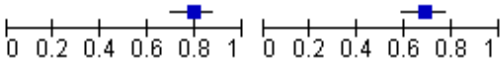
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Freedman 2001a	39	477	5	1096	BM U	>0003 cells/µL	C B OC CC	0.89 [0.75, 0.96]	0.70 [0.67, 0.72]
Freedman 2001b	33	115	11	1458	BM U	>0030 cells/µL	C B OC CC	0.75 [0.60, 0.87]	0.93 [0.91, 0.94]
Sormunen 1999a	49	120	6	62	BM VM	>0100 cells/µL	C	0.89 [0.78, 0.96]	0.34 [0.27, 0.41]
Dubos 2006	16	37	5	109	BM AM	>0200 cells/µL	C B OC CC	0.76 [0.53, 0.92]	0.75 [0.67, 0.81]
Agueda 2013	25	49	6	215	BM AM VM	>0321 cells/µL	C Mic	0.81 [0.63, 0.93]	0.81 [0.76, 0.86]
BenGershom 1986	15	7	2	18	BM VM NM	>0500 cells/µL	C	0.88 [0.64, 0.99]	0.72 [0.51, 0.88]
Corrall 1981	17	2	6	30	BM VM	>0500 cells/µL	C	0.74 [0.52, 0.90]	0.94 [0.79, 0.99]
Sormunen 1999b	43	20	12	162	BM VM	>0500 cells/µL	C	0.78 [0.65, 0.88]	0.89 [0.84, 0.93]
Bonsu 2008	12	4	7	55	BM VM	>0597 cells/µL	C	0.63 [0.38, 0.84]	0.93 [0.84, 0.98]
Sormunen 1999c	41	5	14	177	BM VM	>1000 cells/µL	C	0.75 [0.61, 0.85]	0.97 [0.94, 0.99]
Sormunen 1999d	35	2	20	180	BM VM	>2000 cells/µL	C	0.64 [0.50, 0.76]	0.99 [0.96, 1.00]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; NM: non-meningitis; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 7: Forest plot for sensitivity and specificity of white cell count at >200 cells/µL for diagnosis of bacterial meningitis in children

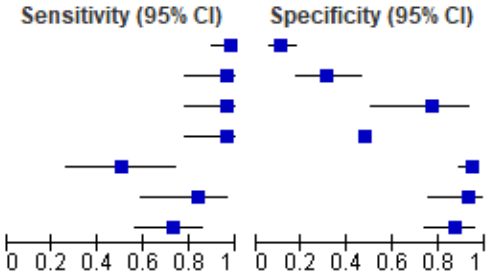
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2008	76	32	20	70	BM AM	>200 cells/µL	C B OC CC	0.79 [0.70, 0.87]	0.69 [0.59, 0.77]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive

Figure 8: Forest plot for sensitivity and specificity of white cell count at all thresholds for diagnosis of bacterial meningitis in adults

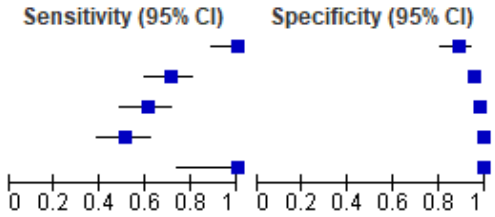
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Buch 2018	50	111	1	14	BM AME	>015 cells/µL	C B Mic Mol	0.98 [0.90, 1.00]	0.11 [0.06, 0.18]
White 2012a	22	31	1	14	BM VM	>090 cells/µL	C Mic Mol	0.96 [0.78, 1.00]	0.31 [0.18, 0.47]
White 2012b	22	4	1	13	BM CM	>090 cells/µL	C Mic Mol	0.96 [0.78, 1.00]	0.76 [0.50, 0.93]
White 2012c	22	1148	1	1059	BM U	>090 cells/µL	C Mic Mol	0.96 [0.78, 1.00]	0.48 [0.46, 0.50]
Ray 2007	9	8	9	125	BM UM	>300 cells/µL	C B OC CC	0.50 [0.26, 0.74]	0.94 [0.88, 0.97]
Giulieri 2015	15	2	3	25	BM VM	>388 cells/µL	C B Mic Mol	0.83 [0.59, 0.96]	0.93 [0.76, 0.99]
Kleine 2003	29	6	11	40	BM AM VM	>5.1 M/L	C B Mic	0.72 [0.56, 0.85]	0.87 [0.74, 0.95]



AM: aseptic meningitis; AME: aseptic meningoencephalitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; CM: cryptococcal meningitis; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis; VM: viral meningitis

Figure 9: Forest plot for sensitivity and specificity of white cell count at all thresholds for diagnosis of bacterial meningitis in all ages

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	32	12	0	91	BM U	>05 cells/µL	C	1.00 [0.89, 1.00]	0.88 [0.81, 0.94]
Lindquist 1988a	56	30	23	602	BM U	>0500 cells/µL	C OC	0.71 [0.60, 0.81]	0.95 [0.93, 0.97]
Lindquist 1988b	48	14	31	618	BM U	>1000 cells/µL	C OC	0.61 [0.49, 0.72]	0.98 [0.96, 0.99]
Lindquist 1988c	40	5	39	627	BM U	>1500 cells/µL	C OC	0.51 [0.39, 0.62]	0.99 [0.98, 1.00]
Boudet 2019	12	4	0	692	BM VM NM	Elevated	C	1.00 [0.74, 1.00]	0.99 [0.99, 1.00]

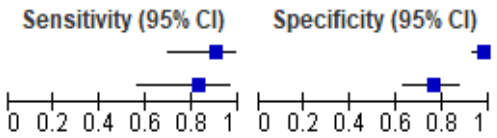


Elevated thresholds defined as >10 cells/µL for premature neonates and >5 cells/µL for other ages
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Neutrophil count

Figure 10: Forest plot for sensitivity and specificity of neutrophil count at all thresholds for diagnosis of bacterial meningitis in neonates, babies and children

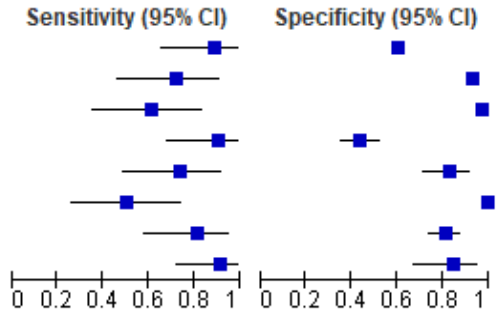
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Benjamin 1984	19	2	2	96	BM AM NM	>50 cells/cm	C	0.90 [0.70, 0.99]	0.98 [0.93, 1.00]
De Cauwer 2007	14	13	3	42	BM VM	>80%	C B P	0.82 [0.57, 0.96]	0.76 [0.63, 0.87]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; P: CSF pleocytosis; TN: true negative; TP: true positive; VM: viral meningitis

Figure 11: Forest plot for sensitivity and specificity of neutrophil count at all thresholds for diagnosis of bacterial meningitis in babies and children

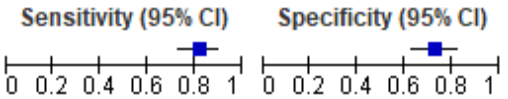
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2005a	16	3034	2	4655	BM U	>001%	C B Mic	0.89 [0.65, 0.99]	0.61 [0.59, 0.62]
Bonsu 2005b	13	549	5	7140	BM U	>025%	C B Mic	0.72 [0.47, 0.90]	0.93 [0.92, 0.93]
Bonsu 2005c	11	221	7	7468	BM U	>050%	C B Mic	0.61 [0.36, 0.83]	0.97 [0.97, 0.97]
Negrini 2000	18	78	2	60	BM AM	>050%	C B P	0.90 [0.68, 0.99]	0.43 [0.35, 0.52]
Bonsu 2008	14	10	5	49	BM VM	>074%	C	0.74 [0.49, 0.91]	0.83 [0.71, 0.92]
Bonsu 2005d	9	66	9	7623	BM U	>075%	C B Mic	0.50 [0.26, 0.74]	0.99 [0.99, 0.99]
Dubos 2006	17	27	4	116	BM AM	>100 cells/µl	C B OC CC	0.81 [0.58, 0.95]	0.81 [0.74, 0.87]
Corrall 1981	21	5	2	27	BM VM NM	>200 cells/µl	C	0.91 [0.72, 0.99]	0.84 [0.67, 0.95]



AM: aseptic meningitis; BM: bacterial meningitis; B: blood bacterial culture; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; NM: non-meningitis; OC: other CSF findings; P: CSF pleocytosis; TN: true negative; TP: true positive; VM: viral meningitis; U: undefined population

Figure 12: Forest plot for sensitivity and specificity of neutrophil count at >100 cells/µL for diagnosis of bacterial meningitis in children

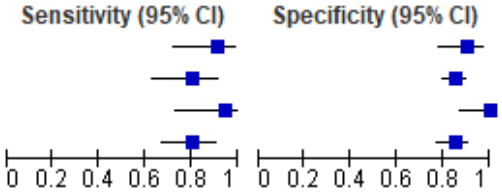
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2008	78	24	17	65	BM AM	>100 cells/µl	C B OC CC	0.82 [0.73, 0.89]	0.73 [0.63, 0.82]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive

Figure 13: Forest plot for sensitivity and specificity of neutrophil count at all thresholds for diagnosis of bacterial meningitis in adults

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dastych 2015	21	5	2	45	BM AM	>037 cells/µL	C OC	0.91 [0.72, 0.99]	0.90 [0.78, 0.97]
Viallon 2011	28	33	7	185	BM VM VME	>118 cells/µl	C	0.80 [0.63, 0.92]	0.85 [0.79, 0.89]
Giulieri 2015	17	0	1	27	BM VM	>260 cells/µl	C B Mic Mol	0.94 [0.73, 1.00]	1.00 [0.87, 1.00]
Buch 2018	41	19	10	106	BM AME	>67%	C B Mic Mol	0.80 [0.67, 0.90]	0.85 [0.77, 0.91]

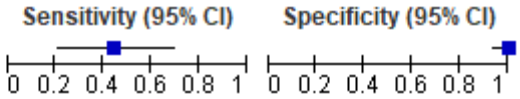


AM: aseptic meningitis; AME: aseptic meningoencephalitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; OC: other CSF findings; TN: true negative; TP: true positive; VM: viral meningitis; VME: viral meningoencephalitis

Microscopy for bacteria

Figure 14: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by all bacteria in neonates

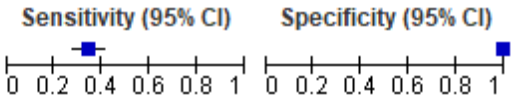
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bonadio 1989	8	0	10	54	BM VM AM	C OC	0.44 [0.22, 0.69]	1.00 [0.93, 1.00]



AM: aseptic meningitis; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; VM: viral meningitis

Figure 15: Forest plot for sensitivity and specificity of Gram staining diagnosis of bacterial meningitis caused by for all bacteria in neonates and younger babies

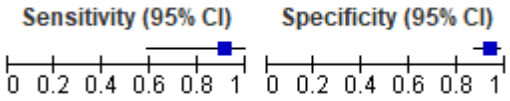
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Balamuth 2021	70	44	134	20699	BM U	C	0.34 [0.28, 0.41]	1.00 [1.00, 1.00]



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

Figure 16: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in neonates, babies and children

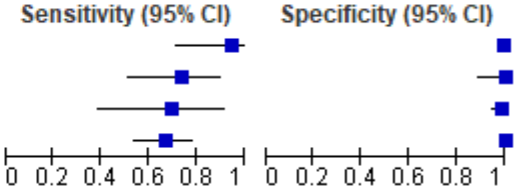
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2012	10	6	1	89	BM U	C	0.91 [0.59, 1.00]	0.94 [0.87, 0.98]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 17: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by all bacteria in babies and children

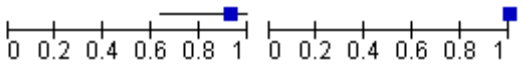
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Brizzi 2012	16	18	1	1903	BM U	C	0.94 [0.71, 1.00]	0.99 [0.99, 0.99]
Corrall 1981	17	0	6	32	BM VM NM	C	0.74 [0.52, 0.90]	1.00 [0.89, 1.00]
Khurana 1987	9	2	4	123	BM AM NM	C	0.69 [0.39, 0.91]	0.98 [0.94, 1.00]
Neuman 2008	42	28	21	17478	BM U	C	0.67 [0.54, 0.78]	1.00 [1.00, 1.00]



AM: aseptic meningitis; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 18: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by all bacteria in adults

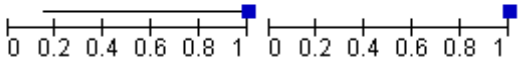
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dunbar 1998	12	0	1	2402	BM U	C	0.92 [0.64, 1.00]	1.00 [1.00, 1.00]



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

Figure 19: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by N. meningitidis in adults

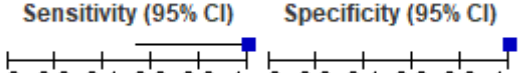
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dunbar 1998	2	0	0	2413	BM U	C	1.00 [0.16, 1.00]	1.00 [1.00, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitidis; TN: true negative; TP: true positive; U: undefined population

Figure 20: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in adults

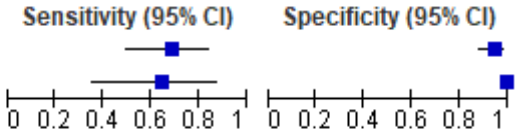
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dunbar 1998	6	0	0	2409	BM U	C	1.00 [0.54, 1.00]	1.00 [1.00, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 21: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by all bacteria in all ages

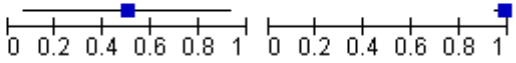
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	22	6	10	97	BM U	C	0.69 [0.50, 0.84]	0.94 [0.88, 0.98]
Deutch 2006	9	1	5	181	BM U	C	0.64 [0.35, 0.87]	0.99 [0.97, 1.00]



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

Figure 22: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by N. meningitidis in all ages

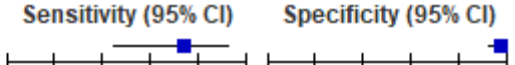
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	2	2	2	129	BM U	C	0.50 [0.07, 0.93]	0.98 [0.95, 1.00]		



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitidis; TN: true negative; TP: true positive; U: undefined population

Figure 23: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in all ages

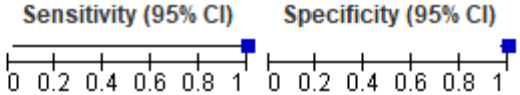
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	11	4	4	116	BM U	C	0.73 [0.45, 0.92]	0.97 [0.92, 0.99]		



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 24: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by group B Streptococcus in all ages

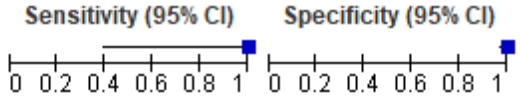
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	1	0	0	134	BM U	C	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]		



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

Figure 25: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by Gram-negative bacilli in all ages

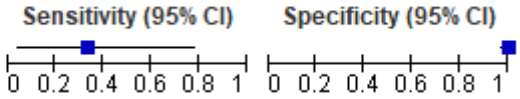
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020*	4	0	0	131	BM U	C	1.00 [0.40, 1.00]	1.00 [0.97, 1.00]		



** Pathogens detected: E. coli and C. koseri*
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; C. koseri: Citrobacter koseri; E. coli: Escherichia coli; FN: false negative; FP: false positive; TN: true negative; TP: true positive; U: undefined population

Figure 26: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by L. monocytogenes in all ages

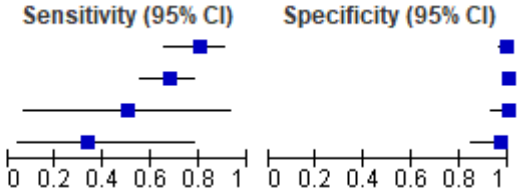
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	2	0	4	129	BM U	C	0.33 [0.04, 0.78]	1.00 [0.97, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; L. monocytogenes: Listeria monocytogenes; TN: true negative; TP: true positive; U: undefined population

Figure 27: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by all bacteria in undefined ages

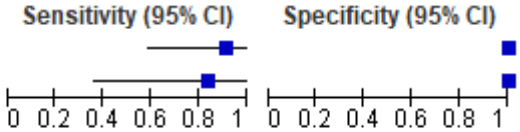
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bortolussi 1982	36	1	9	156	BM U	C	0.80 [0.65, 0.90]	0.99 [0.97, 1.00]
Jorgensen 1978	50	0	24	231	BM UM NM	C	0.68 [0.56, 0.78]	1.00 [0.98, 1.00]
Kotilainen 1998	2	0	2	52	BM UM NM	C	0.50 [0.07, 0.93]	1.00 [0.93, 1.00]
Meyer 2014	2	1	4	33	BM BI UI	C	0.33 [0.04, 0.78]	0.97 [0.85, 1.00]



BI: bacterial CNS infection; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; TN: true negative; TP: true positive; U: undefined population; UI: undefined CNS infection; UM: undefined meningitis

Figure 28: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by N. meningitidis in undefined ages

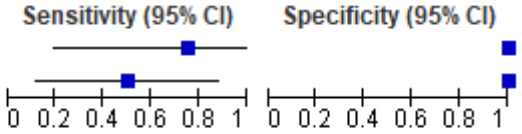
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bortolussi 1982	10	0	1	191	BM U	C	0.91 [0.59, 1.00]	1.00 [0.98, 1.00]
Jorgensen 1978	5	0	1	299	BM UM NM	C	0.83 [0.36, 1.00]	1.00 [0.99, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitidis; NM: non-meningitis; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis

Figure 29: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in undefined ages

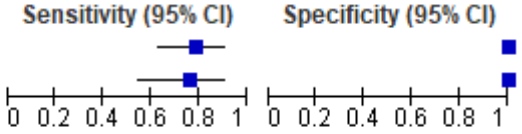
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bortolussi 1982	3	0	1	198	BM U	C	0.75 [0.19, 0.99]	1.00 [0.98, 1.00]
Jorgensen 1978	3	0	3	300	BM UM NM	C	0.50 [0.12, 0.88]	1.00 [0.99, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis

Figure 30: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by H. influenzae in undefined ages

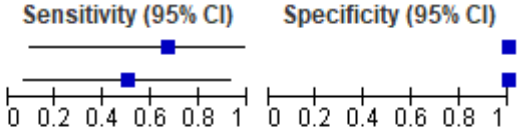
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Jorgensen 1978	30	0	8	267	BM UM NM	C	0.79 [0.63, 0.90]	1.00 [0.99, 1.00]
Bortolussi 1982	19	0	6	177	BM U	C	0.76 [0.55, 0.91]	1.00 [0.98, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; NM: non-meningitis; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis

Figure 31: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by group B Streptococcus in undefined ages

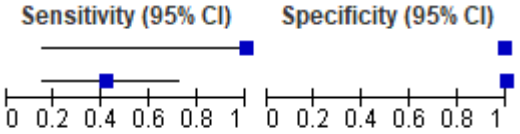
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bortolussi 1982	2	0	1	199	BM U	C	0.67 [0.09, 0.99]	1.00 [0.98, 1.00]
Jorgensen 1978	2	0	2	301	BM UM NM	C	0.50 [0.07, 0.93]	1.00 [0.99, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis

Figure 32: Forest plot for sensitivity and specificity of Gram staining for diagnosis of bacterial meningitis caused by Gram-negative bacilli in undefined ages

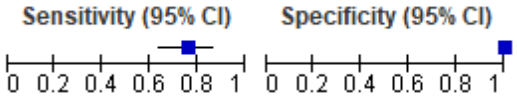
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bortolussi 1982*	2	1	0	199	BM U	C	1.00 [0.16, 1.00]	0.99 [0.97, 1.00]
Jorgensen 1978**	5	0	7	293	BM UM NM	C	0.42 [0.15, 0.72]	1.00 [0.99, 1.00]



** Escherichia coli*
*** Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumoniae*
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis

Figure 33: Forest plot for sensitivity and specificity of Gram and methylene blue staining for diagnosis of bacterial meningitis caused by all bacteria in babies and children

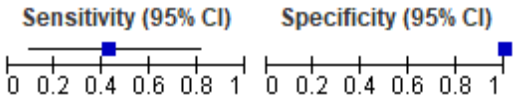
Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
La Scolea Jr 1984	48	0	15	1968	BM U	C	0.76 [0.64, 0.86]	1.00 [1.00, 1.00]



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

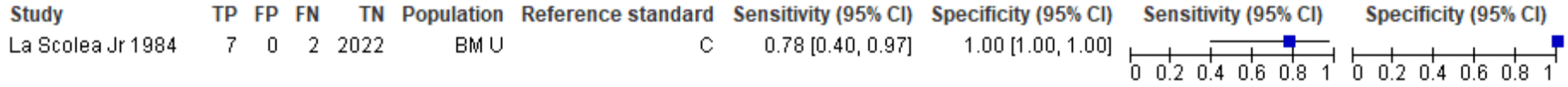
Figure 34: Forest plot for sensitivity and specificity of Gram and methylene blue staining for diagnosis of bacterial meningitis caused by N. meningitidis in babies and children

Study	TP	FP	FN	TN	Population	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
La Scolea Jr 1984	3	0	4	2024	BM U	C	0.43 [0.10, 0.82]	1.00 [1.00, 1.00]



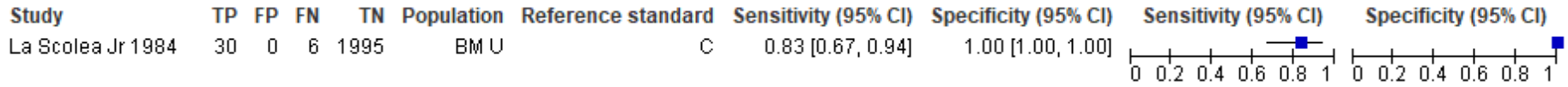
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitidis; TN: true negative; TP: true positive; U: undefined population

Figure 35: Forest plot for sensitivity and specificity of Gram and methylene blue staining for diagnosis of bacterial meningitis caused by S. pneumoniae in babies and children



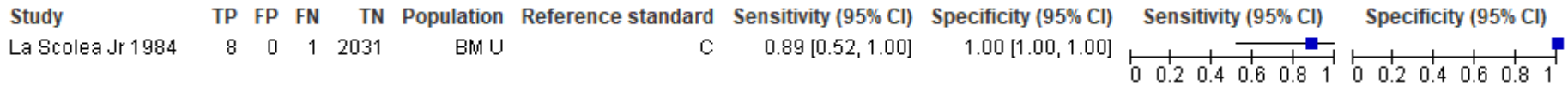
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 36: Forest plot for sensitivity and specificity of Gram and methylene blue staining for diagnosis of bacterial meningitis caused by H. influenzae in babies and children



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; TN: true negative; TP: true positive; U: undefined population

Figure 37: Forest plot for sensitivity and specificity of Gram and methylene blue staining for diagnosis of bacterial meningitis caused by group B Streptococcus in babies and children

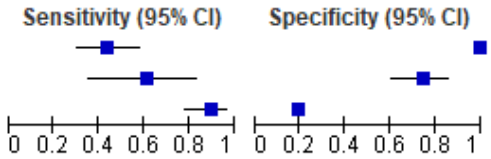


BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive; U: undefined population

Glucose concentration

Figure 38: Forest plot for the sensitivity and specificity of glucose concentration at all thresholds for diagnosis of bacterial meningitis in neonates

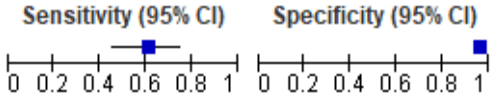
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Garges 2006a	24	25	31	4364	BM U	<1.11 mmol/L	C	0.44 [0.30, 0.58]	0.99 [0.99, 1.00]
Bonadio 1989	11	14	7	40	BM VM AM	<1.89 mmol/L	C OC	0.61 [0.36, 0.83]	0.74 [0.60, 0.85]
Garges 2006b	49	3529	6	860	BM U	<3.33 mmol/L	C	0.89 [0.78, 0.96]	0.20 [0.18, 0.21]



AM: aseptic meningitis; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 39: Forest plot for the sensitivity and specificity of glucose concentration at 'low'* threshold for diagnosis of bacterial meningitis caused by group B Streptococcus in neonates

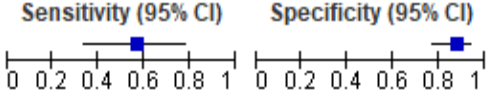
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Ansong 2009	28	578	18	12871	GBM GBS U	Low	C	0.61 [0.45, 0.75]	0.96 [0.95, 0.96]



**Low defined as <23mg/dL for premature neonates and <33mg/dL for term neonates*
C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; TN: true negative; TP: true positive; U: undefined population

Figure 40: Forest plot for the sensitivity and specificity of glucose concentration at <2.94mmol/L for diagnosis of bacterial meningitis in neonates, babies and children

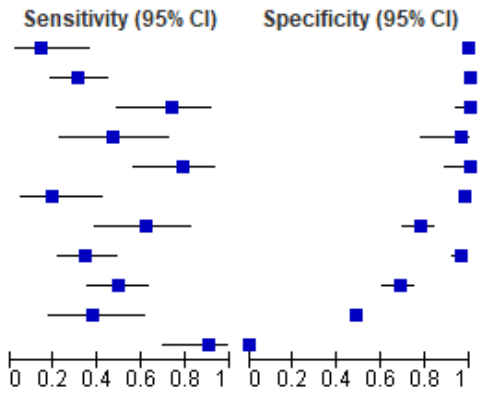
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
De Cauwer 2007	12	9	9	62	BM VM	<2.94 mmol/L	C B P	0.57 [0.34, 0.78]	0.87 [0.77, 0.94]



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

Figure 41: Forest plot for the sensitivity and specificity of glucose concentration at all thresholds for diagnosis of bacterial meningitis in babies and children

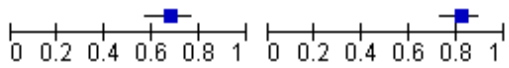
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2005a	3	71	18	7618	BM U	<1.11 mmol/L	C B Mic	0.14 [0.03, 0.36]	0.99 [0.99, 0.99]
Sormunen 1999a	17	0	38	182	BM VM	<2.0 mmol/L	C	0.31 [0.19, 0.45]	1.00 [0.98, 1.00]
Bonsu 2008	14	0	5	59	BM VM	<2.11 mmol/L	C	0.74 [0.49, 0.91]	1.00 [0.94, 1.00]
BenGershom 1986	8	1	9	22	BM VM NM	<2.2 mmol/L	C	0.47 [0.23, 0.72]	0.96 [0.78, 1.00]
Corrall 1981	18	0	5	32	BM VM	<2.22 mmol/L	C	0.78 [0.56, 0.93]	1.00 [0.89, 1.00]
Bonsu 2005b	4	186	17	7503	BM U	<2.22 mmol/L	C B Mic	0.19 [0.05, 0.42]	0.98 [0.97, 0.98]
Dubos 2006	13	32	8	111	BM AM	<2.5 mmol/L	C B OC CC	0.62 [0.38, 0.82]	0.78 [0.70, 0.84]
Sormunen 1999b	19	7	36	175	BM VM	<2.5 mmol/L	C	0.35 [0.22, 0.49]	0.96 [0.92, 0.98]
Sormunen 1999c	27	58	28	124	BM VM	<3.0 mmol/L	C	0.49 [0.35, 0.63]	0.68 [0.61, 0.75]
Bonsu 2005c	8	3947	13	3742	BM U	<3.33 mmol/L	C B Mic	0.38 [0.18, 0.62]	0.49 [0.48, 0.50]
Bonsu 2005d	19	7652	2	37	BM U	<6.66 mmol/L	C B Mic	0.90 [0.70, 0.99]	0.00 [0.00, 0.01]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; NM: non-meningitis; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 42: Forest plot for the sensitivity and specificity of glucose concentration at <2.5 mmol/L for diagnosis of bacterial meningitis in children

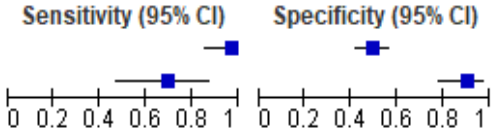
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2008	64	18	31	81	BM AM	<2.5 mmol/L	C B OC CC	0.67 [0.57, 0.77]	0.82 [0.73, 0.89]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive

Figure 43: Forest plot for the sensitivity and specificity of glucose concentration at all thresholds for diagnosis of bacterial meningitis in adults

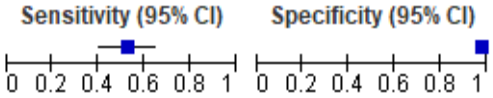
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Viallon 2011	34	111	1	107	BM VM VME	<2.2 mmol/L	C	0.97 [0.85, 1.00]	0.49 [0.42, 0.56]
Dastych 2015	16	5	7	45	BM AM	<2.7 mmol/L	C OC	0.70 [0.47, 0.87]	0.90 [0.78, 0.97]



AM: aseptic meningitis; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; VM: viral meningitis; VME: viral meningoencephalitis

Figure 44: Forest plot for the sensitivity and specificity of glucose concentration at <2.2mmol/L for diagnosis of bacterial meningitis in all ages

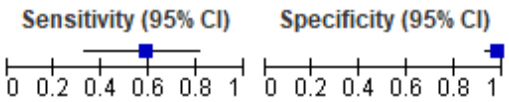
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Lindquist 1988a	37	14	33	587	BM U	<2.2 mmol/L	C OC	0.53 [0.41, 0.65]	0.98 [0.96, 0.99]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population

Figure 45: Forest plot for the sensitivity and specificity of CSF:serum glucose at a ratio of 0.40 for diagnosis of bacterial meningitis in neonates, babies and children

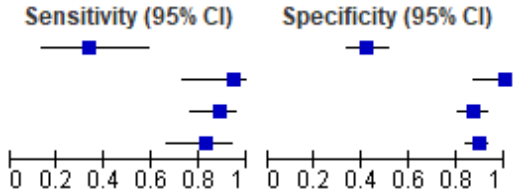
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Nelson 1986	10	2	7	101	BM AM NM	<0.40	C	0.59 [0.33, 0.82]	0.98 [0.93, 1.00]



AM: aseptic meningitis; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; NM: non-meningitis; TN: true negative; TP: true positive

Figure 46: Forest plot for the sensitivity and specificity of CSF:serum glucose at all thresholds for diagnosis of bacterial meningitis in adults

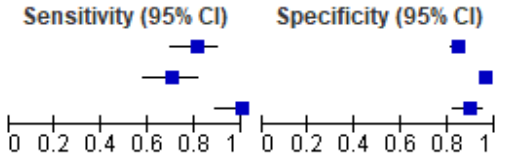
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Ray 2007	6	77	12	56	BM UM	<0.15	C B OC CC	0.33 [0.13, 0.59]	0.42 [0.34, 0.51]
Giulieri 2015	17	0	1	27	BM VM	<0.35	C B Mic Mol	0.94 [0.73, 1.00]	1.00 [0.87, 1.00]
Buch 2018	45	16	6	109	BM AME	<0.40	C B Mic Mol	0.88 [0.76, 0.96]	0.87 [0.80, 0.93]
Viallon 2011	29	24	6	194	BM VM VME	<0.48	C	0.83 [0.66, 0.93]	0.89 [0.84, 0.93]



AME: aseptic meningoencephalitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; OC: other CSF findings; TN: true negative; TP: true positive; UM: undefined meningitis; VM: viral meningitis; VME: viral meningoencephalitis

Figure 47: Forest plot for the sensitivity and specificity of CSF:serum glucose at all thresholds for diagnosis of bacterial meningitis in all ages

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Lindquist 1988a	52	94	12	505	BM U	<0.40	C OC	0.81 [0.70, 0.90]	0.84 [0.81, 0.87]
Lindquist 1988b	45	24	19	575	BM U	<0.50	C OC	0.70 [0.58, 0.81]	0.96 [0.94, 0.97]
D'Inzeo 2020	32	11	0	92	BM U	<0.66	C	1.00 [0.89, 1.00]	0.89 [0.82, 0.95]

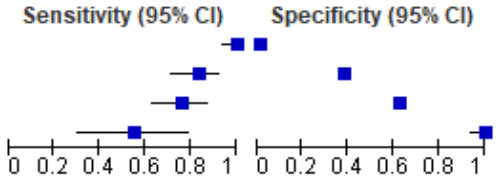


BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; CSF: cerebrospinal fluid; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population

Protein concentration

Figure 48: Forest plot for the sensitivity and specificity of protein concentration at all thresholds for diagnosis of bacterial meningitis in neonates

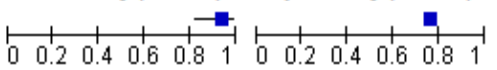
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Garges 2006a	55	4313	0	83	BM U	>040 mg/dL	C	1.00 [0.94, 1.00]	0.02 [0.02, 0.02]
Garges 2006b	46	2697	9	1699	BM U	>090 mg/dL	C	0.84 [0.71, 0.92]	0.39 [0.37, 0.40]
Garges 2006c	42	1624	13	2772	BM U	>120 mg/dL	C	0.76 [0.63, 0.87]	0.63 [0.62, 0.64]
Bonadio 1989	10	0	8	54	BM VM	>170 mg/dL	C OC	0.56 [0.31, 0.78]	1.00 [0.93, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 49: Forest plot for the sensitivity and specificity of protein concentration at elevated* threshold for diagnosis of bacterial meningitis caused by group B Streptococcus in neonates

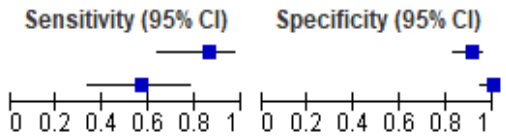
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Ansong 2009	43	3268	3	10181	GBM GBS U	Elevated	C	0.93 [0.82, 0.99]	0.76 [0.75, 0.76]



**Elevated defined as >151mg/dL for premature neonates and >171mg/dL for term neonates*
C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; TN: true negative; TP: true positive; U: undefined population

Figure 50: Forest plot for the sensitivity and specificity of protein concentration at all thresholds for diagnosis of bacterial meningitis in neonates, babies and children

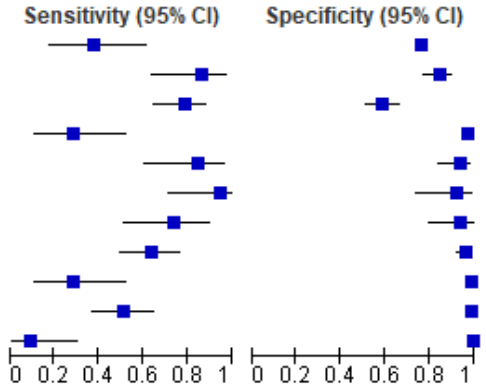
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Benjamin 1984	18	9	3	89	BM AM NM	>040 mg/dL	C	0.86 [0.64, 0.97]	0.91 [0.83, 0.96]
De Cauwer 2007	12	0	9	71	BM VM	>100 mg/dL	C B P	0.57 [0.34, 0.78]	1.00 [0.95, 1.00]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; P: CSF pleocytosis; TN: true negative; TP: true positive; VM: viral meningitis

Figure 51: Forest plot for the sensitivity and specificity of protein concentration at all thresholds for diagnosis of bacterial meningitis in babies and children

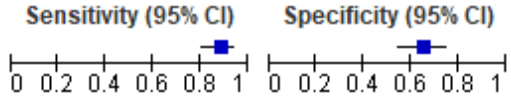
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Bonsu 2005a	8	1827	13	5862	BM U	>040 mg/dL	C B Mic	0.38 [0.18, 0.62]	0.76 [0.75, 0.77]
Dubos 2006	18	21	3	112	BM AM	>050 mg/dL	C B OC CC	0.86 [0.64, 0.97]	0.84 [0.77, 0.90]
Sormunen 1999a	43	75	12	107	BM VM	>050 mg/dL	C	0.78 [0.65, 0.88]	0.59 [0.51, 0.66]
Bonsu 2005b	6	230	15	7459	BM U	>080 mg/dL	C B Mic	0.29 [0.11, 0.52]	0.97 [0.97, 0.97]
Bonsu 2008	16	4	3	55	BM VM	>097 mg/dL	C	0.84 [0.60, 0.97]	0.93 [0.84, 0.98]
BenGershom 1986	16	2	1	23	BM VM NM	>100 mg/dL	C	0.94 [0.71, 1.00]	0.92 [0.74, 0.99]
Corrall 1981	17	2	6	30	BM VM	>100 mg/dL	C	0.74 [0.52, 0.90]	0.94 [0.79, 0.99]
Sormunen 1999b	35	7	20	175	BM VM	>100 mg/dL	C	0.64 [0.50, 0.76]	0.96 [0.92, 0.98]
Bonsu 2005c	6	89	15	7600	BM U	>120 mg/dL	C B Mic	0.29 [0.11, 0.52]	0.99 [0.99, 0.99]
Sormunen 1999c	28	2	27	180	BM VM	>150 mg/dL	C	0.51 [0.37, 0.65]	0.99 [0.96, 1.00]
Bonsu 2005d	2	33	19	7656	BM U	>200 mg/dL	C B Mic	0.10 [0.01, 0.30]	1.00 [0.99, 1.00]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; NM: non-meningitis; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 52: Forest plot for the sensitivity and specificity of protein concentration at >50mg/dL for diagnosis of bacterial meningitis in children

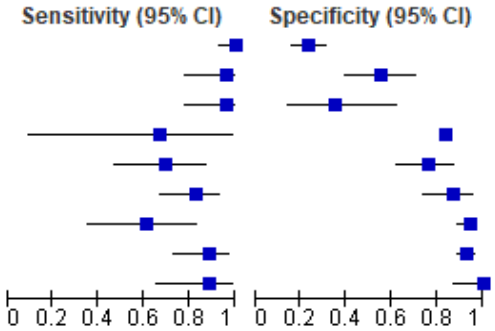
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Dubos 2008	84	35	11	65	BM AM	>050 mg/dL	C B OC CC	0.88 [0.80, 0.94]	0.65 [0.55, 0.74]



AM: aseptic meningitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive

Figure 53: Forest plot for the sensitivity and specificity of protein concentration at all thresholds for diagnosis of bacterial meningitis in adults

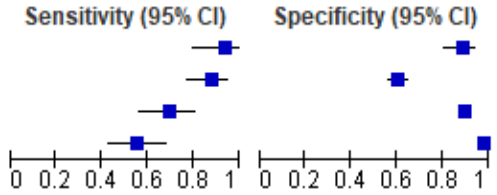
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Buch 2018	51	96	0	29	BM AME	>045 mg/dL	C B Mic Mol	1.00 [0.93, 1.00]	0.23 [0.16, 0.32]
White 2012a	22	20	1	25	BM VM	>060 mg/dL	C Mic Mol	0.96 [0.78, 1.00]	0.56 [0.40, 0.70]
White 2012b	22	11	1	6	BM CM	>060 mg/dL	C Mic Mol	0.96 [0.78, 1.00]	0.35 [0.14, 0.62]
White 2012c	2	362	1	1845	BM U	>060 mg/dL	C Mic Mol	0.67 [0.09, 0.99]	0.84 [0.82, 0.85]
Dastych 2015	16	12	7	38	BM AM	>101 mg/dL	C OC	0.70 [0.47, 0.87]	0.76 [0.62, 0.87]
Kleine 2003	33	6	7	40	BM AM VM	>130 mg/dL	C B Mic	0.82 [0.67, 0.93]	0.87 [0.74, 0.95]
Ray 2007	11	8	7	125	BM UM	>131 mg/dL	C B OC CC	0.61 [0.36, 0.83]	0.94 [0.88, 0.97]
Viallon 2011	31	15	4	203	BM VM VME	>188 mg/dL	C	0.89 [0.73, 0.97]	0.93 [0.89, 0.96]
Giulieri 2015	16	0	2	27	BM VM	>193.4 mg/dL	C B Mic Mol	0.89 [0.65, 0.99]	1.00 [0.87, 1.00]



AM: aseptic meningitis; AME: aseptic meningoencephalitis; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CC: clinical criteria; CI: confidence interval; CM: cryptococcal meningitis; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis: VM; viral meningitis; VME: viral meningoencephalitis

Figure 54: Forest plot for the sensitivity and specificity of protein concentration at all thresholds for diagnosis of bacterial meningitis in all ages

Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	30	12	2	91	BM U	>040 mg/dL	C	0.94 [0.79, 0.99]	0.88 [0.81, 0.94]
Lindquist 1988a	57	208	8	318	BM U	>050 mg/dL	C OC	0.88 [0.77, 0.95]	0.60 [0.56, 0.65]
Lindquist 1988b	45	54	20	472	BM U	>100 mg/dL	C OC	0.69 [0.57, 0.80]	0.90 [0.87, 0.92]
Lindquist 1988c	36	13	29	513	BM U	>150 mg/dL	C OC	0.55 [0.43, 0.68]	0.98 [0.96, 0.99]



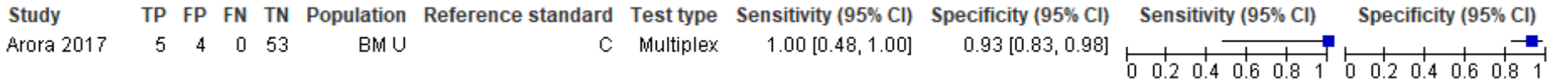
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; OC: other CSF findings; TN: true negative; TP: true positive; U: undefined population

Molecular diagnosis for bacterial pathogens

Figure 55: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in neonates and younger babies

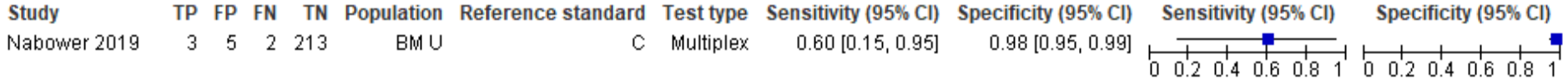
C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; GBM: group B Streptococcus meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 56: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by group B Streptococcus and Gram-negative bacilli* in neonates and younger babies



** Bacteria included in PCR panel: E. coli*
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; E. coli: Escherichia coli; FN: false negative; FP: false positive; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

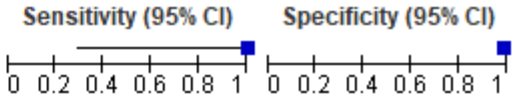
Figure 57: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by all bacteria in neonates, babies and children



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 58: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by N. meningitidis in neonates, babies and children

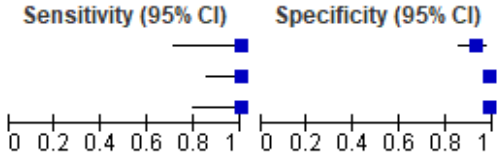
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Lee 2015	3	22	0	1549	MM U	C	Specific	1.00 [0.29, 1.00]	0.99 [0.98, 0.99]



C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 59: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in neonates, babies and children

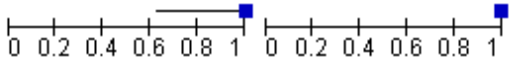
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2012	11	7	0	88	BM U	C	Specific	1.00 [0.72, 1.00]	0.93 [0.85, 0.97]
Kennedy 2007	23	17	0	1023	BM U	C	Specific	1.00 [0.85, 1.00]	0.98 [0.97, 0.99]
Alqayoudhi 2017	16	28	0	1962	BM U	C	Specific	1.00 [0.79, 1.00]	0.99 [0.98, 0.99]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 60: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by H. influenzae in neonates, babies and children

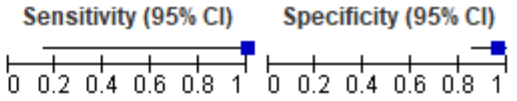
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Kennedy 2007	8	4	0	565	BM U	C	Specific	1.00 [0.63, 1.00]	0.99 [0.98, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 61: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by N. meningitidis in babies and children

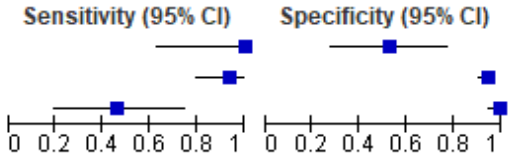
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Bryant 2004	2	2	0	44	MM UM US	C	Multiplex	1.00 [0.16, 1.00]	0.96 [0.85, 0.99]



C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; UM: undefined meningitis; US: undefined septicaemia

Figure 62: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by all bacteria in adults

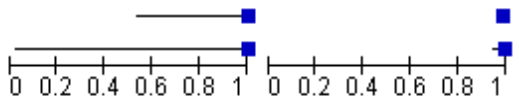
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Piccirilli 2018	8	8	0	9	BM U	C	Multiplex	1.00 [0.63, 1.00]	0.53 [0.28, 0.77]
Favaro 2013	30	15	2	249	BM U	C	Combined	0.94 [0.79, 0.99]	0.94 [0.91, 0.97]
Leli 2019	6	1	7	95	BM VM NM	C	Multiplex	0.46 [0.19, 0.75]	0.99 [0.94, 1.00]



Note. for Piccirilli 2018, the authors considered the false positive cases (according to culture results) as true positive based on results of real-time PCR, which would improve specificity
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 63: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by N. meningitidis in adults

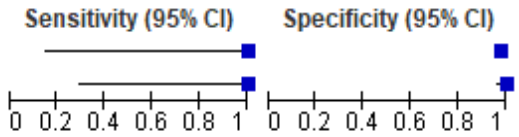
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Favaro 2013	6	5	0	285	BM U	C	Combined	1.00 [0.54, 1.00]	0.98 [0.96, 0.99]
Leli 2019	1	1	0	107	BM VM NM	C	Multiplex	1.00 [0.03, 1.00]	0.99 [0.95, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitidis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 64: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in adults

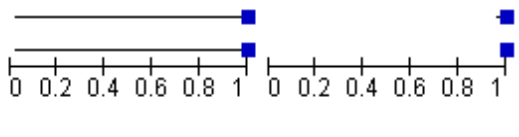
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Favaro 2013	2	6	0	288	BM U	C	Combined	1.00 [0.16, 1.00]	0.98 [0.96, 0.99]
Leli 2019	3	0	0	106	BM VM NM	C	Multiplex	1.00 [0.29, 1.00]	1.00 [0.97, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 65: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in adults

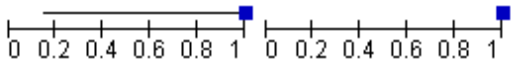
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Leli 2019	1	0	0	108	BM VM NM	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]
Favaro 2013	1	0	0	295	BM U	C	Combined	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 66: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by Gram-negative bacilli in adults

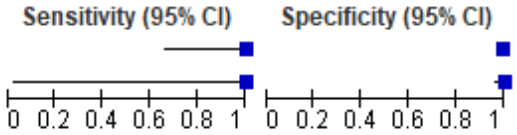
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Favaro 2013*	2	0	0	294	BM U	C	Combined	1.00 [0.16, 1.00]	1.00 [0.99, 1.00]



** Pathogens detected: E. coli*
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; E. coli: Escherichia coli; FN: false negative; FP: false positive; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 67: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by L. monocytogenes in adults

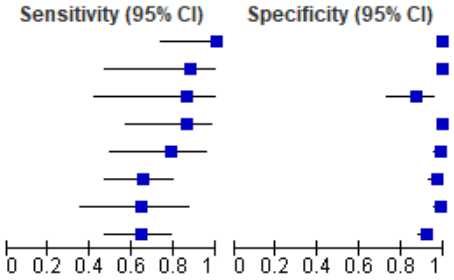
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Favaro 2013	9	2	0	285	BM U	C	Combined	1.00 [0.66, 1.00]	0.99 [0.98, 1.00]
Leli 2019	1	0	0	108	BM VM NM	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; L. monocytogenes: Listeria monocytogenes; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 68: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by all bacteria in all ages

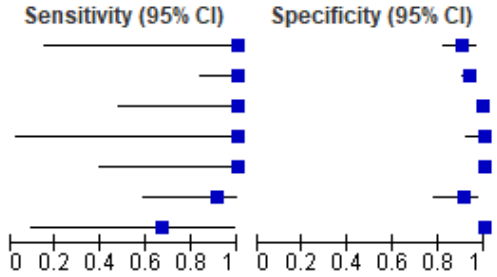
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Boudet 2019	12	6	0	690	BM VM NM	C	Multiplex	1.00 [0.74, 1.00]	0.99 [0.98, 1.00]
Leber 2016	7	15	1	1537	BM VM FM NM	C	Multiplex	0.88 [0.47, 1.00]	0.99 [0.98, 0.99]
Ena 2021	6	5	1	34	BME NBME	C	Multiplex	0.86 [0.42, 1.00]	0.87 [0.73, 0.96]
Vincent 2020	12	4	2	1106	BM U	C Mic Mol	Multiplex	0.86 [0.57, 0.98]	1.00 [0.99, 1.00]
Deutch 2006a	11	3	3	179	BM U	C	Broad-range + DNA	0.79 [0.49, 0.95]	0.98 [0.95, 1.00]
Schuurman 2004	24	6	13	184	BM U	C	Broad-range	0.65 [0.47, 0.80]	0.97 [0.93, 0.99]
Deutch 2006b	9	3	5	179	BM U	C	Broad-range	0.64 [0.35, 0.87]	0.98 [0.95, 1.00]
Welinder-Olsson 2007	25	26	14	280	BM VM UM NM	C	Broad-range	0.64 [0.47, 0.79]	0.92 [0.88, 0.94]



BM: bacterial meningitis; BME: bacterial meningoencephalitis; C: CSF bacterial culture; CI: confidence interval; FM: fungal meningitis; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis; VM: viral meningitis

Figure 69: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by N. meningitidis in all ages

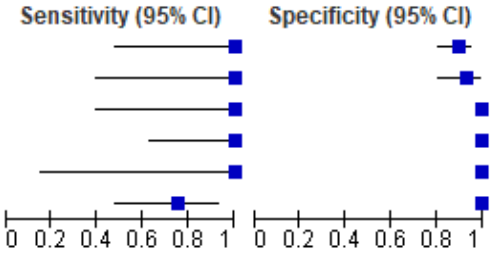
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Abdeldaim 2010	2	8	0	77	BM U	C Mic	Specific	1.00 [0.16, 1.00]	0.91 [0.82, 0.96]
Richardson 2003	21	16	0	244	BM UM	C	Specific	1.00 [0.84, 1.00]	0.94 [0.90, 0.96]
Deutch 2008	5	3	0	1007	BM U	C	Multiplex	1.00 [0.48, 1.00]	1.00 [0.99, 1.00]
Ena 2021	1	0	0	45	BME NBME	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.92, 1.00]
Boudet 2019	4	0	0	704	BM VM NM	C	Multiplex	1.00 [0.40, 1.00]	1.00 [0.99, 1.00]
Ni 1992	10	4	1	39	BM MD VM NM	C Mic	Specific	0.91 [0.59, 1.00]	0.91 [0.78, 0.97]
Vincent 2020	2	0	1	1121	BM U	C Mic Mol	Multiplex	0.67 [0.09, 0.99]	1.00 [1.00, 1.00]



BM: bacterial meningitis; BME: bacterial meningoencephalitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; MD: meningococcal disease; N. meningitidis: Neisseria meningitidis; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis; VM: viral meningitis

Figure 70: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in all ages

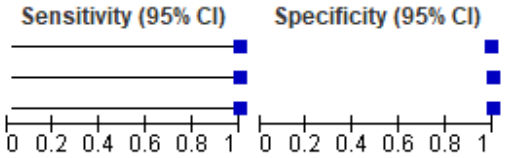
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Abdeldaim 2010	5	9	0	73	BM U	C Mic	Specific	1.00 [0.48, 1.00]	0.89 [0.80, 0.95]
Ena 2021	4	3	0	39	BME NBME	C	Multiplex	1.00 [0.40, 1.00]	0.93 [0.81, 0.99]
Leber 2016	4	12	0	1544	BM VM FM NM	C	Multiplex	1.00 [0.40, 1.00]	0.99 [0.99, 1.00]
Vincent 2020	8	4	0	1112	BM U	C Mic Mol	Multiplex	1.00 [0.63, 1.00]	1.00 [0.99, 1.00]
Boudet 2019	2	2	0	704	BM VM NM	C	Multiplex	1.00 [0.16, 1.00]	1.00 [0.99, 1.00]
Deutch 2008	12	7	4	992	BM U	C	Multiplex	0.75 [0.48, 0.93]	0.99 [0.99, 1.00]



BM: bacterial meningitis; BME: bacterial meningoencephalitis; C: CSF bacterial culture; CI: confidence interval; FM: fungal meningitis; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumonia; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 71: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by H. influenzae in all ages

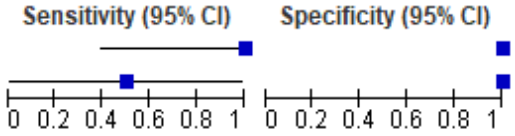
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Boudet 2019	1	2	0	705	BM VM NM	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]
Leber 2016	1	1	0	1558	BM VM FM NM	C	Multiplex	1.00 [0.03, 1.00]	1.00 [1.00, 1.00]
Vincent 2020	1	0	0	1123	BM U	C Mic Mol	Multiplex	1.00 [0.03, 1.00]	1.00 [1.00, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FM: fungal meningitis; FN: false negative; FP: false positive; H. influenzae; Haemophilus influenzae; Mic: microscopy; Mol: molecular diagnosis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 72: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in all ages

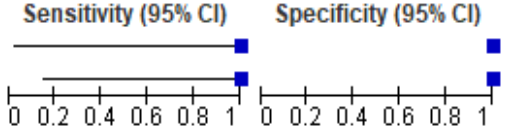
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Boudet 2019	4	1	0	703	BM VM NM	C	Multiplex	1.00 [0.40, 1.00]	1.00 [0.99, 1.00]
Vincent 2020	1	0	1	1122	BM U	C Mic Mol	Multiplex	0.50 [0.01, 0.99]	1.00 [1.00, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 73: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by Gram-negative bacilli in all ages

Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Boudet 2019*	1	1	0	706	BM VM NM	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]
Leber 2016*	2	1	0	1557	BM VM FM NM	C	Multiplex	1.00 [0.16, 1.00]	1.00 [1.00, 1.00]

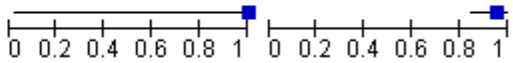


** Pathogens detected: E. coli*
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; E. coli: Escherichia coli; FM: fungal meningitis; FN: false negative; FP: false positive; NM: non-meningitis;

PCR: polymerase chain reaction; TN: true negative; TP: true positive; VM: viral meningitis

Figure 74: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by L. monocytogenes in all ages

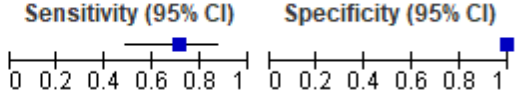
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Ena 2021	1	2	0	43	BME NBME	C	Multiplex	1.00 [0.03, 1.00]	0.96 [0.85, 0.99]



BME: bacterial meningoencephalitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; L. monocytogenes: Listeria monocytogenes; NBME: non-bacterial meningoencephalitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive

Figure 75: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by N. meningitidis and S. pneumoniae in all ages

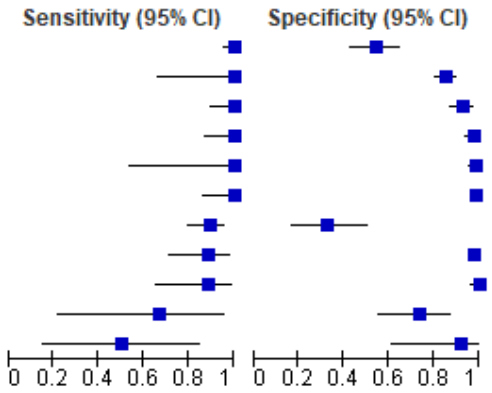
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Deutch 2008	17	10	7	981	BM U	C	Multiplex	0.71 [0.49, 0.87]	0.99 [0.98, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 76: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by all bacteria in undefined ages

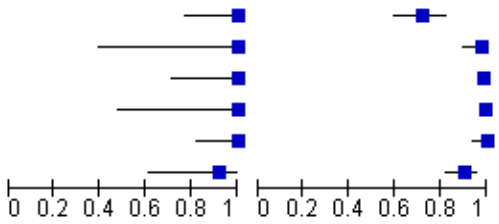
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Chiba 2009	81	40	0	47	BM U	C	Multiplex	1.00 [0.96, 1.00]	0.54 [0.43, 0.65]
Xirogianni 2009	9	37	0	216	BM VM NM	C	Multiplex	1.00 [0.66, 1.00]	0.85 [0.80, 0.89]
Poppert 2005	35	8	0	108	BM U	C	Multiplex	1.00 [0.90, 1.00]	0.93 [0.87, 0.97]
Pfefferle 2020	27	3	0	141	BM VM FM NM	C Mol	Multiplex	1.00 [0.87, 1.00]	0.98 [0.94, 1.00]
Wagner 2018	6	4	0	210	BM U	C	Multiplex	1.00 [0.54, 1.00]	0.98 [0.95, 0.99]
Seward 2000b	25	4	0	265	BM U	C	Multiplex	1.00 [0.86, 1.00]	0.99 [0.96, 1.00]
Esparcia 2011	60	23	7	11	BM U	C	Broad-range	0.90 [0.80, 0.96]	0.32 [0.17, 0.51]
Boving 2009	24	31	3	1129	BM U	C B Mic Mol	Multiplex	0.89 [0.71, 0.98]	0.97 [0.96, 0.98]
Rothman 2010	16	0	2	90	BM U	C	Multiplex	0.89 [0.65, 0.99]	1.00 [0.96, 1.00]
Meyer 2014	4	9	2	25	BM BI UI	C	Broad-range	0.67 [0.22, 0.96]	0.74 [0.56, 0.87]
Leitner 2016	4	1	4	11	BM U	C	Multiplex	0.50 [0.16, 0.84]	0.92 [0.62, 1.00]



Note. for Meyer 2015, the authors considered the false positive cases (according to culture results) as true positive based on clinical features, other CSF findings and antibiotic usage, which would improve specificity
BI: bacterial CNS infection; B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FM: fungal meningitis; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; UI: undefined CNS infection; VM: viral meningitis

Figure 77: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by N. meningitidis in undefined ages

Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Porritt 2000	14	20	0	51	BM U	C	Multiplex	1.00 [0.77, 1.00]	0.72 [0.60, 0.82]
Kotilainen 1998	4	1	0	51	BM UM NM	C	Broad-range	1.00 [0.40, 1.00]	0.98 [0.90, 1.00]
Seward 2000b	11	4	0	279	BM U	C	Multiplex	1.00 [0.72, 1.00]	0.99 [0.96, 1.00]
Boving 2009	5	3	0	1179	BM U	C B Mic Mol	Multiplex	1.00 [0.48, 1.00]	1.00 [0.99, 1.00]
Seward 2000a	19	0	0	55	BM U	C	Multiplex	1.00 [0.82, 1.00]	1.00 [0.94, 1.00]
Esparcia 2011	11	9	1	80	BM U	C	Broad-range	0.92 [0.62, 1.00]	0.90 [0.82, 0.95]

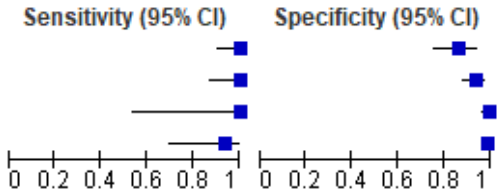


Note. for Porritt 2000, the authors considered the false positive cases (according to culture results) as true positive based on clinical presentation and other CSF findings, which would improve specificity

B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; N. meningitidis: Neisseria meningitidis; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; UM: undefined meningitis

Figure 78: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in undefined ages

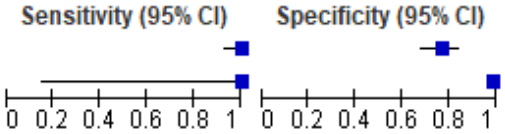
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Esparcia 2011	36	9	0	56	BM U	C	Broad-range	1.00 [0.90, 1.00]	0.86 [0.75, 0.93]
Chiba 2009	27	9	0	132	BM U	C	Multiplex	1.00 [0.87, 1.00]	0.94 [0.88, 0.97]
Wagner 2018	6	2	0	212	BM U	C	Multiplex	1.00 [0.54, 1.00]	0.99 [0.97, 1.00]
Boving 2009	15	13	1	1158	BM U	C B Mic Mol	Multiplex	0.94 [0.70, 1.00]	0.99 [0.98, 0.99]



B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; PCR: polymerase chain reaction; S. pneumoniae: Streptococcus pneumonia; TN: true negative; TP: true positive; U: undefined population

Figure 79: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by H. influenzae in undefined ages

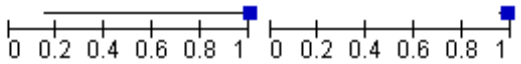
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Chiba 2009	48	28	0	92	BM U	C	Multiplex	1.00 [0.93, 1.00]	0.77 [0.68, 0.84]
Xirogianni 2009	2	3	0	257	BM VM NM	C	Multiplex	1.00 [0.16, 1.00]	0.99 [0.97, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; H. influenzae: Haemophilus influenzae; NM: non-meningitis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 80: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in undefined ages

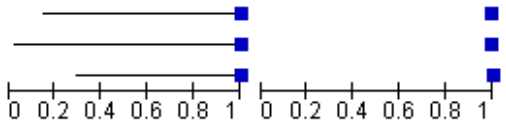
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chiba 2009	2	2	0	164	BM U	C	Multiplex	1.00 [0.16, 1.00]	0.99 [0.96, 1.00]		



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 81: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by Gram-negative bacilli in undefined ages

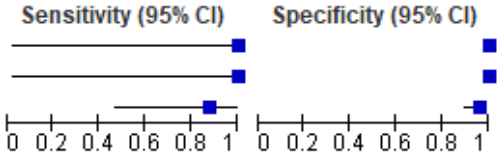
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Xirogianni 2009*	2	2	0	258	BM VM NM	C	Multiplex	1.00 [0.16, 1.00]	0.99 [0.97, 1.00]		
Boving 2009**	1	6	0	1180	BM U	C B Mic Mol	Multiplex	1.00 [0.03, 1.00]	0.99 [0.99, 1.00]		
Chiba 2009**	3	0	0	165	BM U	C	Multiplex	1.00 [0.29, 1.00]	1.00 [0.98, 1.00]		



** Pathogens detected: P. aeruginosa*
*** Pathogens detected: E. coli*
BM: bacterial meningitis; B: blood bacterial culture; C: CSF bacterial culture; CI: confidence interval; E. coli: Escherichia coli; FN: false negative; FP: false positive; Mic: microscopy; Mol: molecular diagnosis; NM: non-meningitis; PCR: polymerase chain reaction; P. aeruginosa: Pseudomonas aeruginosa; TN: true negative; TP: true positive; U: undefined population; VM: viral meningitis

Figure 82: Forest plot for sensitivity and specificity of PCR for diagnosis of bacterial meningitis caused by L. monocytogenes in undefined ages

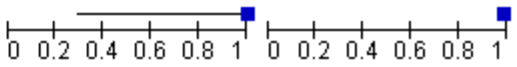
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Boving 2009	1	0	0	1186	BM U	C B Mic Mol	Multiplex	1.00 [0.03, 1.00]	1.00 [1.00, 1.00]
Chiba 2009	1	0	0	167	BM U	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.98, 1.00]
Esparcia 2011	7	4	1	89	BM U	C	Broad-range	0.88 [0.47, 1.00]	0.96 [0.89, 0.99]



B: blood bacterial culture; BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; L. monocytogenes: Listeria monocytogenes; Mic: microscopy; Mol: molecular diagnosis; PCR: polymerase chain reaction; TN: true negative; TP: true positive; U: undefined population

Figure 83: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by N. meningitidis in neonates, babies and children

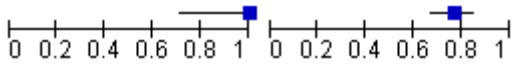
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Lee 2015	3	28	0	1543	MM U	C	Specific	1.00 [0.29, 1.00]	0.98 [0.97, 0.99]



C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; TN: true negative; TP: true positive; U: undefined population

Figure 84: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by S. pneumoniae in neonates, babies and children

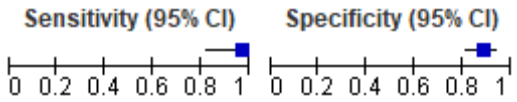
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2012	11	22	0	73	BM U	C	Specific	1.00 [0.72, 1.00]	0.77 [0.67, 0.85]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 85: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by all bacteria in all ages

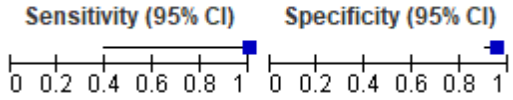
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	28	12	1	94	BM U	C	Multiplex	0.97 [0.82, 1.00]	0.89 [0.81, 0.94]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; TN: true negative; TP: true positive; U: undefined population

Figure 86: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by N. meningitidis in all ages

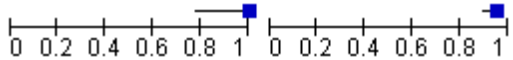
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	4	6	0	125	BM U	C	Multiplex	1.00 [0.40, 1.00]	0.95 [0.90, 0.98]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; N. meningitidis: Neisseria meningitidis; TN: true negative; TP: true positive; U: undefined population

Figure 87: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by S. pneumoniae in all ages

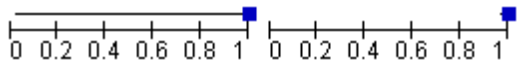
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	15	6	0	114	BM U	C	Multiplex	1.00 [0.78, 1.00]	0.95 [0.89, 0.98]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; S. pneumoniae: Streptococcus pneumoniae; TN: true negative; TP: true positive; U: undefined population

Figure 88: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by group B streptococcus in all ages

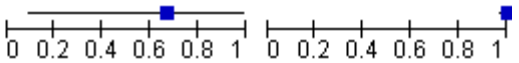
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	1	0	0	134	BM U	C	Multiplex	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; TN: true negative; TP: true positive; U: undefined population

Figure 89: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by Gram-negative bacilli in all ages

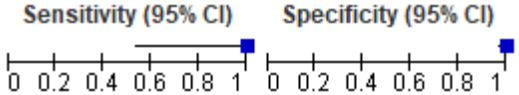
Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020*	2	0	1	132	BM U	C	Multiplex	0.67 [0.09, 0.99]	1.00 [0.97, 1.00]



** Pathogens detected: E. coli*
BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; E. coli: Escherichia coli; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; TN: true negative; TP: true positive; U: undefined population

Figure 90: Forest plot for sensitivity and specificity of LAMP for diagnosis of bacterial meningitis caused by L. monocytogenes in all ages

Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	6	0	0	129	BM U	C	Multiplex	1.00 [0.54, 1.00]	1.00 [0.97, 1.00]

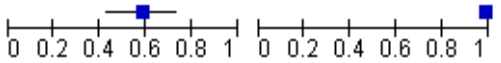


BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; L. monocytogenes: Listeria monocytogenes; TN: true negative; TP: true positive; U: undefined population

Combination index tests

Figure 91: Forest plot for the sensitivity and specificity of combined white cell count plus glucose concentration plus protein concentration at 'elevated'* threshold for diagnosis of bacterial meningitis in neonates

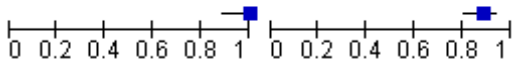
Study	TP	FP	FN	TN	Population	Threshold	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)
Ansong 2009	27	242	19	13207	GBM GBS U	Elevated	C	0.59 [0.43, 0.73]	0.98 [0.98, 0.98]



** Elevated thresholds defined as follows: white cell count >26 cells/µL for premature neonates and >23 cells/µL for term neonates; glucose concentration <1.3mmol/L for premature neonates and <1.8mmol/L for term neonates; protein concentration >151mg/dL for premature neonates and >171mg/dL for term neonates*
C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; TN: true negative; TP: true positive; U: undefined population

Figure 92: Forest plot for the sensitivity and specificity of combined Gram staining and LAMP for diagnosis of meningitis in all ages

Study	TP	FP	FN	TN	Population	Reference standard	Test type	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
D'Inzeo 2020	32	12	0	91	BM U	C	Multiplex	1.00 [0.89, 1.00]	0.88 [0.81, 0.94]		



BM: bacterial meningitis; C: CSF bacterial culture; CI: confidence interval; FN: false negative; FP: false positive; LAMP: loop mediated isothermal amplification; TN: true negative; TP: true positive; U: undefined population

Appendix F GRADE tables

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

White cell count

Table 5: Evidence profile for white cell count at all thresholds for diagnosis of bacterial meningitis in neonates

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 cells/µL										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,624	Sensitivity: 0.97 (0.88 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.01	1.00
			Specificity: 0.11 (0.10 to 0.12)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >8 cells/µL										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,624	Sensitivity: 0.83 (0.71 to 0.91)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.03	1.00
			Specificity: 0.61 (0.60 to 0.63)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >21 cells/µL										
1	Population:	4,624	Sensitivity:	Serious[1]	No serious	No serious	No serious	MODERATE	0.05	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
(Garges 2006)	BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture		0.79 (0.67 to 0.89)							
			Specificity: 0.81 (0.80 to 0.82)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >100 cells/µL										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,624	Sensitivity: 0.66 (0.52 to 0.78)	Serious[1]	No serious	No serious	No serious	MODERATE	0.12	1.00
			Specificity: 0.94 (0.93 to 0.94)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[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 6: Evidence profile for white cell count at 'elevated'* thresholds for diagnosis of bacterial meningitis caused by group B streptococcus in neonates

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: 'Elevated' (>26 cells/µL for premature and >23 cells/µL for term neonates)										
1 (Ansong 2009)	Population: GBM GBS U (neonates with lumbar puncture performed) Reference standard: CSF	13,495	Sensitivity: 0.89 (0.76 to 0.96)	No serious	No serious	No serious	Serious[1]	MODERATE	0.02	1.00
			Specificity: 0.82 (0.81 to 0.82)	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
	bacterial culture									

CI: confidence interval; CSF: cerebrospinal fluid; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 7: Evidence profile for white cell count at all thresholds for diagnosis of bacterial meningitis in neonates and babies

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: >8 cells/µL										
1 (Bonsu 2003)	Population: BM U (routine sepsis evaluation)	5,353	Sensitivity: 0.77 (0.55 to 0.92)	No serious	No serious	No serious	Serious[1]	MODERATE	0.01	1.00
	Reference standard: CSF bacterial culture		Specificity: 0.79 (0.78 to 0.80)	No serious	No serious	No serious	No serious	HIGH		
Threshold: >10 cells/µL										
1 (Bonsu 2003)	Population: BM U (routine sepsis evaluation)	5,353	Sensitivity: 0.73 (0.50 to 0.89)	No serious	No serious	No serious	No serious	HIGH	0.02	1.00
	Reference standard: CSF bacterial culture		Specificity: 0.83 (0.82 to 0.84)	No serious	No serious	No serious	No serious	HIGH		
Threshold: >100 cells/µL										
1 (Bonsu 2003)	Population: BM U (routine sepsis evaluation)	5,353	Sensitivity: 0.41 (0.21 to 0.64)	No serious	No serious	No serious	Serious[1]	MODERATE	0.04	1.00
	Reference standard: CSF bacterial culture		Specificity: 0.96 (0.96 to 0.97)	No serious	No serious	No serious	No serious	HIGH		
Threshold: >1000 cells/µL										
1 (Bonsu	Population: BM U	5,353	Sensitivity:	No	No serious	No serious	No serious	HIGH	0.12	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
2003)	(routine sepsis evaluation) Reference standard: CSF bacterial culture		0.23 (0.08 to 0.45)	serious						
			Specificity: 0.99 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
Threshold: Not applicable										
1 (Bonsu 2003)	Population: BM U (routine sepsis evaluation) Reference standard: CSF bacterial culture	5,353	AUC: 0.82 (0.71 to 0.94)	No serious	No serious	No serious	Serious[1]	MODERATE	NA	NA

AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 8: Evidence profile for white cell count at >8 cells/µL for diagnosis of bacterial meningitis in neonates, 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
Threshold: >8 cells/µL										
1 (Nelson 1986)	Population: BM AM NM Reference standard: CSF bacterial culture	130	Sensitivity: 0.94 (0.73 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.38	0.99
			Specificity: 0.75 (0.66 to 0.83)	No serious	No serious	No serious	No serious	HIGH		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value
[1] 95% CI crosses 1 decision making threshold

Table 9: Evidence profile for white cell count at all thresholds 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
Threshold: >3 cells/µL										
1 (Freedman 2001)	Population: BM U (lumbar puncture for suspected acute meningitis) Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	1,617	Sensitivity: 0.89 (0.75 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.07	1.00
			Specificity: 0.70 (0.67 to 0.72)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >30 cells/µL										
1 (Freedman 2001)	Population: BM U (lumbar puncture for suspected acute meningitis) Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	1,617	Sensitivity: 0.75 (0.60 to 0.87)	Serious[1]	No serious	No serious	No serious	MODERATE	0.22	0.99
			Specificity: 0.93 (0.91 to 0.94)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >100 cells/µL										
1 (Sormunen 1999)	Population: BM VM Reference standard: CSF bacterial culture	237	Sensitivity: 0.89 (0.78 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.29	0.91
			Specificity: 0.34 (0.27 to 0.41)	Serious[1]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: > 200 cells/µL										
1 (Dubos 2006)	Population: BM AM	167	Sensitivity: 0.76 (0.53 to 0.92)	No serious	No serious	No serious	Serious[2]	MODERATE	0.30	0.96
	Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria		Specificity: 0.75 (0.67 to 0.81)	No serious	No serious	No serious	No serious	HIGH		
Threshold: >321 cells/µL										
1 (Agueda 2013)	Population: BM VM AM	295	Sensitivity: 0.81 (0.63 to 0.93)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW	0.34	0.97
	Reference standard: CSF bacterial culture and/or microscopy		Specificity: 0.81 (0.76 to 0.86)	Very serious[3]	No serious	No serious	No serious	LOW		
Threshold: >500 cells/µL										
1 (BenGershom 1986)	Population: BM VM NM	42	Sensitivity: 0.88 (0.64 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.68	0.90
	Reference standard: CSF bacterial culture and/or other undefined reference standard		Specificity: 0.72 (0.51 to 0.88)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Corrall 1981)	Population: BM VM NM	55	Sensitivity: 0.74 (0.52 to 0.90)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.89	0.83

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: CSF bacterial culture		Specificity: 0.94 (0.79 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.78 (0.65 to 0.88)	Serious[1]	No serious	No serious	No serious	MODERATE	0.68	0.93
	Reference standard: CSF bacterial culture		Specificity: 0.89 (0.84 to 0.93)	Serious[1]	No serious	No serious	Serious[2]	LOW		
Threshold: >597 cells/µL										
1 (Bonsu 2008)	Population: BM VM	78	Sensitivity: 0.63 (0.38 to 0.84)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.75	0.89
	Reference standard: CSF bacterial culture		Specificity: 0.93 (0.84 to 0.98)	Serious[1]	No serious	No serious	Serious[2]	LOW		
Threshold: >1000 cells/µL										
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.75 (0.61 to 0.85)	Serious[1]	No serious	No serious	No serious	MODERATE	0.89	0.93
	Reference standard: CSF bacterial culture		Specificity: 0.97 (0.94 to 0.99)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >2000 cells/µL										
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.64 (0.50 to 0.76)	Serious[1]	No serious	No serious	No serious	MODERATE	0.95	0.90
	Reference standard: CSF bacterial culture		Specificity: 0.99 (0.96 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; 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] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 10: Evidence profile for white cell count at >200 cells/µL for diagnosis of bacterial meningitis in children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: >200 cells/µL										
1 (Dubos 2008)	Population: BM AM Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	198	Sensitivity: 0.79 (0.70 to 0.87)	Serious[1]	No serious	No serious	No serious	MODERATE	0.70	0.78
			Specificity: 0.69 (0.59 to 0.77)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 11: Evidence profile for white cell count at all thresholds 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
Threshold: >15 cells/µL										
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	Sensitivity: 0.98 (0.90 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE	0.31	0.93
			Specificity: 0.11 (0.06 to 0.18)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >90 cells/µL										
1 (White 2012)	Population: BM VM Reference standard: CSF	68	Sensitivity: 0.96 (0.78 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.42	0.93
			Specificity:	Serious[1]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	bacterial culture, microscopy and/or molecular diagnosis		0.31 (0.18 to 0.47)							
	Population: BM CM Reference standard: CSF bacterial culture, microscopy and/or molecular diagnosis	40	Sensitivity: 0.96 (0.78 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.85	0.93
			Specificity: 0.76 (0.50 to 0.93)	Serious[1]	No serious	No serious	Serious[2]	LOW		
	Population: BM U (over 5 years of age receiving lumbar puncture) Reference standard: CSF bacterial culture, microscopy and/or molecular diagnosis	2,230	Sensitivity: 0.96 (0.79 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.02	1.00
			Specificity: 0.48 (0.46 to 0.50)	Serious[1]	No serious	No serious	Serious[2]	LOW		
Threshold: >300 cells/µL										
1 (Ray 2007)	Population: BM UM Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	151	Sensitivity: 0.50 (0.26 to 0.74)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW	0.53	0.93
			Specificity: 0.94 (0.88 to 0.97)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: >388 cells/µL										
1 (Giulieri	Population: BM VM	45	Sensitivity:	Very	No serious	No serious	Serious[2]	VERY LOW	0.88	0.89

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
2015)	Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis		0.83 (0.59 to 0.96)	serious[3]						
			Specificity: 0.93 (0.76 to 0.99)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: >5.1 M/L										
1 (Kleine 2003)	Population: BM VM AM Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy	86	Sensitivity: 0.72 (0.56 to 0.85)	No serious	No serious	No serious	No serious	HIGH	0.83	0.78
			Specificity: 0.87 (0.74 to 0.95)	No serious	No serious	No serious	Serious[2]	MODERATE		
Threshold: Not applicable										
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	AUC: 0.80 (0.72 to 0.88)	Serious[1]	No serious	No serious	Serious[2]	LOW	NA	NA
1 (Ray 2007)	Population: BM UM Reference standard: CSF bacterial culture, blood bacterial	151	AUC: 0.59 (0.21 to 0.82)	Very serious[3]	No serious	No serious	Very serious[4]	VERY LOW	NA	NA

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	culture, other CSF findings and/or clinical criteria									
1 (Giulieri 2015)	Population: BM VM Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	45	AUC: 0.89 (0.76 to 1.00)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW	NA	NA

AM: aseptic meningitis; AME: aseptic meningoencephalitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CM: cryptococcal meningitis; CSF: cerebrospinal fluid; NA: not applicable; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; UM: undefined meningitis; 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] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

[4] 95% CI crosses 2 decision making thresholds

Table 12: Evidence profile for white cell count at all thresholds for diagnosis of bacterial meningitis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: >5 cells/µL										
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 1.00 (0.89 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.73	1.00
			Specificity: 0.88 (0.81 to 0.94)	No serious	No serious	No serious	Serious[1]	MODERATE		
Threshold: >500 cells/µL										

1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	711	Sensitivity: 0.71 (0.60 to 0.81)	Serious[2]	No serious	No serious	No serious	MODERATE	0.65	0.96
			Specificity: 0.95 (0.93 to 0.97)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: >1000 cells/µL										
1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	711	Sensitivity: 0.61 (0.49 to 0.72)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.77	0.95
			Specificity: 0.98 (0.96 to 0.99)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: >1500 cells/µL										
1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	711	Sensitivity: 0.51 (0.39 to 0.62)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.89	0.94
			Specificity: 0.99 (0.98 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: Elevated (≥10 cells/µL for neonates and ≥5 cells/µL for adults)										
1 (Boudet 2019)	Population: BM VM NM Reference standard:	708	Sensitivity: 1.00 (0.74 to 1.00)	Very serious[3]	No serious	No serious	Serious[1]	VERY LOW	0.75	1.00
			Specificity:	Very	No serious	No serious	No serious	LOW		

	CSF bacterial culture		0.99 (0.99 to 1.00)	serious[3]						

BM: bacterial meningitis; CI: confidence interval; CNS: central nervous system; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; 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
[3] 95% CI crosses 2 decision making thresholds

Neutrophil count

Table 13: Evidence profile for neutrophil count at all thresholds for diagnosis of bacterial meningitis in neonates, 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
Threshold: >50 cells/cm										
1 (Benjamin 1984)	Population: BM VM AM	119	Sensitivity: 0.90 (0.70 to 0.99)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.90	0.98
	Reference standard: CSF bacterial culture		Specificity: 0.98 (0.93 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >80%										
1 (De Cauwer 2007)	Population: BM VM	72	Sensitivity: 0.82 (0.57 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.52	0.93
	Reference standard: CSF bacterial culture and /or blood bacterial culture with CSF pleocytosis		Specificity: 0.76 (0.63 to 0.87)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; 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: Evidence profile for neutrophil count at all thresholds 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
Threshold >1%										
1 (Bonsu 2005)	Population: BM U	7707	Sensitivity: 0.89 (0.65 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.01	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.61 (0.59 to 0.62)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: >25%										
1 (Bonsu 2005)	Population: BM U	7707	Sensitivity: 0.72 (0.47 to 0.90)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.02	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.93 (0.92 to 0.93)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: >50%										
1 (Negrini 2000)	Population: BM AM	158	Sensitivity: 0.90 (0.68 to 0.99)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.19	0.97
	Reference standard: CSF bacterial culture, blood bacterial culutre and/or CSF pleocytosis		Specificity: 0.43 (0.35 to 0.52)	Serious[3]	No serious	No serious	Serious[2]	LOW		

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 2005)	Population: BM U	7707	Sensitivity: 0.61 (0.36 to 0.83)	Very serious[1]	No serious	No serious	Very serious[4]	VERY LOW	0.05	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.97 (0.97 to 0.97)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: >74%										
1 (Bonsu 2008)	Population: BM VM	78	Sensitivity: 0.74 (0.49 to 0.91)	Serious[3]	No serious	No serious	Very serious[4]	VERY LOW	0.58	0.91
	Reference standard: CSF bacterial culture		Specificity: 0.83 (0.71 to 0.92)	Serious[3]	No serious	No serious	Serious[2]	LOW		
Threshold: >75%										
1 (Bonsu 2005)	Population: BM U	7707	Sensitivity: 0.50 (0.26 to 0.74)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.12	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.99 (0.99 to 0.99)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: >100 cells/µL										
1 (Dubos 2006)	Population: BM AM	164	Sensitivity: 0.81 (0.58 to 0.95)	No serious	No serious	No serious	Serious[2]	MODERATE	0.39	0.97
	Reference		Specificity:	No	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
	standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria		0.81 (0.74 to 0.87)	serious						
Threshold: >200 cells/µl										
1 (Corrall 1981)	Population: BM VM NM	55	Sensitivity: 0.91 (0.72 to 0.99)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.81	0.93
	Reference standard: CSF bacterial culture		Specificity: 0.84 (0.67 to 0.95)	Serious[3]	No serious	No serious	Serious[2]	LOW		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold
[3] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[4] 95% CI crosses 2 decision making thresholds

Table 15: Evidence profile for neutrophil count at >100 cells/µL for diagnosis of bacterial meningitis in children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: >100 cells/µl										
1 (Dubos 2008)	Population: BM AM	184	Sensitivity: 0.82 (0.73 to 0.89)	Serious[1]	No serious	No serious	No serious	MODERATE	0.76	0.79
	Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria		Specificity: 0.73 (0.63 to 0.82)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: Not applicable										

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 2008)	Population: BM AM Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	184	AUC: 0.87 (0.80 to 0.93)	Serious[1]	No serious	No serious	Serious[2]	LOW	NA	NA

AM: aseptic meningitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; 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 1 decision making threshold

Table 16: Evidence profile for neutrophil count at all thresholds 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
Threshold: >37 cells/µl										
1 (Dastych 2015)	Population: BM AM Reference standard: CSF bacterial culture and/or other CSF findings	73	Sensitivity: 0.91 (0.72 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.81	0.96
			Specificity: 0.90 (0.78 to 0.97)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: >118 cells/µl										
1 (Viallon 2011)	Population: BM VM VME Reference standard: CSF bacterial culture	253	Sensitivity: 0.80 (0.63 to 0.92)	Serious[2]	No serious	No serious	Serious[2]	LOW	0.46	0.96
			Specificity: 0.85 (0.79 to 0.89)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: >260 cells/µl										
1 (Giulieri 2015)	Population: BM VM Reference standard: CSF bacterial	45	Sensitivity: 0.94 (0.73 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	1.00	0.96
			Specificity:	Very	No serious	No serious	Serious[2]	VERY LOW		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	culture, blood bacterial culture, microscopy and/or molecular diagnosis		1.00 (0.87 to 1.00)	serious[1]						
Threshold: >67%										
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	Sensitivity: 0.80 (0.67 to 0.90)	Serious[2]	No serious	No serious	Serious[2]	LOW	0.68	0.91
			Specificity: 0.85 (0.77 to 0.91)	Serious[2]	No serious	No serious	Serious[2]	LOW		
Threshold: Not applicable										
1 (Dastych 2015)	Population: BM AM Reference standard: CSF bacterial culture and/or other CSF findings	73	AUC: 0.93 (0.85 to 0.98)	Very serious[1]	No serious	No serious	No serious	LOW	NA	NA
1 (Viallon 2011)	Population: BM VM VME Reference standard: CSF bacterial culture	253	AUC: 0.86 (0.86 to 0.94)	Serious[2]	No serious	No serious	No serious	MODERATE	NA	NA
1 (Giulieri 2015)	Population: BM VM Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	45	AUC: 0.97 (0.91 to 1.00)	Very serious[2]	No serious	No serious	No serious	LOW	NA	NA

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	AUC: 0.89 (0.84 to 0.94)	Serious[2]	No serious	No serious	No serious	MODERATE	NA	NA

AM: aseptic meningitis; AME: aseptic meningoencephalitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; VM: viral meningitis; VME: viral meningoencephalitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] 95% CI crosses 1 decision making threshold

Microscopy for bacteria

Table 17: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by all bacteria in neonates

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bonadio 1989)	Population: BM VM AM	72	Sensitivity: 0.44 (0.22 to 0.69)	No serious	Serious[1]	No serious	Serious[2]	LOW	1.00	0.84
	Reference standard: CSF bacterial culture and/or other CSF findings		Specificity: 1.00 (0.93 to 1.00)	No serious	Serious[1]	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; 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 18: Evidence profile for Gram staining diagnosis of bacterial meningitis caused by for all bacteria in neonates and younger babies

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 (Balamuth 2021)	Population: BM U (Babies aged ≤60 days with CSF culture obtained). Reference standard: CSF bacterial culture	20947	Sensitivity: 0.34 (0.28 to 0.41)	No serious	No serious	No serious	No serious	HIGH	0.61	0.99
			Specificity: 1.00 (1.00 to 1.00	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population

Table 19: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in neonates, 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 (Kim 2012)	Population: BM U (< 5 years old with suspected meningitis) Reference standard: CSF bacterial culture	106	Sensitivity: 0.91 (0.59 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.63	0.99
			Specificity: 0.94 (0.87 to 0.98)	No serious	No serious	No serious	Serious[1]	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 20: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by all bacteria 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 (Brizzi 2012)	Population: BM U (<18 years old with lumbar puncture performed)	1938	Sensitivity: 0.94 (0.71 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.47	1.00
			Specificity: 0.99 (0.99 to	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: CSF bacterial culture		0.99)							
1 (Corrall 1981)	Population: BM VM NM	55	Sensitivity: 0.74 (0.52 to 0.90)	Serious[2]	No serious	No serious	Serious[1]	LOW	1.00	0.84
	Reference standard: CSF bacterial culture		Specificity: 1.00 (0.89 to 1.00)	Serious[2]	No serious	No serious	Serious[1]	LOW		
1 (Khurana 1987)	Population: BM AM NM	138	Sensitivity: 0.69 (0.39 to 0.91)	No serious	No serious	No serious	Very serious[3]	LOW	0.82	0.97
	Reference standard: CSF bacterial culture		Specificity: 0.98 (0.94 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Neuman 2008)	Population: BM U (≤21 years of age admitted to emergency department and lumbar puncture performed.)	17569	Sensitivity: 0.67 (0.54 to 0.78)	No serious	No serious	No serious	No serious	HIGH	0.60	1.00
	Reference standard: CSF bacterial culture		Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; 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
[3] 95% CI crosses 2 decision making thresholds

Table 21: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by all bacteria 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

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Dunbar 1998)	Population: BM U (CSF specimens submitted to study laboratory) Reference standard: CSF bacterial culture	2415	Sensitivity: 0.92 (0.64 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[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 22: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by N. meningitidis 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 (Dunbar 1998)	BM U (CSF specimens submitted to study laboratory) Reference standard: CSF bacterial culture	2415	Sensitivity: 1.00 (0.16 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[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 23: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae 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 (Dunbar	Population: BM	2415	Sensitivity:	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	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
1998)	U (CSF specimens submitted to study laboratory) Reference standard: CSF bacterial culture		1.00 (0.54 to 1.00)							
			Specificity: 1.00 (1.00 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population
[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 24: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by all bacteria in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 0.69 (0.50 to 0.84)	No serious	No serious	No serious	No serious	HIGH	0.79	0.91
			Specificity: 0.94 (0.88 to 0.98)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Deutch 2006)	Population: BM U (All CSF specimens from clinical departments)	196	Sensitivity: 0.64 (0.35 to 0.87)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.90	0.97
			Specificity: 0.99 (0.97 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		

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: CSF bacterial culture									

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[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 25: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by N. meningitidis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 0.50 (0.07 to 0.93)	No serious	No serious	No serious	Very serious[1]	LOW	0.50	0.98
			Specificity: 0.98 (0.50 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; N. meningitidis: Neisseria meningitidis; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 26: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical	135	Sensitivity: 0.73 (0.45 to 0.92)	No serious	No serious	No serious	Very serious[1]	LOW	0.73	0.97
			Specificity: 0.97 (0.93 to	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
	suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture		0.99)							

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; S. pneumoniae: Streptococcus pneumoniae; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 27: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by group B Streptococcus in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	1.00
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 28: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by Gram-negative bacilli in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)*	Population: BM U (CSF samples	135	Sensitivity: 1.00 (0.40 to	No serious	No serious	No serious	Very serious[1]	LOW	1.00	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
	from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture		1.00)							
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

** Pathogens detected: E. coli and C. koseri*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; C. koseri: Citrobacter koseri; E.coli: Escherichia coli; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 29: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by L. monocytogenes in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 0.33 (0.04 to 0.78)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	0.97
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; L. monocytogenes: Listeria monocytogenes; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 30: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by all bacteria in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bortolussi 1982)	Population: BM U (Patients with suspected bacterial meningitis) Reference standard: CSF bacterial culture	202	Sensitivity: 0.80 (0.65 to 0.90)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.97	0.95
			Specificity: 0.99 (0.97 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Jorgensen 1978)	Population: BM UM NM Reference standard: CSF bacterial culture	305	Sensitivity: 0.68 (0.56 to 0.78)	No serious	No serious	No serious	No serious	HIGH	1.00	0.91
			Specificity: 1.00 (0.98 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Kotilainen 1998)	Population: BM UM NM Reference standard: CSF bacterial culture	56	Sensitivity: 0.50 (0.07 to 0.93)	Serious[1]	No serious	No serious	Very serious[3]	VERY LOW	1.00	0.96
			Specificity: 1.00 (0.93 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Meyer 2014)	Population: BM BI UI Reference standard: CSF bacterial culture	40	Sensitivity: 0.33 (0.04 to 0.78)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.67	0.89
			Specificity: 0.97 (0.85 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		

AM: aseptic meningitis; BI: bacterial CNS infection; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; UI: undefined CNS infection; UM: undefined 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 31: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by N. meningitidis in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bortolussi 1982)	Population: BM U (Patients with suspected bacterial meningitis) Reference standard: CSF bacterial culture	202	Sensitivity: 0.91 (0.59 to 1.00)	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		
1 (Jorgensen 1978)	Population: BM UM NM Reference standard: CSF bacterial culture	305	Sensitivity: 0.83 (0.36 to 1.00)	No serious	No serious	No serious	Very serious[3]	LOW	1.00	1.00
			Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; N. meningitis: Neisseria meningitidis; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; UM: undefined 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 32: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by S. pneumoniae in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bortolussi 1982)	Population: BM U (Patients with suspected bacterial meningitis) Reference standard: CSF bacterial culture	202	Sensitivity: 0.75 (0.19 to 0.99)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	1.00
			Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Jorgensen 1978)	Population: BM UM NM	305	Sensitivity: 0.50 (0.12 to	No serious	No serious	No serious	Very 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
			0.88)							
	Reference standard: CSF bacterial culture		Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive valuer; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population; UM: undefined 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

Table 33: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by H. influenzae in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Jorgensen 1978)	Population: BM UM NM	305	Sensitivity: 0.79 (0.63 to 0.90)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	0.97
	Reference standard: CSF bacterial culture		Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Bortolussi 1982)	Population: BM U (Patients with suspected bacterial meningitis)	202	Sensitivity: 0.76 (0.55 to 0.91)	Serious[2]	No serious	No serious	Serious[1]	LOW	1.00	0.97
	Reference standard: CSF bacterial culture		Specificity: 1.00 (0.98 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; H. influenzae: Haemophilus influenzae; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; UM: undefined meningitis
[1] 95% CI crosses 2 decision making thresholds
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 34: Evidence profile for Gram staining for diagnosis of bacterial meningitis caused by group B Streptococcus in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bortolussi	Population: BM U	202	Sensitivity:	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	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
1982)	(Patients with suspected bacterial meningitis) Reference standard: CSF bacterial culture		0.67 (0.09 to 0.99)							
			Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Jorgensen 1978)	Population: BM UM NM Reference standard: CSF bacterial culture	305	Sensitivity: 0.50 (0.07 to 0.93)	No serious	No serious	No serious	Very serious[2]	LOW	1.00	0.99
			Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; UM: undefined 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

Table 35: Evidence profile for Gram staining for Gram staining for diagnosis of bacterial meningitis caused by Gram-negative bacilli in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bortolussi 1982)*	Population: BM U (Patients with suspected bacterial meningitis) Reference standard: CSF bacterial culture	202	Sensitivity: 1.00 (0.16 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.67	1.00
			Specificity: 0.99 (0.97 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Jorgensen 1978)**	Population: BM UM NM Reference standard: CSF	305	Sensitivity: 0.42 (0.15 to 0.72)	No serious	No serious	No serious	Serious[3]	MODERATE	1.00	0.98
			Specificity: 1.00 (0.99	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
	bacterial culture		to 1.00)							

** Pathogens detected: E. coli*
*** Pathogens detected: E. coli, P. aeruginosa, K. pneumoniae*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; E. coli: Escherichia coli; K. pneumoniae: Klebsiella pneumoniae; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; P. aeruginosa: Pseudomonas aeruginosa; U: undefined population; UM: undefined 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
[3] 95% CI crosses 1 decision making threshold

Table 36: Evidence profile for Gram and methylene blue staining for diagnosis of bacterial meningitis caused by all bacteria 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 (La Scolea Jr 1984)	Population: BM U (Paediatric inpatient and outpatient patients) Reference standard: CSF bacterial culture	2031	Sensitivity: 0.76 (0.64 to 0.86)	No serious	No serious	No serious	No serious	HIGH	1.00	0.99
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population

Table 37: Evidence profile for Gram and methylene blue staining for diagnosis of bacterial meningitis caused by N. meningitidis 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 (La Scolea Jr 1984)	Population: BM U (Paediatric inpatient and outpatient patients) Reference standard: CSF bacterial culture	2031	Sensitivity: 0.43 (0.10 to 0.82)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 38: Evidence profile for Gram and methylene blue staining 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 (La Scolea Jr 1984)	Population: BM U (Paediatric inpatient and outpatient patients) Reference standard: CSF bacterial culture	2031	Sensitivity: 0.78 (0.40 to 0.97)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 39: Evidence profile for Gram and methylene blue staining for diagnosis of bacterial meningitis caused by H. influenzae 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 (La Scolea Jr 1984)	Population: BM U (Paediatric inpatient and outpatient patients) Reference standard: CSF bacterial culture	2031	Sensitivity: 0.83 (0.67 to 0.94)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; H. influenzae: Haemophilus influenzae; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 40: Evidence profile for Gram and methylene blue staining for diagnosis of bacterial meningitis caused by group B Streptococcus 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 (La Scolea Jr 1984)	Population: BM U (Paediatric inpatient and outpatient patients) Reference standard: CSF bacterial culture	2031	Sensitivity: 0.89 (0.52 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

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

Glucose concentration

Table 41: Evidence profile for glucose concentration at all thresholds for diagnosis of bacterial meningitis in neonates

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: <1.11 mmol/L										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,444	Sensitivity: 0.44 (0.30 to 0.58)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.49	0.99
			Specificity: 0.99 (0.99 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: <1.89 mmol/L										
1 (Bonadio 1989)	Population: BM VM AM Reference standard: CSF bacterial culture and/or other CSF	72	Sensitivity: 0.61 (0.36 to 0.83)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.44	0.85
			Specificity: 0.74 (0.60 to 0.85)	Serious[1]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	findings									
Threshold: <3.33 mmol/L										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,444	Sensitivity: 0.89 (0.78 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.01	0.99
			Specificity: 0.20 (0.18 to 0.21)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; 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 42: Evidence profile for glucose concentration at 'low' threshold for diagnosis of bacterial meningitis caused by group B Streptococcus in neonates

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: 'Low' (<1.28 mmol/L for premature and <1.83 mmol/L term neonates)										
1 (Ansong 2009)	Population: GBM GBS U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	13,495	Sensitivity: 0.61 (0.45 to 0.75)	No serious	No serious	No serious	Serious[1]	MODERATE	0.05	1.00
			Specificity: 0.96 (0.95 to 0.96)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; NPV: negative predictive value'; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 43: Evidence profile for glucose concentration at <2.94mmol/L for diagnosis of bacterial meningitis in neonates, 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
Threshold: <2.94 mmol/L										
1 (De Cauwer 2007)	Population: BM VM Reference standard: CSF bacterial culture and/or blood bacterial culture with CSF pleocytosis	92	Sensitivity: 0.57 (0.34 to 0.78)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.57	0.87
			Specificity: 0.87 (0.77 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; 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 44: Evidence profile for glucose concentration at all thresholds 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
Threshold: <1.11 mmol/L										
1 (Bonsu 2005)	Population: BM U Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy	7710	Sensitivity: 0.14 (0.03 to 0.36)	Very serious[1]	No serious	No serious	No serious	LOW	0.04	1.00
			Specificity: 0.99 (0.99 to 0.99)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: <2.00 mmol/L										
1 (Sormunen 1999)	Population: BM VM Reference standard: CSF bacterial culture	237	Sensitivity: 0.31 (0.19 to 0.45)	Serious[2]	No serious	No serious	No serious	MODERATE	1.00	0.83
			Specificity: 1.00 (0.98 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: <2.11 mmol/L										
1 (Bonsu	Population: BM	78	Sensitivity:	Serious[2]	No serious	No serious	Very serious[3]	VERY LOW	1.00	0.92

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
2008)	VM		0.74 (0.49 to 0.91)							
	Reference standard: CSF bacterial culture		Specificity: 1.00 (0.94 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: <2.20 mmol/L										
1 (BenGershom 1986)	Population: BM VM NM	40	Sensitivity: 0.47 (0.23 to 0.72)	Serious[2]	No serious	No serious	Serious[4]	LOW	0.89	0.71
	Reference standard: CSF bacterial culture		Specificity: 0.96 (0.78 to 1.00)	Serious[2]	No serious	No serious	Serious[4]	LOW		
Threshold: <2.22 mmol/L										
1 (Corrall 1981)	Population: BM VM NM	55	Sensitivity: 0.78 (0.56 to 0.93)	Serious[2]	No serious	No serious	Serious[4]	LOW	1.00	0.86
	Reference standard: CSF bacterial culture		Specificity: 1.00 (0.89 to 1.00)	Serious[2]	No serious	No serious	Serious[4]	LOW		
1 (Bonsu 2005)	Population: BM U	7710	Sensitivity: 0.19 (0.05 to 0.42)	Very serious[1]	No serious	No serious	No serious	LOW	0.02	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.98 (0.97 to 0.98)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: <2.50 mmol/L										
1 (Dubos 2006)	Population: BM AM	164	Sensitivity: 0.62 (0.38 to 0.82)	No serious	No serious	No serious	Serious[4]	MODERATE	0.29	0.93
	Reference standard: CSF		Specificity: 0.78 (0.70 to	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
	bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria		0.84)							
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.35 (0.22 to 0.49)	Serious[2]	No serious	No serious	No serious	MODERATE	0.73	0.83
	Reference standard: CSF bacterial culture		Specificity: 0.96 (0.92 to 0.98)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: <3.00 mmol/L										
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.49 (0.35 to 0.63)	Serious[2]	No serious	No serious	Serious[4]	LOW	0.32	0.82
	Reference standard: CSF bacterial culture		Specificity: 0.68 (0.61 to 0.75)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: <3.33 mmol/L										
1 (Bonsu 2005)	Population: BM U	7710	Sensitivity: 0.38 (0.18 to 0.62)	Very serious[1]	No serious	No serious	Serious[4]	VERY LOW	0.00	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.49 (0.48 to 0.50)	Very serious[1]	No serious	No serious	Serious[4]	LOW		
Threshold: <6.66 mmol/L										
1 (Bonsu 2005)	Population: BM U	7707	Sensitivity: 0.90 (0.70 to 099)	Very serious[1]	No serious	No serious	Serious[4]	LOW	0.00	0.95
	Reference		Specificity:	Very	No serious	No serious	No serious	LOW		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	standard: CSF bacterial culture, blood bacterial culture and/or microscopy		0.00 (0.00 to 0.01)	serious[1]						

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; VM: viral meningitis; U: undefined population
[1] Very serious risk of bias in the evidence contributing to the outcomes
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] 95% CI crosses 2 decision making thresholds
[4] 95% CI crosses 1 decision making threshold

Table 45: Evidence profile for glucose concentration at <2.5mmol/L for diagnosis of bacterial meningitis in children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: <2.50 mmol/L										
1 (Dubos 2008)	Population: BM AM Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	194	Sensitivity: 0.67 (0.57 to 0.77)	Serious[1]	No serious	No serious	No serious	MODERATE	0.78	0.72
			Specificity: 0.82 (0.73 to 0.89)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 46: Evidence profile for glucose concentration at all thresholds 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
Threshold: <2.20 mmol/L										
1 (Viallon 2011)	Population: BM VM VME Reference standard:	253	Sensitivity: 0.97 (0.85 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.23	0.99
			Specificity: 0.49 (0.42 to	Serious[1]	No serious	No serious	Serious[2]	LOW		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	CSF bacterial culture		0.56)							
Threshold: <2.70 mmol/L										
1 (Dastych 2015)	Population: BM AM	73	Sensitivity: 0.70 (0.47 to 0.87)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.76	0.87
	Reference standard: CSF bacterial culture and/or other CSF findings		Specificity: 0.90 (0.78 to 0.97)	Serious[1]	No serious	No serious	Serious[2]	LOW		
Threshold: Not applicable										
1 (Viallon 2011)	Population: BM VM VME Reference standard: CSF bacterial culture	253	AUC: 0.69 (0.69 to 0.76)	Serious[1]	No serious	No serious	Serious[2]	LOW	NA	NA
1 (Dastych 2015)	Population: BM AM Reference standard: CSF bacterial culture and/or other CSF findings	73	AUC: 0.81 (0.70 to 0.89)	Serious[1]	No serious	No serious	Serious[2]	LOW	NA	NA

AM: aseptic meningitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; VM: viral meningitis; VME: viral meningoencephalitis
[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 47: Evidence profile for glucose concentration at <2.2mmol/L for diagnosis of bacterial meningitis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: <2.20 mmol/L										
1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	671	Sensitivity: 0.53 (0.41 to 0.65)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.73	0.95
			Specificity: 0.98 (0.96 to 0.99)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[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 48: Evidence profile for CSF:serum glucose at a ratio of 0.40 for diagnosis of bacterial meningitis in neonates, 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
Threshold: <0.40										
1 (Nelson 1986)	Population: BM AM NM Reference standard: CSF bacterial culture	120	Sensitivity: 0.59 (0.33 to 0.82)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.83	0.94
			Specificity: 0.98 (0.93 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; 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 1 decision making threshold

Table 49: Evidence profile for CSF:serum glucose at all thresholds 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
Threshold: <0.15										

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Ray 2007)	Population: BM UM Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	151	Sensitivity: 0.33 (0.13 to 0.59)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.07	0.82
			Specificity: 0.42 (0.34 to 0.51)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: <0.35										
1 (Giulieri 2015)	Population: BM VM Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	45	Sensitivity: 0.94 (0.73 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	1.00	0.96
			Specificity: 1.00 (0.87 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: <0.40										
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	Sensitivity: 0.88 (0.76 to 0.96)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.74	0.95
			Specificity: 0.87 (0.80 to 0.93)	Serious[3]	No serious	No serious	Serious[2]	LOW		
Threshold: <0.48										
1 (Viallon 2011)	Population: BM VM VME Reference standard: CSF bacterial culture	253	Sensitivity: 0.83 (0.66 to 0.93)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.55	0.97
			Specificity: 0.89 (0.84 to 0.93)	Serious[3]	No serious	No serious	Serious[2]	LOW		
Threshold: Not applicable										
1 (Ray 2007)	Population: BM UM Reference standard: CSF bacterial culture, blood	151	AUC: 0.11 (0.06 to 0.10)	Very serious[1]	No serious	No serious	No serious	LOW	NA	NA

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	bacterial culture, other CSF findings and/or clinical criteria									
1 (Giulieri 2015)	Population: BM VM Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	45	AUC: 0.96 (0.88 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW	NA	NA
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	AUC: 0.91 (0.87 to 0.96)	Serious[3]	No serious	No serious	No serious	MODERATE	NA	NA
1 (Viallon 2011)	Population: BM VM VME Reference standard: CSF bacterial culture	253	AUC: 0.87 (0.86 to 0.91)	Serious[3]	No serious	No serious	No serious	MODERATE	NA	NA

AME: aseptic meningoencephalitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; UM: undefined meningitis; VM: viral meningitis; VME: viral meningoencephalitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold
[3] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 50: Evidence profile for CSF:serum glucose at all thresholds for diagnosis of bacterial meningitis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: <0.40										
1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected	663	Sensitivity: 0.81 (0.70 to 0.90)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.36	0.98
			Specificity: 0.84 (0.81 to	Serious[1]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings		0.87)							
Threshold: <0.50										
1 (Lindquist 1988)	Population: BMU (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	663	Sensitivity: 0.70 (0.58 to 0.81)	Serious[1]	No serious	No serious	No serious	MODERATE	0.65	0.97
			Specificity: 0.96 (0.94 to 0.97)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: <0.66										
1 (D'Inzeo 2020)	Population: BMU (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis)	135	Sensitivity: 1.00 (0.89 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE	0.74	1.00
			Specificity: 0.89 (0.82 to 0.95)	No serious	No serious	No serious	Serious[2]	MODERATE		

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: CSF bacterial culture									

BM: bacterial meningitis; CI: confidence interval; CNS: central nervous system; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold

Protein concentration

Table 51: Evidence profile for protein concentration at all thresholds for diagnosis of bacterial meningitis in neonates

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/dL										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,451	Sensitivity: 1.00 (0.94 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE	0.13	1.00
			Specificity: 0.02 (0.02 to 0.02)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >90 mg/dL										
1 (Garges 2006)	Population: BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	4,451	Sensitivity: 0.84 (0.71 to 0.92)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.02	0.99
			Specificity: 0.39 (0.37 to 0.40)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >120 mg/dL										
1 (Garges	Population:	4,451	Sensitivity:	Serious[1]	No serious	No serious	No serious	MODERATE	0.03	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
2006)	BM U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture		0.76 (0.63 to 0.87)							
			Specificity: 0.63 (0.62 to 0.64)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >170 mg/dL										
1 (Bonadio 1989)	Population: BM VM AM Reference standard: CSF bacterial culture and/or other CSF findings	72	Sensitivity: 0.56 (0.31 to 0.78)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.87
			Specificity: 1.00 (0.93 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; 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 52: Evidence profile for protein concentration at 'elevated' threshold for diagnosis of bacterial meningitis caused by group B Streptococcus in neonates

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: 'Elevated' (>151 mg/dL for premature and >171 mg/dL for term neonates)										
1 (Ansong 2009)	Population: GBM GBS U (neonates with lumbar puncture performed) Reference standard: CSF bacterial culture	13,495	Sensitivity: 0.93 (0.82 to 0.99)	No serious	No serious	No serious	Serious[1]	MODERATE	0.01	1.00
			Specificity: 0.76 (0.75 to 0.76)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 53: Evidence profile for protein concentration at all thresholds for diagnosis of bacterial meningitis in neonates, 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
Threshold: >40 mg/dL										
1 (Benjamin 1984)	Population: BM VM AM Reference standard: CSF bacterial culture	119	Sensitivity: 0.86 (0.64 to 0.97)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.67	0.97
			Specificity: 0.91 (0.83 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW		
Threshold: >100 mg/dL										
1 (De Cauwer 2007)	Population: BM VM Reference standard: CSF bacterial culture and /or blood bacterial culture with CSF pleocytosis	92	Sensitivity: 0.57 (0.34 to 0.78)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.89
			Specificity: 1.00 (0.95 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

AM: aseptic meningitis; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; 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 54: Evidence profile for protein concentration at all thresholds 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
Threshold: > 40 mg/dL										
1 (Bonsu 2005)	Population: BM U Reference	7710	Sensitivity: 0.38 (0.18 to 0.62)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.00	1.00
			Specificity:	Very	No serious	No serious	No serious	LOW		

	standard: CSF bacterial, blood bacterial culture and/or microscopy		0.76 (0.75 to 0.77)	serious[1]						
Threshold: >50 mg/dL										
1 (Dubos 2006)	Population: BM AM	154	Sensitivity: 0.86 (0.64 to 0.97)	No serious	No serious	No serious	Serious[2]	MODERATE	0.46	0.97
	Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria		Specificity: 0.84 (0.77 to 0.90)	No serious	No serious	No serious	Serious[2]	MODERATE		
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.78 (0.65 to 0.88)	Serious[3]	No serious	No serious	No serious	MODERATE	0.36	0.90
	Reference standard: CSF bacterial culture		Specificity: 0.59 (0.51 to 0.66)	Serious[3]	No serious	No serious	No serious	MODERATE		
Threshold: 80 mg/dL										
1 (Bonsu 2005)	Population: BM U	7710	Sensitivity: 0.29 (0.11 to 0.52)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.03	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.97 (0.97 to 0.97)	Very serious[1]	No serious	No serious	No serious	LOW		
Threshold: >97 mg/dL										

1 (Bonsu 2008)	Population: BM VM Reference standard: CSF bacterial culture	78	Sensitivity: 0.84 (0.60 to 0.97)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.80	0.95
			Specificity: 0.93 (0.84 to 0.98)	Serious[3]	No serious	No serious	Serious[2]	LOW		
Threshold: >100 mg/dL										
1 (BenGershom 1986)	Population: BM VM NM Reference standard: CSF bacterial culture	42	Sensitivity: 0.94 (0.71 to 1.00)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.89	0.96
			Specificity: 0.92 (0.74 to 0.99)	Serious[3]	No serious	No serious	Serious[2]	LOW		
1 (Corrall 1981)	Population: BM VM NM Reference standard: CSF bacterial culture	55	Sensitivity: 0.74 (0.52 to 0.90)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.89	0.83
			Specificity: 0.94 (0.79 to 0.99)	Serious[3]	No serious	No serious	Serious[2]	LOW		
1 (Sormunen 1999)	Population: BM VM Reference standard: CSF bacterial culture	237	Sensitivity: 0.64 (0.50 to 0.76)	Serious[3]	No serious	No serious	No serious	MODERATE	0.83	0.90
			Specificity: 0.96 (0.92 to 0.98)	Serious[3]	No serious	No serious	No serious	MODERATE		
Threshold: 120 mg/dL										
1 (Bonsu 2005)	Population: BM U Reference standard: CSF bacterial	7710	Sensitivity: 0.29 (0.11 to 0.52)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.06	1.00
			Specificity: 0.99 (0.99 to 0.99)	Very serious[1]	No serious	No serious	No serious	LOW		

	culture, blood bacterial culture and/or microscopy									
Threshold: >150 mg/dL										
1 (Sormunen 1999)	Population: BM VM	237	Sensitivity: 0.51 (0.37 to 0.65)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.93	0.87
	Reference standard: CSF bacterial culture		Specificity: 0.99 (0.96 to 1.00)	Serious[3]	No serious	No serious	No serious	MODERATE		
Threshold: >200 mg/dL										
1 (Bonsu 2005)	Population: BM U	7710	Sensitivity: 0.10 (0.01 to 0.30)	Very serious[1]	No serious	No serious	No serious	LOW	0.06	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 1.00 (0.99 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PPV: positive predictive value; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold
[3] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 55: Evidence profile for protein concentration at >50mg/dL for diagnosis of bacterial meningitis in children

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/dL										
1 (Dubos 2008)	Population: BM AM Reference standard: CSF (bacterial culture, blood	195	Sensitivity: 0.88 (0.80 to 0.94)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.71	0.86
			Specificity: 0.65 (0.55	Serious[2]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	bacterial culture, other CSF findings and/or clinical criteria		to 0.74)							
Threshold: Not applicable										
1 (Dubos 2008)	Population: BM AM Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria	195	AUC: 0.86 (0.79 to 0.94)	Serious[2]	No serious	No serious	Serious[1]	LOW	NA	NA

AM: aseptic meningitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value
[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 56: Evidence profile for protein concentration at all thresholds 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
Threshold: >45 mg/dL										
1 (Buch 2018)	Population: BM AME	176	Sensitivity: 1.00 (0.93 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE	0.35	1.00
	Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis		Specificity: 0.23 (0.16 to 0.32)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >60 mg/dL										
1 (White	Population: BM VM (over 5 years	68	Sensitivity: 0.96 (0.78 to	Serious[1]	No serious	No serious	Serious[2]	LOW	0.52	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
2012)	of age receiving lumbar puncture) Reference standard: CSF bacterial culture, microscopy and/or molecular diagnosis		1.00)							
			Specificity: 0.56 (0.40 to 0.70)	Serious[1]	No serious	No serious	Serious[2]	LOW		
	Population: BM CM Reference standard: CSF bacterial culture, microscopy and/or molecular diagnosis	40	Sensitivity: 0.96 (0.78 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.67	0.86
			Specificity: 0.35 (0.14 to 0.62)	Serious[1]	No serious	No serious	Serious[2]	LOW		
	Population: BM U (over 5 years of age receiving lumbar puncture) Reference standard: CSF bacterial culture, microscopy and/or molecular diagnosis	2,210	Sensitivity: 0.67 (0.09 to 0.99)	Serious[1]	No serious	No serious	Very serious[3]	VERY LOW	0.01	1.00
			Specificity: 0.84 (0.82 to 0.85)	Serious[1]	No serious	No serious	No serious	MODERATE		
Threshold: >101 mg/dL										
1 (Dastych 2015)	Population: BM AM Reference standard: CSF	73	Sensitivity: 0.70 (0.47 to 0.87)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.57	0.84
			Specificity: 0.76 (0.62 to	Serious[1]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	bacterial culture and/or other CSF findings		0.87)							
Threshold: >130 mg/dL										
1 (Kleine 2003)	Population: BM VM AM	86	Sensitivity: 0.82 (0.67 to 0.93)	No serious	No serious	No serious	Serious[2]	MODERATE	0.85	0.85
	Reference standard: CSF bacterial culture, blood bacterial culture and/or microscopy		Specificity: 0.87 (0.74 to 0.95)	No serious	No serious	No serious	Serious[2]	MODERATE		
Threshold: >131 mg/dL										
1 (Ray 2007)	Population: BM UM	151	Sensitivity: 0.61 (0.36 to 0.83)	Very serious[4]	No serious	No serious	Serious[2]	VERY LOW	0.58	0.95
	Reference standard: CSF bacterial culture, blood bacterial culture, other CSF findings and/or clinical criteria		Specificity: 0.94 (0.88 to 0.97)	Very serious[4]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: >188 mg/dL										
1 (Viallon 2011)	Population: BM VM VME	253	Sensitivity: 0.89 (0.73 to 0.97)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.67	0.98
	Reference standard: CSF bacterial culture		Specificity: 0.93 (0.89 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW		
Threshold: >193.4 mg/dL										
1 (Giulieri	Population: BM VM	45	Sensitivity: 0.89 (0.65 to	Very serious[4]	No serious	No serious	Serious[2]	VERY LOW	1.00	0.93

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
2015)			0.99)							
	Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis		Specificity: 1.00 (0.87 to 1.00)	Very serious[4]	No serious	No serious	Serious[2]	VERY LOW		
Threshold: Not applicable										
1 (Buch 2018)	Population: BM AME Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	176	AUC: 0.91 (0.87 to 0.96)	Serious[1]	No serious	No serious	No serious	MODERATE	NA	NA
1 (Dastych 2015)	Population: BM AM Reference standard: CSF bacterial culture and/or other CSF findings	73	AUC: 0.74 (0.63 to 0.83)	Serious[1]	No serious	No serious	Very serious[3]	VERY LOW	NA	NA
1 (Ray 2007)	Population: BM UM Reference standard: CSF bacterial culture,	151	AUC: 0.70 (0.30 to 0.89)	Very serious[4]	No serious	No serious	Very serious[3]	VERY LOW	NA	NA

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	blood bacterial culture, other CSF findings and/or clinical criteria									
1 (Viallon 2011)	Population: BM VM VME Reference standard: CSF bacterial culture	253	AUC: 0.93 (0.92 to 0.98)	Serious[1]	No serious	No serious	No serious	MODERATE	NA	NA
1 (Giulieri 2015)	Population: BM VM Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	45	AUC: 0.95 (0.88 to 1.00)	Very serious[4]	No serious	No serious	No serious	LOW	NA	NA

AM: aseptic meningitis; AME: aseptic meningoencephalitis; AUC: area under the curve; BM: bacterial meningitis; CI: confidence interval; CM: cryptococcal meningitis; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; U: undefined population; UM: undefined meningitis: VM; viral meningitis; VME: viral meningoencephalitis

[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

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

Table 57: Evidence profile for protein concentration at all thresholds for diagnosis of bacterial meningitis in all ages

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/dL										
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult,	135	Sensitivity: 0.94 (0.79 to 0.99)	No serious	No serious	No serious	Serious[1]	MODERATE	0.71	0.98

	paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture		Specificity: 0.88 (0.81 to 0.94)	No serious	No serious	No serious	Serious[1]	MODERATE		
Threshold: >50 mg/dL										
1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	591	Sensitivity: 0.88 (0.77 to 0.95)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.22	0.98
			Specificity: 0.60 (0.56 to 0.65)	Serious[2]	No serious	No serious	No serious	MODERATE		
Threshold: >100 mg/dL										
1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	591	Sensitivity: 0.69 (0.57 to 0.80)	Serious[2]	No serious	No serious	No serious	MODERATE	0.45	0.96
			Specificity: 0.90 (0.87 to 0.92)	Serious[2]	No serious	No serious	Serious[1]	LOW		
Threshold: >150 mg/dL										

1 (Lindquist 1988)	Population: BM U (≥2 months old receiving lumbar puncture due to suspected CNS infection) Reference standard: CSF bacterial culture and/or other CSF findings	591	Sensitivity: 0.55 (0.43 to 0.68)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.73	0.95
			Specificity: 0.98 (0.96 to 0.99)	Serious[2]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CNS: central nervous system; CSF: cerebrospinal fluid; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Molecular diagnosis for bacterial pathogens

Table 58: Evidence profile for PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in neonates and younger 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: GBM U (Babies (aged 7–90 days) with a blood or CSF sample tested by group B Streptococcus PCR) PCR type: Specific Reference standard: CSF bacterial culture	827	Sensitivity: 1.00 (0.48 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.23	1.00
			Specificity: 0.98 (0.97 to 0.99)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; GBM: group B Streptococcus meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 59: Evidence profile for PCR for diagnosis of bacterial meningitis caused by group B Streptococcus and Gram-negative bacilli* in neonates and younger 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 (Arora 2017)	Population: BM U (Babies with undergoing suspected meningitis) PCR type: Multiplex Reference standard: CSF bacterial culture	62	Sensitivity: 1.00 (0.48 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.56	1.00
			Specificity: 0.93 (0.83 to 0.98)	No serious	No serious	No serious	Serious[2]	MODERATE		

** Bacteria included in PCR panel: E. coli*
CI: confidence interval; CSF: cerebrospinal fluid; BM: bacterial meningitis; E. coli: Escherichia coli; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds
[2] 95% CI crosses 1 decision making threshold

Table 60: Evidence profile for PCR for diagnosis of bacterial meningitis caused by all bacteria in neonates, 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 (Nabower 2019)	Population: BM U (Children 0-18 years old who had a CSF culture or FA-M/E panel obtained within 48 hours of admission, to evaluate potential infectious aetiology) PCR type: Multiplex Reference standard: CSF bacterial culture	223	Sensitivity: 0.60 (0.15 to 0.95)	No serious	No serious	No serious	Very serious[1]	LOW	0.38	0.99
			Specificity: 0.98 (0.95 to 0.99)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; FA-M/E: FilmArray Meningitis/Encephalitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 61: Evidence profile for PCR for diagnosis of bacterial meningitis caused by N. meningitidis in neonates, 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 (Lee 2015)	Population: MM U PCR type: Specific Reference standard: CSF bacterial culture	1574	Sensitivity: 1.00 (0.29 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.12	1.00
			Specificity: 0.99 (0.98 to 0.99)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 62: Evidence profile for PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in neonates, 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 (Kim 2012)	Population: BM U (Children with suspected meningitis who were less than five years old) PCR type: Specific Reference standard: CSF bacterial culture	106	Sensitivity: 1.00 (0.72 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.61	1.00
			Specificity: 0.93 (0.85 to 0.97)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Kennedy 2007)	Population: BM U (Children <5 years old with suspected meningitis) PCR type: Specific Reference standard: CSF bacterial culture	1063	Sensitivity: 1.00 (0.85 to 1.00)	Very serious[2]	No serious	No serious	Serious[1]	VERY LOW	0.58	1.00
			Specificity: 0.98 (0.97 to 0.99)	Very serious[2]	No serious	No serious	No serious	LOW		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Alqayoudhi 2017)	Population: PM U (Patients <16 years old with suspected meningitis, and with a CSF sample tested for S. pneumoniae DNA by PCR) PCR type: Specific Reference standard: CSF bacterial culture	2006	Sensitivity: 1.00 (0.79 to 1.00)	Serious[3]	No serious	No serious	Serious[1]	LOW	0.36	1.00
			Specificity: 0.99 (0.98 to 0.99)	Serious[3]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; UM: undefined meningitis; US: undefined septicaemia
[1] 95% CI crosses 2 decision making thresholds
[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 63: Evidence profile for PCR for diagnosis of bacterial meningitis caused by H. influenzae in neonates, 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 (Kennedy 2007)	Population: BM U (Children <5 years old with suspected meningitis) PCR type: Specific Reference standard: CSF bacterial culture	577	Sensitivity: 1.00 (0.63 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.67	1.00
			Specificity: 0.99 (0.98 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; H. influenzae: Haemophilus influenzae; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold

Table 64: Evidence profile for PCR for diagnosis of bacterial meningitis caused by N. meningitidis 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 (Bryant 2004)	Population: MM UM US PCR type: Multiplex Reference standard: CSF bacterial culture	48	Sensitivity: 1.00 (0.16 to 1.00)	Very serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.50	1.00
			Specificity: 0.96 (0.85 to 0.99)	Very serious[1]	No serious	No serious	Serious[3]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; N. meningitidis: Neisseria meningitidis; PCR: polymerase chain reaction; PPV: positive predictive value; UM: undefined meningitis: US: undefined septicaemia
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds
[3] 95% CI crosses 1 decision making threshold

Table 65: Evidence profile for PCR for diagnosis of bacterial meningitis caused by all bacteria 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 (Piccirilli 2018)	Population: BM U (suspected meningitis or encephalitis) PCR type: Multiplex Reference standard: CSF bacterial culture	39	Sensitivity: 1.00 (0.83 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.50	1.00
			Specificity: 0.53 (0.28 to 0.77)*	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Favaro 2013)	Population: BM U (Patients with suspected meningitis) PCR type: Combined Reference standard:	296	Sensitivity: 0.94 (0.79 to 0.99)	No serious	No serious	No serious	Serious[2]	MODERATE	0.67	0.99
			Specificity: 0.94 (0.91 to 0.97)	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
	CSF bacterial									
1 (Leli 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	109	Sensitivity: 0.46 (0.19 to 0.75)	No serious	No serious	No serious	Serious[2]	MODERATE	0.86	0.93
			Specificity: 0.99 (0.94 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

** The authors considered the false positive cases (according to culture results) as true positive based on results of real-time PCR, which would improve specificity*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; 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 66: Evidence profile for PCR for diagnosis of bacterial meningitis caused by N. meningitidis 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 (Favaro 2013)	Population: BM U (Patients with suspected meningitis) PCR type: Combined Reference standard: CSF bacterial culture	296	Sensitivity: 1.00 (0.54 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.55	1.00
			Specificity: 0.98 (0.96 to 0.99)	No serious	No serious	No serious	No serious	HIGH		
1 (Leli 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	109	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	0.50	1.00
			Specificity: 0.99 (0.95 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; N. meningitidis: Neisseria meningitidis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; VM: viral meningitis
[1] 95% CI crosses 1 decision making threshold

[2] 95% CI crosses 2 decision making thresholds

Table 67: Evidence profile for PCR for diagnosis of bacterial meningitis caused by S. pneumoniae 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 (Favaro 2013)	Population: BM U (Patients with suspected meningitis) PCR type: Combined Reference standard: CSF bacterial culture	296	Sensitivity: 1.00 (0.16 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.25	1.00
			Specificity: 0.98 (0.96 to 0.99)	No serious	No serious	No serious	No serious	HIGH		
1 (Leli 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	109	Sensitivity: 1.00 (0.29 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	1.00
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population; VM: viral meningitis
[1] 95% CI crosses 2 decision making thresholds

Table 68: Evidence profile for PCR for diagnosis of bacterial meningitis caused by group B Streptococcus 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 (Favaro 2013)	Population: BM U (Patients with suspected meningitis) PCR type: Combined Reference standard: CSF bacterial culture	296	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	1.00
			Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Leli	Population: BM VM NM	109	Sensitivity:	No	No serious	No serious	Very serious[1]	LOW	1.00	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
2019)	PCR type: Multiplex Reference standard: CSF bacterial culture		1.00 (0.03 to 1.00)	serious						
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; VM: viral meningitis
[1] 95% CI crosses 1 decision making threshold

Table 69: Evidence profile for PCR for diagnosis of bacterial meningitis caused by Gram-negative bacilli 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 (Favaro 2013)*	Population: BM U (Patients with suspected meningitis) PCR type: Combined Reference standard: CSF bacterial culture	296	Sensitivity: 1.00 (0.16 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	1.00
			Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

** Pathogens detected: E. coli*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; E. coli: Escherichia coli; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 70: Evidence profile for PCR for diagnosis of bacterial meningitis caused by L. monocytogenes 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 (Favaro 2013)	Population: BM U (Patients with suspected meningitis) PCR type: Combined	296	Sensitivity: 1.00 (0.66 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.82	1.00
			Specificity: 0.99 (0.98 to 1.00)	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: CSF bacterial culture									
1 (Leli 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	109	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	1.00	1.00
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; L. monocytogenes: Listeria monocytogenes; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; VM: viral meningitis
[1] 95% CI crosses 1 decision making threshold
[2] 95% CI crosses 2 decision making thresholds

Table 71: Evidence profile for PCR for diagnosis of bacterial meningitis caused by all bacteria in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Boudet 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	708	Sensitivity: 1.00 (0.74 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.67	1.00
			Specificity: 0.99 (0.98 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Leber 2016)	Population: BM VM FM NM PCR type: Multiplex Reference standard: CSF bacterial culture	1560	Sensitivity: 0.88 (0.47 to 1.00)	No serious	No serious	No serious	Very serious[3]	LOW	0.32	1.00
			Specificity: 0.99 (0.98 to 0.99)	No serious	No serious	No serious	No serious	HIGH		
1 (Ena 2021)	Population: BME NMBE PCR type: Multiplex	46	Sensitivity: 0.86 (0.42 to 1.00)	Serious[4]	No serious	No serious	Very serious[3]	VERY LOW	0.55	0.97
			Specificity:	Serious[4]	No serious	No serious	Serious[2]	LOW		

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: CSF bacterial culture		0.87 (0.73 to 0.96)							
1 (Vincent 2020)	Population: BM U (CSF samples from patients submitted for the diagnosis of infectious meningitis at study laboratory) PCR type: Multiplex Reference standard: CSF bacterial culture, microscopy and molecular diagnosis	1124	Sensitivity: 0.86 (0.57 to 0.98)	No serious	No serious	No serious	Serious[2]	MODERATE	0.75	1.00
			Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Deutch 2006a)	Population: BM U (All CSF specimens from clinical departments) PCR type: Broad-range plus DNA sequencing Reference standard: CSF bacterial culture	196	Sensitivity: 0.79 (0.49 to 0.95)	Serious[4]	No serious	No serious	Very serious[3]	VERY LOW	0.79	0.98
			Specificity: 0.98 (0.95 to 1.00)	Serious[4]	No serious	No serious	No serious	MODERATE		
1 (Schuurman 2004)	Population: BM U (Patients who had meningitis as part of their differential diagnosis) PCR type: Broad-range	277	Sensitivity: 0.65 (0.47 to 0.80)	No serious	No serious	No serious	Serious[2]	MODERATE	0.80	0.93
			Specificity: 0.97 (0.93 to 0.99)	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: CSF bacterial culture									
1 (Deutch 2006b)	Population: BM U (All CSF specimens from clinical departments) PCR type: Broad-range plus DNA sequencing Reference standard: CSF bacterial culture	196	Sensitivity: 0.64 (0.35 to 0.87)	Serious[4]	No serious	No serious	Serious[2]	LOW	0.75	0.97
			Specificity: 0.98 (0.95 to 1.00)	Serious[4]	No serious	No serious	No serious	MODERATE		
1 (Welinder-Olsson 2007)	Population: BM VM UM NM PCR type: Broad-range Reference standard: CSF bacterial culture	345	Sensitivity: 0.64 (0.47 to 0.79)	No serious	No serious	No serious	Serious[2]	MODERATE	0.49	0.95
			Specificity: 0.92 (0.88 to 0.94)	No serious	No serious	No serious	Serious[2]	MODERATE		

BM: bacterial meningitis; BME: bacterial meningoencephalitis; CI: confidence interval; CSF: cerebrospinal fluid; FM: fungal meningitis; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; UM: undefined meningitis; VM: viral meningitis

[1] Very 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

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

Table 72: Evidence profile for PCR for diagnosis of bacterial meningitis caused by N. meningitidis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Abdeldaim 2010)	Population: BM U (CSF samples sent for culture at study	87	Sensitivity: 1.00 (0.16 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.20	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
	laboratory with CSF white blood cell count was ≥10 cells/µl) PCR type: Specific Reference standard: CSF bacterial culture and microscopy		Specificity: 0.91 (0.82 to 0.96)	Serious[1]	No serious	No serious	Serious[3]	LOW		
1 (Richardson 2003)	Population: BM UM PCR type: Specific Reference standard: CSF bacterial culture	281	Sensitivity: 1.00 (0.84 to 1.00)	No serious	No serious	No serious	Serious[3]	MODERATE	0.57	1.00
			Specificity: 0.94 (0.90 to 0.96)	No serious	No serious	No serious	No serious	HIGH		
1 (Deutch 2008)	Population: BM U (Routine CSF samples sent to study centre) PCR type: Multiplex Reference standard: CSF bacterial culture	1015	Sensitivity: 1.00 (0.48 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.63	1.00
			Specificity: 1.00 (0.99 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Boudet 2019)	Population: BM VM NM PCR type: Multiplex Reference	708	Sensitivity: 1.00 (0.40 to 1.00)	Very serious[4]	No serious	No serious	Very serious[2]	VERY LOW	1.00	1.00
			Specificity: 1.00 (0.99 to 1.00)	Very serious[4]	No serious	No serious	No serious	LOW		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
	standard: CSF bacterial culture									
1 (Ena 2021)	Population: BME NMBE PCR type: Multiplex Reference standard: CSF bacterial culture	46	Sensitivity: 1.00 (0.03 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	1.00
			Specificity: 1.00 (0.92 to 1.00)	Serious[1]	No serious	No serious	No serious	LOW		
1 (Ni 1992)	Population: BM MD VM NM PCR type: Specific Reference standard: CSF bacterial culture and microscopy	54	Sensitivity: 0.91 (0.59 to 1.00)	No serious	No serious	No serious	Serious[3]	MODERATE	0.71	0.98
			Specificity: 0.91 (0.78 to 0.97)	No serious	No serious	No serious	Serious[3]	MODERATE		
1 (Vincent 2020)	Population: BM U (CSF samples from patients submitted for the diagnosis of infectious meningitis) PCR type: Multiplex Reference standard: CSF bacterial culture, microscopy and molecular diagnosis	1124	Sensitivity: 0.67 (0.09 to 0.99)	No serious	No serious	No serious	Very serious[2]	LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; BME: bacterial meningoencephalitis; CI: confidence interval; CSF: cerebrospinal fluid; MMD: meningococcal disease; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; UM: undefined meningitis; 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
[3] 95% CI crosses 1 decision making threshold
[4] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 73: Evidence profile for PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Abdeldaim 2010)	Population: BM U (CSF samples sent for culture at study laboratory with CSF WCC ≥10 cells/µL) PCR type: Specific Reference standard: CSF bacterial culture and microscopy	87	Sensitivity: 1.00 (0.48 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.36	1.00
			Specificity: 0.89 (0.80 to 0.95)	Serious[1]	No serious	No serious	Serious[3]	LOW		
1 (Ena 2021)	Population: BME NBME PCR type: Multiplex Reference standard: CSF bacterial culture	46	Sensitivity: 1.00 (0.40 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.57	1.00
			Specificity: 0.93 (0.91 to 0.99)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Leber 2016)	Population: BM VM FM NM PCR type: Multiplex Reference standard: CSF bacterial culture	1560	Sensitivity: 1.00 (0.40 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	0.25	1.00
			Specificity: 0.99 (0.99 to 1.00)	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
1 (Vincent 2020)	Population: BM U (CSF samples from patients submitted for the diagnosis of infectious meningitis at study laboratory) PCR type: Multiplex Reference standard: CSF bacterial culture, microscopy and molecular diagnosis	1124	Sensitivity: 1.00 (0.63 to 1.00)	No serious	No serious	No serious	Serious[3]	MODERATE	0.67	1.00
			Specificity: 1.00 (0.99 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Boudet 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	708	Sensitivity: 1.00 (0.16 to 1.00)	Very serious[4]	No serious	No serious	Very serious[2]	VERY LOW	0.50	1.00
			Specificity: 1.00 (0.99 to 1.00)	Very serious[4]	No serious	No serious	No serious	LOW		
1 (Deutch 2008)	Population: BM U (Routine CSF samples sent to study centre) PCR type: Multiplex Reference standard: CSF bacterial culture	1015	Sensitivity: 0.75 (0.48 to 0.93)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.63	1.00
			Specificity: 0.99 (0.99 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; BME: bacterial meningoencephalitis; CI: confidence interval; CSF: cerebrospinal fluid; FM: fungal meningitis; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population; VM: viral meningitis; WCC: white cell count

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

[2] 95% CI crosses 2 decision making thresholds

[3] 95% CI crosses 1 decision making threshold
[4] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 74: Evidence profile for PCR for diagnosis of bacterial meningitis caused by H. influenzae in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Boudet 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	708	Sensitivity: 1.00 (0.03 to 1.00)	Very serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.33	1.00
			Specificity: 1.00 (0.99 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Leber 2016)	Population: BM VM FM NM PCR type: Multiplex Reference standard: CSF bacterial culture	1560	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	0.50	1.00
			Specificity: 1.00 (1.00 to 1.00	No serious	No serious	No serious	No serious	HIGH		
1 (Vincent 2020)	Population: BM U (CSF samples from patients submitted for the diagnosis of infectious meningitis at study laboratory) PCR type: Multiplex Reference standard: CSF bacterial culture, microscopy and	1124	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	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
	molecular diagnosis									

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; FM: fungal meningitis; H. influenzae: Haemophilus influenzae; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds

Table 75: Evidence profile for PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Boudet 2019)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	708	Sensitivity: 1.00 (0.40 to 1.00)	Very serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.80	1.00
			Specificity: 1.00 (0.99 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Vincent 2020)	Population: BM U (CSF samples from patients submitted for the diagnosis of infectious meningitis at study laboratory) PCR type: Multiplex Reference standard: CSF bacterial culture, microscopy and molecular diagnosis	1124	Sensitivity: 0.50 (0.01 to 0.99)	No serious	No serious	No serious	Very serious[2]	LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; UM: undefined meningitis; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds

Table 76: Evidence profile for PCR for diagnosis of bacterial meningitis caused by Gram-negative bacilli in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Boudet 2019)*	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	708	Sensitivity: 1.00 (0.03 to 1.00)	Very serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.50	1.00
			Specificity: 1.00 (0.99 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Leber 2016)*	Population: BM VM FM NM PCR type: Multiplex Reference standard: CSF bacterial culture	1560	Sensitivity: 1.00 (0.16 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	0.67	1.00
			Specificity: 1.00 (1.00 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

** Pathogens detected: E.coli*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; E. coli: Escherichia coli; FM: fungal meningitis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds

Table 77: Evidence profile for PCR for diagnosis of bacterial meningitis caused by L. monocytogenes in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Ena 2021)	Population: BME NBME PCR type: Multiplex Reference standard: CSF bacterial culture	46	Sensitivity: 1.00 (0.03 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.33	1.00
			Specificity: 0.96 (0.85 to 0.99)	Serious[1]	No serious	No serious	Serious[3]	LOW		

BM: bacterial meningitis; BME: bacterial meningoencephalitis; CI: confidence interval; CSF: cerebrospinal fluid; L. monocytogenes; Listeria monocytogenes; NBME: non-bacterial meningoencephalitis: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[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 78: Evidence profile for PCR for diagnosis of bacterial meningitis caused by N. meningitidis and S. pneumoniae in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Deutch 2008)	Population: BM U (Routine CSF samples sent to study centre) PCR type: Multiplex Reference standard: CSF bacterial culture	1015	Sensitivity: 0.71 (0.49 to 0.87)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.63	0.99
			Specificity: 0.99 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population
[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 79: Evidence profile for PCR for diagnosis of bacterial meningitis caused by all bacteria in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Chiba 2009)	Population: BM U (Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing) PCR type: Multiplex Reference standard: CSF bacterial culture	168	Sensitivity: 1.00 (0.96 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE	0.67	1.00
			Specificity: 0.54 (0.43 to 0.65)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Xirogianni 2009)	Population: BM VM NM PCR type: Multiplex	262	Sensitivity: 1.00 (0.66 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE	0.20	1.00
			Specificity: 0.85 (0.80	No serious	No serious	No serious	No serious	HIGH		

	Reference standard: CSF bacterial culture		to 0.89)							
1 (Poppert 2005)	Population: BM U (CSF samples from patients with suspected meningitis, which had been sent for routine diagnosis) PCR type: Multiplex Reference standard: CSF bacterial culture	151	Sensitivity: 1.00 (0.90 to 1.00)	No serious	No serious	No serious	No serious	HIGH	0.81	1.00
			Specificity: 0.93 (0.87 to 0.97)	No serious	No serious	No serious	Serious[2]	MODERATE		
1 (Pfefferle 2020)	Population: BM VM FM NM PCR type: Multiplex Reference standard: CSF bacterial culture and molecular diagnosis	171	Sensitivity: 1.00 (0.87 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.90	1.00
			Specificity: 0.98 (0.94 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Wagner 2018)	Population: BM U (CSF samples from patients with meningitis symptoms collected in secondary and tertiary care hospitals in study area) PCR type: Multiplex Reference standard: CSF bacterial culture	220	Sensitivity: 1.00 (0.54 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE	0.60	1.00
			Specificity: 0.98 (0.95 to 0.99)	No serious	No serious	No serious	No serious	HIGH		
1 (Seward	Population: BM U	294	Sensitivity:	No	No serious	No serious	Serious[2]	MODERATE	0.86	1.00

2000b)	(Patients with suspected meningitis) PCR type: Multiplex Reference standard: CSF bacterial culture		1.00 (0.86 to 1.00)	serious						
			Specificity: 0.99 (0.96 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Esparcia 2011)	Population: BM U (Patients with clinical suspicion of bacterial meningitis) PCR type: Broad-range Reference standard: CSF bacterial culture	191	Sensitivity: 0.90 (0.80 to 0.96)	No serious	No serious	No serious	Serious[2]	MODERATE	0.72	0.61
			Specificity: 0.32 (0.17 to 0.51)	No serious	No serious	No serious	Serious[2]	MODERATE		
1 (Boving 2009)	Population: BM U (CSF samples sent to study centre for analysis) PCR type: Multiplex Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	1087	Sensitivity: 0.89 (0.71 to 0.98)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.44	1.00
			Specificity: 0.97 (0.96 to 0.98)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Rothman 2010)	Population: BM U (Patients with suspected meningitis and obtained from study laboratory)	108	Sensitivity: 0.89 (0.65 to 0.99)	No serious	No serious	No serious	Serious[2]	MODERATE	0.89	1.00
			Specificity: 1.00 (0.96 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

	PCR type: Multiplex Reference standard: CSF bacterial culture									
1 (Meyer 2014)	Population: BM BI UI PCR type: Broad-range Reference standard: CSF bacterial culture	40	Sensitivity: 0.67 (0.22 to 0.96)	Serious[1]	No serious	No serious	Very serious[3]	VERY LOW	0.31	0.93
			Specificity: 0.74 (0.56 to 0.87)*	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Leitner 2016)	Population: BM U (Patients with clinically suspected community acquired or drainage associated meningitis) PCR type: Multiplex Reference standard: CSF bacterial culture	20	Sensitivity: 0.50 (0.16 to 0.84)	No serious	No serious	No serious	Serious[2]	MODERATE	0.80	0.73
			Specificity: 0.92 (0.62 to 1.00)	No serious	No serious	No serious	Serious[2]	MODERATE		

** The authors considered the false positive cases (according to culture results) as true positive based on clinical features, other CSF findings and antibiotic usage, which would improve specificity*
BI: bacterial CNS infection; BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; FM: fungal meningitis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; UI: undefined CNS infection; UM: undefined meningitis; 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 80: Evidence profile for PCR for diagnosis of bacterial meningitis caused by N. meningitidis in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Porritt 2000)	Population: MM U (CSF samples from patients with	81	Sensitivity: 1.00 (0.77 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.41	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
	suspected meningococcal disease) PCR type: Multiplex Reference standard: CSF bacterial culture		Specificity: 0.72 (0.60 to 0.82)*	No serious	No serious	No serious	No serious	HIGH		
1 (Kotilainen 1998)	Population: BM UM NM PCR type: Broad-range Reference standard: CSF bacterial culture	56	Sensitivity: 1.00 (0.40 to 1.00)	Serious[2]	No serious	No serious	Very serious[3]	VERY LOW	0.80	1.00
			Specificity: 0.98 (0.90 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		
1 (Seward 2000b)	Population: BM U (Patients with suspected meningitis) PCR type: Multiplex Reference standard: CSF bacterial culture	294	Sensitivity: 1.00 (0.72 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.73	1.00
			Specificity: 0.99 (0.96 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Boving 2009)	Population: BM U (CSF samples sent to study centre for analysis) PCR type: Multiplex	1087	Sensitivity: 1.00 (0.48 to 1.00)	Serious[2]	No serious	No serious	Very serious[3]	VERY LOW	0.63	1.00
			Specificity: 1.00 (0.99 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		

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: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis									
1 (Seward 2000a)	Population: MM U (CSF samples from patients suspected of meningococcal meningitis) PCR type: Multiplex Reference standard: CSF bacterial culture	74	Sensitivity: 1.00 (0.82 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	1.00
			Specificity: 1.00 (0.94 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Esparcia 2011)	Population: BM U (Patients with clinical suspicion of bacterial meningitis) PCR type: Broad-range Reference standard: CSF bacterial culture	101	Sensitivity: 0.92 (0.62 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.55	0.99
			Specificity: 0.90 (0.82 to 0.95)	No serious	No serious	No serious	Serious[1]	MODERATE		

** The authors considered the false positive cases (according to culture results) as true positive based on clinical presentation and other CSF findings, which would improve specificity*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; UM: undefined meningitis; 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
[3] 95% CI crosses 2 decision making thresholds
[4] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 81: Evidence profile for PCR for diagnosis of bacterial meningitis caused by S. pneumoniae in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Esparcia 2011)	Population: BM U (Patients with clinical suspicion of bacterial meningitis) PCR type: Broad range Reference standard: CSF bacterial culture	101	Sensitivity: 1.00 (0.90 to 1.00)	No serious	No serious	No serious	No serious	HIGH	0.80	1.00
			Specificity: 0.86 (0.75 to 0.93)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Chiba 2009)	Population: BM U (Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing) PCR type: Multiplex Reference standard: CSF bacterial culture	168	Sensitivity: 1.00 (0.87 to 1.00)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.75	1.00
			Specificity: 0.94 (0.88 to 0.97)	Serious[2]	No serious	No serious	Serious[1]	LOW		
1 (Wagner 2018)	Population: BM U (CSF samples from patients with meningitis symptoms) PCR type: Multiplex	220	Sensitivity: 1.00 (0.54 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.75	1.00
			Specificity: 0.99 (0.97 to 1.00)	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: CSF bacterial culture									
1 (Boving 2009)	Population: BM U (CSF samples sent to study centre for analysis) PCR type: Multiplex Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	1087	Sensitivity: 0.94 (0.70 to 1.00)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.54	1.00
			Specificity: 0.99 (0.98 to 0.99)	Serious[2]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population
[1] 95% CI crosses 1 decision making threshold
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] 95% CI crosses 2 decision making thresholds

Table 82: Evidence profile for PCR for diagnosis of bacterial meningitis caused by H. influenzae in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Chiba 2009)	Population: BM U (Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing) PCR type: Multiplex	168	Sensitivity: 1.00 (0.93 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE	0.63	1.00
			Specificity: 0.77 (0.68 to 0.84)	Serious[1]	No serious	No serious	No serious	MODERATE		

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: CSF bacterial culture									
1 (Xirogianni 2009)	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	262	Sensitivity: 1.00 (0.16 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	0.40	1.00
			Specificity: 0.99 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; FM: fungal meningitis; H. influenzae: Haemophilus influenzae; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population; 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

Table 83: Evidence profile for PCR for diagnosis of bacterial meningitis caused by group B Streptococcus in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Chiba 2009)	Population: BM U (Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing.) PCR type: Multiplex Reference standard: CSF bacterial culture	168	Sensitivity: 1.00 (0.16 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	0.50	1.00
			Specificity: 0.99 (0.96 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population

[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 84: Evidence profile for PCR for diagnosis of bacterial meningitis caused by Gram-negative bacilli in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Xirogianni 2009)*	Population: BM VM NM PCR type: Multiplex Reference standard: CSF bacterial culture	262	Sensitivity: 1.00 (0.16 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.50	1.00
			Specificity: 0.99 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		
1 (Boving 2009)**	Population: BM U (CSF samples sent to study centre for analysis) PCR type: Multiplex Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	1187	Sensitivity: 1.00 (0.03 to 1.00)	Serious[2]	No serious	No serious	Very serious[1]	VERY LOW	0.14	1.00
			Specificity: 0.99 (0.99 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		
1 (Chiba 2009)**	Population: BM U (Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing) PCR type: Multiplex Reference standard:	168	Sensitivity: 1.00 (0.29 to 1.00)	Serious[2]	No serious	No serious	Very serious[1]	VERY LOW	1.00	1.00
			Specificity: 1.00 (0.98 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		

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

**Pathogens detected: P. aeruginosa*
*** Pathogens detected: E. coli*
BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; E. coli: Escherichia coli; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; P. aeruginosa: Pseudomonas aeruginosa; U: undefined population; VM: viral meningitis
[1] 95% CI crosses 2 decision making thresholds
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 85: Evidence profile for PCR for diagnosis of bacterial meningitis caused by L. monocytogenes in undefined ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Boving 2009)	Population: BM U (CSF samples sent to study centre for analysis) PCR type: Multiplex Reference standard: CSF bacterial culture, blood bacterial culture, microscopy and/or molecular diagnosis	1087	Sensitivity: 1.00 (0.03 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	1.00
			Specificity: 1.00 (1.00 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Chiba 2009)	Population: BM U (Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood examination testing) PCR type: Multiplex Reference standard: CSF bacterial culture	168	Sensitivity: 1.00 (0.03 to 1.00)	Serious[1]	No serious	No serious	Very serious[2]	VERY LOW	1.00	1.00
			Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Esparcia 2011)	Population: BM U (Patients with clinical suspicion of bacterial meningitis) PCR type: Broad-range Reference standard: CSF bacterial culture	101	Sensitivity: 0.88 (0.47 to 1.00)	No serious	No serious	No serious	Very serious[2]	LOW	0.64	0.99
			Specificity: 0.96 (0.89 to 0.99)	No serious	No serious	No serious	Serious[3]	MODERATE		

BM: bacterial meningitis; BME: bacterial meningoencephalitis; CI: confidence interval; CSF: cerebrospinal fluid; L. monocytogenes; Listeria monocytogenes; NBME: non-bacterial meningoencephalitis; NM: non-meningitis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; U: undefined population
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 2 decision making thresholds
[3] 95% CI crosses 1 decision making threshold

Table 86: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by N. meningitidis in neonates, 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 (Lee 2015)	Population: MM U (Children with suspected meningitis who were less than 5 years old.) Reference standard: CSF bacterial culture	1574	Sensitivity: 1.00 (0.29 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.10	1.00
			Specificity: 0.98 (0.97 to 0.99)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; LAMP: loop-mediated isothermal amplification; MM: meningococcal meningitis; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 87: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by S. pneumoniae in neonates, 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 (Kim	Population: BM U	106	Sensitivity:	No	No serious	No serious	Serious[1]	MODERATE	0.33	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
2015)	(Children with suspected meningitis who were less than five years old.) Reference standard: CSF bacterial culture		1.00 (0.72 to 1.00)	serious						
			Specificity: 0.77 (0.67 to 0.85)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LAMP: loop-mediated isothermal amplification; NPV: negative predictive value; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumoniae; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 88: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by all bacteria in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 0.97 (0.82 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.70	0.99
			Specificity: 0.89 (0.81 to 0.94)	No serious	No serious	No serious	Serious[1]	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebral spinal fluid; LAMP: loop mediated isothermal amplification; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 89: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by N. meningitidis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo	Population: BM U (CSF samples	135	Sensitivity: 1.00 (0.40 to	No serious	No serious	No serious	Very serious[1]	LOW	0.40	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
2020)	from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture		1.00)							
			Specificity: 0.95 (0.90 to 0.98)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebral spinal fluid; LAMP: loop mediated isothermal amplification; N. meningitidis: Neisseria meningitidis; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 90: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by S. pneumoniae in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 1.00 (0.78 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.71	1.00
			Specificity: 0.95 (0.89 to 0.98)	No serious	No serious	No serious	Serious[1]	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebral spinal fluid; LAMP: loop mediated isothermal amplification; NPV: negative predictive value; PPV: positive predictive value; S. pneumoniae; Streptococcus pneumonia; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 91: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by group B streptococcus in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 1.00 (0.03 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	1.00
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebral spinal fluid; LAMP: loop mediated isothermal amplification; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 92: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by Gram-negative bacilli* in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 0.67 (0.09 to 0.99)	No serious	No serious	No serious	Very serious[1]	LOW	1.00	0.99
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

** Pathogens detected: E. coli*

BM: bacterial meningitis; CI: confidence interval; CSF: cerebral spinal fluid; E. coli: Escherichia coli; LAMP: loop mediated isothermal amplification; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 2 decision making thresholds

Table 93: Evidence profile for LAMP for diagnosis of bacterial meningitis caused by L. monocytogenes in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 1.00 (0.54 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	1.00	1.00
			Specificity: 1.00 (0.97 to 1.00)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebral spinal fluid; LAMP: loop mediated isothermal amplification; L. monocytogenes: Listeria monocytogenes; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Combination index tests

Table 94: Evidence profile for white cell count plus protein concentration plus glucose concentration at 'elevated' threshold for the diagnosis of group B Streptococcus bacterial meningitis in neonates

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
Threshold: Elevated white cell count (<26 cells/µL for premature neonates and <23 cells/µL for term neonates) and protein concentration (<151 mg/dL for premature neonates and <171 mg/dL for term neonates), low glucose concentration (>23 mg/dL for premature neonates and >33 mg/dL for term neonates)										
1 (Ansong 2009)	Population: GBM GBS U (neonates with lumbar puncture	13,495	Sensitivity: 0.59 (0.43 to 0.73)	No serious	No serious	No serious	Serious[1]	MODERATE	0.10	1.00
			Specificity:	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
	performed) Reference standard: CSF bacterial culture		0.98 (0.98 to 0.98)							

CI: confidence interval; CSF: cerebrospinal fluid; GBM: group B Streptococcus meningitis; GBS: group B Streptococcus septicaemia; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Table 95: Evidence profile for combined Gram staining and LAMP for diagnosis of meningitis in all ages

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (D'Inzeo 2020)	Population: BM U (CSF samples from adult, paediatric and neonatal patients with a clinical suspicion of meningitis or encephalitis) Reference standard: CSF bacterial culture	135	Sensitivity: 1.00 (0.89 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.73	1.00
			Specificity: 0.88 (0.81 to 0.94)	No serious	No serious	No serious	Serious[1]	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LAMP: loop-mediated isothermal amplification; NPV: negative predictive value; PPV: positive predictive value; U: undefined population
[1] 95% CI crosses 1 decision making threshold

Appendix G Economic evidence study selection

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

A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 93).

Figure 93: Study selection flow chart

Appendix H Economic evidence tables

Economic evidence tables for review question: What is the accuracy and effectiveness of cerebrospinal fluid 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 cerebrospinal fluid 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 cerebrospinal fluid investigations in diagnosing bacterial meningitis?

Excluded diagnostic studies

Table 96: Excluded studies and reasons for their exclusion

Study	Reason
Abdel-Salam, H. A. (1999) Direct PCR assay for detection of Neisseria meningitidis in human cerebrospinal fluid. Folia microbiologica 44: 689-694	- Study country not in protocol *Non-OECD, high income country (Egypt)*
Abelian, A, Mund, T, Curran, M. D et al. (2020) Towards accurate exclusion of neonatal bacterial meningitis: A feasibility study of a novel 16S rDNA PCR assay. BMC Infectious Diseases 20 (1)	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Abelian, A and Pritchard, I. (2011) Neonatal bacterial meningitis: Has time come for polymerase chain reaction?. Journal of Pediatric Infectious Diseases 6: 227-229	- Study design not in protocol *Non-comparative study*
Agnememel, A, Traincard, F, Dartevelle, S et al. (2015) Development and evaluation of a dipstick diagnostic test for Neisseria meningitidis serogroup X. Journal of clinical microbiology 53: 449-54	- Reference standard not in protocol *PCR testing of CSF samples*
Aguiar-Nogueira, J; Lecour, H; Luz-Dias, M. (1989) Use of a latex agglutination test in rapid diagnosis of acute meningitis. Enfermedades Infecciosas y Microbiologia Clinica 7: 186-8	- Non-English language article
Ahmed, Mahmoud Abdelfattah, Askar, Gamal A, Farghaly, Hekma S et al. (2022) Evaluation of the accuracy of multiplex polymerase chain reaction in differentiation between bacterial and viral meningitis. Irish journal of medical science	- Reference standard not in protocol *Multiplex PCR compared to diagnosis based on clinical signs and symptoms*
Ahmet, Z, Stanier, P, Harvey, D et al. (1999) New PCR primers for the sensitive detection and specific identification of Group B beta-hemolytic streptococci in cerebrospinal fluid. Molecular and Cellular Probes 13: 349-357	- Population does not meet inclusion criteria *CSF samples from historical prevalence study of infants with confirmed meningitis*
Akkaya, O, Guvenc, H. I, Yuksekkaya, S et al. (2017) Real-time PCR Detection of the Most Common Bacteria and Viruses Causing Meningitis. Clinical LaboratoryClin Lab 63: 827-832	- Study country not in protocol *Non-OECD, high income country (Turkey)*
Aksoy, F, Yilmaz, G, Nur Aydin, N et al. (2017) Are new biomarkers useful in the diagnosis of meningitis in adults?. Open Forum Infectious	- Study design not in protocol *Conference abstract*

Study	Reason
Diseases 4 (Supplement 1): 303	
Al-Mekhlafi, A, Suhs, K. W, Schuchardt, S et al. (2021) Elevated free phosphatidylcholine levels in cerebrospinal fluid distinguish bacterial from viral cns infections. Cells 10 (5)	- Study design not in protocol *No reference standard comparison*
Ala, A, Rahmani, F, Abdollahi, S et al. (2018) Accuracy of neck stiffness, Kernig, Brudzinski, and jolt accentuation of headache signs in early detection of meningitis. Emergency 6 (1)	- Study country not in protocol *Non-OECD high income country (Iran)*
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: 435-443	- Study country not in protocol *Non-OECD, high income country (Brazil)*
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: 14-18	- Study country not in protocol *Non-OECD high income country (Egypt)*
Alkmin, M. D. G. A; Landgraf, I. M; Shimizu, S. H. (1996) Detection of N. meningitidis Group B antigens by MB-Dot-ELISA in patients with meningitis. Bulletin of the Pan American Health Organization 30: 212-217	- Study country not in protocol *Non-OECD, high income country (Brazil)*
Alnomasy, S. F, Alotaibi, B. S, Mujamammi, A. H et al. (2021) Microbial aspects and potential markers for differentiation between bacterial and viral meningitis among adult patients. 16: e0251518	- Study country not in protocol *Non-OECD high income country (Egypt)*
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: e00545	- Index test not in protocol *Procalcitonin levels in CSF samples*
Andersen, J, Backer, V, Jensen, E et al. (1995) Acute meningitis of unknown aetiology: analysis of 219 cases admitted to hospital between 1977 and 1990. Journal of Infection 31: 115-122	- Population does not meet inclusion criteria *Patients with CSF samples culture-negative for bacterial meningitis*
Andreola, B, Bressan, S, Callegaro, S et al. (2007) Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatric Infectious Disease Journal 26: 672-677	- Population does not meet inclusion criteria *Patients with severe bacterial infections. Only 7/435 (7.5%) diagnosed with bacterial meningitis. Results presented as serious bacterial infection compared to non-serious bacterial infection so unable to calculate for bacterial meningitis*
Angelin, J. M, Prabhat, Agiesh Kumar, B. P, Soundravally, R et al. (2015) Novel diagnostic model using iron homeostatic proteins for differentiating acute bacterial meningitis from acute viral meningitis in infants. Indian Journal of Clinical Biochemistry 1: 25	- Study design not in protocol *Conference abstract*

Study	Reason
Anne, R, Dutta, S, Aggarwal, A et al. (2019) Accuracy of cerebrospinal fluid white blood cell count glucose and protein in rapid diagnosis of meningitis in neonates and young infants less than 90 days old. Journal of Perinatal Medicine 47 (Supplement 1): eA494-eA495	- Study design not in protocol *Conference abstract*
Anne, R, Dutta, S, Aggarwal, A et al. (2019) Accuracy of cerebrospinal fluid white blood cell count glucose and protein for rapid diagnosis of meningitis in neonates and young infants. Journal of Perinatal Medicine 47 (Supplement 1): eA252-eA253	- Study design not in protocol *Conference abstract*
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: 839-844	- Study country not in protocol *Non-OECD, high income country (People's Republic of China)*
Arosio, M, Nozza, F, Rizzi, M et al. (2008) Evaluation of the MICROSEQ 500 16S rDNA-based gene sequencing for the diagnosis of culture-negative bacterial meningitis. New Microbiologica 31: 343-349	- Population does not meet inclusion criteria *Patients with CSF samples culture-negative for bacterial meningitis*
Atobe, J. H, Hirata, M. H, Hoshino-Shimizu, S et al. (2000) One-step heminested PCR for amplification of Neisseria meningitidis DNA in cerebrospinal fluid. Journal of Clinical Laboratory Analysis 14: 193-199	- Study country not in protocol *Non-OECD high income country (Brazil)*
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: 489-496	- Index test not in protocol *PCR testing of blood samples. Included studies checked for possible includes*
Ayyagari, A, Kumar, L, Agarwal, K. C et al. (1979) Counter current immunoelectrophoresis in the diagnosis of Haemophilus influenzae meningitis in children. Indian Journal of Medical Research 70: 168-72	- Study country not in protocol *Non-OECD high income country (India)*
Ayyagari, A, Kumar, L, Sharma, M et al. (1980) Counter current immunoelectrophoresis in the rapid diagnosis of pneumococcal meningitis. Indian Journal of Medical Research 72: 627-631	- Study country not in protocol *Non-OECD high income country (India)*
Azuma, H, Tsuda, N, Sasaki, K et al. (1997) Clinical significance of cytokine measurement for detection of meningitis. Journal of Pediatrics 131: 463-465	- Index test not in protocol *CSF levels of TNF-alpha and IL-6*
Babalola, A. A and Coker, A. O. (1981) Pyogenic meningitis: A re-appraisal of microbiological tests used in establishing the diagnosis. East African Medical Journal 58: 601-607	- Study country not in protocol *Non-OECD, high income country (Nigeria)*

Study	Reason
Babenko, Dmitriy, Seidullayeva, Aliya, Bayesheva, Dinagul et al. (2021) Ability of Procalcitonin and C-Reactive Protein for Discriminating between Bacterial and Enteroviral Meningitis in Children Using Decision Tree. BioMed research international 2021: 5519436	- Study country not in protocol *Non-OECD high income country (Kazakhstan)*
Backman, A, Lantz, P. G, Radstrom, P et al. (1999) 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: 49-60	- Study design not in protocol *Two gate-study and sufficient single-gate studies are available for this index test*
Bador, J, Nicolas, B, Chapuis, A et al. (2020) 16S rRNA PCR on clinical specimens: Impact on diagnosis and therapeutic management. Medecine et Maladies Infectieuses 50: 63-73	- Population does not meet inclusion criteria *Unclear. Patients who had a 16S PCR test performed during study period. No further information given and no final diagnosis provided.*
Baethgen, L. F, Moraes, C, Weidlich, L et al. (2003) Direct-test PCR for detection of meningococcal DNA and its serogroup characterization: Standardization and adaptation for use in a public health laboratory. Journal of Medical Microbiology 52: 793-799	- Study country not in protocol *Non-OECD high income country (Brazil)*
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: 393-395	- Reference standard not in protocol *Countercurrent immunoelectrophoresis testing of CSF samples*
Baker, R. C and Lenane, A. M. (1989) The predictive value of cerebrospinal fluid differential cytology in meningitis. Pediatric infectious disease journal 8: 329-330	- Paper unavailable
Bal, A, Anil, M, Gokalp, G et al. (2015) Comparison of the eosinophil count to C - reactive protein, leukocyte count, and neutrophil count for the detection of bacterial infection in ill-appearing children with fever admitted to the emergency department. Signa Vitae 10: 163-176	- Study design not in protocol *Non-OECD high income country (Turkey)*
Balasubramanin, P, Bandiya, P, Niranjan, S. H et al. (2018) Role of CSF-CRP as a Diagnostic Marker in Neonatal Meningitis. Journal of Neonatology 32: 112-117	- Study country not in protocol *Non-OECD, high income country (India)*
Balganesh, M; Lalitha, M. K; Nathaniel, R. (2000) Rapid diagnosis of acute pyogenic meningitis by a combined PCR dot-blot assay. Molecular and Cellular Probes 14: 61-69	- Study country not in protocol *Non-OECD high income country (India)*
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: 630-634	- Reference standard not in protocol *Counterimmunoelectrophoresis and Gram stain testing of CSF samples*

Study	Reason
Banniettis, N, Joshi, S, Kaushik, S et al. (2019) Diagnostic Practices for Suspected Community-Acquired Central Nervous System Infection in the Post-Conjugate Vaccine Era. Pediatric Emergency Care 35: 774-776	- Study design not in protocol *Non comparative study*
Barros Domingues, Renan, Mendes-Correa, Maria Cassia, Vilela de Moura Leite, Fernando Brunale et al. (2022) Evaluation of the Utilization of FilmArray Meningitis/Encephalitis in Children With Suspected Central Nervous System Infection: A Retrospective Case Series. Pediatric emergency care 38(2): 58-61	- Study country not in protocol *Non-OECD high income country (Brazil)*
Barsoum, Z. (2012) Lumbar puncture(LP) in infants and children with suspected meningitis-diagnostic yield over 15 years. Archives of disease in childhood 2: a447	- Study design not in protocol *Conference abstract*
Batista Munoz, A, Hadley, S, Iriondo Sanz, M et al. (2019) Role of beta-2-microglobulin as a biomarker in very preterm and extremely preterm infants with CNS inflammation. 14: e0216498	- Population does not meet inclusion criteria *Mixed. All infants undergoing lumbar puncture for suspected CNS infection or post-hemorrhagic ventricular dilatation. Results presented separately for meningitis population but not for bacterial meningitis*
Baty, V, Viel, J. F, Schuhmacher, H et al. (2000) Prospective validation of a diagnosis model as an aid to therapeutic decision-making in acute meningitis. European Journal of Clinical Microbiology and Infectious Diseases 19: 422-426	- Index test not in protocol *Mixed. Diagnostic model uses CSF protein level and polymorphonuclear cell count, and blood glucose level and leucocyte count*
Beaver, R, Powell, P, Brigmon, M et al. (2021) Approach to a reflex-based meningitis testing pathway. Laboratory Investigation 101 (SUPPL 1): 1022-1023	- Study design not in protocol *Conference abstract*
Behzad-Behbahani, A, Abbas, B. B, Abdolvahab, A et al. (2003) Clinical signs as a guide for performing HSV-PCR in correct diagnosis of herpes simplex virus encephalitis. Neurology India 51: 341-344	- Study country not in protocol *Non-OECD high income country (Iran)*
Belmaaza, A, Hamel, J, Mousseau, S et al. (1986) Rapid diagnosis of severe Haemophilus influenzae serotype b infections by monoclonal antibody enzyme immunoassay for outer membrane proteins. Journal of clinical microbiology 24: 440-5	- Index test not in protocol *Enzyme immunoassay testing of CSF samples*
Belogurov, A. A, Ivanova, O. M, Lomakin, Y. A et al. (2016) Mediators and Biomarkers of Inflammation in Meningitis: Cytokine and Peptidome Profiling of Cerebrospinal Fluid. Biochemistry biokhimiia81: 1293-1302	- Study country not in protocol *Non-OECD high income country (Russia)*
Ben, R. J, Kung, S, Chang, F. Y et al. (2008) Rapid diagnosis of bacterial meningitis using a	- Study country not in protocol *Non-OECD high income country*

Study	Reason
microarray. Journal of the Formosan Medical Association 107: 448-453	*(Taiwan/Republic of China)*
Beratis, N. G; Eliopoulou, M. I; Syrogiannopoulos, G. A. (2003) Beta-glucuronidase in the diagnosis of bacterial meningitis and response to treatment. Acta PaediatricaActa Paediatr 92: 1272-6	- Study design not in protocol *No reference standard comparison*
Berg, B; Gardsell, P; Skansberg, P. (1982) Cerebrospinal fluid lactate in the diagnosis of meningitis. Diagnostic value compared to standard biochemical methods. Scandinavian Journal of Infectious Diseases 14: 111-115	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Bhansali, P, Wiedermann, B. L, Pastor, W et al. (2015) Management of hospitalized febrile neonates without csf analysis: A study of us pediatric hospitals. Hospital Pediatrics 5: 528-533	- Paper unavailable
Bhatia, R, Vibha, D, Prasad, K et al. (2010) Validation of diagnostic algorithm to differentiate tuberculous meningitis and acute bacterial meningitis. Annals of Indian Academy of Neurology 1: 19	- Paper unavailable
Bhisitkul, D. M; Hogan, A. E; Tanz, R. R. (1994) The role of bacterial antigen detection tests in the diagnosis of bacterial meningitis. Pediatric Emergency Care 10: 67-71	- Index test not in protocol *Bacterial antigen detection testing of CSF samples*
Bianchi, L, Napoli, Z, Donati, S et al. (2014) Filmarray system versus RT-PCR method in meningitidis and sepsis management: An example of routine-emergency integration. Clinical Chemistry and Laboratory Medicine 52 (11): ea393	- Study design not in protocol *Conference abstract*
Bianchi, L, Napoli, Z, Donati, S et al. (2013) Real-time PCR and turn around time: Clinical relapse in true microbiological emergencies management. Biochimica Clinica 1: 133	- Study design not in protocol *Conference abstract*
Bianchi, L, Napoli, Z, Niccolai, M et al. (2012) Management of real microbiological emergencies: Real time PCR platform as integration tool among clinical biochemistry, microbiology and clinical molecular biology. Biochimica Clinica 36 (6): 482	- Study design not in protocol *Conference abstract*
Biesterfeld, S, Bernhard, B, Bamborschke, S et al. (1993) DNA single cell cytometry in lymphocytic pleocytosis of the cerebrospinal fluid. Acta NeuropathologicaActa Neuropathol (Berl) 86: 428-32	- Study design not in protocol *No reference standard comparison*
Bingen, E, Lambert-Zechovsky, N, Mariani-Kurkdjian, P et al. (1990) Bacterial counts in cerebrospinal fluid of children with meningitis. European Journal of Clinical Microbiology &	- Study design not in protocol *No reference standard comparison*

Study	Reason
Infectious DiseasesEur J Clin Microbiol Infect Dis 9: 278-81	
Bishop, B, Geffen, Y, Plaut, A et al. (2018) The use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for rapid bacterial identification in patients with smear-positive bacterial meningitis. Clinical Microbiology and Infection 24: 171-174	- Population does not meet inclusion criteria *Mixed. Post-neurosurgical bacterial meningitis (34/44) and community acquired bacterial meningitis (10/44) patients. Results not presented separately for target population*
Bitaraf, F. S; Rasooli, I; Mousavi Gargari, S. L. (2016) DNA aptamers for the detection of Haemophilus influenzae type b by cell SELEX. European journal of clinical microbiology & infectious diseases 35: 503-10	- Study country not in protocol *Non-OECD high income country (Iran)*
Bociaga-Jasik, M, Garlicki, A, Ciesla, A et al. (2012) The diagnostic value of cytokine and nitric oxide concentrations in cerebrospinal fluid for the differential diagnosis of meningitis. Advances in Medical Sciences 57: 142-147	- Study design not in protocol *No reference standard comparison*
Boden, K, Sachse, S, Baier, M et al. (2011) 16s rDNA-PCR and Sequencing improves diagnosis of bacterial infection of the central nervous system. Open Critical Care Medicine Journal 4: 44-46	- Population does not meet inclusion criteria *Patients with suspected bacterial CSF infection. Only 8/26 (31%) diagnosed with bacterial meningitis*
Bonadio, W. A. (1992) The cerebrospinal fluid: Physiologic aspects and alterations associated with bacterial meningitis. Pediatric infectious disease journal 11: 423-432	- Study design not in protocol *Non-systematic review*
Bonadio, W. A; Smith, D; Carmody, J. (1992) Correlating CBC profile and infectious outcome: A study of febrile infants evaluated for sepsis. Clinical pediatrics 31: 578-582	- Population does not meet inclusion criteria *Patients with serious bacterial infection. Only 21/1009 (2.1%) diagnosed with bacterial meningitis. Results presented as serious bacterial infection compared to non-serious bacterial infection so unable to calculate outcomes for bacterial meningitis*
Bonadio, W.A, Webster, H, Wolfe, A et al. (1993) Correlating infectious outcome with clinical parameters of 1130 consecutive febrile infants aged zero to eight weeks. Pediatric Emergency Care 9: 84-86	- Study design not in protocol *Conference abstract*
Bonsu, B. K and Harper, M. B. (2004) Differentiating acute bacterial meningitis from acute viral meningitis among children with cerebrospinal fluid pleocytosis: A multivariable regression model. Pediatric infectious disease journal 23: 511-517	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Borrow, R, Claus, H, Guiver, M et al. (1997) Non-culture diagnosis and serogroup determination of meningococcal B and C infection by a sialyltransferase (siaD) PCR ELISA.	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*

Study	Reason
Epidemiology & InfectionEpidemiol Infect 118: 111-7	
Borrow, R, Guiver, M, Sadler, F et al. (1998) False positive diagnosis of meningococcal infection by the IS1106 PCR ELISA. FEMS Microbiology Letters 162: 215-218	- Study design not in protocol *Pathogen identification of 4 false positive PCR tests from previous study results.*
Boskheti, V and Kyssela (1960) Electrophoresis of the cerebrospinal fluid and the blood serum in neuro-infections. Zh neuropatpsikhiat60: 974-981	- Paper unavailable
Boulos, A, Fairley, D, McKenna, J et al. (2017) Evaluation of a rapid antigen test for detection of Streptococcus pneumoniae in cerebrospinal fluid. Journal of Clinical PathologyJ Clin Pathol 70: 448-450	- Index test not in protocol *Rapid antigen testing of CSF samples*
Bressan, S, Gomez, B, Mintegi, S et al. (2012) Diagnostic performance of the Lab-score in predicting severe and invasive bacterial infections in well-appearing young febrile infants. Pediatric Infectious Disease Journal 31: 1239-1244	- Population does not meet inclusion criteria *Patients with serious bacterial infections and invasive bacterial infections. Only 1/274 (<1%) diagnosed with bacterial meningitis (reference standard for this participant was positive blood culture plus pleocytosis, and negative CSF culture). Unable to calculate outcomes for bacterial meningitis*
Briem, H. (1983) Comparison between cerebrospinal fluid concentrations of glucose, total protein, chloride, lactate, and total amino acids for the differential diagnosis of patients with meningitis. Scandinavian Journal of Infectious Diseases 15: 277-284	- Index test not in protocol *Total free amino acid concentrations in CSF samples*
Briem, H, Hultman, E. H, Kalin, M. E et al. (1982) Increased total concentration of amino acids in the cerebrospinal fluid of patients with purulent meningitis. Journal of infectious diseases 145: 346-350	- Index test not in protocol *Total free amino acid concentrations in CSF samples*
Bronska, E, Dzupova, O, Krizova, P et al. (2005) Invasive meningococcal disease and latex agglutination test - Is it still beneficial for diagnosis?. Folia Microbiologica 50: 453-456	- Population does not meet inclusion criteria *Patients with laboratory-confirmed invasive meningococcal disease. Bacterial meningitis not reported*
Bronska, E, Kalmusova, J, Dzupova, O et al. (2006) Dynamics of PCR-based diagnosis in patients with invasive meningococcal disease. Clinical Microbiology and Infection 12: 137-141	- Population does not meet inclusion criteria *Patients with laboratory-confirmed invasive meningococcal disease. Bacterial meningitis not reported*
Bugden, S. A; Coles, C; Mills, G. D. (2004) The potential role of procalcitonin in the emergency department management of febrile young adults during a sustained meningococcal epidemic. EMA - Emergency Medicine Australasia 16: 114-119	- Population does not meet inclusion criteria *Patients with suspected meningococcal disease. Only 4/183 (2.2%) diagnosed with bacterial meningitis. Results presented as meningococcal disease compared to non-meningococcal disease so unable to calculate outcomes for bacterial meningitis*

Study	Reason
Buoro, S, Esposito, S. A, Ottomano, C et al. (2014) Automated screening of bacterial meningitis by cytofluorimetric analysis of cerebrospinal fluid: Preliminary results. Biochimica Clinica 38: 208-212	- Reference standard not in protocol *Comparing cytometric analysis of CSF samples using automated particle analyzer with optical microscopy*
Buoro, S, Ottomano, C, Esposito, S. A et al. (2013) Analytical and clinical evaluation of sysmex UF1000i for automated screening of cerebrospinal fluids. Journal of Medical Biochemistry 33: 191-196	- Reference standard not in protocol *Comparing cytometric analysis of CSF samples using automated particle analyzer with optical microscopy*
Burdash, N. M; Smith, K. A; Welborn, A. L. (1982) Rapid detection of Haemophilus influenzae type b in cerebrospinal fluid by commercial coagglutination and latex agglutination kits. European Journal of Clinical Microbiology 1: 131-3	- Population does not meet inclusion criteria *Unclear. CSF samples submitted to the clinical microbiology laboratory for culture No further information given*
Butzler, J. P. (1979) Rapid etiologic diagnosis of bacterial meningitis. Acta Clinica Belgica 34: 51-54	- Study design not in protocol *Book chapter. No original data presented*
Calderaro, A, Martinelli, M, Motta, F et al. (2014) Comparison of peptide nucleic acid fluorescence in situ hybridization assays with culture-based matrix-assisted laser desorption/ionization-time of flight mass spectrometry for the identification of bacteria and yeasts from blood cultures and cerebrospinal fluid cultures. Clinical Microbiology & InfectionClin Microbiol Infect 20: O468-75	- Population does not meet inclusion criteria *Unclear. Patients with suspected sepsis and other severe infections (of which meningitis is an example). Proportions of meningitis not reported*
Camara-Lemarroy, C, Delgado-Garcia, G, De La Cruz-Gonzalez, J et al. (2016) Mean platelet volume in the differential diagnosis of tuberculous and bacterial meningitis. Neurology. Conference: 68th American Academy of Neurology Annual Meeting, AAN 86	- Study design not in protocol *Conference abstract*
Canillas Munoz, B, Rubio Arias, S, Hernandez Alvarez, M et al. (2011) Procalcitonin in infants under 3 months with fever of unknown origin. Clinical Chemistry and Laboratory Medicine 1: 519	- Study design not in protocol *Conference abstract*
Cargill, J. S. (1975) Previous antibiotic treatment and meningitis diagnosis. Lancet 2: 665-666	- Study design not in protocol *Letter to the editor*
Carrol, E. D, Thomson, A. P. J, Riordan, F. A. I et al. (2000) Increasing microbiological confirmation and changing epidemiology of meningococcal disease on Merseyside, England. Clinical Microbiology and Infection 6: 259-262	- Population does not meet inclusion criteria *Unclear. Patients with probable meningococcal disease. Proportions of meningitis not reported*
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	- Population does not meet inclusion criteria *Unclear. Patients with probable meningococcal disease. Proportions of meningitis not reported*

Study	Reason
Disease in Childhood 83: 271-273	
Casal, J; Perez Brena, P; Martin Bourgon, C. (1973) A comparative study of precipitating serological techniques for the detection of meningococcal polysaccharide. Microbiologia Espanola 26: 85-97	- Index test not in protocol *Gel diffusion and immunoelectrophoresis testing of CSF samples*
Caugant, D. A, Hoiby, E. A, Froholm, L. O et al. (1996) Polymerase chain reaction for case ascertainment of meningococcal meningitis: application to the cerebrospinal fluids collected in the course of the Norwegian meningococcal serogroup B protection trial. Scandinavian Journal of Infectious DiseasesScand J Infect Dis 28: 149-53	- Population does not meet inclusion criteria *Patients with diseases of 'various aetiology'. Only 11/87 (12.6%) diagnosed with meningitis. Unable to calculate outcomes for bacterial meningitis*
Cavallazzi, R, Bennin, C. L, Hirani, A et al. (2010) Is the band count useful in the diagnosis of infection? An accuracy study in critically ill patients. Journal of Intensive Care Medicine 25: 353-7	- Population does not meet inclusion criteria *Patients admitted to medical intensive care unit. Meningitis not listed as diagnosis*
Chakrabarti, P; Das, B. K; Kapil, A. (2009) Application of 16S rDNA based seminested PCR for diagnosis of acute bacterial meningitis. Indian Journal of Medical Research 129: 182-188	- Study country not in protocol *Non-OECD, high income country (India)*
Chan, Y. L, Tseng, C. P, Tsay, P. K et al. (2004) Procalcitonin as a marker of bacterial infection in the emergency department: an observational study. Critical care (London, England) 8: R12-20	- Study country not in protocol *Non-OECD high income country (Taiwan, People's Republic of China)*
Chang, D, Okulicz, J. F, Nielsen, L. E et al. (2018) A Tertiary Care Center's Experience with Novel Molecular Meningitis/Encephalitis Diagnostics and Implementation with Antimicrobial Stewardship. Military medicine 183: e24-e27	- Population does not meet inclusion criteria *Unclear. Patients that had index test performed during study period. Proportions of meningitis not reported*
Chanteau, S, Dartevelle, S, Mahamane, A. E et al. (2006) New rapid diagnostic tests for Neisseria meningitidis serogroups A, W135, C, and Y. PLoS Medicine / Public Library of SciencePLoS Med 3: e337	- Study country not in protocol *Non-OECD high income country (Niger)*
Chao, Y.N; Chiu, N.C; Huang, F.Y. (2008) Clinical features and prognostic factors in childhood pneumococcal meningitis. Journal of Microbiology, Immunology and Infection 41: 48-53	- Study country not in protocol *Non-OECD high income country (Taiwan)*
Chatzopoulos, K; Shannon, S; Schuetz, A. N. (2020) Clinical utility of anaerobic culture of cerebrospinal fluid. Anaerobe 64 (no pagination)	- Population does not meet inclusion criteria *Unclear. Patients that had index test performed during study period. Proportions of meningitis not reported*
Chauhan, D, Mokta, K, Kanga, A et al. (2018) Epidemiology, clinical profile and role of rapid tests in the diagnosis of acute bacterial meningitis	- Study country not in protocol *Non-OECD high income country (India)*

Study	Reason
in children (aged 1-59 months). Neurology india 66: 1045-1049	
Chavanet, P, Schaller, C, Levy, C et al. (2007) Performance of a predictive rule to distinguish bacterial and viral meningitis. Journal of infection 54: 328-336	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Chen, Juncao, Huang, Weiben, Zhang, Hong et al. (2022) Quantitative proteomics on the cerebrospinal fluid of hydrocephalus in neonatal bacterial meningitis. Frontiers in pediatrics 10: 972032	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Chen, Yin-Ting, Chang, Yu-Jun, Liu, Bang-Yan et al. (2021) Severe bacterial infection in young infants with pyrexia admitted to the emergency department. Medicine 100(27): e26596	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Chen, Z, Wang, Y, Zeng, A et al. (2012) The clinical diagnostic significance of cerebrospinal fluid d-lactate for bacterial meningitis. Clinica Chimica Acta 413: 1512-1515	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Cherian, T, Lalitha, M. K, Manoharan, A et al. (1998) PCR-Enzyme immunoassay for detection of Streptococcus pneumoniae DNA in cerebrospinal fluid samples from patients with culture-negative meningitis. Journal of clinical microbiology 36: 3605-8	- Study country not in protocol *Non-OECD high income country (India)*
Chew, G. L. N. (1973) A simple laboratory diagnosis of meningitis: The causative organism and therapy. Ghana Medical Journal 12: 219-222	- Study country not in protocol *Non-OECD, high income country (Ghana)*
Choi, H. S and Anderson, P. J. (1979) Diagnostic cytology of cerebrospinal fluid by the cytocentrifuge method. American Journal of Clinical Pathology 72: 931-43	- Population does not meet inclusion criteria *Unclear. Patients with neurological and non-neurological disorders. Bacterial meningitis not listed as a diagnosis*
Chong, B. S. W and Kennedy, K. J. (2021) Comparison of a commercial real-time PCR panel to routine laboratory methods for the diagnosis of meningitis-encephalitis. Pathology 17: 17	- Population does not meet inclusion criteria *Unclear. Includes patients with history of neurological impairment and/or significant immunosuppression. Proportions not reported and results not presented separately for target population*
Chowdhury, Z. U, Rahman, K. M, Miah, R. A et al. (1990) Evaluation of co-agglutination (COA), counter immunoelectrophoresis (CIE), culture and direct microscopic (Dm) examination of cere-brospinal fluid (CSF) for detection of meningitis caused by common bacterial pathogens. Bangladesh Medical Research Council bulletin 16: 34-41	- Study country not in protocol *Non-OECD high income country (Bangladesh)*
Close, R.M, Ejidokun, O.O, Verlander, N.Q et al. (2011) Early diagnosis model for meningitis	- Population does not meet inclusion criteria *Mixed. Suspected cases of meningitis and*

Study	Reason
supports public health decision making. Journal of Infection 63: 32-38	*meningococcal septicaemia. Results not presented separately for target population*
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 in protocol *Conference abstract*
Colding, H and Lind, I. (1977) Counterimmunoelectrophoresis in the diagnosis of bacterial meningitis. Journal of Clinical Microbiology 5: 405-409	- Index test not in protocol *Counter immunoelectrophoresis testing of CSF samples*
Coll, P, Borche, L, Ausina, V et al. (1986) Dot-immunobinding assay with a monoclonal antibody for detection of group B meningococcal antigen. European Journal of Clinical Microbiology 5: 44-6	- Index test not in protocol *Mixed. Gram stain of CSF and urine samples. Results not presented separately for target index test*
Congeni, B. L; Igel, H. J; Platt, M. S. (1984) Evaluation of a latex particle agglutination kit in pneumococcal disease. Pediatric infectious disease 3: 417-9	- Index test not in protocol *Latex agglutination and countercurrent immunoelectrophoresis testing of CSF samples*
Converse, G. M, Gwaltney, J. M, Jr et al. (1973) Alteration of cerebrospinal fluid findings by partial treatment of bacterial meningitis. Journal of pediatrics 83: 220-5	- Study design not in protocol *Investigating the effect of anti-bacterial treatment on CSF parameters in children with acute meningitis, rather than using these parameters as a diagnostic test*
Converse, G. M; Stewart, P. M; Hendley, J. O. (1977) Clinical use of counterimmunoelectrophoresis in diagnosis of meningitis. Journal of the Medical Association of the State of Alabama 46: 29-30	- Index test not in protocol *Countercurrent immunoelectrophoresis testing of CSF samples*
Coonrod, J. D and Rylko, Bauer (1976) Latex agglutination in the diagnosis of pneumococcal infection. Journal of clinical microbiology 4: 168-174	- Index test not in protocol *Latex agglutination and countercurrent immunoelectrophoresis testing of CSF samples*
Coonrod, J. D and Rytel, M. W. (1972) Specificity of counter-immunoelectrophoresis in bacterial meningitis. Lancet 2: 829	- Study design not in protocol *Letter to editor*
Coovadia, Y. M and Naidu, K. K. (1985) Evaluation of Bactigen latex agglutination and Phadebact coagglutination for detection of bacterial antigens in cerebrospinal fluid. Journal of Clinical Pathology 38: 561-564	- Study country not in protocol *Non-OECD high income country (South Africa)*
Corless, C. E, Guiver, M, Borrow, R et al. (2001) Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. Journal of clinical microbiology 39: 1553-1558	- Population does not meet inclusion criteria *Unclear. Patients with CSF samples culture-positive for meningococcal disease. Proportions of meningitis not reported*

Study	Reason
Correia Barbosa, S. F; Alkmin, M. G; Landgraf, I. M. (2000) Detecting polysaccharide antigen of Neisseria meningitidis group C in cerebrospinal fluid by dot-ELISA assay. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases 4: 144-150	- Study country not in protocol *Non-OECD, high income country (Brazil)*
Cruciani, M and Mengoli, C. (2009) An Overview of Meta-analyses of Diagnostic Tests in Infectious Diseases. Infectious Disease Clinics of North America 23: 225-267	- Population does not meet inclusion criteria *Includes all infectious diseases (bacterial, fungal, viral, protozoan, and different clinical syndromes and conditions). Included studies checked for possible includes*
Cuadros-Munoz, J. F, Santotoribio, J. D, Canavate-Solano, C et al. (2017) Biomarkers of inflammation in cerebrospinal fluid and serum to differentiate between bacterial and viral meningitis. Clinical Chemistry 63 (Supplement 1): 205	- Study design not in protocol *Conference abstract*
Da Costa Castro, J. M, Deschamps, F, Benbachir, M et al. (1987) Highly sensitive biotin-avidin sandwich ELISA for the rapid detection of pneumococcal capsular polysaccharide antigens. Journal of Immunological Methods 104: 265-270	- Study country not in protocol *Non-OECD high income country (Morocco)*
Dagan, R, Shriker, O, Hazan, I et al. (1998) Prospective study to determine clinical relevance of detection of pneumococcal DNA in sera of children by PCR. Journal of clinical microbiology 36: 669-73	- Index test not in protocol *Mixed. PCR testing of serum and CSF samples. Only 4/284 (1.4%) CSF samples*
Dalton, H. P and Allison, M. J. (1968) Modification of laboratory results by partial treatment of bacterial meningitis. American Journal of Clinical Pathology 49: 410-413	- Study design not in protocol *Investigating the effect of anti-bacterial treatment on CSF parameters in children with acute meningitis, rather than using these parameters as a diagnostic test*
Daly, J. A; Gooch, W. M; 3rd, Matsen, J. M. (1985) Evaluation of the Wayson variation of a methylene blue staining procedure for the detection of microorganisms in cerebrospinal fluid. Journal of Clinical Microbiology 21: 919-21	- Reference standard not in protocol *Microscopy of CSF samples prepared with Wayson stain compared to those prepared with Gram stain*
Dano, I. D, Sadou, H, Issaka, B et al. (2016) Measurement of Interleukin-6 in Cerebrospinal Fluid for the Diagnosis of Bacterial Meningitis. Pakistan journal of biological sciences : PJBS 19: 185-190	- Study country not in protocol *Non-OECD high income country (Niger)*
Das, B. K, Gurubacharya, R. L, Mohapatra, T. M et al. (2003) Bacterial antigen detection test in meningitis. Indian journal of pediatrics 70: 799-801	- Study country not in protocol *Non-OECD high income country (India)*
Dasgupta, J; Rao, R. S; Kanungo, R. (1990) Counter immuno electrophoresis for the early	- Study country not in protocol *Non-OECD, high income country (India)*

Study	Reason
diagnosis of acute pyogenic meningitis. Indian journal of pathology & microbiology 33: 239-243	
Dash, S. K, Sharma, M, Khare, S et al. (2013) rmpM genosensor for detection of human brain bacterial meningitis in cerebrospinal fluid. Applied Biochemistry & BiotechnologyAppl Biochem Biotechnol 171: 198-208	- Study country not in protocol *Non-OECD high income country (India)*
De Almeida, S. M, Furlan, S. M. P, Cretella, A. M. M et al. (2020) Comparison of Cerebrospinal Fluid Biomarkers for Differential Diagnosis of Acute Bacterial and Viral Meningitis with Atypical Cerebrospinal Fluid Characteristics. Medical Principles and Practice 29: 244-254	- Study country not in protocol *Non-OECD high income country (Brazil)*
de Almeida, Sergio Monteiro, Barros, Nagyla, Fernandes Dos Santos, Alisson et al. (2021) Clinical performance of amperometry compared with enzymatic ultra violet method for lactate quantification in cerebrospinal fluid. Diagnosis (Berlin, Germany) 8(4): 510-514	- Study country not in protocol *Non-OECD high income country (Brazil)*
de Blauw, D, Bruning, A, Vijn, L. J et al. (2019) Blood and cerebrospinal fluid characteristics in neonates with a suspected central nervous system infection. Medicine 98: e16079	- Study design not in protocol *Non-comparative study*
de Filippis, I, do Nascimento, C. R, Clementino, M. B et al. (2005) Rapid detection of Neisseria meningitidis in cerebrospinal fluid by one-step polymerase chain reaction of the nspA gene. Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis 51: 85-90	- Study country not in protocol *Non-OECD, high income country (Brazil)*
de Kruif, M. D, Limper, M, Gerritsen, H et al. (2010) Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department. Critical Care Medicine 38: 457-63	- Study design not in protocol *PhD thesis*
de Zoysa, A, Edwards, K, Gharbia, S et al. (2012) Non-culture detection of Streptococcus agalactiae (Lancefield group B Streptococcus) in clinical samples by real-time PCR. Journal of Medical Microbiology 61: 1086-1090	- Population does not meet inclusion criteria *Infants with CSF samples culture-negative for S. agalactiae*
De Zoysa, A, Vickers, A, Edwards, K et al. (2011) Non-culture diagnosis of neonatal sepsis caused by Streptococcus agalactiae. Clinical Microbiology and Infection 17: 554	- Study design not in protocol *Conference proceeding*
Dean, N. P, Carpenter, J. L, Campos, J. M et al. (2014) A systematic approach to the differential diagnosis of encephalitis in children. Journal of the Pediatric Infectious Diseases Society 3: 175-179	- Study design not in protocol *Clinical decision tree. No original data presented*

Study	Reason
Debray, A, Nathanson, S, Moulin, F et al. (2019) Eosinopenia as a marker of diagnosis and prognostic to distinguish bacterial from aseptic meningitis in pediatrics. European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis 38: 1821-1827	- Index test not in protocol *Eosinophil count of CSF samples. AUC reported for C-reactive protein and procalcitonin levels of CSF samples. Protein and glucose levels of CSF samples also measured but insufficiently reported*
Deivanayagam, B. N, Ashok, T. P, Nedunchelian, K et al. (1993) Evaluation of CSF variables as a diagnostic test for bacterial meningitis. Journal of Tropical Pediatrics 39: 284-287	- Study country not in protocol *Non-OECD high income country (India)*
Deivanayagam, N, Ashok, T. P, Nedunchelian, K et al. (1993) Bacterial meningitis: diagnosis by latex agglutination test and clinical features. Indian pediatrics 30: 495-500	- Study country not in protocol *Non-OECD, high income country (India)*
Dekker, P. A. (1970) Pyogenic meningitis in infancy and childhood. Ethiopian Medical Journal 8: May-15	- Study country not in protocol *Non-OECD high income country (Ethiopia)*
Delannoy, Q, Pean-De-Ponfilly, G, Mesnil, C et al. (2020) Validation of the Bacterial Meningitis Score in adults consulting at an emergency department: a retrospective multicentric study. European Journal of Emergency Medicine: 447-453	- Index test not in protocol *Mixed. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure*
Delevaux, I, Andre, M, Colombier, M et al. (2003) Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes?. Annals of the Rheumatic Diseases 62: 337-340	- Population does not meet inclusion criteria *Patients with fever and/or inflammatory syndrome. Meningitis not listed as a diagnosis*
DeLozier, J. S and Auerbach, P. S. (1989) The leukocyte esterase test for detection of cerebrospinal fluid leukocytosis and bacterial meningitis. Annals of Emergency MedicineAnn Emerg Med 18: 1191-8	- Population does not meet inclusion criteria *Unclear. CSF samples collected during lumbar puncture for routine indications. Proportion of suspected bacterial meningitis not reported*
Demissie, D. E, Kaplan, S. L, Romero, J. R et al. (2013) Altered neutrophil counts at diagnosis of invasive meningococcal infection in children. Pediatric Infectious Disease Journal 32: 1070-2	- Reference standard not in protocol *Unclear. Questionnaire used to gather demographic and clinical information, and outcome*
Denis, F, Mounier, M, Gaye, A et al. (1989) Detection of bacterial and viral antigens in CSF: Detection and quantification of bacterial antigen in cerebrospinal fluid for aetiological diagnosis, prognosis and therapeutic survey of purulent meningitis. Journal of Clinical Chemistry and Clinical Biochemistry 27: 899-900	- Study design not in protocol *Conference proceeding*
DeVincenzo, J, Cornaghie, M, Utkov, G et al. (2011) Evaluation of a nucleic acid amplification-based molecular diagnosis of invasive pneumococcal (PNEUMO) infections. Journal of Investigative Medicine 59 (2): 489-490	- Study design not in protocol *Conference proceeding*

Study	Reason
Diawara, I, Katfy, K, Zerouali, K et al. (2016) A duplex real-time PCR for the detection of Streptococcus pneumoniae and Neisseria meningitidis in cerebrospinal fluid. Journal of Infection in Developing Countries 10: 53-61	- Study country not in protocol *Non-OECD, high income country (Morocco)*
Dicuonzo, G, Lorino, G, Lilli, D et al. (1999) Use of oligoprobes on amplified DNA in the diagnosis of bacterial meningitis. European Journal of Clinical Microbiology and Infectious Diseases 18: 352-357	- Study design not in protocol *Two gate-study and sufficient single-gate studies are available for this index test*
Dole, M, Maniar, P, Lahiri, K et al. (1989) Enzyme-linked immuno-assay for the detection of mycobacterium tuberculosis specific IgG antibody in the cerebrospinal fluid in cases of tuberculous meningitis. Journal of Tropical Pediatrics 35: 218-220	- Study country not in protocol *Non-OECD high income country (India)*
Domingues, R. B; Fernandes, G. B. P; Leite, Fbvm, Senne, C. (2019) Performance of lactate in discriminating bacterial meningitis from enteroviral meningitis. Revista do Instituto de Medicina Tropical de Sao Paulo 61: e24	- Study country not in protocol *Non-OECD high income country (Brazil)*
Domingues, R. B; Santos, M. V. D; Leite, Fbvm, Senne, C. (2019) FilmArray Meningitis/Encephalitis (ME) panel in the diagnosis of bacterial meningitis. Brazilian Journal of Infectious Diseases 23: 468-470	- Study country not in protocol *Non-OECD, high income country (Brazil)*
Donald, P. R; Malan, C; van der Walt, A. (1983) Simultaneous determination of cerebrospinal fluid glucose and blood glucose concentrations in the diagnosis of bacterial meningitis. Journal of Pediatrics 103: 413-5	- Study country not in protocol *Non-OECD high income country (South Africa)*
Dou, M, Sanjay, S. T, Dominguez, D. C et al. (2017) Multiplexed instrument-free meningitis diagnosis on a polymer/paper hybrid microfluidic biochip. Biosensors & BioelectronicsBiosens Bioelectron 87: 865-873	- Population does not meet inclusion criteria *Previously prepared microorganism samples. No clinical CSF samples tested*
Drakopoulou, Z, Kesanopoulos, K, Sioumala, M et al. (2008) Simultaneous single-tube PCR-based assay for the direct identification of the five most common meningococcal serogroups from clinical samples. FEMS Immunology and Medical Microbiology 53: 178-182	- Study design not in protocol *Two gate-study and sufficient single-gate studies are available for this index test*
Drow, D. L; Maki, D. G; Manning, D. D. (1979) Indirect sandwich enzyme-linked immunosorbent assay for rapid detection of Haemophilus influenzae type b infection. Journal of clinical microbiology 10: 442-50	- Index test not in protocol *Enzyme-linked immunosorbent assay testing of CSF samples*
Drow, D. L, Welch, D. F, Hensel, D et al. (1983) Evaluation of the Phadebact CSF test for	- Index test not in protocol *Counter immunoelectrophoresis and*

Study	Reason
detection of the four most common causes of bacterial meningitis. Journal of Clinical Microbiology 18: 1358-61	*coagglutination testing of CSF samples*
Duan, Q. J; Shang, S. Q; Wu, Y. D. (2009) Rapid diagnosis of bacterial meningitis in children with fluorescence quantitative polymerase chain reaction amplification in the bacterial 16S rRNA gene. European Journal of Pediatrics 168: 211-216	- Study country not in protocol *Non-OECD, high income country (People's Republic of China)*
Dubos, F, De la Rocque, F, Levy, C et al. (2008) Sensitivity of the bacterial meningitis score in 889 children with bacterial meningitis. Journal of Pediatrics 152: 378-82	- Index test not in protocol *Mixed. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure*
Duff, S, Hasbun, R, Balada-Llasat, J. M et al. (2019) Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in adult patients. InfectionInfection 20: 20	- Study design not in protocol *Health economic analysis with no presentation of original clinical data. References of included clinical data checked for possible inclusion*
Duff, S, Hasbun, R, Ginocchio, C. C et al. (2018) Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in pediatric patients. Future MicrobiologyFuture Microbiol 13: 617-629	- Study design not in protocol *Health economic analysis with no presentation of original clinical data. References of included clinical data checked for possible inclusion*
Dutta, Sourabh, Sachdeva, Naresh, Pal, Arnab et al. (2022) Cerebrospinal fluid and plasma procalcitonin for the diagnosis of neonatal bacterial meningitis. Journal of paediatrics and child health 58(8): 1425-1430	- Study country not in protocol *Non-OECD high income country (India)*
Dyson, D and Cassady, G. (1976) Use of Limulus lysate for detecting gram-negative neonatal meningitis. Pediatrics 58: 105-9	- Index test not in protocol *Limulus lystate testing of CSF samples*
Eckerle, M; Lahni, P; Wong, H. (2016) Estimating the probability of bacterial infection using a novel biomarker among pediatric patients in the emergency department. Biomarkers 21: 404-408	- Index test not in protocol *IL-27 and procalcitonin levels in CSF samples*
Edwards, E. A; Muehl, P. M; Peckinpaugh, R. O. (1972) Diagnosis of bacterial meningitis by counterimmunoelectrophoresis. The Journal of laboratory and clinical medicine 80: 449-454	- Index test not in protocol *Counter immunoelectrophoresis testing of CSF samples*
Edwards, K. J, Logan, J. M. J, Langham, S et al. (2012) Utility of real-time amplification of selected 16S rRNA gene sequences as a tool for detection and identification of microbial signatures directly from clinical samples. Journal of Medical Microbiology 61: 645-652	- Index test not in protocol *Mixed. PCR testing of a variety of clinical samples. Only 19/213 (8.9%) CSF samples. Results not presented separately*
Edwards, M. S; Kasper, D. L; Baker, C. J. (1979)	- Index test not in protocol

Study	Reason
Rapid diagnosis of type III group B streptococcal meningitis by latex particle agglutination. Journal of pediatrics 95: 202-5	*Latex agglutination and countercurrent immunoelectrophoresis testing of CSF samples*
Ellis, J, Luintel, A, Chandna, A et al. (2019) Community-acquired acute bacterial meningitis in adults: A clinical update. British Medical Bulletin 131: 57-70	- Study design not in protocol *Narrative review*
Ellis, Jayne, Harvey, David, Defres, Sylviane et al. (2022) Clinical management of community-acquired meningitis in adults in the UK and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR). BMJ open 12(7): e062698	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
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: 920-924	- Study country not in protocol *Non-OECD, high income country (Brazil)*
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: 525	- Index test not in protocol *LAMP assay testing of a variety of body fluids (including CSF, blood and urine). Included studies checked for possible includes*
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: 261-265	- Study country not in protocol *Non-OECD high income country (Iran)*
Feuerborn, S. A; Capps, W. I; Jones, J. C. (1992) Use of latex agglutination testing in diagnosing pediatric meningitis. Journal of Family Practice 34: 176-9	- Index test not in protocol *Latex agglutination testing of CSF samples. CSF leukocytes, protein and glucose also measured but insufficiently reported to construct 2x2 table for review*
Fleischer, E and Aronson, P. L. (2020) Rapid diagnostic tests for meningitis and encephalitis - Biofire. Pediatric Emergency Care 36: 397-403	- Study design not in protocol *Narrative review*
Forward, K. R. (1988) Prospective evaluation of bacterial antigen detection in cerebral spinal fluid in the diagnosis of bacterial meningitis in a predominantly adult hospital. Diagnostic microbiology and infectious disease 11: 61-63	- Index test not in protocol *Latex agglutination testing of CSF samples*
Fossieck Jr, B; Craig, R; Paterson, P. Y. (1973) Counterimmunoelectrophoresis for rapid diagnosis of meningitis due to Diplococcus pneumoniae. The Journal of infectious diseases 127: 106-109	- Index test not in protocol *Countercurrent immunoelectrophoresis testing of CSF samples*

Study	Reason
Fouad, R, Khairy, M, Fathalah, W et al. (2014) Role of clinical presentations and routine CSF analysis in the rapid diagnosis of acute bacterial meningitis in cases of negative gram stained smears. Journal of Tropical Medicine 2014 (no pagination)	- Study country not in protocol *Non-OECD high income country (Egypt)*
Franz, A.R, Kron, M, Pohlandt, F et al. (1999) Comparison of procalcitonin with interleukin 8, C-reactive protein and differential white blood cell count for the early diagnosis of bacterial infections in newborn infants. Pediatric Infectious Disease Journal 18: 666-671	- Population does not meet inclusion criteria *Infants admitted to study centre with suspected bacterial infection. Meningitis not listed as a diagnosis*
Fretzayas, A, Moustaki, M, Stefos, E et al. (2010) Differential diagnosis of meningococcal meningitis based on common clinical and laboratory findings: Are there criterion standards?. Infectious Diseases in Clinical Practice 18: 253-257	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Friedman, C. A; Wender, D. F; Rawson, J. E. (1984) Rapid diagnosis of group B streptococcal infection utilizing a commercially available latex agglutination assay. Pediatrics 73: 27-30	- Index test not in protocol *Latex agglutination testing of CSF samples*
Frohna, J. G; Park, S. M; Gopal, S. (2001) Diagnosing bacterial meningitis after the Haemophilus influenzae vaccine. Archives of Pediatrics and Adolescent Medicine 155: 1307-1310	- Results reported elsewhere *Reports results already presented in Freedman 2001. Excluded to prevent double counting*
Frosch, M; Peuckert, W; Bitter-Suermann, D. (1986) Diagnostic use of monoclonal IgG antibody to meningococcal B polysaccharide in cerebrospinal fluid. Antonie van Leeuwenhoek, International Journal of General and Molecular Microbiology 52: 253-254	- Index test not in protocol *Latex agglutination and enzyme-linked immunosorbent assay testing of CSF samples*
Garcia-De la Rosa, Gema, De Las Heras-Florez, Silvia, Rodriguez-Afonso, Jorge et al. (2022) Interpretation of white blood cell counts in the cerebrospinal fluid of neonates with traumatic lumbar puncture: a retrospective cohort study. BMC pediatrics 22(1): 488	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Garty, B. Z, Berliner, S, Liberman, E et al. (1997) Cerebrospinal fluid leukocyte aggregation in meningitis. Pediatric infectious disease journal 16: 647-51	- Index test not in protocol *Leukocyte aggregation score of CSF samples*
Gendrel, D and Bohuon, C. (2000) Procalcitonin in pediatrics for differentiation of bacterial and viral infections. Intensive Care Medicine, Supplement 26: S178-S181	- Index test not in protocol *Levels of procalcitonin, C-reactive protein and and IL6 in CSF samples*
Giannopoulou, P, Charalambaki, N, Grafakos, I et al. (2009) Meningococcal meningitis: A review of laboratory features during an 8-year period in a	- Study design not in protocol *Conference abstract*

Study	Reason
general hospital. Clinical Microbiology and Infection 15 (S4): S336-S337	
Gokalp, G, Bal, A, Anil, M et al. (2014) The children with a diagnosis of meningitis in emergency department. Pediatric Critical Care Medicine 1: 20	- Study design not in protocol *Conference abstract*
Goktas, Sibel Yorulmaz, Oral, Arzu Yilmaztepe, Yilmaz, Emel et al. (2021) Diagnostic value of the CSF levels of D-Lactate and pro-inflammatory cytokines (TNF-alpha, IL-6, IL-8 and IL-17) in the patients with suspected nosocomial meningitis. Singapore medical journal	- Index test not in protocol *IL-6, IL-8, IL-17, TNF-α and D-lactate levels in CSF*
Goldfinch, C, Korman, T, Kotsanas, D et al. (2015) Should inflammatory markers inform the decision to perform a lumbar puncture in infants with suspected neonatal sepsis?. Journal of Paediatrics and Child Health 1: 84	- Study design not in protocol *Conference abstract*
Gong, Zhe, Zhang, Chaopeng, Li, Yanfei et al. (2021) NLRP3 in the Cerebrospinal Fluid as a Potential Biomarker for the Diagnosis and Prognosis of Community-Acquired Bacterial Meningitis in Adults. Frontiers in cellular and infection microbiology 11: 803186	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Gonzalez Londono, J, Lorencio Cardenas, C, Sanchez Gines, A et al. (2016) Quick diagnose of pneumococcal meningitis in adults. Sensitivity and specificity of the Streptococcus pneumoniae antigen in CSF. Intensive Care Medicine Experimental. Conference: 29th Annual Congress of the European Society of Intensive Care Medicine, ESICM 4	- Study design not in protocol *Conference abstract*
Goonetilleke, U. R, Scarborough, M, Ward, S. A et al. (2010) Proteomic analysis of cerebrospinal fluid in pneumococcal meningitis reveals potential biomarkers associated with survival. Journal of infectious diseases 202: 542-550	- Study country not in protocol *Non-OECD high income country (Malawi)*
Gowin, E, Januszkiewicz-Lewandowska, D, Slowinski, R et al. (2017) With a little help from a computer: Discriminating between bacterial and viral meningitis based on dominance-based rough set approach analysis. Medicine 96	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Graf, E. H; Farquharson, M. V; Cardenas, A. M. (2017) Comparative evaluation of the FilmArray meningitis/encephalitis molecular panel in a pediatric population. Diagnostic microbiology and infectious disease 87: 92-94	- Population does not meet inclusion criteria *Selected CSF samples culture-positive and culture-negative for bacterial meningitis*
Gray, S. J, Sobanski, M. A, Kaczmarski, E. B et al. (1999) Ultrasound-enhanced latex immunoagglutination and PCR as complementary	- Index test not in protocol *Mixed. PCR testing of blood/serum (113/125) and CSF (12/125) samples. Results not presented*

Study	Reason
methods for non-culture-based confirmation of meningococcal disease. Journal of Clinical MicrobiologyJ Clin Microbiol 37: 1797-801	*separately for target index test*
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: e0212922	- Population does not meet inclusion criteria *Patients with laboratory confirmed diagnosis o invasive meningococcal disease*
Guiver, M, Borrow, R, Marsh, J et al. (2000) Evaluation of the Applied Biosystems automated Taqman polymerase chain reaction system for the detection of meningococcal DNA. FEMS Immunology and Medical Microbiology 28: 173-179	- Index test not in protocol *Unclear. PCR testing of blood, serum and CSF samples. Proportions not reported and results not presented separately for target index test*
Guo, Lei, Qiu, Zhongzhi, Wang, Yue et al. (2021) Volatile Organic Compounds to Identify Infectious (Bacteria/Viruses) Diseases of the Central Nervous System: A Pilot Study. European neurology 84(5): 325-332	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Gupta, A and Dwivedi, T. (2019) Reagent strips test: A simplified method for prompt analysis of cerebrospinal fluid in neurological disorders in emergency. Practical Laboratory Medicine 16 (no pagination)	- Study country not in protocol *Non-OECD high income country (India)*
Gupta, R, Singh, V, Patrikar, S et al. (2013) Is procalcitonin useful in early diagnosis of serious bacterial infections in children?. Journal of Nepal Paediatric Society 33: 106-109	- Study country not in protocol *Non-OECD high income country (India)*
Hadadi, A; Masuadi, E; Tamimi, W. (2017) Evaluation of biochemical and hematological markers of cerebrospinal fluid in suspected patients with meningitis. Clinical Chemistry 63 (Supplement 1): 191	- Study design not in protocol *Conference abstract*
Haddar, C. H, Terrade, A, Verhoeven, P et al. (2020) Validation of a new rapid detection test for detection of neisseria meningitidis A/C/W/X/Y antigens in cerebrospinal fluid. Journal of clinical microbiology 58 (3)	- Index test not in protocol *Lateral flow immunochromatographic testing (MeningoSpeed RDT) of CSF samples*
Hagedorn, P. A; Shah, S. S; Kirkendall, E. S. (2016) Following the (Clinical Decision) Rules: Opportunities for Improving Safety and Resource Utilization With the Bacterial Meningitis Score. Hospital PediatricsHosp 6: 305-9	- Index test not in protocol *Mixed. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure*
Hallgren, J. D, Zakaria, S, Stephens, M et al. (2007) Can you differentiate bacterial from viral pediatric infections based on the CBC?. Journal of Family Practice 56: 390-392	- Index test not in protocol *Complete blood count of blood samples*

Study	Reason
Hamedi, A. (2014) Value of serum procalcitonin level in differentiation of viral and bacterial meningitis in children admitted emergency room. Archives of disease in childhood 2: a308	- Study design not in protocol *Conference abstract*
Harris, K. A and Hartley, J. C. (2003) Development of broad-range 16S rDNA PCR for use in the routine diagnostic clinical microbiology service. Journal of Medical Microbiology 52: 685-691	- Index test not in protocol *Mixed. PCR testing of variety of clinical samples. Only 123/382 (32.2%) CSF samples. Results not presented separately for target index test*
Harris, M. A. (1971) The diagnosis and treatment of acute meningitis, excluding tuberculosis, in infancy and childhood. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 45: 686-694	- Study country not in protocol *Non-OECD high income country (South Africa)*
Hasbun, R, Bijlsma, M, Brouwer, M. C et al. (2013) Risk score for identifying adults with CSF pleocytosis and negative CSF Gram stain at low risk for an urgent treatable cause. Journal of infection 67: 102-110	- Population does not meet inclusion criteria *Patients presenting at study centre presenting with urgent treatable cause symptoms. Only 31/760 (4.1%) diagnosed with bacterial meningitis. Results presented as urgent treatable cause compared to non-urgent serious cause so unable to calculate outcomes for bacterial meningitis*
Hashim, I. A, Walsh, A, Hart, C. A et al. (1995) Cerebrospinal fluid interleukin-6 and its diagnostic value in the investigation of meningitis. Annals of Clinical Biochemistry 32: 289-296	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Hashim, Q.M., Muhsin, H.J., Majeed, S.A. et al. (2021) The role of CSF-CRP in diffrentation between bacterial from nonbacterial meningitis. Current Pediatric Research 25(8): 755-761	- Study country not in protocol *Non-OECD high income country (Iraq)*
Hassan, E. M, Ezzat, H. O, Saleh, L. H et al. (1989) Diagnosis of tuberculous meningitis by immunofluorescence and enzyme immunoassay. The Journal of the Egyptian Public Health Association 64: 45-54	- Paper unavailable
Hill, R. B, Adams, S, Gunn, B. A et al. (1994) The effects of nonclassic pediatric bacterial pathogens on the usefulness of the Directigen latex agglutination test. American Journal of Clinical Pathology 101: 729-732	- Index test not in protocol *Latex agglutination testing of CSF samples*
Hoban, D. J; Witwicki, E; Hammond, G. W. (1985) Bacterial antigen detection in cerebrospinal fluid of patients with meningitis. Diagnostic Microbiology & Infectious DiseaseDiagn Microbiol Infect Dis 3: 373-9	- Index test not in protocol *Coagglutination, latex agglutination, counterimmunoelectrophoresis and limulus amebocyte lysate testing of CSF samples*
Hoeboer, S. H, Alberts, E, van den Hul, I et al. (2012) Old and new biomarkers for predicting high and low risk microbial infection in critically ill patients with new onset fever: a case for	- Population does not meet inclusion criteria *Patients with new onset fever in intensive care unit. Meningitis not listed as a diagnosis*

Study	Reason
procalcitonin. Journal of Infection 64: 484-93	
Hoen, B, Viel, J. F, Paquot, C et al. (1995) Multivariate approach to differential diagnosis of acute meningitis. European Journal of Clinical Microbiology and Infectious Diseases 14: 267-274	- Index test not in protocol *Mixed. Statistical model including protein levels and polymorphonuclear counts in CSF, and glucose levels and leukocyte counts in blood*
Holub, M, Beran, O, Dzupova, O et al. (2007) Cortisol levels in cerebrospinal fluid correlate with severity and bacterial origin of meningitis. Critical care (london, england) 11: r41	- Index test not in protocol *Cortisol levels in CSF samples. CSF leukocytes. neutrophils, protein and glucose also measured but insufficiently reported*
Holub, M, Beran, O, Kasprikova, N et al. (2012) Neutrophil to lymphocyte count ratio as a biomarker of bacterial infections. Central European Journal of Medicine 7: 258-261	- Population does not meet inclusion criteria *Patients hospitalised with febrile illnesses. Meningitis not listed as a diagnosis*
Hong, E, Barraud, O, Bidet, P et al. (2012) Proficiency of PCR in hospital settings for nonculture diagnosis of invasive meningococcal infections. Clinical Laboratory 58: 343-6	- Study design not in protocol *Validation of 10 PCR testing protocols*
Hou, Y, Zhang, X, Hou, X et al. (2018) Rapid pathogen identification using a novel microarray-based assay with purulent meningitis in cerebrospinal fluid. Scientific reports 8: 15965	- Study country not in protocol *Non-OECD, high income country (People's Republic of China)*
Huttunen, P, Lappalainen, M, Salo, E et al. (2009) Differential diagnosis of acute central nervous system infections in children using modern microbiological methods. Acta Paediatrica 98: 1300-1306	- Population does not meet inclusion criteria *Children with suspected CNS infection. Only 21/213 (9.9%) diagnosed with bacterial meningitis. Unable to calculate outcomes for bacterial meningitis*
Huy, N. T, Hang le, T. T, Boamah, D et al. (2012) Development of a single-tube loop-mediated isothermal amplification assay for detection of four pathogens of bacterial meningitis. FEMS Microbiology Letters 337: 25-30	- Study design not in protocol *Design and development article. No clinical samples included*
Inaba, Y; Ishiguro, A; Shimbo, T. (1997) The production of macrophage inflammatory protein-1alpha in the cerebrospinal fluid at the initial stage of meningitis in children. Pediatric Research 42: 788-793	- Index test not in protocol *Cytokine levels in CSF samples*
Jaeger, F, Leroy, J, Duchene, F et al. (2000) Validation of a diagnosis model for differentiating bacterial from viral meningitis in infants and children under 3.5 years of age. European Journal of Clinical Microbiology and Infectious Diseases 19: 418-421	- Index test not in protocol *Mixed. Statistics model including protein levels and polymorphonuclear counts in CSF, and glucose levels and leukocyte counts in blood*
Jafari, M, Mohammadzadeh Jahani, P, Choopanizadeh, M et al. (2020) Investigating the role of T helper related cytokines in cerebrospinal fluid for the differential diagnosis of bacterial meningitis in pre-treated paediatric patients. Biomarkers 25: 171-178	- Study country not in protocol *Non-OECD high income country (Iran)*

Study	Reason
Jana Broadhurst, M, Dujari, S, Budvytiene, I et al. (2020) Utilization, yield, and accuracy of the filmarray meningitis/encephalitis panel with diagnostic stewardship and testing algorithm. Journal of clinical microbiology 58 (9)	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review (culture results for PCR negative samples not presented)*
Jaton, K; Sahli, R; Bille, J. (1992) Development of polymerase chain reaction assays for detection of Listeria monocytogenes in clinical cerebrospinal fluid samples. Journal of clinical microbiology 30: 1931-1936	- Study design not in protocol *Two gate-study and sufficient single-gate studies are available for this index test*
Javadinia, S, Tabasi, M, Naghdalipour, M et al. (2019) C - reactive protein of cerebrospinal fluid, as a sensitive approach for diagnosis of neonatal meningitis. African Health Sciences 19: 2372-2377	- Study country not in protocol *Non-OECD high income country (Iran)*
Javali, M, Acharya, P, Mehta, A et al. (2017) Use of multiplex PCR based molecular diagnostics in diagnosis of suspected CNS infections in tertiary care setting-A retrospective study. Clinical Neurology and Neurosurgery 161: 110-116	- Study country not in protocol *Non-OECD high income country (India)*
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: 191-200	- Index test not in protocol *Ultrasound-enhanced particle agglutination testing of CSF samples*
Jin, D, Heo, T. H, Byeon, J. H et al. (2015) Analysis of clinical information and reverse transcriptase-polymerase chain reaction for early diagnosis of enteroviral meningitis. Korean Journal of Pediatrics 58: 446-450	- Study design not in protocol *Non-comparative study*
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: 1013-1019	- Study country not in protocol *Non-OECD, high income country (People's Republic of China)*
John, A. J. P, Lalitha, M. K, Cherian, T et al. (2001) A polymerase chain reaction-enzyme immunoassay for diagnosis of pneumococcal meningitis in children & adults. Indian Journal of Medical Research 113: 48-52	- Study country not in protocol *Non-OECD, high income country (India)*
John, T, Ittycheria, C, George, J et al. (2011) CSF LDH estimation to differentiate pyogenic and viral meningitis and its role in tuberculous meningitis. Clinical Microbiology and Infection 4: 463	- Study design not in protocol *Conference abstract*
Jordan, G. W; Statland, B; Halsted, C. (1983) CSF lactate in diseases of the CNS. Archives of Internal Medicine 143: 85-7	- Index test not in protocol *Lactate levels in CSF samples*
Joshi, D, Kundana, K, Puranik, A et al. (2013) Diagnostic accuracy of urinary reagent strip to	- Study country not in protocol *Non-OECD high income country (India)*

Study	Reason
determine cerebrospinal fluid chemistry and cellularity. Journal of Neurosciences in Rural Practice 4: 140-5	
Juarez Aragon, G; Games Esternod, J; Cetina Sauri, G. (1979) Assessment of five laboratory tests for differential diagnosis in bacterial and viral meningoencephalitides. Archivos de Investigacion Medica 10: 111-119	- Study country not in protocol *Non-OECD, high income country (Mexico)*
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: 105-113	- Non-English language article *Spanish language*
Kalghatgi, A. T, Praharaj, A. K, Sahni, A. K et al. (2008) Detection of bacterial pathogens in cerebrospinal fluid using restriction fragment length polymorphism. Medical Journal Armed Forces India 64: 29-32	- Study country not in protocol *Non-OECD high income country (India)*
Kanegaye, J. T, Nigrovic, L. E, Malley, R et al. (2009) Diagnostic value of immature neutrophils (bands) in the cerebrospinal fluid of children with cerebrospinal fluid pleocytosis. Pediatrics 123: e967-e971	- Reference standard not in protocol *Mixed. Culture of CSF samples or culture of blood samples and CSF pleocytosis or latex agglutination testing of CSF samples. Results not presented separately for target reference standard*
Karanika, M, Vasilopoulou, V.A, Katsioulis, A.T et al. (2009) Diagnostic clinical and laboratory findings in response to predetermining bacterial pathogen: data from the Meningitis Registry. PLoS ONE [Electronic Resource] 4: e6426	- Study design not in protocol *Non-comparative study*
Kashaki, M, Norouzi, E, Heidarali, S et al. (2020) Is there any correlation between cerebrospinal fluid and serum c-reactive protein in neonates suspected to meningitis?. Journal of Kerman University of Medical Sciences 27: 389-393	- Study country not in protocol *Non-OECD high income country (Iran)*
Kaufhold, A. (1989) Rapid detection of microbial antigens for the diagnosis of meningitis. Journal of Clinical Chemistry and Clinical Biochemistry 27: 900-901	- Study design not in protocol *Conference abstract*
Kim, D. W, Kilgore, P. E, Kim, E. J et al. (2011) Loop-mediated isothermal amplification assay for detection of Haemophilus influenzae type b in cerebrospinal fluid. Journal of Clinical MicrobiologyJ Clin Microbiol 49: 3621-6	- Reference standard not in protocol *Loop-mediated isothermal amplification (LAMP) testing compared to PCR testing of CSF samples. CSF culture also performed but reported in insufficient detail*
Kim, Y. O, Kang, J. S, Youm, M. H et al. (2003) Diagnostic capability of CSF ferritin in children with meningitis. Pediatric Neurology 28: 271-276	- Index test not in protocol *Ferritin levels in CSF samples*
King, J. C, Jr, Berman, E. D et al. (1987) Evaluation of fever in infants less than 8 weeks	- Population does not meet inclusion criteria *Infants with fever hospitalised during the study*

Study	Reason
old. Southern Medical Journal 80: 948-52	*period. Only 16/342 (5%) diagnosed with bacterial meningitis. Not able to calculate outcomes for bacterial meningitis*
Knight, J. A; Dudek, S. M; Haymond, R. E. (1981) Early (chemical) diagnosis of bacterial meningitis - Cerebrospinal fluid glucose, lactate, and lactate dehydrogenase compared. Clinical Chemistry 27: 1431-1434	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Kokici, M, Kone, E, Marku, N et al. (2014) Significance of LDH (lactatdehydrogenasis) determination in cerebrospinal fluid (CSF) in the early differential diagnosis of acute bacterial meningitis from the tubercular one. Clinical Chemistry and Laboratory Medicine 1: 962	- Study design not in protocol *Conference abstract*
Komolpis, P and Rungpitarangsi, B. (1989) Comparison of culture and latex agglutination in the diagnosis of bacterial meningitis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 72: 37-40	- Study country not in protocol *Non-OECD, high income country (Thailand)*
Komorowski, R. A; Farmer, S. G; Knox, K. K. (1986) Comparison of cerebrospinal fluid C-reactive protein and lactate for diagnosis of meningitis. Journal of clinical microbiology 24: 982-985	- Index test not in protocol *C-reactive protein and lactate levels in CSF samples*
Kong, Yueyue, Ye, Yi, Ma, Jiawei et al. (2022) Accuracy of heparin-binding protein for the diagnosis of nosocomial meningitis and ventriculitis. Critical care (London, England) 26(1): 56	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Konstantinidis, T, Cassimos, D, Gioka, T et al. (2015) Can Procalcitonin in Cerebrospinal Fluid be a Diagnostic Tool for Meningitis?. Journal of Clinical Laboratory Analysis 29: 169-174	- Index test not in protocol *Procalcitonin levels of CSF samples. Leukocytes, protein and glucose also measured but insufficiently reported*
Krishnan, C and Wylie, J. S. (1978) Countercurrent immunoelectrophoresis (CIEP) in the diagnosis of childhood meningitis. Indian Pediatrics 15: 703-706	- Index test not in protocol *Countercurrent immunoelectrophoresis testing of CSF samples*
Kulik, D. M; Uleryk, E. M; Maguire, J. L. (2013) Does this child have bacterial meningitis? A systematic review of clinical prediction rules for children with suspected bacterial meningitis. Journal of Emergency Medicine 45: 508-19	- Index test not in protocol *Clinical predictions rules included a variety of factors (CSF parameters, blood parameters and clinical symptoms). Included studies checked for possible includes*
Kurdyumova, N, Danilov, G, Shifrin, M et al. (2013) Efficiency of clinical and laboratory criterion for the diagnosis of bacterial meningitis. Antimicrobial Resistance and Infection Control. Conference: 2nd International Conference on Prevention and Infection Control, ICPIC 2	- Study design not in protocol *Conference abstract*

Study	Reason
Kurzynski, T. A, Kimball, J. L, Polyak, M. B et al. (1985) Evaluation of the phadebact and bactigen reagents for detection of Neisseria meningitidis in cerebrospinal fluid. Journal of clinical microbiology 21: 989-90	- Index test not in protocol *Latex agglutination testing of CSF samples*
Kuzemenska, P, Kominkova, B, Macku, M et al. (1982) The Slidex-meningite-Kit (Bio-Merieux) tested for exoantigen detection in spinal fluids from purulent meningitis cases. Journal of Hygiene, Epidemiology, Microbiology & ImmunologyJ Hyg Epidemiol Microbiol Immunol 26: 57-64	- Index test not in protocol *Latex agglutination testing of CSF samples*
Lagi, F, Bartalesi, F, Pecile, P et al. (2016) Proposal for a new score-based approach to improve efficiency of diagnostic laboratory workflow for acute bacterial meningitis in adults. Journal of clinical microbiology 54: 1851-1854	- Index test not in protocol *Mixed. Blood (neutrophil leukocyte) and CSF (luekocyte count, protein concentration, lactate concentration and glucose-to-serum glucose ratio) levels*
Landaas, S and Von Der Lippe, B. (1985) Chemical analyses for early differential diagnosis between bacterial and viral meningitis. Scandinavian Journal of Clinical and Laboratory Investigation 45: 525-529	- Study design not in protocol *No reference standard comparison*
Landgraf, I. M; Alkmin, M. G; Vieira, M. F. (1995) Bacterial antigen detection in cerebrospinal fluid by the latex agglutination test. Revista do Instituto de Medicina Tropical de Sao Paulo 37: 257-260	- Study country not in protocol *Non-OECD high income country (Brazil)*
Law, D. K and Tsang, R. S. (2013) Real-time polymerase chain reaction for detection of encapsulated Haemophilus influenzae using degenerate primers to target the capsule transport gene bexA. Canadian Journal of Microbiology 59: 359-61	- Study design not in protocol *Design and test study for RT-PCR assay. No clinical data presented*
Le Monnier, A, Abachin, E, Beretti, J. L et al. (2011) Diagnosis of Listeria monocytogenes meningoencephalitis by real-time PCR for the hly gene. Journal of clinical microbiology 49: 3917-3923	- Population does not meet inclusion criteria *Unclear. Patients with suspected CNS listeriosis. Proportions of meningitis not reported*
Lee, J, Kwon, H, Lee, J. S et al. (2015) Applying the bacterial meningitis score in children with cerebrospinal fluid pleocytosis: A single center's experience. Korean Journal of Pediatrics 58: 251-255	- Index test not in protocol *Mixed. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure*
Leinonen, M and Herva, E. (1977) The latex agglutination test for the diagnosis of meningococcal and Haemophilus influenzae meningitis. Scandinavian Journal of Infectious Diseases 9: 187-191	- Index test not in protocol *Latex agglutination and countercurrent immunoelectrophoresis testing of CSF samples*
Lembo, R.M and Marchant, C.D. (1991) Acute	- Index test not in protocol

Study	Reason
phase reactants and risk of bacterial meningitis among febrile infants and children. Annals of Emergency Medicine,Ann.Emerg.Med. 20: 36-40	*C-reactive protein levels in CSF samples and total peripheral white blood cell count in blood samples*
Leroy, Anne-Gaelle, Persyn, Elise, Gibaud, Sophie-Anne et al. (2021) Assessment of a Multiplex LAMP Assay (Eazyplex R CSF Direct M) for Rapid Molecular Diagnosis of Bacterial Meningitis: Accuracy and Pitfalls. Microorganisms 9(9)	- Reference standard not in protocol *Mixed. Culture of CSF samples or CSF parameters indicative of infection (association of WBC and protein concentration, or CSF and blood glucose levels). Results not presented separately for target reference standard*
Li, H, Xiao, R, Javed, R et al. (2020) Evaluation of cerebrospinal fluid and blood parameters finding in early diagnosis and drug therapy of suspected bacterial meningitis in neonates. Journal of Research in Medical Sciences 25: 77	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Li, W, Sun, X, Yuan, F et al. (2017) Diagnostic accuracy of cerebrospinal fluid procalcitonin in bacterial meningitis patients with empiric antibiotic pretreatment. Journal of clinical microbiology 55: 1193-1204	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Linder, A, Akesson, P, Brink, M et al. (2011) Heparin-binding protein: A diagnostic marker of acute bacterial meningitis. Critical care medicine 39: 812-817	- Study design not in protocol *Non-comparative study*
Long, F, Kong, M, Wu, S et al. (2019) Development and validation of an advanced fragment analysis-based assay for the detection of 22 pathogens in the cerebrospinal fluid of patients with meningitis and encephalitis. Journal of Clinical Laboratory Analysis 33 (3)	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Long, James R, Mitchell, Kara, Edwards, Justine et al. (2022) Laboratory diagnosis of bacterial meningitis by direct detection, serotyping and Next Generation Sequencing: How 10 years of testing in New York State has evolved to improve laboratory diagnosis and public health. Molecular and cellular probes 61: 101786	- Population does not meet inclusion criteria *Included culture-negative specimens*
Lorino, G, Lilli, D, Rivanera, D et al. (1999) Polymerase chain reaction, with sequencing, as a diagnostic tool in culture---negative bacterial meningitis. Clinical Microbiology & InfectionClin Microbiol Infect 5: 92-96	- Population does not meet inclusion criteria *Patients with CSF samples culture-negative for bacterial meningitis*
Lu, J. J, Perng, C. L, Lee, S. Y et al. (2000) Use of PCR with universal primers and restriction endonuclease digestions for detection and identification of common bacterial pathogens in cerebrospinal fluid. Journal of clinical microbiology 38: 2076-2080	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Luo, Ting, Yang, Sai, Chen, Yan et al. (2022) Quantitative proteomic analysis of cerebrospinal	- Study country not in protocol *Non-OECD high income country (People's*

Study	Reason
fluid reveals CD163, A2M and full-length APP as potential diagnostic biomarkers of paediatric bacterial meningitis. Proteome science 20(1): 8	*Republic of China)*
Lyons, T. W, Garro, A. C, Cruz, A. T et al. (2020) Performance of the Modified Boston and Philadelphia Criteria for Invasive Bacterial Infections. Pediatrics 145: 4	- Index test not in protocol *Mixed. Boston high-risk predictor (peripheral white blood count ≥20000 cells/mm3, CSF WBC ≥ 10 cells/mm3, and urinalysis with >10 white blood cell count per high-power field or positive urine dip result) and Philadelphia high-risk predictor (peripheral white blood count ≥15000 cells/mm3, CSF WBC ≥ 8 cells/mm3, positive Gram stain, and urinalysis with >10 white blood cell count per high-power field or positive urine dip result)*
Mahmoudvand, G., Ebrahimzadeh, F., Mahmoudvand, B. et al. (2021) Epidemiology of findings of lumbar puncture among pediatric patients. Annals of Medicine and Surgery 72: 103093	- Study country not in protocol *Non-OECD high income country (Iran)*
Mamani, M, Hashemi, S, Niayesh, A et al. (2009) Rapid diagnosis of acute meningitis using reagent strips. International journal of antimicrobial agents 2: 62	- Study design not in protocol *Conference abstract*
Marcon, M. J; Hamoudi, A. C; Cannon, H. J. (1984) Comparative laboratory evaluation of three antigen detection methods for diagnosis of haemophilus influenzae type b disease. Journal of clinical microbiology 19: 333-337	- Index test not in protocol *Coagglutination, latex agglutination and counterimmunoelectrophoresis testing of CSF samples*
Margall Coscojuela, N, Majo Moreno, M, Latorre Otin, C et al. (2002) Use of universal PCR on cerebrospinal fluid to diagnose bacterial meningitis in culture-negative patients. European Journal of Clinical Microbiology and Infectious Diseases 21: 67-69	- Population does not meet inclusion criteria *Patients with CSF samples culture-negative for bacterial meningitis*
Martinot, M, Greigert, V, Souply, L et al. (2018) Cerebrospinal fluid monocytes in bacterial meningitis, viral meningitis, and neuroborreliosis. Medecine et Maladies Infectieuses 48: 286-290	- Study design not in protocol *Non-comparative study*
Matos, J. D. A, Madureira, D. J, Rebelo, M. C et al. (2006) Diagnosis of Streptococcus pneumoniae meningitis by polymerase chain reaction amplification of the gene for pneumolysin. Memorias do Instituto Oswaldo Cruz 101: 559-563	- Study country not in protocol *Non-OECD, high income country (Brazil)*
Maxson, S; Lewno, M. J; Schutze, G. E. (1994) Clinical usefulness of cerebrospinal fluid bacterial antigen studies. Journal of PediatricsJ Pediatr 125: 235-8	- Index test not in protocol *Bacterial antigen testing of CSF samples*
Mazumder, S; Ramya, B; Biligi, D. (2018) Utility of urine reagent strips in cerebrospinal fluid analysis:	- Study country not in protocol *Non-OECD high income country (India)*

Study	Reason
An aid to bedside diagnosis of meningitis. Indian Journal of Pathology and Microbiology 61: 356-359	
McArthur, R; Edlow, J. A; Nigrovic, L. E. (2016) Validation of the bacterial meningitis score in adults presenting to the ED with meningitis. American journal of emergency medicine 34: 1265-1267	- Index test not in protocol *Mixed. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure*
McArthur, R; Edlow, J; Nigrovic, L. (2015) Identification of adults with cerebrospinal fluid pleocytosis at low risk for bacterial meningitis. Annals of emergency medicine 1: 92	- Study design not in protocol *Conference abstract*
McGraw, T. P and Bruckner, D. A. (1983) Sensitivity of commercial agglutination and counterimmunoelectrophoresis methods for the detection of Haemophilus influenzae Type b capsular polysaccharide. American Journal of Clinical Pathology 80: 703-706	- Index test not in protocol *Coagglutination, latex agglutination and counterimmunoelectrophoresis testing of CSF samples*
McLaughlin, Wesley N; Lamb, Molly; Gaensbauer, James (2022) Reassessing the Value of CSF Protein and Glucose Measurement in Pediatric Infectious Meningitis. Hospital pediatrics 12(5): 481-490	- Population does not meet inclusion criteria *Infectious meningitis microbiologically-confirmed in 6% of sample*
Meddeb, M, Koebel, C, Jaulhac, B et al. (2016) Comparison between a broad-range real-time and a broad-range end-point PCR assays for the detection of bacterial 16S rRNA in clinical samples. Annals of Clinical and Laboratory Science 46: 18-25	- Index test not in protocol *Mixed. PCR testing of a variety of clinical specimens. 34/144 (23.6%) CSF and brain samples. Results not reported separately for target index test*
Mehta, A, Mahale, R. R, Sudhir, U et al. (2015) Utility of cerebrospinal fluid cortisol level in acute bacterial meningitis. Annals of Indian Academy of Neurology 18: 210-214	- Study country not in protocol *Non-OECD high income country (India)*
Mein, J and Lum, G. (1999) CSF bacterial antigen detection tests offer no advantage over Gram's stain in the diagnosis of bacterial meningitis. PathologyPathology 31: 67-9	- Index test not in protocol *Bacterial antigen detection testing of CSF samples. Gram stain also performed but insufficient presentation of results*
Mentis, A. A, Garcia, I, Jimenez, J et al. (2021) Artificial Intelligence in Differential Diagnostics of Meningitis: A Nationwide Study. Diagnostics 11: 28	- Reference standard not in protocol *Unclear. Described as mainly non-culture methods using PCR testing of CSF samples. Results not presented separately for target reference standard*
Mentis, A. F. A, Kyprianou, M. A, Xirogianni, A et al. (2016) Neutrophil-to-lymphocyte ratio in the differential diagnosis of acute bacterial meningitis. European Journal of Clinical Microbiology and Infectious Diseases 35: 397-403	- Index test not in protocol *Neutrophil count of CSF and blood samples. Results not presented separately for target index test*

Study	Reason
Merisescu, M. M, Luminos, M, Jugulete, G et al. (2013) Plex id role in the diagnosis of acute bacterial meningitis with haemophilus influenzae in children. Intensive Care Medicine 1: 88	- Study design not in protocol *Conference abstract*
Messacar, K, Breazeale, G, Robinson, C. C et al. (2016) Potential clinical impact of the film array meningitis encephalitis panel in children with suspected central nervous system infections. Diagnostic microbiology and infectious disease 86: 118-120	- Population does not meet inclusion criteria *Patients with suspected CNS infections. Bacterial meningitis not listed as a diagnosis*
Meyer, T, Franke, G, Polywka, S. K. A et al. (2013) Detection of CNS infections using commercial broad range PCR. Infection, Supplement 1: 34	- Study design not in protocol *Conference abstract*
Mintegi, S, Garcia, S, Martin, M. J et al. (2020) Clinical Prediction Rule for Distinguishing Bacterial From Aseptic Meningitis. Pediatrics 146: 9	- Index test not in protocol *Mixed. Prediction rule including levels of procalcitonin and C-reactive protein in serum samples, and protein levels and absolute neutrophil count in CSF samples*
Mizu, Daisuke, Matsuoka, Yoshinori, Huh, Ji-Young et al. (2022) The necessity of lumbar puncture in adult emergency patients with fever-associated seizures. The American journal of emergency medicine 58: 120-125	- Insufficient presentation of results *Insufficient information to calculate 2x2 tables for review*
Modol, J, Gimenez, M, Mesalles, E et al. (2009) Accuracy of clinical presentation in predicting the aetiology of acute bacterial meningitis. Clinical Microbiology and Infection 15 (S4): 672	- Study design not in protocol *Conference abstract*
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: 35-40	- Study country not in protocol *Non-OECD high income country (Egypt)*
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: 645-649	- Study country not in protocol *Non-OECD, high income country (India)*
Molero-Luis, M, Casas-Alba, D, Orellana, G et al. (2020) Cerebrospinal fluid neopterin as a biomarker of neuroinflammatory diseases. Scientific reports 10: 18291	- Population does not meet inclusion criteria *Patients with neuroinflammatory disorders. Only 15/277 (5.4%) diagnosed with bacterial meningitis. Unable to calculate outcomes for bacterial meningitis*
Moosa, A. A; Quortum, H. A; Ibrahim, M. D. (1995) Rapid diagnosis of bacterial meningitis with reagent strips. Lancet 345: 1290-1291	- Index test not in protocol *Urine reagent strip testing of CSF samples*
Morel, A. S, Dubourg, G, Prudent, E et al. (2015) Complementarity between targeted real-time	- Reference standard not in protocol *Conventional broad-range 16S rDNA PCR*

Study	Reason
specific PCR and conventional broad-range 16S rDNA PCR in the syndrome-driven diagnosis of infectious diseases. European Journal of Clinical Microbiology and Infectious Diseases 34: 561-570	*compared to real-time specific PCR of CSF samples*
Mukai, A. O, Krebs, V. L, Bertoli, C. J et al. (2006) TNF-alpha and IL-6 in the diagnosis of bacterial and aseptic meningitis in children. Pediatric Neurology 34: 25-Sep	- Study country not in protocol *Non-OECD high income country (Brazil)*
Myhre, E. B. (1974) Rapid diagnosis of bacterial meningitis. Demonstration of bacterial antigen by counterimmunoelectrophoresis. Scandinavian Journal of Infectious Diseases 6: 237-239	- Index test not in protocol *Counter immunoelectrophoresis testing of CSF samples*
Mylonakis, E; Hohmann, E.L; Calderwood, S.B. (1998) Central nervous system infection with Listeria monocytogenes: 33 Years' experience at a general hospital and review of 776 episodes from the literature. Medicine 77: 313-336	- Study design not in protocol *Non comparative study*
Naccache, S. N, Lustestica, M, Fahit, M et al. (2018) One Year in the Life of a Rapid Syndromic Panel for Meningitis/Encephalitis: a Pediatric Tertiary Care Facility's Experience. Journal of clinical microbiology 56: 5	- Reference standard not in protocol *CSF culture testing only performed on FA/ME positive CSF samples. FA/ME negative CSF samples had no reference standard*
Nagaraj, Meghana, Bandiya, Prathik, Jagannatha, Bhavana et al. (2022) Diagnostic Utility of Cerebrospinal Fluid Procalcitonin in Neonatal Meningitis. Journal of tropical pediatrics 68(3)	- Study country not in protocol *Non-OECD high income country (India)*
Nagdev, K. J, Bhagchandani, S. P, Bhullar, S. S et al. (2015) Rapid diagnosis and simultaneous identification of tuberculous and bacterial meningitis by a newly developed duplex polymerase chain reaction. Indian Journal of MicrobiologyIndian J Microbiol 55: 213-8	- Study country not in protocol *Non-OECD high income country (India)*
Nazir, M, Wani, W. A, Malik, M. A et al. (2018) Cerebrospinal fluid lactate: a differential biomarker for bacterial and viral meningitis in children. Jornal de Pediatria 94: 88-92	- Study country not in protocol *Non-OECD high income country (India)*
Nestor, D, Thulin Hedberg, S, Lignell, M et al. (2019) Evaluation of the FilmArray TM Meningitis/Encephalitis panel with focus on bacteria and Cryptococcus spp. Journal of Microbiological Methods 157: 113-116	- Index test not in protocol *Mixed. Culture (4/17, 23.5%) and PCR of CSF samples (13/17, 76.5%). Results not presented separately for target index test*
Newman, R. B; Stevens, R. W; Gaafar, H. A. (1970) Latex agglutination test for the diagnosis of haemopfcih inflwcnxae. J.Lab.Clin.Med 76: 1179-1182	- Index test not in protocol *Latex agglutination testing of CSF samples*
Newman, R. B; Stevens, R. W; Gaafar, H. A. (1970) Latex agglutination test for the diagnosis of haemophilus influenzne meniagitis. Journal of	- Index test not in protocol *Latex agglutination testing of CSF samples*

Study	Reason
Laboratory and Clinical Medicine 7671: 107-113	
Nigrovic, L. E; Malley, R; Kuppermann, N. (2011) Multi-study validation of the bacterial meningitis score. Pediatric Emergency Care 27 (10): 999	- Study design not in protocol *Conference abstract*
Nigrovic, L. E; Malley, R; Kuppermann, N. (2012) Meta-analysis of bacterial meningitis score validation studies. Archives of Disease in ChildhoodArch Dis Child 97: 799-805	- Index test not in protocol *Mixed. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure. Included studies checked for possible includes*
Njuguna, P, Lonergan, T, Erskine, S et al. (2015) A novel multiplexed qPCR assay for the detection of 10 bacterial and viral causes of meningitis. Clinical Chemistry 1: 148	- Study design not in protocol *Conference abstract*
Nour, M and Alaidarous, A. (2018) Clinical usefulness and accuracy of polymerase chain reaction in the detection of bacterial meningitis agents in pediatric cerebrospinal fluid. Current Research in Translational Medicine 66: 15-18	- Study design not in protocol *Non-OECD high income country (Saudi Arabia)*
Nuutila, J, Hohenthal, U, Laitinen, I et al. (2006) Quantitative analysis of complement receptors, CR1 (CD35) and CR3 (CD11b), on neutrophils improves distinction between bacterial and viral infections in febrile patients: comparison with standard clinical laboratory data. Journal of Immunological Methods 315: 191-201	- Index test not in protocol *Microbiological testing of blood samples from febrile infants*
O, M, Seo, D, Kwak, M et al. (2012) Serum procalcitonin and c-reactive protein level as a early diagnostic marker of bacterial meningitis in the emergency department. Annals of emergency medicine 1: 22	- Study design not in protocol *Conference abstract*
Obreja, Maria, Miftode, Egidia Gabriela, Stoleriu, Iulian et al. (2022) Heparin-Binding Protein (HBP), Neutrophil Gelatinase-Associated Lipocalin (NGAL) and S100 Calcium-Binding Protein B (S100B) Can Confirm Bacterial Meningitis and Inform Adequate Antibiotic Treatment. Antibiotics (Basel, Switzerland) 11(6)	- Study country not in protocol *Non-OECD high income country (Romania)*
Ogunbi, O and Odugbemi, T. O. (1976) Counter immunoelectrophoresis technique in laboratory diagnosis of bacterial meningitis. Tropical and Geographical Medicine 28: 141-144	- Study country not in protocol *Non-OECD high income country (Nigeria)*
Omene, J. A, Okolo, A. A, Longe, A. C et al. (1985) The specificity and sensitivity of CSF and blood glucose concentration in the diagnosis of neonatal meningitis. Annals of Tropical Paediatrics 5: 37-9	- Study country not in protocol *Non-OECD high income country (Nigeria)*

Study	Reason
Onal, H, Onal, Z, Ozdil, M et al. (2008) A new parameter in the differential diagnosis of bacterial and viral meningitis. Neurosciences 13: 91-92	- Study country not in protocol *Non-OECD and/or non-high income country (Turkey)*
Ostergaard, C, Benfield, T. L, Sellebjerg, F et al. (1996) Interleukin-8 in cerebrospinal fluid from patients with septic and aseptic meningitis. European journal of clinical microbiology & infectious diseases 15: 166-9	- Index test not in protocol *Levels of IL-8, IL-1β and TNF-α in CSF samples*
Paciorek, Marcin, Bienkowski, Carlo, Krogulec, Dominika et al. (2020) Differences and similarities in clinical manifestations of Listeria monocytogenes and Mycobacterium tuberculous meningitis. Przeglad epidemiologiczny 74(2): 326-335	- Population does not meet inclusion criteria *Mixed. Diagnosis of meningitis based on CSF culture or blood culture with coexisting CSF findings typical for bacterial meningitis*
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: 109-113	- Study design not in protocol *Non-comparative study*
Park, S. E, Lim, T. J, Nam, S. O et al. (2021) Clinical utility of the FilmArray meningitis/encephalitis panel in children at a tertiary center in South Korea. Brain and Development 43: 234-243	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review (culture results for PCR negative samples not presented)*
Parmar, R. C, Warke, S, Sira, P et al. (2004) Rapid diagnosis of meningitis using reagent strips. Indian Journal of Medical Sciences 58: 62-66	- Study country not in protocol *Non-OECD, high income country (India)*
Pasolescu, O and Mihalcu, F. (1975) A latex agglutination test for meningococcal infection diagnosis. Developments in biological standardization 28: 439-442	- Index test not in protocol *Latex agglutination testing of CSF samples*
Peltola, H, Roine, I, Leinonen, M et al. (2010) Diagnosis of streptococcus pneumoniae and haemophilus influenzae type B meningitis by identifying dna from cerebrospinal fluid-impregnated filter paper strips. Pediatric infectious disease journal 29: 111-114	- Study country not in protocol *Non-OECD high income country (Paraguay and Venezuela)*
Perkins, M. D; Mirrett, S; Reller, L. B. (1995) Rapid bacterial antigen detection is not clinically useful. Journal of Clinical MicrobiologyJ Clin Microbiol 33: 1486-91	- Index test not in protocol *Latex agglutination (molecular diagnosis technique superseded by PCR testing) testing of CSF samples*
Pollard, A. J, Probe, G, Trombley, C et al. (2002) Evaluation of a diagnostic polymerase chain reaction assay for Neisseria meningitidis in North America and field experience during an outbreak. Archives of Pathology and Laboratory Medicine 126: 1209-1215	- Reference standard not in protocol *Mixed. Culture or smear or antigen testing of CSF and blood samples*

Study	Reason
Pollock, S. S; Pollock, T. M; Harrison, M. J. (1984) Infection of the central nervous system by Listeria monocytogenes: a review of 54 adult and juvenile cases. Quarterly Journal of Medicine 53: 331-40	- Study design not in protocol *Non-comparative study*
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: 61-4	- Index test not in protocol *Ultrasound-enhanced latex immunoagglutination testing of CSF samples*
Posnakoglou, L, Siahanidou, T, Syriopoulou, V et al. (2020) Impact of cerebrospinal fluid syndromic testing in the management of children with suspected central nervous system infection. European Journal of Clinical Microbiology and Infectious Diseases 39: 2379-2386	- Study design not in protocol *Case control study*
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: 13-15	- Study country not in protocol *Non-OECD, high income country (India)*
Prasad, R, Kapoor, R, Srivastava, R et al. (2014) Cerebrospinal fluid TNF-alpha, IL-6, and IL-8 in children with bacterial meningitis. Pediatric Neurology 50: 60-65	- Study country not in protocol *Non-OECD high income country (India)*
Qurbanalizadegan, M, Ranjbar, R, Ataee, R et al. (2010) Specific PCR Assay for Rapid and Direct Detection of Neisseria meningitidis in Cerebrospinal Fluid Specimens. Iranian Journal of Public HealthIran J Public Health 39: 45-50	- Study country not in protocol *Non-OECD high income country (Iran)*
Raba, A and Donnelly, J. (2019) Cell ratios in traumatic cerebrospinal fluid. Do they have predictive value for meningitis?. Archives of disease in childhood 104 (Supplement 3): a111	- Study design not in protocol *Conference abstract*
Radstrom, P, Backman, A, Qian, N et al. (1994) Detection of bacterial DNA in cerebrospinal fluid by an assay for simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and streptococci using a seminested PCR strategy. Journal of clinical microbiology 32: 2738-2744	- Study design not in protocol *Two gate-study and sufficient single-gate studies are available for this index test*
Rafi, W, Chandramuki, A, Mani, R et al. (2010) Rapid diagnosis of acute bacterial meningitis: role of a broad range 16S rRNA polymerase chain reaction. Journal of Emergency MedicineJ Emerg Med 38: 225-30	- Study country not in protocol *Non-OECD, high income country (India)*
Rahimkhani, M; Khavari Daneshvar, H; Velayati, A. A. (2011) Detection and evaluation of haemophilus influenza in CSF. European Journal of Neurology 2: 404	- Study design not in protocol *Conference abstract*

Study	Reason
Rai, G. P, Zachariah, K, Sharma, R et al. (2003) Pneumococcal antigen detection in cerebrospinal fluid: A comparative study on counter immunoelectrophoresis, latex agglutination and coagglutination. Comparative Immunology, Microbiology and Infectious Diseases 26: 261-267	- Study country not in protocol *Non-OECD high income country (India)*
Rajial, Tanuja, Batra, Prerna, Harit, Deepika et al. (2022) Utility of Cerebrospinal Fluid and Serum Procalcitonin for the Diagnosis of Neonatal Meningitis. American journal of perinatology 39(4): 373-378	- Study country not in protocol *Non-OECD high income country (India)*
Ramalingam, R. K and Chakraborty, D. (2016) Retrospective analysis of multiplex polymerase chain reaction-based molecular diagnostics (SES) in 70 patients with suspected central nervous system infections: A single-center study. Annals of Indian Academy of Neurology 19: 482-490	- Study country not in protocol *Non-OECD high income country (India)*
Rantakokko-Jalava, K, Nikkari, S, Jalava, J et al. (2000) Direct amplification of rRNA genes in diagnosis of bacterial infections. Journal of Clinical Microbiology 38: 32-9	- Index test not in protocol *Mixed. PCR testing of biopsy specimens, body fluid specimens (including CSF) and abscesses. Results not presented separately for target index test*
Rathore, M. H, Rathore, S, Easley, M. A et al. (1995) Latex particle agglutination tests on the cerebrospinal fluid. A reappraisal. Journal of the Florida Medical AssociationJ Fla Med Assoc 82: 21-Mar	- Index test not in protocol *Latex particle agglutination testing of CSF samples*
Rench, M. A; Metzger, T. G; Baker, C. J. (1984) Detection of group B streptococcal antigen in body fluids by a latex-coupled monoclonal antibody assay. Journal of clinical microbiology 20: 852-854	- Study design not in protocol *No reference standard comparison*
Requejo, H. I. Z, Das Gracas, M, Alkmin, A et al. (2001) Immunodiagnosis of pneumococcal meningitis using dot-enzyme-linked immunosorbent assay. Journal of Tropical Pediatrics 47: 288-290	- Study country not in protocol *Non-OECD high income country (Brazil)*
Reshi, Z, Nazir, M, Wani, W et al. (2017) Cerebrospinal fluid procalcitonin as a biomarker of bacterial meningitis in neonates. Journal of Perinatology 37: 927-931	- Study country not in protocol *Non-OECD high income country (India)*
Rodewald, L. E, Woodin, K. A, Szilagyi, P. G et al. (1991) Relevance of common tests of cerebrospinal fluid in screening for bacterial meningitis. Journal of Pediatrics 119: 363-9	- Index test not in protocol *CSF nucleated blood cell count*
Rosenberg, N. M and Bobowski, T. (1988) Clinical indicators for lumbar puncture. Pediatric Emergency Care 4: 05-Aug	- Index test not in protocol *Clinical impression score (consisting of temperature elevation; inability to be consoled or increased crying; level of alertness; nuchal*

Study	Reason
	rigidity; bulging fontanel; decreased appetite; rash; referral; febrile seizures; other)
Rousseau, G, Asmolov, R, Grammatico-Guillon, L et al. (2017) Rapid diagnosis of bacterial meningitis using a point-of-care glucometer. Annals of Intensive Care 7 (1 Supplement 1): 164	- Study design not in protocol *Conference abstract*
Sacca, R, Shaikh, J, Wood, N et al. (2017) Detecting meningococcal disease amongst children presenting with fever and petechiae. Journal of Paediatrics and Child Health 53 (Supplement 3): 23-24	- Study design not in protocol *Conference abstract*
Sadarangani, M, Willis, L, Kadambari, S et al. (2015) Childhood meningitis in the conjugate vaccine era: a prospective cohort study. Archives of disease in childhood 100: 292-4	- Study design not in protocol *Non-comparative study*
Salih, M. A. M, Ahmed, H. S, Hofvander, Y et al. (1989) Rapid diagnosis of bacterial meningitis by an enzyme immunoassay of cerebrospinal fluid. Epidemiology and Infection 103: 301-310	- Study country not in protocol *Non-OECD, high income country (Sudan)*
Samra, Z, Shmuely, H, Nahum, E et al. (2003) Use of the NOW Streptococcus pneumoniae urinary antigen test in cerebrospinal fluid for rapid diagnosis of pneumococcal meningitis. Diagnostic microbiology and infectious disease 45: 237-240	- Index test not in protocol *Direct antigen testing of CSF samples*
Sanborn, W. R. (1969) Meningitis diagnostic bacteriology. The Journal of the Egyptian Public Health Association 44: 385-407	- Paper unavailable
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: 40-5	- Population does not meet inclusion criteria *Unclear. CSF samples from lumbar puncture and ventricular shunts. Proportions of neurology samples not reported*
Sarookhani, M. R, Ayazi, P, Alizadeh, S et al. (2010) Comparison of 16s rdna-pcr amplification and culture of cerebrospinal fluid for diagnosis of bacterial meningitis. Iranian Journal of Pediatrics 20: 471-475	- Study country not in protocol *Non-OECD, high income country (Iran)*
Saubolle, M. A. (1985) Chromogenic Limulus amebocyte lysate assay as an aid in the diagnosis of meningitis. Progress in Clinical & Biological ResearchProg Clin Biol Res 189: 369-85	- Index test not in protocol *Limulus amebocyte lysate testing of CSF sample*
Schwarz, S, Bertram, M, Schwab, S et al. (2000) Serum procalcitonin levels in bacterial and abacterial meningitis. Critical care medicine 28: 1828-1832	- Index test not in protocol *Procalcitonin levels, C-reactive protein levels and white blood cell count in serum samples, and lactate levels of CSF samples. Cell counts, protein levels and glucose levels of CSF samples also measured but insufficiently reported*

Study	Reason
Seki, M, Kilgore, P. E, Kim, E. J et al. (2018) Loop-Mediated Isothermal Amplification Methods for Diagnosis of Bacterial Meningitis. Frontiers in Pediatrics 6: 57	- Study design not in protocol *Non-systematic review*
Shackelford, P. G; Campbell, J; Feigin, R. D. (1974) Countercurrent immunoelectrophoresis in the evaluation of childhood infections. Journal of Pediatrics 85: 478-81	- Index test not in protocol *Countercurrent immunoelectrophoresis testing of CSF samples*
Sharma, Nupur, Gautam, Hitender, Tyagi, Sonu et al. (2022) Clinical use of multiplex-PCR for the diagnosis of acute bacterial meningitis. Journal of family medicine and primary care 11(2): 593-598	- Study country not in protocol *Non-OECD high income country (India)*
Shenoy, A; Desai, H; Mandvekar, A. (2017) Cerebrospinal Fluid - A Clinicopathologic Analysis. Journal of the Association of Physicians of India 65: 40-43	- Study country not in protocol *Non-OECD high income country (India)*
Shin, D, Baek, S, Lee, Y et al. (2014) Usefulness of C-reactive protein in distinguishing forms of adult meningitis. Headache 1: 63	- Study design not in protocol *Conference abstract*
Shivaprakash, M. R; Rajagopal, V; Nagarathna, S. (2004) Latex Agglutination Test in the diagnosis of pyogenic meningitis. Journal of Communicable Diseases 36: 127-131	- Study country not in protocol *Non-OECD high income country (India)*
Shokouhi, S, Karamipour, M, Darazam, I. A et al. (2018) Diagnostic value of the leukocyte esterase test for early detection of pleocytosis in cerebrospinal fluid of patients with suspected acute bacterial meningitis. Infectious Disorders - Drug Targets 18: 29-34	- Study country not in protocol *Non-OECD high income country (Iran)*
Shrikanth, V, Salazar, L, Khoury, N et al. (2015) Hypoglycorrhachia in adults with community-acquired meningitis: Etiologies and prognostic significance. International journal of infectious diseases 39: 39-43	- Study design not in protocol *Prognostic study*
Sillanpaa, M; Vaha Eskeli, E; Willman, K. (1975) Immunoelectroosmophoresis (IEOP) for detection of bacterial antigens in cerebrospinal fluid. Scandinavian Journal of Infectious Diseases 7: 113-115	- Index test not in protocol *Immunoelectroosmophoresis testing of CSF samples*
Singh, H, Sarkar, R, Sachdev, H. P et al. (1988) Immunological tests in acute bacterial meningitis. Indian Pediatrics 25: 323-328	- Study country not in protocol *Non-OECD, high income country (India)*
Singh, Lovelina, Javali, Mahendra, Mehta, Anish et al. (2022) Study of cerebrospinal fluid levels of lactate, lactate dehydrogenase and adenosine deaminase in the diagnosis and outcome of acute meningitis. Neurological research 44(5): 463-467	- Study country not in protocol *Non-OECD high income country (India)*

Study	Reason
Singh, M; Paul, S.S; Gill, P. (1980) Effect of partial treatment on purulent meningitis. Tropical and Geographical Medicine 32: 16-18	- Paper unavailable
Singhal, A, Lalitha, M. K, Jacob John, T et al. (1996) Modified latex agglutination test for rapid detection of Streptococcus pneumoniae and Haemophilus influenzae in cerebrospinal fluid and direct serotyping of Streptococcus pneumoniae. European Journal of Clinical Microbiology and Infectious Diseases 15: 472-477	- Study country not in protocol *Non-OECD high income country (India)*
Singhi, S. C, Pratibhad, D. M, Singhi, P. D et al. (2002) Evaluation of polymerase chain reaction (PCR) for diagnosing Haemophilus influenzae b meningitis. Annals of tropical paediatrics 22: 347-353	- Study country not in protocol *Non-OECD, high income country (India)*
Smith, P.B, Garges, H.P, Cotton, C.M et al. (2008) Meningitis in preterm neonates: importance of cerebrospinal fluid parameters. American Journal of Perinatology 25: 421-426	- Population does not meet inclusion criteria *Patients with meningitis rather than bacterial meningitis (plus other types of meningitis)*
Sobanski, M. A; Barnes, R. A; Coakley, W. T. (2001) Detection of meningococcal antigen by latex agglutination. Methods in Molecular MedicineMethods Mol Med 67: 41-59	- Study design not in protocol *Book chapter. No original data presented*
Sono, L. and Velaphi, S. (2022) The profile of ancillary laboratory tests in neonates with positive blood and/or cerebrospinal fluid cultures. SAJCH South African Journal of Child Health 16(1): 22-27	- Study country not in protocol *Non-OECD high income country (South Africa)*
Spanos, A; Harrell Jr, F. E; Durack, D. T. (1989) Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. Journal of the American Medical Association 262: 2700-2707	- Insufficient presentation of results *Insufficient information to calculate 2x2 tables for review*
Srinivasan, L, Kilpatrick, L, Shah, S. S et al. (2016) Cerebrospinal fluid cytokines in the diagnosis of bacterial meningitis in infants. Pediatric Research 80: 566-572	- Population does not meet inclusion criteria *Mixed population. Included patients with prior neurosurgical procedures and only 5/11 (45.5%) diagnosed with bacterial meningitis. Results not presented separately for target population*
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: 609-620.e2	- Study country not in protocol *Mixture of OECD and non-OECD countries. Included studies checked for possible inclusion.*
Standage, S, Lahni, P, Ma, W et al. (2010) Cerebrospinal fluid (CSF) HSP72 levels are a potential biomarker for bacterial meningitis in critically ill children. Critical care medicine 12: a15	- Study design not in protocol *Conference abstract*

Study	Reason
Stearman, M and Southgate, H. J. (1994) The use of cytokine and C-reactive protein measurements in cerebrospinal fluid during acute infective meningitis. Annals of Clinical Biochemistry 31: 255-261	- Index test not in protocol *CSF levels of C-reactive protein, tumour necrosis factor α and interleukin-6. Protein and white cell count also measured but insufficiently presented*
Sujaya, M; Ramya, B. S; Biligi Dayananda, S. (2018) Utility of urine reagent strips in cerebrospinal fluid analysis: An aid to bedside diagnosis of meningitis. Indian Journal of Pathology and Microbiology 61 (5): 45	- Study design not in protocol *Conference abstract*
Sunbul, M, Atilla, A, Esen, S et al. (2005) Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. Medical Principles and Practice 14: 151-154	- Study country not in protocol *Non-OECD high income country (Turkey)*
Surinder, K; Bineeta, K; Megha, M. (2007) Latex particle agglutination test as an adjunct to the diagnosis of bacterial meningitis. Indian Journal of Medical Microbiology 25: 395-397	- Study country not in protocol *Non-OECD high income country (India)*
Tamimi, W, Al-Kharji, N. H, Alanazi, M et al. (2008) Cerebrospinal creatinine kinase level in children with meningitis. Clinical Biochemistry 41: 1025-1027	- Study country not in protocol *Non-OECD high income country (Saudi Arabia)*
Tatara, R and Imai, H. (2000) Serum C-reactive protein in the differential diagnosis of childhood meningitis. Pediatrics International 42: 541-546	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review. ROC curves calculated but only Az (area under the best-fit binormal ROC curve) reported*
Thong, K. L, Lai, M. Y, Teh, C. S. J et al. (2011) Simultaneous detection of methicillin-resistant Staphylococcus aureus, Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae and pseudomonas aeruginosa by multiplex PCR. Tropical Biomedicine 28: 21-31	- Study country not in protocol *Non-OECD high income country (Malaysia)*
Tokuda, Y, Koizumi, M, Stein, G. H et al. (2009) Identifying low-risk patients for bacterial meningitis in adult patients with acute meningitis. Internal Medicine 48: 537-543	- Index test not in protocol *Mixed. CSF gram stain, CSF neutrophil count and mental status change. Outcomes can only be calculated for high-risk and low-risk levels of bacterial meningitis, rather than confirmed diagnosis*
Tomasiuk, R, Lipowski, D, Szlufik, S et al. (2016) Higher level of NT-proCNP in cerebrospinal fluid of patients with meningitis. Neuroscience Letters 614: 29-32	- Index test not in protocol *Levels of aminoterminal pro-C type natriuretic peptide in CSF samples, and levels of C-reactive protein and procalcitonin in serum samples. CSF protein and glucose also measured but not reported*
Trung, Ngo Tat, Son, Le Huu Phuc, Hien, Trinh Xuan et al. (2022) CRISPR-Cas12a combination to alleviate the false-positive in loop-mediated isothermal amplification-based diagnosis of Neisseria meningitidis. BMC infectious diseases	- Study country not in protocol *Non-OECD high income country (Vietnam)*

Study	Reason
22(1): 429	
Tsukahara, H, Haruta, T, Hori, C et al. (1999) Evaluation of a rapid reagent strip test for the diagnosis of childhood meningitis. Pediatrics International 41: 443-446	- Index test not in protocol *Urine reagent strip testing of CSF samples*
Tuerlinckx, D, El Hayeck, J, Van der Linden, D et al. (2012) External validation of the bacterial meningitis score in children hospitalized with meningitis. Acta Clinica Belgica 67: 282-285	- Index test not in protocol *Mixed index test. Bacterial Meningitis Score consists of 5 predictors: positive CSF Gram stain, increased CSF absolute neutrophil count, increased CSF protein levels, increased blood absolute neutrophil count and history of seizure*
Tzanakaki, G, Tsopanomichalou, M, Kesanopoulos, K et al. (2005) Simultaneous single-tube PCR assay for the detection of Neisseria meningitidis, Haemophilus influenzae type b and Streptococcus pneumoniae. Clinical Microbiology & InfectionClin Microbiol Infect 11: 386-90	- Index test not in protocol *PCR testing on blood samples*
Uduman, S. A, Adeyemi, E, El-Khadir, A et al. (2000) Haemophilus influenzae type b still remains a leading cause of meningitis among unvaccinated children - A prospective CSF analysis study. Journal of Tropical Pediatrics 46: 331-334	- Study country not in protocol *Non-OECD high income country (United Arab Emirates)*
Van Den Bruel, A, Thompson, M. J, Haj-Hassan, T et al. (2011) Diagnostic value of laboratory tests in identifying serious infections in febrile children: Systematic review. BMJ 342: d3082	- Index test not in protocol *Diagnostic testing of blood samples. Included studies checked for possible inclusions*
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: 651-653	- Reference standard not in protocol *Mixed. Positive Gram staining of CSF samples OR CSF or blood samples culture positive for N. meningitidis or S. pneumoniae OR CSF or blood samples PCR positive for N. meningitidis or S. pneumoniae. Results not reported separately for target reference standard*
Van Ketel, R. J; De Wever, B; Van Alphen, L. (1990) Detection of Haemophilus influenzae in cerebrospinal fluids by polymerase chain reaction DNA amplification. Journal of Medical Microbiology 33: 271-276	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
van Soest, T.M., Horst, L.T., Chekrouni, N. et al. (2022) A risk score for identifying patients at a low risk of bacterial meningitis amongst adults with cerebrospinal fluid leucocytosis and a negative gram stain result: a derivation and validation study. Clinical Microbiology and Infection	- Population does not meet inclusion criteria *Mixed. Diagnosis of bacterial meningitis made based on CSF bacterial culture, a positive Gram stain result, or positive blood culture*
van Soest, Thijs M, Chekrouni, Nora, van Sorge, Nina M et al. (2022) Community-acquired bacterial meningitis in patients of 80 years and	- Study design not in protocol *Comparing older and younger people with bacterial meningitis*

Study	Reason
older. Journal of the American Geriatrics Society 70(7): 2060-2069	
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: 1313-1316	- Insufficient presentation of results *Not enough data to construct 2x2 tables for review*
Viswanath, G, Praveen, Hanumanthappa, A. R, Chandrappa, N. R et al. (2007) Bacteriological study of pyogenic meningitis with special reference to latex agglutination. Indian Journal of Pathology and Microbiology 50: 97-100	- Study country not in protocol *Non-OECD, high income country (India)*
Von Dohlen, M and Jones, J. (2019) A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections: Kuppermann N, Dayan PS, Levine DA, et al. JAMA Pediatrics. 2019;173(4):342-351. Journal of emergency medicine 57 (3): 421	- Study design not in protocol *Conference abstract*
Wakhle, L and Saigal, S. R. (1997) Rapid and specific diagnosis of group B streptococcal infection by the polymerase chain reaction (PCR). Advances in Experimental Medicine & BiologyAdv Exp Med Biol 418: 347-9	- Study design not in protocol *Conference abstract*
Waltman, W. D, 2nd, Gray, B, McDaniel, L. S et al. (1988) Cross-reactive monoclonal antibodies for diagnosis of pneumococcal meningitis. Journal of clinical microbiology 26: 1635-40	- Index test not in protocol *Dot blot assay of CSF samples*
Wang, M. E, Neuman, M. I, Nigrovic, L. E et al. (2021) Characteristics of Afebrile Infants <=60 Days of Age With Invasive Bacterial Infections. Hospital Pediatrics 11: 100-105	- Paper unavailable
Wang, Ying, Cao, Mei, Zhu, Xi et al. (2022) The cerebrospinal fluid neutrophil to lymphocyte ratio is a sensitive biomarker for bacterial meningitis in children. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery 38(6): 1165-1171	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Whittle, H. C and Greenwood, B. M. (1975) A revival of the older methods of diagnosis and treatment of pyogenic meningitis. Journal of tropical pediatrics and environmental child health 21: 58-59	- Study country not in protocol *Non-OECD high income country (Nigeria)*
Whittle, H. C; Greenwood, B. M; Davidson Mc, D. N. (1975) Meningococcal antigen in diagnosis and treatment of group A meningococcal infections. American Journal of Medicine 58: 823-828	- Study country not in protocol *Non-OECD, high income country (Nigeria)*
Whittle, H. C, Tugwell, P, Egler, L. J et al. (1974) Rapid bacteriological diagnosis of pyogenic meningitis by latex agglutination. Lancet 2: 619-	- Study country not in protocol *Non-OECD high income country (Nigeria)*

Study	Reason
621	
Wilson, M. R, Sample, H. A, Zorn, K. C et al. (2019) Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. New England journal of medicine 380: 2327-2340	- Index test not in protocol
Worrall, C, Hare, C, Freeman, P et al. (2020) The utility of a rapid, in house method of CSF analysis involving sedimentation and cytological evaluation direct from the spinal needle. Journal of Veterinary Internal Medicine 34 (1): 493	- Study design not in protocol *Conference abstract*
Yadhav Ml, K. (2014) Study of bacterial meningitis in children below 5 years with comparative evaluation of gram staining, culture and bacterial antigen detection. Journal of Clinical and Diagnostic Research JCDRJ Clin Diagn Res 8: DC04-6	- Study country not in protocol *Non-OECD, high income country (India)*
Yahia, M. A and Balach, O. (2014) Comparison of multiplex PCR, gram stain, and culture for diagnosis of acute bacterial meningitis. International Journal of Pharmacy and Pharmaceutical Sciences 6: 425-429	- Study country not in protocol *Non-OECD, high income country (Syria)*
Yang, Y, Qu, X. H, Zhang, K. N et al. (2020) A Diagnostic Formula for Discrimination of Tuberculous and Bacterial Meningitis Using Clinical and Laboratory Features. Frontiers in Cellular and Infection Microbiology 9 (no pagination)	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Ye, Q, Shao, W. X, Shang, S. Q et al. (2016) Clinical value of assessing cytokine levels for the differential diagnosis of bacterial meningitis in a pediatric population. Medicine (United States) 95: e3222	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Yetkin, F, Bayraktar, M. R, Ersoy, Y et al. (2011) A New Diagnostic Scoring for Discrimination of Tuberculous and Bacterial Meningitis on the Basis of Clinical and Laboratory Findings. Medical Principles and Practice. 1	- Study design not in protocol *Conference abstract*
Yetkin, F, Kayabas, U, Ersoy, Y et al. (2010) Evaluation of cerebrospinal fluid viscosity as a novel diagnostic measure for acute meningitis. Clinical Microbiology and Infection 2: S518-S519	- Study country not in protocol *Non-OECD high income country (Turkey)*
Yetkin, F, Kayabas, U, Ersoy, Y et al. (2010) Cerebrospinal fluid viscosity: A novel diagnostic measure for acute meningitis. Southern Medical Journal 103: 892-895	- Study country not in protocol
Zhang, L, Ma, L, Zhou, X et al. (2019) Diagnostic Value of Procalcitonin for Bacterial Meningitis in Children: A Comparison Analysis Between Serum	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*

Study	Reason
and Cerebrospinal Fluid Procalcitonin Levels. Clinical pediatrics 58: 159-165	
Zhang, Y. (2019) Early diagnosis and clinical characteristics of neonatal purulent meningitis. Acta Medica Mediterranea 35: 615-619	- Study design not in protocol *Non-OECD high income country (People's Republic of China)*
Zhang, Y. C. (2013) Pathogen diagnosis of children sepsis by LAMP technology. Asian Pacific Journal of Tropical Medicine 6: 242-245	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Zhang, Y, Cui, P, Zhang, H. C et al. (2020) Clinical application and evaluation of metagenomic next-generation sequencing in suspected adult central nervous system infection. Journal of Translational Medicine 18 (1)	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Zhao, C, Wang, X, Zhang, C et al. (2019) Development of a TaqMan Array card to target 21 purulent meningitis-related pathogens. BMC Infectious Diseases 19 (1)	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Zhou, L, Wu, R, Shi, X et al. (2016) Simultaneous detection of five pathogens from cerebrospinal fluid specimens using Luminex technology. International Journal of Environmental Research and Public Health 13 (2)	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*
Zhu, H, Wang, Q, Wen, L et al. (2012) Development of a multiplex PCR assay for detection and genogrouping of Neisseria meningitidis. Journal of clinical microbiology 50: 46-51	- Study country not in protocol *Non-OECD high income country (People's Republic of China)*

AUC: area under the curve; CNS: central nervous system; CSF: cerebrospinal fluid; FA/ME: FilmArray – Meningitis/Encephalitis; IL: interleukin; LAMP: loop-mediated isothermal amplification; N. meningitidis: Neisseria meningitidis; OECD: Organisation for Economic Co-operation and Development; PCR: polymerase chain reaction; RDT: rapid diagnostic test; ROC: receiver operating characteristic; RT: real-time; S. agalactiae: Streptococcus agalactiae; S. pneumoniae; Streptococcus pneumoniae; TNF: tumour necrosis factor; WBC: white blood count

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

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

Research question

Can novel host biomarker or metagenomic techniques applied to blood or cerebrospinal fluid be used to diagnose bacterial meningitis?

Why this is important

In the context of changing epidemiology and an aging population, a definitive diagnosis of bacterial meningitis is increasingly hard to make. Currently available diagnostics such as culture and PCR, take time to give a definitive answer and have a low sensitivity. There is insufficient evidence on whether novel host biomarker or metagenomic techniques could fill this diagnostic gap. Further research would provide greater clarity about the role of these techniques in the diagnosis of meningitis.

Table 97: Research recommendation rationale

Research question	**Can novel host biomarker or metagenomic techniques applied to blood or cerebrospinal fluid be used to diagnose bacterial meningitis?**
Why is this needed	
Importance to 'patients' or the population	Making an accurate diagnosis of bacterial meningitis is likely to improve outcome, antibiotic stewardship and patient confidence.
Relevance to NICE guidance	There was insufficient evidence on whether novel host biomarker or metagenomic techniques could fill this diagnostic gap.
Relevance to the NHS	Bacterial meningitis is a medical emergency associated with a high rate of death and disability.
National priorities	Antimicrobial stewardship
Current evidence base	These techniques are in the early stages of development and there is very limited diagnostic accuracy data for validation in a clinical setting
Equality	No equality issues were identified
Feasibility	These diagnostics are currently in development
Other comments	None

CSF: cerebrospinal fluid

Table 98: Research recommendation characteristics

Criterion	**Explanation**
Population	People with suspected bacterial meningitis
Index tests	Novel host biomarker or metagenomic techniques
Reference standard	Standard diagnostics
Outcomes	Sensitivity and specificity

Criterion	Explanation
Study design	Multicentre prospective cohort study