National Institute for Health and Care Excellence

Final

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

[A1] Evidence review for symptoms and signs associated with bacterial meningitis

NICE guideline NG240

Evidence review underpinning recommendations 1.1.1 to 1.1.7, 1.1.16, 1.1.17, 1.2.1 and 1.2.2 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Symptoms and signs associated with bacterial meningitis

Review question

What symptoms and signs, individually or in combination, are associated with 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. The diagnosis of bacterial meningitis is difficult, particularly as the early symptoms and signs may mimic those found in other serious conditions or milder viral illnesses.

The aim of this review is to evaluate the symptoms and signs (and combinations thereof) that are useful to healthcare professionals in deciding whether bacterial meningitis should be considered in the initial differential diagnosis.

Summary of the protocol

See Table 1 for a summary of the Population, Risk markers, Comparison and Outcome characteristics of this review.

Table 1: Summary of the protocol

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis.
Risk markers	Any signs and symptoms, alone or in combination
Comparison	**Binary accuracy data** N/A **Association data (if insufficient accuracy data)** Absence of sign(s)/symptom(s)
Outcome	**Critical** **Binary accuracy data** • Sensitivity for diagnosis of bacterial meningitis* • Specificity for diagnosis of bacterial meningitis* **Association data (if insufficient accuracy data)** • Risk ratios for diagnosis of bacterial meningitis* • Odds ratios for diagnosis of bacterial meningitis* * Diagnosis of bacterial meningitis must be made based on lumbar puncture **Important** None

N/A: Not applicable

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

Sixteen studies were included in the diagnostic test accuracy review, 5 single-gate, cross-sectional, diagnostic test accuracy (DTA) studies (Borchsenius 1991, Fretzayas 2010, Krishna 1983, Lembo 1991, Walsh-Kelly 1992), 9 single-gate retrospective DTA studies (Behrman 1989, De Cauwer 2007, Gowin 2017, Joffe 1983, Levy 1990, Magazzini 2012, Magnussen 1980, Nielsen 1988, Oostenbrink 2001), and 2 two-gate, cross-sectional, DTA studies (Bilavsky 2013, Brivet 2005). Studies with univariate analyses were included as no studies with multivariate analyses were identified.

The included studies are summarised in Table 2.

Eleven studies included babies and children (Bilavsky 2013, De Cauwer 2007, Fretzayas 2010, Gowin 2017, Joffe 1983, Krishna 1983, Lembo 1991, Levy 1990, Nielsen 1988, Oostenbrink 2001, Walsh-Kelly 1992); 2 studies included adults of any age (Brivet 2005, Magazzini 2012) and 1 study only older adults (Behrman 1989); 1 study included older children and adults and reported combined results (Magnussen 1980); and 1 study had an undefined age range and reported results for the whole sample (Borchsenius 1991).

The signs and symptoms of bacterial meningitis in babies and children reported by the studies can be categorised as follows: general signs of illness and duration of illness (Bilavsky 2013, De Cauwer 2007, Joffe 1983, Krishna 1983, Levy 1990, Nielsen 1988, Walsh-Kelly 1992); unusual, abnormal, or pale skin colour (Oostenbrink 2001); presence, and type and size, of rash (De Cauwer 2007, Fretzayas 2010, Gowin 2017, Krishna 1983, Nielsen 1988, Oostenbrink 2001); signs or symptoms of meningism (Bilavsky 2013, De Cauwer 2007, Fretzayas 2010, Gowin 2017, Lembo 1991, Levy 1990, Nielsen 1988, Oostenbrink 2001, Walsh-Kelly 1992); neurological deficits (Bilavsky 2013, De Cauwer 2007, Gowin 2017, Joffe 1983, Krishna 1983, Levy 1990, Nielsen 1988, Oostenbrink 2001); altered mental state (Krishna 1983, Nielsen 1988, Oostenbrink 2001); signs of shock (Walsh-Kelly 1992); respiratory symptoms (Fretzayas 2010, Krishna 1983); gastrointestinal symptoms and food refusal (Bilavsky 2013, De Cauwer 2007, Fretzayas 2010, Gowin 2017, Krishna 1983, Levy 1990, Nielsen 1988). One study also reported on the presence of one of a number of signs/symptoms across categories (Joffe 1983). No studies reported on the distribution or duration of rash, limb or body pain, or cardiac symptoms, as signs/symptoms of bacterial meningitis in babies and children.

The signs and symptoms of bacterial meningitis in adults reported by the studies can be categorised as follows: general signs of illness (Behrman 1989); signs or symptoms of meningism (Behrman 1989, Magazzini 2012); neurological deficits (Behrman 1989, Brivet 2005, Magazzini 2012); altered mental state (Behrman 1989, Brivet 2005, Magazzini 2012); signs of shock (Brivet 2005, Magazzini 2012). One study also reported on the presence of 1 of a number of signs/symptoms across categories (Brivet 2005). No studies reported on unusual/abnormal/pale skin colour, or presence/type/size/distribution/duration of rash, or limb/body pain, or cardiac or respiratory symptoms, or gastrointestinal symptoms or food refusal, as signs/symptoms of bacterial meningitis in adults.

One study (Magnussen 1980) reported on fever, neck stiffness, headache, focal neurological deficits, and altered mental state, as potential signs/symptoms of bacterial meningitis in older children and adults.

One study (Borchsenius 1991) reported the following signs and symptoms of bacterial meningitis in an undefined age range: reduced general condition; cyanosis; petechiae (≤4 mm); ecchymoses (>4 mm); neck stiffness; reduced consciousness; cold extremities; and body pain.

One study restricted the reference standard to positive bacterial CSF culture (Bilavsky 2013). One study attempted to restrict the reference standard to positive bacterial CSF culture but included 1/10 where CSF culture was negative (Krishna 1983). One study used bacterial pathogens identified in both CSF and blood cultures, CSF culture alone, or blood culture alone as the reference standard, although the majority of patients had positive bacterial CSF culture (95%; Brivet 2005). One study used CSF pleocytosis as the reference standard, although 85% of those diagnosed with meningitis had positive CSF bacterial cultures (Joffe 1983). One study diagnosed bacterial meningitis based on high cell counts (predominantly polymorphonuclear cells), low or normal sugar levels, and elevated protein, but reported that for the majority of patients bacteria were recovered from the CSF culture (Levy 1990). One study diagnosed bacterial meningitis based on positive CSF culture and/or CSF pleocytosis and a positive blood culture, and 67% of the bacterial meningitis group had positive CSF culture (De Cauwer 2007). One study used CSF Gram stain, CSF culture, other CSF findings, or blood culture as the reference standard and included 36% of diagnoses made without positive culture (Magnussen 1980). The following studies did not report details on the proportion of the population diagnosed with CSF culture, but used a combination of CSF culture and other methods as the reference standard: CSF culture, other CSF findings and/or blood culture (Behrman 1989); CSF culture, blood culture, Gram stain, and/or PCR (Fretzayas 2010); CSF culture, blood culture, and/or CSF leukocyte count (Borchsenius 1991, Oostenbrink 2001); CSF culture, CSF latex agglutination and/or Gram stain (Walsh-Kelly 1992); CSF culture, CSF latex agglutination, Gram stain, and/or PCR (Gowin 2017); CSF culture, or identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive culture (Lembo 1991). Two studies performed lumbar puncture on all patients but did not report criteria for diagnosis or the proportion of the population diagnosed with CSF culture (Magazzini 2012; Nielsen 1988).

Three studies compared those with bacterial meningitis to those with no meningitis (Bilavsky 2013, Borchsenius 1991, Joffe 1983). Six studies compared patients with bacterial meningitis to those with viral meningitis (Brivet 2005, De Cauwer 2007, Gowin 2017, Magazzini 2012, Magnussen 1980, Walsh-Kelly 1992). One study compared those with bacterial meningitis to patients with other types of meningitis, including aseptic, tuberculous, suspected tuberculous, fungal and viral meningitis (Behrman 1989). For 6 studies, the comparison was between those with bacterial meningitis and a mixed comparison group including both those without meningitis and those with other types of meningitis (Fretzayas 2010, Krishna 1983, Lembo 1991, Levy 1990, Nielsen 1988, Oostenbrink 2001).

Signs and symptoms were identified or reported by healthcare professionals in all 16 studies.

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
Behrman 1989 Single-gate, cross-sectional (retrospective) DTA study US	N=50 Older adults (≥65 years) with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess Bacterial meningitis, including partially treated bacterial meningitis (n=30) Other types of meningitis (n=20): Aseptic (n=3); tuberculous (n=3); suspected tuberculous (n=3); fungal (n=2); viral (n=1); unknown (n=8) 50 episodes of meningitis occurred in 48 patients: Age in years (mean; range in parentheses): 72 (65-89) Sex: male: 22 (46%); female: 26 (54%)	Signs and symptoms (taken from medical records): • Fever (≥37°C) • Meningismus • Headache • Change in mental status • Motor or cranial nerve deficits	Positive CSF culture or CSF examination revealing hypoglycorrachia and/or CSF pleocytosis associated with a positive Gram's stain, a positive blood culture, or a positive counterimmunoelectrophoresis assay for Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae. Partially treated bacterial meningitis defined as results of CSF investigation showing pleocytosis, and evidence of bacterial otitis media or pneumonia in patients who received antibacterial therapy prior to lumbar puncture	• Sensitivity • Specificity	Causative organisms: Gram-positive (21/28; 75%): S. pneumoniae (12/28; 43%); Other streptococci, including Streptococcus bovis, Streptococcus viridans, Streptococcus faecalis, and S pyogenes (4/28; 14%); Listeria monocytogenes (2/28; 7%); Staphylococci (2/28; 7%); Propionlbacterium acnes (1/28; 4%). Gram-negative (7/28; 25%): Klebsiella species (2/28; 7%); Others, including Haemophilus influenzae, Enterobacter cloacae, Serratia species, Pseudomonas aeruginosa, and an undefined gram-negative rod (5/28; 18%)
Bilavsky 2013 Two-gate, cross-sectional DTA	N=86 Babies and children (3 months-17	Signs and symptoms in clinical history: • Fever (≥38°C)	Presence of a positive bacterial CSF culture	• Sensitivity • Specificity	Causative organisms: S. pneumoniae (23/40; 57.5%); N. meningitidis (17/40; 42.5%)

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
study Israel	years) with a confirmed diagnosis of bacterial meningitis compared with matched controls without a diagnosis of bacterial meningitis Bacterial meningitis (n=40): Age (in months): Median 27 (range 5-180); aged <12 months (n=7; 17%) Sex: male 19 (47.5%); female: 21 (52.5%) No meningitis (n=46) Age (in months): Median 24 (range 7-204); aged <12 months (n=10; 20.7%) Sex: male 29 (63%); female: 17 (37%)	• Nausea/ vomiting • Headache • Convulsions Signs and symptoms at presentation identified by healthcare professional: • Fever (between 38°C and 39°C) • Fever (≥ 39.1°C) • Nuchal rigidity • Brudzinski's sign • Kernig's sign • Kernig's sign and nuchal rigidity • Kernig's sign and Brudzinski's sign • Nuchal rigidity and Brudzinski's sign • Kernig's sign, nuchal rigidity, and Brudzinski's sign			Excluded children treated with antibiotics prior to hospital admission, which may not reflect clinical practice
Borchsenius 1991 Single-gate, cross-sectional DTA study Norway	N=92 Patients with suspected systemic meningococcal disease admitted to hospital (those with meningitis only are included in this review, and those with	Signs and symptoms recorded by healthcare professional on the day of admission to hospital: • Petechiae (≤4mm) • Reduced general condition • Ecchymoses	Method of diagnosis was reported for the whole sample only (including those with meningococcal disease): growth of meningococci in blood and/or CSF (for 62%), or based on the clinical	• Sensitivity • Specificity	5% of full sample (that included those with meningococcal disease) included retrospectively Data was not reported for clinical symptoms that were non-significant

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	septicaemia only or meningitis and septicemia are included in the review on signs and symptoms of meningococcal disease) Meningococcal meningitis (n=56): Age: Reported for whole sample only (including those with meningococcal disease); Mean/median not reported; 50% aged < 12 years. No meningococcal or bacterial infection (n=36): Age: Reported for whole sample only (including control participants not included in this review; Mean/median not reported; 79% aged < 12 years	(cutaneous haemorrhages >4 mm) • Reduced consciousness • Cold extremities • Cyanosis • Neck stiffness • Body pain	picture, meningococcal antigen in CSF, or growth of N. meningitidis in pharyngeal swab specimens (for 38%)		(presence of convulsions, back rigidity, headache, nausea, chills, fever, diarrhoea, irritability, systolic blood pressure <100, heart rate ≥120, rectal temperature≥40.0)
Brivet 2005 Two-gate, cross-sectional (retrospective) DTA study France	N=144 Adults hospitalized with a confirmed diagnosis of bacterial meningitis (in medical records) compared with adults hospitalized	Signs and symptoms (taken from medical records): • Presence of at least 1 sign of severity at presentation (altered mental status; focal neurological deficits;	At least 2 of: • a CSF Gram-stained smear positive for bacterial pathogen, • CSF pleocytosis and a positive blood culture	• Sensitivity • Specificity	Causative organisms: S. pneumoniae (44/90; 49%); N. meningitidis (19/90; 21%); Listeria monocytogenes (6/90; 7%); other streptococci (7/90; 8%); Staphylococcus aureus (5/90; 6%); other

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	with a confirmed diagnosis of viral meningitis (in medical records) Bacterial meningitis (n=90 analysed): Age (in years): Mean 49.7 (SD=20.5) Viral meningitis (n=54 analysed): Age (in years): Mean 34.9 (SD=14.0)	seizures at or before presentation ; or shock) • Altered mental status (defined as Glasgow Coma Scale [GCS] score <14) • Focal neurological deficits • Seizures at or before presentation • Shock	• a positive CSF culture for bacterial pathogen • a positive CSF latex agglutination test or PCR assay for N. meningitidis		bacteria (9/90; 10%) Bacterial pathogens identified in both CSF and blood cultures (n=61), CSF culture alone (n=24), and blood culture alone (n=4) 20/90 of those with bacterial meningitis received antibiotics before referral 10/90 of those with bacterial meningitis (and none of those with viral meningitis) were immunocompromised Data cannot be extracted for: duration of symptoms (<24 hours); headache; nausea/vomiting ; photophobia; neck stiffness
De Cauwer 2007 Single-gate, cross-sectional (retrospective) DTA study Belgium	N=92 Children (0-15 years old) admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of viral or bacterial meningitis Bacterial meningitis	Signs and symptoms (reported by the paediatrician): • Headache • Neck strain • Photophobia • Fever • Neck stiffness • Nausea • Vomiting • Sick for >2 days • Convulsions	Positive CSF culture or a pleocytosis ≥ 10 white blood cells in the CSF and a positive blood culture	• Sensitivity • Specificity	Bacterial aetiology: Meningococcal meningitis (n=16; 76%); pneumococcal meningitis (n=5; 24%) 14/21 in bacterial meningitis group had positive CSF culture

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	(n=21): Age in years (mean; range in parentheses): 3.9 (0-13) Sex: male: 12 (57%); female 9 (43%) Viral meningitis (n=71): Age in years (mean; range in parentheses): 6.1 (0-15) Sex: male 46 (65%); female: 25 (35%)	• Petechiae			
Fretzayas 2010 Single-gate, cross-sectional DTA study Greece	N=145 Children (1 month-14 years) who underwent diagnostic lumbar puncture for infectious meningitis Meningococcal meningitis (n=40): Age in months (mean; standard deviation in parentheses): 75.3 (39.7) Sex: male: 25 (62.5%); female: 15 (37.5%) Viral meningitis/no meningitis (n=105): Viral meningitis (n=32); No meningitis	Signs and symptoms (recorded in a pre-coded questionnaire on admission): • Respiratory symptoms • Gastrointestinal symptoms • Vomiting • Neck stiffness • Kernig's sign • Brudzinski's sign • Hemorrhagic rash • Headache	Blood or CSF culture and/or Gram stain, or PCR for meningococcus	• Sensitivity • Specificity	Excluded children treated with antibiotics within 72 hours before evaluation

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	(n=73) Age in months (mean; standard deviation in parentheses): 50.3 (53.3) Sex: male: 54 (51%); female: 51 (49%)				
Gowin 2007 Single-gate, cross-sectional (retrospective) DTA study Poland	N=148 Children hospitalised with meningitis Bacterial meningitis (n=84): Age in months (mean; standard deviation in parentheses): 61.6 (64.9) Viral meningitis (n=64): Age in months (mean; standard deviation in parentheses): 117.7 (57.2) Total sample (N=148): Sex: male: 78 (53%); female: 70 (47%)	Signs and symptoms present on admission taken from medical records: • Headache • Rash • Vomiting • Seizures	Positive CSF culture (or detection of bacterial genetic material by PCR) along with typical clinical symptoms: fever, headache, and existing meningeal signs. The gold standard was positive culture. For rapid diagnosis, fast latex tests and direct examination of Gram stain were performed	• Sensitivity • Specificity	No breakdown of bacterial or viral pathogens isolated
Joffe 1983 Single-gate, cross-sectional (retrospective) DTA study US	N=241 Children (6 months-6 years) presenting at the emergency room with a first episode of seizure and fever	Signs and symptoms (taken from medical records): • Visit to a physician in the 48 hours prior to the seizure • Seizure at presentation	CSF pleocytosis	• Sensitivity • Specificity	Very small number of participants with bacterial meningitis enrolled in the study 11/13 of children with CSF pleocytosis had positive CSF

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Meningitis (n=13) Age in months: Mean 22 (SD not reported) Sex: male 6 (46%); female: 7 (54%) No meningitis/febrile seizures (n=228) Age in months: Mean 23 (SD not reported) Sex: male 144 (63%); female: 84 (37%)	• Focal seizure • Presence of rash/petechiae, cyanosis, hypotension, or grunting respirations • Abnormal neurologic findings • Presence of ≥1 of: visit to physician within 48 hours or focal type of seizure • Presence of ≥1 of: visit to physician within 48 hours or abnormal neurologic finding • Presence of ≥1 of: visit to physician within 48 hours or seizure at presentation • Presence of ≥1 of: focal type of seizure or presence of abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations) • Presence of ≥1 of: focal type of seizure or abnormal neurologic findings • Presence of ≥1 of: visit to			bacterial cultures

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
		physician within 48 hours; seizure at presentation ; focal type of seizure; abnormal physical finding (rash/petechiae, cyanosis, hypotension , or grunting respirations) ; abnormal neurologic findings			
Krishna 1983 Single-gate, cross-sectional (retrospective) DTA study US	N=168 Paediatric patients (<18 years) who had undergone a lumbar puncture Bacterial meningitis (n=10): Age in months (mean; range in parentheses): 7.8 (9 days to 18 months) Sex: male: 6 (60%); female: 4 (40%) Other type of meningitis/no meningitis (n=158): Bacteremia only n=3; aseptic meningitis n=10; no meningitis n=145. Age in months (mean; range in	Signs and symptoms taken from medical records: • Fever • Upper respiratory symptoms • Diarrhoea • Loss of appetite • Vomiting • Seizures • Constipation • Reduced consciousness • Irritable • Lethargic • Toxic or ill • Petechiae	Positive bacterial cultures of the CSF, regardless of blood culture results	• Sensitivity • Specificity	Very small number of participants with bacterial meningitis enrolled in the study For 1/10 of bacterial meningitis group, CSF culture was negative, but the patient developed a subdural effusion and a mild communicating hydrocephalus. Blood culture yielded H influenzae B, and CSF was interpreted as abnormal by 2 independently working expert judges. Positive CSF culture (n=9): H. influenzae B (n=3); H. influenzae nontypeable (n=1); S pneumoniae

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	parentheses): 7.3 (4 days to 9 years) Sex: male: 93 (59%); female: 65 (41%)				meningitis (n=2); N. meningitidis C (n=1); group D streptococcus (n=1); Listeria monocytogenes (n=1)
Lembo 1991 Single-gate, cross-sectional DTA study US	N=160 Children presenting to hospital for evaluation of an acute febrile episode Bacterial meningitis (n=10) Other illnesses (n=150): Aseptic meningitis (n=14); other bacterial infections (n=10); other illnesses (n=126) Total sample (N=160): Age in months (median): 6 Sex: male 84 (52.5%); female: 76 (47.5%)	Signs and symptoms recorded at presentation: • Any sign of meningeal irritation (for example, nuchal rigidity, Kernig's sign, or Brudzinski's sign) or increased intracranial pressure (full/bulging anterior fontanelle) • Any symptom of CNS infection, defined as irritability, lethargy, headache, or stiff neck	Recovery of a bacterial pathogen from CSF by standard culture techniques, or by the identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive culture	• Sensitivity • Specificity	Very small number of participants with bacterial meningitis enrolled in the study Causative organisms: H. influenzae type B (5/10; 50%); S. pneumoniae (3/10; 30%); group A streptococci (1/10; 10%); Listeria monocytogenes (1/10; 10%)
Levy 1990 Single-gate, cross-sectional (retrospective) DTA study Israel	N=650; Data analysed for N=630 Children undergoing lumbar puncture for presumed diagnosis of meningitis Bacterial meningitis	Signs and symptoms (recorded at presentation, and taken from medical records): • Fever • Convulsion with fever • Convulsion without fever • Irritability	High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	• Sensitivity • Specificity	Paper reports that 'in most such instances bacteria were recovered from the CSF culture' but proportion not reported All of the children with bacterial meningitis were treated with

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	(n=50) Other type of meningitis/no meningitis (n=580): Viral meningitis (n=212); normal CSF findings (n=368) Total sample (N=630): Age: Mean/median not reported; 0-8 weeks (n=58; 9%); 8 weeks to 24 months (n=213; 34%); 2 years to 5 years (n=217; 34%); 5 years to 12 years (n=142; 23%)	• Lethargy • Headache • Vomiting • Nuchal rigidity • Budzinski sign • Kernig sign • Bulging fontanelle			antibiotics No details on bacterial aetiology of patients diagnosed with bacterial meningitis
Magazzini 2012 Single-gate, cross-sectional (retrospective) DTA study Italy	N=202 Adults presenting to the ED and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial (including meningoencephalitis) Bacterial meningitis (n=40): Age in years (mean; standard deviation in parentheses): 55.7 (18.2)	Signs and symptoms (recorded from physical examination performed by emergency physicians in the ED, and taken from medical record): • Reduced consciousness (GCS score <15) • Kernig or Brudzinski signs • Neck stiffness • Kernig or Brudzinski signs or neck stiffness • Neurological complaints, including seizure and	Lumbar puncture performed on all participants. The diagnosis of meningitis and its aetiology were established by the infectious disease specialist or the intensivist based on all laboratory and instrumental investigations performed during the hospital stay, and on the basis of hospital course	• Sensitivity • Specificity	Some patients were immunocompromised (15% of bacterial meningitis group and 6% of viral meningitis group) No details on bacterial aetiology of patients diagnosed with bacterial meningitis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Viral meningitis (n=162): Age in years (mean; standard deviation in parentheses): 39.5 (17.4) Whole sample (N=202): Sex: male: 105 (52%); female: 97 (48%)	focal neurological deficits • Severe sepsis or shock			
Magnussen 1980 Single-gate, cross-sectional (retrospective) DTA study US	N=59 Older children and adults with a discharge diagnosis of acute meningitis. Data only analysed for those with bacterial or aseptic meningitis. Bacterial meningitis (n=25): Age in years (mean): 53.6 Sex: male: 13 (52%); female: 12 (48%) Aseptic meningitis (n=34): Age in years (mean): 28.6 Sex: male: 13 (38%); female: 21 (62%)	Signs and symptoms (recorded at presentation, and taken from medical records): • Fever (>38.9°C) • Headache • Nuchal rigidity • Moderate or severe mentation changes • Focal neurologic signs	Known aetiology: positive result on CSF gram stain or a CSF culture and/or positive blood culture Unknown aetiology: negative CSF gram stain and negative CSF culture or blood cultures, but CSF lab results showing total WBC >1,000 per cubic mm with more than 50% PMNs, and total protein ≥80mg/100ml and/or glucose ≤40mg/100ml	• Sensitivity • Specificity	Study includes 9/25 diagnoses made without positive culture Bacterial aetiology: Pneumococcal (n=9; 36%); meningococcal (n=2; 8%); Pseudomonas species (n=1; 4%); S. epidermidis (n=1; 4%); Gamma-streptococcus (n=1; 4%); Alpha-streptococcus (n=1; 4%); H. influenzae (n=1; 4%); unknown (n=9; 36%) Papilledema also reported as an outcome but no events in either arm
Nielsen 1988 Single-gate, cross-sectional	N=160 Children (<16 years) admitted for	Signs and symptoms (taken from referral letters from GPs and	Criteria for diagnosis not reported (all those with PM underwent	• Sensitivity • Specificity	Very small number of participants with purulent meningitis

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
(retrospective) DTA study Denmark	observation for suspected meningitis to the paediatric ward Purulent meningitis (n=17) Other types of meningitis/non-meningitis (n=143): Aseptic meningitis (n=5; 3%); aseptic meningitis with parotitis (n=10; 7%); parotitis (uncomplicated; n=2; 1%); encephalitis/radiculomyelitis (n=5; 3%); upper respiratory tract infections (n=45; 31%); fever of unknown origin (n=42; 29%); pneumonia (n=21; 15%); gastroenteritis (n=4; 3%); measles (n=4; 3%); urinary tract infection (n=2; 1%); other (n=3; 2%) Total sample (N=160): Age in years (median; lower and upper quartiles parentheses): 5 (2-9) Sex: male: 111 (69%); female: 49	hospital discharge letters): • Duration of symptoms of 24 hours or less • Fever • Neck stiffness • Kernig's sign • Rash • Petechiae • Nausea/vomiting • Impaired consciousness • Convulsions	LP)		enrolled in the study Causative organisms: H. influenzae (n=2; 12%); N. meningitidis (n=8; 47%); S. pneumoniae (n=2; 12%); unknown organisms (n=2; 12%); n=3 (18%) with PM due to N. meningitidis were admitted with a different

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	(31%) 78/160 (49%) underwent lumbar puncture				
Oostenbrink 2001 Single-gate, cross-sectional (retrospective) DTA study Netherlands	N=286 Babies and children (1 month-15 years) visiting the ED, who were retrospectively coded as having meningeal signs Bacterial meningitis (n=84): Age in years (mean; 95% confidence interval in parentheses): 3.6 (2.8–4.3) Sex: male: 42 (50%); female: 42 (50%) Other types of meningitis/non-meningitis (n=202): Viral/aseptic meningitis (n=34; 17%); pneumonia (n=20; 10%); other bacterial infections, including septicaemia, urinary tract infections and gastroenteritis (n=8; 4%); self-limiting diseases, upper respiratory tract infections, non-specified	Signs and symptoms taken from medical records (based on clinical history and physical examination): • Complex convulsion • Disturbed consciousness • Cyanosis • Petechiae or ecchymoses • Meningeal irritation • Focal neurological disorders	Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood	• Sensitivity • Specificity	Data could not be extracted for signs/symptoms with missing data as only overall percentage of sample reported and n's per group unclear

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	viral infection and myogenic torticollis (n=140; 69%) Age in years (mean; 95% confidence interval in parentheses): 3.5 (3.0–4.0) Sex: male: 133 (66%); female: 69 (34%)				
Walsh-Kelly 1992 Single-gate, cross-sectional DTA study US	N=172 Children undergoing lumbar puncture Bacterial meningitis (n=53): Age in months (mean; range in parentheses): 30 (3 weeks to 16 years) Aseptic meningitis (n=119): Age in months (mean; range in parentheses): 31 (1 week to 17 years)	Signs and symptoms (recorded by paediatric emergency attending physicians in the emergency department): • Bulging fontanelle • Nuchal rigidity • Kernig's sign • Brudzinski's sign • Nuchal rigidity or Kernig's sign or Brudzinski's sign • Toxic/ moribund • Lethargic/ comatose • Shock	CSF culture, CSF latex agglutination or Gram stain	• Sensitivity • Specificity	Causative organisms: H. influenzae (n=35; 66%); S. pneumoniae (n=12; 23%); N. meningitidis (n=3; 6%); Group B Streptococcus (n=2; 4%); Escherichia coli (n=1; 2%)

CNS: central nervous system; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; ED: emergency department; GCS: Glasgow coma scale; H. influenzae: Haemophilus influenzae; LP: lumbar puncture; N. Meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction; PM: purulent meningitis; PMN: polymorphonuclear; S. pneumoniae: Streptococcus pneumoniae; SD: standard deviation; WBC: white blood cell

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, with the majority rated as low or very low. Downgrading of the evidence was due to risk of bias and imprecision (95% confidence intervals crossing decision making thresholds). No meta-analyses were conducted for any of the index tests due to insufficient evidence after stratifying for age, and the comparison group. For many of the index tests the evidence came from single studies and all index tests were individual signs and symptoms (no multivariate analysis). See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

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

Signs and symptoms of bacterial meningitis in babies and children

General signs of illness and duration of illness

There was evidence that lethargy was both moderately to highly specific, and moderately to highly sensitive, for a diagnosis of bacterial meningitis in babies and children.

Duration of symptoms of less than 24 hours was both a moderately specific and moderately sensitive index test.

A toxic or ill appearance was a very specific, but not sensitive, symptom of bacterial meningitis in babies and children. Irritability was a moderately to highly specific, but not sensitive, symptom.

Fever (defined as a temperature over 39°C), visiting a physician within 48 hours, and a duration of illness of over 2 days were moderately specific, but not sensitive, index tests of bacterial meningitis in babies and children.

There was evidence that the clinical history including fever (≥38°C) and a fever at clinical presentation (threshold undefined) were very sensitive, but not specific, index tests for a diagnosis of bacterial meningitis in babies and children.

Fever, defined as a temperature between 38°C and 39°C, was a moderately sensitive, but not specific, sign of bacterial meningitis in babies and children.

Unusual, abnormal, or pale skin colour

There was some evidence that cyanosis was a very specific, but not sensitive, sign of bacterial meningitis in babies and children.

Presence, and type and size, of rash

There was evidence that the presence of any rash, and a haemorrhagic rash, were very specific, but not sensitive, index tests for bacterial meningitis in babies and children.

The evidence for petechiae was somewhat mixed, with studies with a comparator group combining those with other types of meningitis and no meningitis showing petechiae to be a very specific but not sensitive sign of bacterial meningitis in babies and children. While a study with a viral meningitis comparator group showed petechiae to be neither specific nor sensitive.

Signs or symptoms of meningism

There was inconsistent evidence for a composite factor of signs or symptoms of meningism, which could not be explained by planned subgroup analyses. One study showed signs or

symptoms of meningism to be both moderately specific and moderately sensitive, and another study showed this index test to be very sensitive but not specific for a diagnosis of bacterial meningitis in babies and children.

There was some evidence showing Brudzinski's sign to be a generally moderately to highly specific, and moderately sensitive, index test for a diagnosis of bacterial meningitis in babies and children.

There was some evidence showing Kernig's sign to be a moderately to highly specific sign of bacterial meningitis in babies and children, although the evidence for sensitivity was more mixed (ranging from non-significant to moderately sensitive, and inconsistency cannot be explained by planned subgroup analyses).

There was some evidence that Brudzinski's sign and Kernig's sign in combination, was a very specific but not sensitive index test for a diagnosis of bacterial meningitis in babies and children.

Neck stiffness was shown to be generally both moderately specific and moderately sensitive, for a diagnosis of bacterial meningitis in babies and children. Neck strain was shown to be moderately specific but not sensitive.

There was some evidence showing photophobia to be a very specific, but not sensitive, symptom of bacterial meningitis in babies and children.

Bulging fontanelle was shown to be moderately to highly specific, but not sensitive, for a diagnosis of bacterial meningitis in babies.

Neck stiffness and Brudzinski's sign in combination, was shown to be both moderately specific and moderately sensitive.

Neck stiffness and Kernig's sign in combination, was shown to be very specific and moderately sensitive for a diagnosis of bacterial meningitis in babies and children.

Presence of all 3 factors of Brudzinski's sign and Kernig's sign and neck stiffness, was a very specific but not sensitive index test for bacterial meningitis in babies and children.

Presence of at least 1 of Brudzinski's sign or Kernig's sign or neck stiffness was both moderately specific and moderately sensitive.

Evidence for headache was very mixed and inconsistency could not be explained by planned subgroup analyses, estimates for both specificity and sensitivity ranged from non-significant to a moderately useful index test.

Any symptom of CNS infection (irritability, lethargy, headache, or stiff neck) was very sensitive, but not specific, for a diagnosis of bacterial meningitis in babies and children.

Neurological deficits

The following signs were very specific but not sensitive for a diagnosis of bacterial meningitis in babies and children: focal neurological deficits; focal seizures; complex convulsions; and convulsion without fever.

Seizure, and convulsions, were moderately to highly specific, but not sensitive, signs of bacterial meningitis in babies and children.

The presence of any abnormal neurological finding was a very sensitive, and moderately specific, index test for bacterial meningitis in babies and children.

Convulsion with fever was a moderately specific, but not sensitive, sign of bacterial meningitis in babies and children.

Altered mental state

Evidence was mixed for reduced consciousness as a symptom of bacterial meningitis in babies and children, and inconsistency could not be explained by planned subgroup analyses. For specificity estimates ranged from non-significant to very specific, and for sensitivity moderately to highly sensitive.

Signs of shock

There was some evidence that shock was a very specific, but not sensitive, index test for a diagnosis of bacterial meningitis in babies and children.

Respiratory symptoms

The evidence for respiratory symptoms was mixed. One study showed respiratory symptoms to be moderately specific but not sensitive, while another study showed high specificity and moderate sensitivity, for bacterial meningitis in babies and children.

Gastrointestinal symptoms and food refusal

There was some evidence that gastrointestinal symptoms, and nausea, were both moderately specific and moderately sensitive index tests for a diagnosis of bacterial meningitis in babies and children.

The evidence for vomiting as a sign of bacterial meningitis in babies and children was mixed, and the inconsistency could not be explained by planned subgroup analyses. Estimates for both specificity and sensitivity ranged from non-significant to a moderately useful test.

Presence of nausea or vomiting was moderately to highly specific, and moderately sensitive, for a diagnosis of bacterial meningitis in babies and children.

Constipation was a very specific, but not sensitive, symptom of bacterial meningitis in babies and children.

Diarrhoea and loss of appetite were moderately specific, but not sensitive, index tests for bacterial meningitis in babies and children.

Cross-category signs and symptoms

There was some evidence that the presence of any abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations) was very specific, but not sensitive, for a diagnosis of bacterial meningitis in babies and children:

The following index tests were both moderately specific and moderately sensitive: presence of at least 1 of visit to physician within 48 hours or focal type of seizure; at least 1 of visit to physician within 48 hours or seizure at presentation.

The following index tests were very sensitive and moderately specific for a diagnosis of bacterial meningitis in babies and children: presence of at least 1 of visit to physician within 48 hours or abnormal neurologic finding; presence of at least 1 of focal seizure or abnormal neurologic findings; presence of at least 1 of visit to physician within 48 hours, seizure, focal seizure, abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations), or abnormal neurologic findings.

Presence of at least 1 of focal seizure or abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations) was a moderately specific, but not sensitive, index test for a diagnosis of bacterial meningitis in babies and children.

Signs and symptoms of bacterial meningitis in adults

General signs of illness

There was some evidence showing fever to be a very sensitive, but not specific, sign of bacterial meningitis in adults.

Signs or symptoms of meningism

The following signs and symptoms were moderately sensitive but not specific for a diagnosis of bacterial meningitis in adults: a composite factor of signs or symptoms of meningism; neck stiffness; presence of at least 1 of Brudzinski's sign, or Kernig's sign, or neck stiffness.

Presence of 1 of Brudzinski's sign or Kernig's sign, and headache, were moderately specific but not sensitive index tests for a diagnosis of bacterial meningitis in adults.

Neurological deficits

There was some evidence that focal neurological deficits, and neurological complaints, were moderately to highly specific, but not sensitive, index tests for a diagnosis of bacterial meningitis in adults.

Seizures were very specific, but not sensitive, for a diagnosis of bacterial meningitis in adults.

Altered mental state

There was some evidence showing altered mental state was a moderately to highly sensitive symptom of bacterial meningitis in adults. The specificity estimates were more mixed (and the inconsistency could not be explained by planned subgroup analyses) with estimates ranging from not specific to very specific.

Signs of shock

Shock, and severe sepsis or shock, were very specific and moderately sensitive index tests for a diagnosis of bacterial meningitis in adults.

Cross-category signs and symptoms

There was some evidence that the presence of at least 1 of altered mental status, or focal neurological deficits, or seizures, or shock, was both very specific and very sensitive for a diagnosis of bacterial meningitis in adults.

Signs and symptoms of bacterial meningitis in older children and adults

Fever was both moderately specific and moderately sensitive for a diagnosis of bacterial meningitis in older children and adults.

Focal neurological deficits, and altered mental state, were very specific but not sensitive index tests for a diagnosis of bacterial meningitis in older children and adults.

Neck stiffness was moderately sensitive but not specific, for a diagnosis of bacterial meningitis in older children and adults.

Headache was neither specific nor sensitive for a diagnosis of bacterial meningitis in older children and adults.

Signs and symptoms of bacterial meningitis in an undefined age range

Reduced general condition, and reduced consciousness, were very specific and moderately sensitive index tests for a diagnosis of bacterial meningitis in an undefined age range.

The presence of petechiae, and neck stiffness, were both moderately specific and moderately sensitive index tests of bacterial meningitis in an undefined age range.

Cyanosis, and cold extremities, were very specific but not sensitive signs of bacterial meningitis in an undefined age range.

The presence of ecchymoses, and body pain, were moderately specific but not sensitive index tests for a diagnosis of bacterial meningitis in an undefined age range.

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. This was because this review does not involve a comparison of competing courses of action.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The objective of this review was to assess the diagnostic accuracy of signs and symptoms (index tests) to determine if a person presenting in the community or to hospital has bacterial meningitis. The reference standard was a confirmed diagnosis of bacterial meningitis made based on lumbar puncture. The committee considered the impact of true positives (correctly identifying bacterial meningitis and starting the appropriate management), true negatives (being able to provide reassurance that the person does not have bacterial meningitis), false positives (potentially starting unnecessary treatments) and false negatives (failing to identify people that require further interventions and intensive management). The committee agreed that both sensitivity and specificity were important. Sensitivity was important as failing to identify bacterial meningitis could lead to treatment being delayed until the condition worsens with potentially serious implications (including death). Specificity was important, particularly when considering signs and symptoms that might lead a clinician to *strongly* suspect bacterial meningitis, as the misdiagnosis of bacterial meningitis would result in the initiation of inappropriate treatment.

The quality of the evidence

The quality of the evidence ranged from high to very low, with the majority rated as low or very low quality, and evidence was typically downgraded due to risk of bias (for example, it was unclear if inappropriate exclusions were avoided or exclusions did not reflect clinical practice, limited detail on how signs and symptoms defined and measured and index tests often not systematically quantified, and unclear interval between index tests and reference standard) and imprecision (95% confidence intervals crossing decision making thresholds). For many of the index tests the evidence came from single studies and all index tests were individual signs and symptoms (no multivariate analysis).

Evidence was found for: general signs of illness and duration of illness; unusual, abnormal, or pale skin colour; presence and type and size of rash; signs or symptoms of meningism; neurological deficits; signs of shock; body pain; respiratory symptoms; gastrointestinal symptoms and food refusal.

No meta-analyses were conducted for any of the index tests due to insufficient evidence after stratifying for age, and the comparison group.

Benefits and harms

The committee noted that all the evidence was based on individual signs and symptoms and agreed that none of these signs or symptoms alone would be sufficient to make a diagnosis of bacterial meningitis. The committee considered the evidence for sensitivity and specificity of the individual signs and symptoms in this review and drew on their clinical knowledge and experience to define combinations of signs and symptoms that might increase suspicion that a person has bacterial meningitis.

The committee emphasised that bacterial meningitis can be fatal if treatment is delayed but can be difficult to diagnose, and drew on their clinical knowledge and experience to include recommendations to help reduce the chance that bacterial meningitis will be missed, by raising awareness that bacterial meningitis: is a rapidly evolving condition; can be difficult to distinguish from other infections with similar signs and symptoms; can occur at the same time as sepsis, particularly in people with a rash; and may be harder to detect in some age groups, for example, signs or symptoms may be less common and/or less apparent in young babies and older adults, or teenagers or young adults may be less likely to appear unwell.

The committee considered evidence showing that neck stiffness was generally both moderately specific and moderately sensitive, reduced consciousness was generally at least moderately specific and moderately sensitive, and altered mental state was overall at least moderately specific and moderately sensitive, for a diagnosis of bacterial meningitis. Evidence showed that the presence of fever was largely moderately to highly sensitive (but not specific), and evidence was mixed for the diagnostic accuracy of the presence of headache. Based on the evidence, and their clinical knowledge and experience, the committee agreed that fever, headache, neck stiffness and altered level of consciousness or cognition (including confusion or delirium), should be considered as a red flag combination for strongly suspecting that a person has bacterial meningitis. However, the committee emphasised that bacterial meningitis should not be ruled out just because a person does not have one or more of the symptoms in the red flag combination, or can be strongly suspected based on clinical assessment even in people who do not have the red flag combination.

Based on their clinical knowledge and experience the committee highlighted that the signs or symptoms included in the red flag combination may be less common and/or harder to detect in certain ages and included notes in the tables (of symptoms and signs) to raise awareness of the different ways in which bacterial meningitis can present. Drawing on their experience and expertise, the committee discussed that: babies and young children, or those with cognitive impairment or communication difficulties may not be able to report headache; neck stiffness is less common and harder to detect in babies and older adults, neck stiffness may present as more subtle discomfort or reluctance to move the neck, and neck stiffness is harder to identify in people with cognitive impairment, communication difficulties, dementia or arthritis; fever is less common as a sign in babies and older adults, receipt of antipyretic treatment should be checked as it may make fever harder to identify, and for young children other possible causes of fever should be considered in line with relevant NICE guidance (Fever in under 5s: assessment and initial management); and bacterial meningitis may be missed in older adults with delirium or altered consciousness, and in young people and young adults where altered level of consciousness may be assumed to be caused by alcohol or substance misuse.

As discussed above, the committee noted that while people with bacterial meningitis may present in the community or to hospital with the red flag combination (fever, headache, neck stiffness and altered level of consciousness or cognition), bacterial meningitis can present in different ways particularly in babies and older adults or if people are presenting early in the condition. Based on the evidence reviewed and their clinical knowledge and experience, the committee included signs and symptoms that may be associated with bacterial meningitis in tables for babies and children, and for adults. The committee agreed based on expert consensus opinion that bacterial meningitis can present with any of the signs and symptoms

included in the tables, and outside of the red flag combination the evidence was not clear enough to rank other signs or symptoms in order of importance. However, the more symptoms and signs a person has, the more likely it is that they have bacterial meningitis.

The committee took into account the rapidly evolving nature of bacterial meningitis, and that people can present with subtle signs or symptoms that might be missed if not considered in the context of the patient's usual state. Based on their clinical knowledge and experience the committee agreed that the assessment of signs and symptoms (and risk factors) should include family member and carer reports of symptoms. For people with reduced consciousness or communication difficulties it was considered particularly important that family members or carers are asked about recent or rapid changes in symptoms.

There was some evidence that a bulging fontanelle was a moderately to highly specific (but not sensitive) sign of bacterial meningitis in babies and this was included in the table as a sign that might increase the index of suspicion for bacterial meningitis in babies and young children where the fontanelle is still open.

The committee considered the evidence showing that a toxic or ill appearance was a very specific (but not sensitive) symptom of bacterial meningitis in babies and children, and reduced general condition was a very specific and moderately sensitive symptom in an undefined age range, and agreed to include ill appearance as a symptom that might support a diagnosis of bacterial meningitis.

There was some evidence that the presence of any rash, and a haemorrhagic rash, were very specific (but not sensitive) index tests for a diagnosis of bacterial meningitis in babies and children, and a petechial rash was both moderately specific and moderately sensitive for a diagnosis of bacterial meningitis in an undefined age range. The committee emphasised that a non-blanching rash is mainly associated with meningococcal disease with or without meningococcal meningitis, and this was consistent with the evidence reviewed. The committee noted that rashes may be difficult to see on brown, black or tanned skin, and included this in the notes section of the table to increase awareness for the healthcare professional who is undertaking the physical examination. The committee noted that healthcare professionals may need to check the conjunctivae (the membranes lining the inside of the eyelids and covering the eyeballs) when checking for petechiae in people with darker skin.

There was some evidence from babies and children and from an undefined age range that cyanosis was a very specific (but not sensitive) sign of bacterial meningitis. The committee agreed that these findings were consistent with their clinical experience that pale or unusual skin colour (including cyanosis) can be associated with bacterial meningitis and they agreed to include this sign in the tables but to maintain consistent terminology with the NICE Fever in under 5s guideline (pale, mottled skin or cyanosis). It is again flagged in the notes section of the table that skin changes may be difficult to see on brown, black or tanned skin.

There was some evidence that irritability was a moderately to highly specific (but not sensitive) symptom of bacterial meningitis in babies and children. The committee agreed that although irritability may be more common as a symptom associated with bacterial meningitis in babies and young children, the evidence could be extrapolated to older age groups. Drawing on their clinical knowledge and experience the committee agreed that unusual behaviour more broadly, particularly being agitated, aggressive or subdued, can be associated with bacterial meningitis at any age. The committee discussed that changes to behaviour can be subtle, particularly to people that are not familiar with the patient's usual state and added to the notes section of the table that family members or carers should be asked about changes in the person's behaviour. The committee highlighted that bacterial meningitis can be missed because delirium may be assumed to be due to cognitive impairment in older adults, whereas altered behaviour may be attributed to alcohol or substance misuse (rather than bacterial meningitis) in young people and young adults.

Based on expert clinical consensus the committee also agreed to include weak, high-pitched or continuous crying as a sign that might be associated with bacterial meningitis in babies.

The evidence showed that lethargy was at least moderately specific and moderately sensitive for a diagnosis of bacterial meningitis in babies and children. Based on their clinical knowledge and experience the committee agreed that lethargy can be associated with bacterial meningitis at any age, but they highlighted that lethargy is often one of the symptoms that babies, young children and older adults can present with and included this in the table.

There was some evidence showing that loss of appetite was a moderately specific (but not sensitive) index test in babies and children and given that bacterial meningitis can be harder to detect and present differently in babies, reduced feeding was included as a symptom that might be associated with bacterial meningitis in this age group.

There was some evidence that shock was a very specific, but not sensitive, index test for a diagnosis of bacterial meningitis in babies and children. Shock, and severe sepsis or shock, were also very specific (and moderately sensitive) index tests for a diagnosis of bacterial meningitis in adults. There was also some evidence from an undefined age range that cold extremities were a very specific (but not sensitive) sign of bacterial meningitis. Based on this evidence and their clinical knowledge and experience the committee included early signs of sepsis and signs of shock, as signs that might support a diagnosis of bacterial meningitis in babies, children, and adults.

Evidence showed that focal neurological deficits were at least moderately specific (but not sensitive) signs of bacterial meningitis in babies and children, adults, and a combined older children and adult population, and the committee agreed to include focal neurological deficits in the tables.

The committee considered evidence showing photophobia to be a very specific, but not sensitive, symptom of bacterial meningitis in babies and children. Based on their clinical knowledge and experience, the committee agreed that photophobia can also be associated with bacterial meningitis in older age groups. The committee included photophobia as a symptom that might support the diagnosis of bacterial meningitis in babies, children, and adults, but highlighted that this can be harder to identify in babies.

There was some evidence that focal seizures and seizures were at least moderately specific (but not sensitive) signs of bacterial meningitis in babies and children. Seizures were also shown to be a very specific (but not sensitive) index test in adults. Based on this evidence, and their clinical knowledge and experience, the committee agreed to include seizures as a sign that might support a diagnosis of bacterial meningitis for all age groups.

Respiratory symptoms were shown to be at least moderately specific (with more mixed sensitivity estimates) for a diagnosis of bacterial meningitis in babies and children. There was no evidence for respiratory symptoms in older age groups and based on their clinical knowledge and experience the committee agreed that this was not a common symptom for adults and should not be included in the table for that age group. Based on clinical expert consensus the committee agreed to include tachypnoea (raised respiratory rate), apnoea (slowed or stopped breathing), and grunting as respiratory symptoms that may support the diagnosis of bacterial meningitis in babies and children.

There was some evidence showing body pain was a moderately specific (but not sensitive) index test for a diagnosis of bacterial meningitis in an undefined age range. Based on clinical expert consensus the committee agreed to include limb, back and abdominal pain as examples of unexplained body pain that may support the diagnosis of bacterial meningitis in any age group.

The evidence for vomiting as a sign of bacterial meningitis in babies and children was mixed with estimates ranging from non-significant to a moderately useful test for both specificity and

sensitivity. There was no evidence for vomiting in adults. The committee agreed that vomiting was not reliably associated with a diagnosis of bacterial meningitis. However, given the variability in the symptoms that people present with, the committee included vomiting as a symptom that might support a diagnosis of bacterial meningitis for any age group but considered the position towards the bottom of the tables as appropriate based on the evidence and their expert clinical opinion.

The committee considered the evidence showing that Brudzinski's sign was at least moderately specific and moderately sensitive, and Kernig's sign was moderately to highly specific (with more mixed sensitivity) for a diagnosis of bacterial meningitis in babies and children, and presence of 1 of Brudzinski's sign or Kernig's sign was a moderately specific (but not sensitive) index test in adults. However, the committee discussed that Kernig's and Brudzinski's signs are very difficult to elicit, and in current clinical practice subtler presentations of bacterial meningitis are more common. The committee emphasised that these signs were introduced at a time when people presented after a few days and antibiotics did not exist. The committee agreed not to include Kernig's or Brudzinski's signs in the recommendations given how hard they are to elicit (particularly in babies), and that their inclusion would take the focus away from other signs and symptoms that are more likely to be helpful.

Given the potentially serious implications of a delay to treatment (including death), the committee agreed based on expert clinical consensus that people with suspected bacterial meningitis should be transferred to hospital as an emergency, and the hospital should be alerted and informed that an assessment by a senior clinical decision maker will be required.

The committee agreed that it was also important to provide safety netting for people returning home after a clinical assessment for bacterial meningitis. Based on their clinical knowledge and experience and considering the rapidly evolving nature of bacterial meningitis, the committee agreed that safety netting advice should be given, and people should be asked to return for further assessment if new symptoms develop, if a rash changes from blanching to non-blanching or if existing symptoms or signs get worse. The committee also wanted to raise awareness that although a person might not have bacterial meningitis, they may have another serious condition. The committee specifically wanted to highlight sepsis (other than meningococcal disease), non-bacterial causes of meningitis and pneumonia, but also intracranial bleed or ischaemia that is often overlooked, as potential alternative diagnoses.

Cost effectiveness and resource use

This review question did not consider decisions between competing alternatives and therefore is not directly relevant to the tools of economic evaluation. The recommendations primarily provide advice to health care professionals on the recognition and diagnosis of bacterial meningitis rather than specific courses of action. However, the committee considered that early and correct identification of bacterial meningitis was a prerequisite of cost-effective management. They also reflected that the recommendations largely reinforce current best practice and knowledge and therefore they did not believe they would have a significant resource impact.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 to 1.1.7, 1.1.16, 1.1.17, 1.2.1 and 1.2.2. Other evidence supporting these recommendations can be found in the evidence review on symptoms and signs associated with meningococcal disease [A3].

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Economic

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

Appendices

Appendix A Review protocols

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021245975
Review title	Symptoms and signs associated with bacterial meningitis
Review question	What symptoms and signs, individually or in combination, are associated with bacterial meningitis?
Objective	To determine the signs and symptoms (individually or in combination) that are associated bacterial meningitis
Searches	The following databases will be searched: Embase MEDLINE Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Searches will be restricted by: Date limitations: No date limit English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis Exclusion:

Field	Content
	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 Note. The meningitis exclusion criteria applies to those that are identified as having condition of interest (bacterial meningitis), but may be included in the population that were not identified as having bacterial meningitis.
Risk markers	Any signs and symptoms, alone or in combination
Comparator/Reference standard/Confounding factors for prognostic estimates	1. Binary accuracy data: N/A 2. Association data (if insufficient accuracy data): Absence of sign(s)/symptom(s)
Types of study to be included	1. Binary accuracy data • Systematic reviews of cross-sectional diagnostic accuracy studies. • Individual cross-sectional diagnostic accuracy studies. Studies with prospective and retrospective data collection will be included. Two-gate studies will only be included if there are insufficient single-gate studies for a given sign, symptom or combination) Conference abstracts will not be considered. 2. Association data (if insufficient accuracy data for a given sign, symptom or combination) • Systematic reviews • Prospective cohort studies with multivariate analyses

Field	Content
	• If insufficient prospective cohort studies: retrospective cohort studies with multivariate analyses Studies with univariate analyses will only be included if there are insufficient studies with multivariate analyses for a given sign, symptom or combination. Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: age (if not possible to stratify) Conference abstracts will not be considered.
Other exclusion criteria	Countries other than OECD high income countries Studies published not in English-language
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	1. Binary accuracy data • Sensitivity for diagnosis of bacterial meningitis* • Specificity for diagnosis of bacterial meningitis* 2. Association data (if insufficient accuracy data) • Risk ratios for diagnosis of bacterial meningitis* • Odds ratios for diagnosis of bacterial meningitis* * Diagnosis of bacterial meningitis must be made based on lumbar puncture
Secondary outcomes (important outcomes)	N/A
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

Field	Content
	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 signs and symptoms, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklist: • ROBIS tool for systematic reviews • QUADAS-2 tool for diagnostic test accuracy studies Quality in Prognostic Studies (QUIPS) tool for prognostic studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	**Binary accuracy data** 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 and specificity 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. **Association data** Quantitative findings will be formally summarised in the review. Where multiple studies report on the same factors and the definitions used and approach to analysis in the primary papers is sufficiently consistent, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies). Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using

Field	Content
	an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/" **Minimally important differences:** **Decision making thresholds (for binary accuracy data)** • Sensitivity: ○ Very useful test: ≥90% ○ Moderately useful test: ≥50% ○ Not a useful test <50% • Specificity: ○ Very useful test: ≥90% ○ Moderately useful test: ≥50% ○ Not a useful test <50% **Minimally important differences (for association data)** ○ Strong association: <0.5 and >2.00 ○ Moderate association: <0.80 and >1.25 ○ Small association: any statistically significant association ○ No association: no statistically significant association
Analysis of sub-groups	**Evidence will be stratified by:** **Stratifications:** • Population that do not receive a diagnosis of bacterial meningitis: ○ Viral, tuberculous or fungal meningitis ○ Absence of meningitis • Person identifying signs/symptoms: ○ Healthcare professionals ○ Non-healthcare professionals • Age: ○ Younger Infants: >28 days to ≤3 months of age

Field	Content	
	○ Older infants: >3 months to <1 year of age ○ Children: ≥1 year 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. Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age: ○ Young and middle aged adults ○ Older adults* • Population that do receive a diagnosis of meningococcal disease: ○ Non-specific meningococcal disease ○ Meningococcal disease excluding meningitis alone *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☐	Intervention
	☒	Diagnostic
	☒	Prognostic

Field	Content			
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	11/03/2021			
Anticipated completion date	07/12/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal @nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance			
Review team members	National Guideline Alliance			
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.			

Field	Content	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=245975	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE	
Keywords	Prognostic, diagnostic, bacterial meningitis, signs and symptoms, risk factors, systematic review	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued

Field	Content
Additional information	None
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PRESS: Peer Review of Electronic Search Strategies; QUADAS: quality assessment of diagnostic accuracy studies; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

Clinical Search

This was a combined search to cover both this review (A1) and also evidence reviews on signs and symptoms and risk factors associated with meningococcal disease (A3 and A4); and risk factors associated with bacterial meningitis (A2).

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 = Ovid 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/
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/
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	Meningococcal Infections/ or exp Neisseria meningitidis/
10	9 use medall
11	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
12	11 use emczd
13	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
14	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
15	(Neisseria* mening* or n mening*).ti,ab.
16	or/2,4-8,10,12-15
17	"Signs and Symptoms"/ or Fever/ or Vomiting/ or Nausea/ or Diarrhea/ or Chills/ or Shivering/ or Sleepiness/ or Headache/ or Photophobia/ or Intracranial Pressure/ or exp Consciousness Disorders/ or *Coma/ or Seizures/ or Seizures, Febrile/ or Irritable Mood/ or Crying/ or Decerebrate State/ or Lethargy/ or Fatigue/ or Confusion/ or Malnutrition/ or exp Purpura/ or Muscle Hypotonia/ or exp Tachycardia/
18	17 use medall
19	*physical disease by body function/ or *fever/ or *vomiting/ or *nausea/ or *diarrhea/ or *chill/ or *shivering/ or *somnolence/ or *headache/ or *photophobia/ or *intracranial pressure/ or exp *consciousness disorder/ or *coma/ or *seizure/ or *febrile convulsion/ or *irritability/ or *crying/ or *decerebration/ or *lethargy/ or *fatigue/ or *confusion/ or *malnutrition/ or exp *purpura/ or *muscle hypotonia/ or exp *tachycardia/
20	19 use emczd
21	((head or cranial or intracranial) adj3 pain*).ti,ab.
22	((stiff* or rigid*) adj3 (neck* or nuchal or cervical or spine or spinal)).ti,ab.
23	(light adj3 (intoleran* or sensitiv*)).ti,ab.
24	((tense or bulge or bulging or full*) adj3 fontanelle?).ti,ab.
25	((raise? or rise or high or elevat*) adj3 intracranial pressure?).ti,ab.
26	((level? or decreas*) adj3 consciousness).ti,ab.
27	(irritab* or petulan* or bad mood or moody).ti,ab.
28	((symphyseal or cheek) adj3 sign?).ti,ab.
29	(abnormal adj3 postur*).ti,ab.
30	(muscle? adj3 (atonic or flaccid*)).ti,ab.
31	((decreas* or alter* or chang*) adj3 (conscious* or mental state?)).ti,ab.
32	((hemorrhagic or haemorrhagic) adj3 rash).ti,ab.
33	(capillar* adj2 refill*).ti,ab.
34	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.
35	((limb? or extremities or arms or legs) adj3 pain*).ti,ab.
36	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.
37	((elevated or rapid* or fast*) adj3 (heart?beat or heart rate)).ti,ab.

#	Searches
38	(sign? or symptom* or complain*).ti,ab.
39	(clinical adj3 (manifestation* or feature* or finding* or aspect*)).ti,ab.
40	(present* adj3 (feature* or finding* or factor*)).ti,ab. or presentation*.ti.
41	(physical* adj3 (manifest* or characteristic* or featur* or finding*)).ti,ab.
42	or/18,20-41
43	exp "SENSITIVITY AND SPECIFICITY"/ or Likelihood Functions/ or Diagnostic Test Routine/ or Differential Diagnosis/
44	43 use medall
45	"sensitivity and specificity"/ or statistical model/ or differential diagnosis/ or *diagnostic accuracy/ or diagnostic test accuracy study/
46	45 use emczd
47	Prognosis/
48	(sensitivity or specificity).ti,ab.
49	((pre test or pretest or post test or posttest) adj probability).ti,ab.
50	((predict* adj3 (value* or factor*)) or (PPV or NPV)).ti,ab.
51	likelihood ratio*.ti,ab.
52	(ROC curve* or AUC).ti,ab.
53	diagnos*.ti.
54	((diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)) or (accurat* adj5 diagnos*)).ti,ab.
55	gold standard.ab.
56	di.fs.
57	or/44,46-56
58	Obstetric Labor, Premature/ or Premature Birth/ or Infant, Premature/ or Fetal Membranes, Premature Rupture/ or Ear, Inner/ or exp Smoking/ or Tobacco Smoke Pollution/ or Cochlear Implants/ or Spleen/ or Splenectomy/ or *Socioeconomic Factors/ or Environment/ or Crowding/ or exp Otitis Media/ or exp Sinusitis/ or exp Pneumonia/ or Mastoiditis/ or Cochlear Implantation/ or Streptococcal Infections/
59	58 use medall
60	*premature labor/ or *prematurity/ or *premature fetus membrane rupture/ or *inner ear/ or exp *smoking/ or *passive smoking/ or *cochlea prosthesis/ or *spleen/ or *splenectomy/ or *socioeconomics/ or *environment/ or "crowding (area)"/ or exp *otitis media/ or exp *sinusitis/ or exp *pneumonia/ or *mastoiditis/ or *cochlear implantation/ or *streptococcus infection/
61	60 use emczd
62	((preterm* or pre-term* or premature*) adj10 (birth* or born* or deliver* or labour* or labor* or infant* or newborn* or new-born* or neonate* or neo-nate* or baby or babies or child or children)).ti,ab.
63	((premature* or prolong*) adj2 rupture*).ti,ab.
64	(inner adj ear).ti,ab.
65	smok*.ti,ab.
66	(cochlea* adj2 implant*).ti,ab.
67	((spleen* or splen*) adj3 (impair* or dysfunc* or absen* or non-function* or nonfunction*)).ti,ab.
68	splenectom*.ti,ab.
69	asplenia.ti,ab.
70	((crowd* or over-crowd* or overcrowd*) adj3 (environment* or place* or premise* or house* or household* or venue* or condition* or living or setting* or transport* or sleep* or room*)).ti,ab.
71	((partial or incomplet*) adj2 immuni*).ti,ab.
72	((vaccin* or immuni*) adj coverage*).ti,ab.
73	(contiguous* adj (spread or foci)).ti,ab.
74	(contiguous adj3 infection*).ti,ab.
75	(otitis media* or sinusitis* or pneumonia* or mastoiditis*).ti,ab.
76	(streptococc* adj (infect* or diseas*)).ti,ab.
77	or/59,61-76
78	Risk/ or Risk Factors/
79	78 use medall
80	*risk/ or *risk factor/
81	80 use emczd
82	risk?.ti.
83	risk factor?.ab.
84	or/79,81-83
85	16 and 77 and 84
86	16 and 42 and 57
87	16 and 42 and 84
88	*"Signs and Symptoms"/ use medall
89	*physical disease by body function/ use emczd
90	(signs adj2 symptom*).ti,ab.
91	or/88-90
92	16 and 91
93	85 or 86 or 87 or 92
94	limit 93 to English language [General Exclusions filter applied]

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: [Signs and Symptoms] this term only
#18	MeSH descriptor: [Fever] this term only
#19	MeSH descriptor: [Vomiting] this term only
#20	MeSH descriptor: [Nausea] this term only
#21	MeSH descriptor: [Diarrhea] this term only
#22	MeSH descriptor: [Chills] this term only
#23	MeSH descriptor: [Shivering] this term only
#24	MeSH descriptor: [Sleepiness] this term only
#25	MeSH descriptor: [Headache] this term only
#26	MeSH descriptor: [Photophobia] this term only
#27	MeSH descriptor: [Intracranial Pressure] this term only
#28	MeSH descriptor: [Consciousness Disorders] explode all trees
#29	MeSH descriptor: [Coma] this term only
#30	MeSH descriptor: [Seizures] this term only
#31	MeSH descriptor: [Seizures, Febrile] this term only
#32	MeSH descriptor: [Irritable Mood] this term only
#33	MeSH descriptor: [Crying] this term only
#34	MeSH descriptor: [Decerebrate State] this term only
#35	MeSH descriptor: [Lethargy] this term only
#36	MeSH descriptor: [Fatigue] this term only
#37	MeSH descriptor: [Confusion] this term only
#38	MeSH descriptor: [Malnutrition] this term only
#39	MeSH descriptor: [Purpura] explode all trees
#40	MeSH descriptor: [Muscle Hypotonia] this term only
#41	MeSH descriptor: [Tachycardia] explode all trees
#42	((head or cranial or intracranial) near/3 pain*):ti,ab,kw
#43	((stiff* or rigid*) near/3 (neck* or nuchal or cervical or spine or spinal)):ti,ab,kw
#44	(light near/3 (intoleran* or sensitiv*)):ti,ab,kw
#45	((tense or bulge or bulging or full*) near/3 fontanelle*):ti,ab,kw
#46	((raise* or rise or high or elevat*) near/3 intracranial pressure*):ti,ab,kw
#47	((level* or decreas*) near/3 consciousness):ti,ab,kw
#48	(irritab* or petulan* or "bad mood" or moody):ti,ab,kw
#49	((symphyseal or cheek) near/3 sign*):ti,ab,kw
#50	(abnormal near/3 postur*):ti,ab,kw
#51	(muscle* near/3 (atonic or flaccid*)):ti,ab,kw
#52	((decreas* or alter* or chang*) near/3 (conscious* or "mental state" or "mental states")):ti,ab,kw
#53	((hemorrhagic or haemorrhagic) near/3 rash):ti,ab,kw
#54	(capillar* near/2 refill*):ti,ab,kw
#55	((cold or clammy or temperature) near/3 (hand* or feet or extremities)):ti,ab,kw
#56	((limb* or extremities or arms or legs) near/3 pain*):ti,ab,kw
#57	((mottled or mottling) near/3 (skin or epidermal)):ti,ab,kw
#58	((elevated or rapid* or fast*) near/3 (heartbeat or "heart beat" or "heart rate")):ti,ab,kw
#59	(sign? or symptom* or complain*):ti,ab,kw
#60	(clinical near/3 (manifest* or featur* or finding* or aspect*)):ti,ab,kw
#61	(present* near/3 (feature* or finding* or factor*)):ti,ab,kw or presentation*:ti
#62	(physical* near/3 (manifest* or characteristic* or featur* or finding*)):ti,ab,kw
#63	{or #17-#62}
#64	MeSH descriptor: [Sensitivity and Specificity] explode all trees
#65	MeSH descriptor: [Likelihood Functions] this term only

#	Searches
#66	MeSH descriptor: [Diagnostic Tests, Routine] this term only
#67	MeSH descriptor: [Diagnosis, Differential] this term only
#68	MeSH descriptor: [Prognosis] this term only
#69	((sensitivity or specificity)):ti,ab,kw
#70	((("pre test" or pretest or "post test" or posttest) next probability)):ti,ab,kw
#71	(((predict* near/3 (value* or factor*)) or (PPV or NPV))):ti,ab,kw
#72	("likelihood ratio*"):ti,ab,kw
#73	(("ROC curve*" or AUC)):ti,ab,kw
#74	diagnos*:ti
#75	(((diagnos* near/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)) or (accurat* near/5 diagnos*))):ti,ab,kw
#76	"gold standard":ab
#77	MeSH descriptor: [] explode all trees and with qualifier(s): [diagnosis - DI]
#78	{or #64-#77}
#79	MeSH descriptor: [Obstetric Labor, Premature] this term only
#80	MeSH descriptor: [Premature Birth] this term only
#81	MeSH descriptor: [Infant, Premature] this term only
#82	MeSH descriptor: [Fetal Membranes, Premature Rupture] this term only
#83	MeSH descriptor: [Ear, Inner] this term only
#84	MeSH descriptor: [Smoking] explode all trees
#85	MeSH descriptor: [Tobacco Smoke Pollution] this term only
#86	MeSH descriptor: [Cochlear Implants] this term only
#87	MeSH descriptor: [Spleen] this term only
#88	MeSH descriptor: [Splenectomy] this term only
#89	MeSH descriptor: [Socioeconomic Factors] this term only
#90	MeSH descriptor: [Environment] this term only
#91	MeSH descriptor: [Crowding] this term only
#92	MeSH descriptor: [Otitis Media] this term only
#93	MeSH descriptor: [Sinusitis] this term only
#94	MeSH descriptor: [Pneumonia] explode all trees
#95	MeSH descriptor: [Mastoiditis] this term only
#96	MeSH descriptor: [Cochlear Implantation] this term only
#97	MeSH descriptor: [Cochlear Implantation] this term only
#98	(((preterm* or "pre term*" or prematur*) near/10 (birth* or born* or deliver* or labour* or labor* or infant* or newborn* or "new born*" or neonate* or "neo nate*" or baby or babies or child or children))):ti,ab,kw
#99	(((premature* or prolong*) near/2 rupture*)):ti,ab,kw
#100	((inner next ear)):ti,ab,kw
#101	smok*:ti,ab,kw
#102	((cochlea* near/2 implant*)):ti,ab,kw
#103	(((spleen* or splen*) near/3 (impair* or dysfunc* or absen* or "non function*" or nonfunction*))):ti,ab,kw
#104	(splenectom*):ti,ab,kw
#105	(asplenia):ti,ab,kw
#106	(((crowd* or "over crowd*" or overcrowd*) near/3 (environment* or place* or premise* or house* or household* or venue* or condition* or living or setting* or transport* or sleep* or room*))):ti,ab,kw
#107	(((partial or incomplet*) near/2 immuni*)):ti,ab,kw
#108	(((vaccin* or immuni*) next coverage*)):ti,ab,kw
#109	((contiguous* next (spread or foci))):ti,ab,kw
#110	((contiguous near/3 infection*)):ti,ab,kw
#111	(("otitis media*" or sinusitis* or pneumonia* or mastoiditis*)):ti,ab,kw
#112	((streptococc* next (infect* or diseas*))):ti,ab,kw
#113	{or #79-#112}
#114	MeSH descriptor: [Risk] this term only
#115	MeSH descriptor: [Risk Factors] this term only
#116	risk*:ti
#117	"risk factor*":ab
#118	{or #114-#117}
#119	#16 and #63
#120	#16 and #113
#121	MeSH descriptor: [Signs and Symptoms] this term only
#122	((signs near/2 symptom*)):ti,ab,kw
#123	#121 or #122
#124	#16 and #123
#125	#119 or #120 or #124
#126	"conference":pt or (clinicaltrials or trialsearch):so
#127	#125 not #126

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.
15	(meningococcus* or meningococci* or meningococ?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

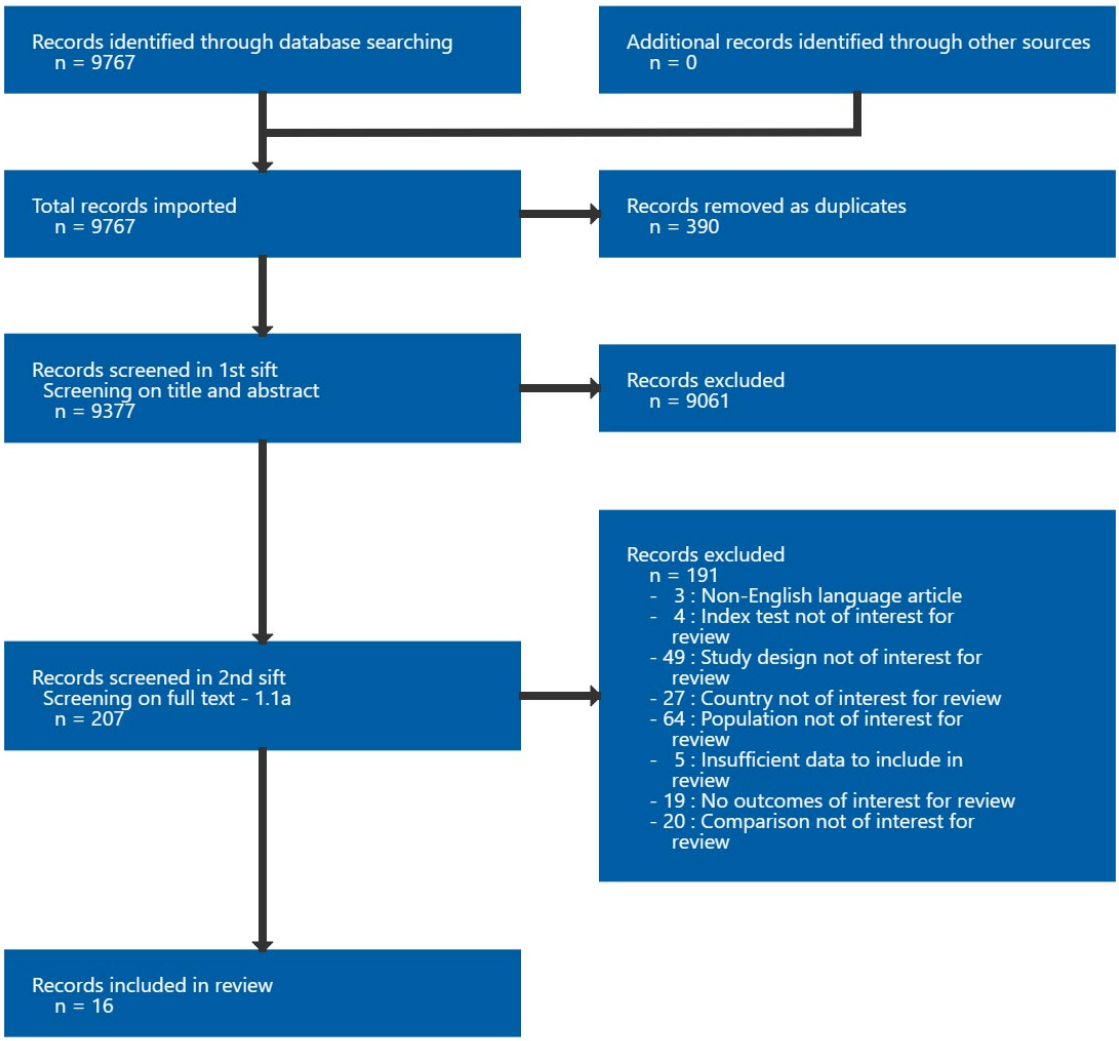
#	Searches
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
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/
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/

#	Searches
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 symptoms and signs, individually or in combination, are associated with bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

Table 4: Evidence tables

Behrman, 1989

Bibliographic Reference	Behrman, R. E; Meyers, B. R; Mendelson, M. H; Sacks, H. S; Hirschman, S. Z.; Central nervous system infections in the elderly; Archives of internal medicine; 1989; vol. 149 (no. 7); 1596-1599

Study details

Country/ies where study was carried out	US
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	1970 to 1985
Inclusion criteria	Older adults (≥65 years) with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess
Exclusion criteria	Not reported
Patient characteristics	N=50 Bacterial meningitis, including partially treated bacterial meningitis (n=30) Causative organisms: Gram-positive (21/28; 75%): S. pneumoniae (12/28; 43%); Other streptococci, including Streptococcus bovis, Streptococcus viridans, Streptococcus faecalis, and S pyogenes (4/28; 14%); Listeria monocytogenes (2/28; 7%); Staphylococci (2/28; 7%); Propionlbacterium acnes (1/28; 4%). Gram-negative (7/28; 25%): Klebsiella species (2/28; 7%); Others, including Haemophilus influenzae, Enterobacter cloacae, Serratia species, Pseudomonas aeruginosa,

	and an undefined gram-negative rod (5/28; 18%). Other types of meningitis (n=20): Aseptic (n=3); tuberculous (n=3); suspected tuberculous (n=3); fungal (n=2); viral (n=1); unknown (n=8) 50 episodes of meningitis occurred in 48 patients: Age in years (mean; range in parentheses): 72 (65-89) Sex: male: 22 (46%); female: 26 (54%)
Index test(s)	Signs and symptoms (taken from medical records): (a) Fever (defined as a rectal temperature of at least 37°C documented on the patient's medical record or the patient's history of fever at home) (b) Meningismus (c) Headache (d) Change in mental status (e) Motor or cranial nerve deficits
Reference standard(s)	Positive CSF culture or CSF examination revealing hypoglycorrachia and/or CSF pleocytosis associated with a positive Gram's stain, a positive blood culture, or a positive counterimmunoelectrophoresis assay for Streptococcus pneumoniae, Neisseria meningitidis, or Haemophilus influenzae. Partially treated bacterial meningitis defined as results of CSF investigation showing pleocytosis, and evidence of bacterial otitis media or pneumonia in patients who received antibacterial therapy prior to lumbar puncture
Duration of follow-up	Not reported
Sources of funding	Not reported

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; N. Meningitidis: Neisseria Meningitidis; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 50**
Fever Custom value	TP 30; FP 16; FN 0; TN 4
Meningismus Custom value	TP 17; FP 11; FN 13; TN 9
Headache Custom value	TP 8; FP 10; FN 22; TN 10
Change in mental status Custom value	TP 28; FP 15; FN 2; TN 5
Motor or cranial nerve deficits Custom value	TP 13; FP 7; FN 17; TN 13

Critical appraisal - QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Records of all eligible patients admitted during study period reviewed, but unclear if the study avoided inappropriate exclusions (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?	High *(No information about whether index tests were interpreted without knowledge of the reference standard, index tests poorly defined, and retrospective study over 15*

Section	Question	Answer
		years with various investigators assessing signs and symptoms without clear definitions)
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?	High *(Reference standard CSF culture, other CSF findings or blood culture. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard)*

Bilavsky, 2013

Bibliographic Reference	Bilavsky, E; Leibovitz, E; Elkon-Tamir, E; Fruchtman, Y; Ifergan, G; Greenberg, D.; The diagnostic accuracy of the 'classic meningeal signs' in children with suspected bacterial meningitis; European Journal of Emergency Medicine; 2013; vol. 20 (no. 5); 361-363

Study details

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

	Babies and children with a confirmed diagnosis of bacterial meningitis compared with matched controls without a diagnosis of bacterial meningitis.
Study dates	January 2001 to December 2004
Inclusion criteria	Babies and children aged 3 months to 17 years diagnosed with bacterial meningitis. The control group included children who underwent lumbar puncture with a suspicion of meningitis, but were eventually diagnosed with diseases other than bacterial or aseptic meningitis.
Exclusion criteria	Antibiotic treatment before arrival to the emergency department
Patient characteristics	N=86 Bacterial meningitis (n=40) Age (in months): Median 27 (range 5-180); aged <12 months (n=7; 17%) Sex: male 19 (47.5%); female: 21 (52.5%) Causative species: S. pneumoniae (N=23; 57.5%), and N. Meningitidis (N=17; 42.5%). No meningitis (n=46) Age (in months): Median 24 (range 7-204); aged <12 months (N=10; 20.7%) Sex: male 29 (63%); female: 17 (37%)
Index test(s)	Signs and symptoms in clinical history: (a) Clinical history included fever (≥38°C) (b) Clinical history included nausea/vomiting (c) Clinical history included headache

	(d) Clinical history included convulsions Signs and symptoms at presentation identified by healthcare professional: (a) Fever (between 38°C and 39°C) (b) Fever (≥ 39.1°C) (c) Nuchal rigidity (d) Brudzinski's sign (e) Kernig's sign (f) Presence of 2 factors (Kernig's sign and nuchal rigidity) (g) Presence of 2 factors (Kernig's sign and Brudzinski's sign) (h) Presence of 2 factors (nuchal rigidity and Brudzinski's sign) (i) Presence of 3 factors (Kernig's sign, nuchal rigidity, and Brudzinski's sign)
Reference standard(s)	Presence of a positive bacterial CSF culture
Duration of follow-up	Not reported
Sources of funding	Not reported (no conflicts of interest reported)

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; N. Meningitidis: Neisseria Meningitidis; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 86**
Clinical history included fever (≥38°C) Custom value	TP 39; FN 1; FP 38; TN 8
Clinical history included nausea/vomiting Custom value	TP 28; FN 12; FP 4; TN 42
Clinical history included headache Custom value	TP 10; FN 30; FP 12; TN 34
Clinical history included convulsions Custom value	TP 12; FN 28; FP 6; TN 40
Fever (between 38°C and 39°C) Custom value	TP 25; FN 15; FP 28; TN 18
Fever (≥ 39.1°C) Custom value	TP 4; FN 36; FP 10; TN 36
Nuchal rigidity Custom value	TP 26; FN 14; FP 21; TN 25
Brudzinski's sign Custom value	TP 21; FN 19; FP 10; TN 36
Kernig's sign Custom value	TP 21; FN 19; FP 2; TN 44

Outcome	N = 86
Presence of 2 factors (Kernig's sign and nuchal rigidity) Custom value	TP 21; FN 19; FP 2; TN 44
Presence of 2 factors (Kernig's sign and Brudzinski's sign) Custom value	TP 18; FN 22; FP 2; TN 44
Presence of 2 factors (nuchal rigidity and Brudzinski's sign) Custom value	TP 20; FN 20; FP 10; TN 36
Presence of 3 factors (Kernig's sign, nuchal rigidity, and Brudzinski's sign) Custom value	TP 18; FN 22; FP 2; TN 44

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 comparing patients with confirmed bacterial meningitis to matched controls without a diagnosis of bacterial meningitis, and excluded children treated with antibiotics prior to hospital admission)*
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 *(Signs and symptoms were identified at referral to hospital, before lumbar puncture carried out. However, limited detail provided on how signs and symptoms were defined and measured.)*
Index tests:	Are there concerns that the index test, its	Low

Section	Question	Answer
applicability	conduct, or 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 *(Interval between index test and reference standard is not clear)*

Borchsenius, 1991

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

Study details

Country/ies where study was carried out	Norway
Study type	Single-gate, cross-sectional DTA study (a very small number of patients [5% of full sample that included those with meningococcal disease] included retrospectively)
Study dates	December 1981 to April 1982
Inclusion criteria	Patients with suspected systemic meningococcal disease admitted to hospital (those with meningitis only are included in this review, and those with septicemia or meningitis and septicemia are included in the review on signs and symptoms of

	meningococcal disease). The control group (n=61) included those where meningococcal disease could be ruled out (with n=2 who were difficult to categorize included in the control group as meningitis of unknown microbiological etiology). For this review, the control participants (n=25) with bacterial meningitis or septicemia (excluding those due to N. meningitidis) and other bacterial infections were not included.
Exclusion criteria	Not reported
Patient characteristics	N=92 Meningococcal meningitis (n=56): Age: Reported for whole sample only (including those with meningococcal disease); Mean/median not reported; 50% aged < 12 years. No meningococcal or bacterial infection (n=36): Age: Reported for whole sample only (including control participants not included in this review; Mean/median not reported; 79% aged < 12 years Viral infections (positive viral isolation or serious meningitis; n=14); other diseases (n=22; includes n=15 with upper respiratory tract infections of unknown aetiology). n=2 who were difficult to categorize included in the control group as meningitis of unknown microbiological aetiology).
Index test(s)	Signs and symptoms recorded by healthcare professional on the day of admission to hospital: (a) Petechiae (≤4mm) (b) Reduced general condition (c) Ecchymoses (cutaneous haemorrhages >4 mm) (d) Reduced consciousness

	(e) Cold extremities (f) Cyanosis (g) Neck stiffness (h) Body pain
Reference standard(s)	Method of diagnosis was reported for the whole sample only (including those with meningococcal disease): growth of meningococci in blood and/or CSF (for 62%), or based on the clinical picture, meningococcal antigen in CSF, or growth of N. meningitidis in pharyngeal swab specimens (for 38%).
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	Data was not reported for clinical symptoms that were non-significant (presence of convulsions, back rigidity, headache, nausea, chills, fever, diarrhoea, irritability, systolic blood pressure <100, heart rate ≥120, rectal temperature≥40.0)

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; N. Meningitidis: Neisseria Meningitidis

Outcomes

Signs and symptoms of meningococcal meningitis

Outcome	**N = 92**
Petechiae (<=4mm) Custom value	TP 29; FP 9; FN 27; TN 27
Reduced general condition Custom value	TP 35; FP 0; FN 21; TN 36
Ecchymoses (cutaneous haemorrhages >4 mm) Custom value	TP 6; FP 18; FN 50; TN 18

Outcome	N = 92
Reduced consciousness Custom value	TP 30; FP 1; FN 26; TN 35
Cold extremities Custom value	TP 9; FP 3; FN 47; TN 33
Cyanosis Custom value	TP 3; FP 0; FN 53; TN 36
Neck stiffness Custom value	TP 50; FP 13; FN 6; TN 23
Body pain Custom value	TP 15; FP 6; FN 41; TN 30

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Generally a consecutive sample enrolled (5% included retrospectively), but exclusion criteria not reported. Inclusion criteria limited to patients hospitalized with suspected systemic meningococcal disease, but no further details reported.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(No information about whether index tests were interpreted without knowledge of the reference standard, and no detail on how clinical features measured and many of these factors are subjective (for example, reduced general condition and reduced consciousness). Data not reported for non-significant signs and symptoms)*
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?	High *(Study includes patients without bacteriological proof (N=44, 38% of the full sample that includes those with meningitis only), and in the full sample there is a statistically significant difference between these patients and those with growth of N. meningitidis from CSF or blood in terms of neck stiffness (69% of culture proven cases had neck stiffness relative to 48% in culture negative cases))*
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 *(Unclear interval between index test and reference standard)*

Brivet, 2005

Bibliographic Reference Brivet, F. G; Ducuing, S; Jacobs, F; Chary, I; Pompier, R; Prat, D; Grigoriu, B. D; Nordmann, P.; Accuracy of clinical presentation for differentiating bacterial from viral meningitis in adults: A multivariate approach; Intensive Care Medicine; 2005; vol. 31 (no. 12); 1654-1660

Study details

Country/ies where study was carried out	France
Study type	Two-gate, cross-sectional (retrospective) DTA study. Adults hospitalized with a confirmed diagnosis of bacterial meningitis (in medical records) compared with adults hospitalized with a confirmed diagnosis of viral meningitis (in medical records).
Study dates	Bacterial meningitis: January 1982 - March 2005 Viral meningitis: June 1996 - January 2003
Inclusion criteria	Adults aged over 16 years hospitalized at the participating hospital with a diagnosis of community-acquired bacterial meningitis or viral meningitis recorded in the hospital discharge diagnostic database.
Exclusion criteria	Bacterial meningitis: Patients with mycobacterial meningitis or with bacterial pathogens associated with contamination Viral meningitis: Receipt of antibiotics within 4 days before lumbar puncture, concurrent bacterial infection.
Patient characteristics	N=144 Bacterial meningitis (n=90 analysed): Age (in years): Mean 49.7 (SD=20.5). Causative organisms: S. pneumoniae (44/90; 49%); N. meningitidis (19/90; 21%); Listeria monocytogenes (6/90; 7%); other streptococci (7/90; 8%); Staphylococcus aureus (5/90; 6%); other bacteria (9/90; 10%) Viral meningitis (n=54 analysed): Age (in years): Mean 34.9 (SD=14.0). n=28 (52%) had proportion of CSF neutrophils greater than 35%; and n=26 (48%) CSF PMN <35%.

Index test(s)	Signs and symptoms (taken from medical records): (a) Presence of a least 1 sign of severity at presentation (altered mental status; focal neurological deficits; seizures at or before presentation; or shock) (b) Altered mental status (defined as Glasgow Coma Scale [GCS] score <14) (c) Focal neurological deficits (d) Seizures at or before presentation (e) Shock Data cannot be extracted for the following signs/symptoms as missing data and N per arm is not reported: duration of symptoms (<24 hours); headache; nausea/vomiting; photophobia; neck stiffness.
Reference standard(s)	Patients were considered to have bacterial meningitis if they fulfilled 2 of the following: (a) a CSF Gram-stained smear positive for bacterial pathogen (b) CSF pleocytosis (>7 white blood cells/mm3) and a positive blood culture (c) a positive CSF culture for bacterial pathogen (d) a positive CSF latex agglutination test or PCR assay for N. meningitidis. Bacterial pathogens identified in both CSF and blood cultures (n=61; 67.8%); CSF culture alone (n=24; 26.7%); blood culture alone (n=4; 4.4%); CSF latex agglutination and PCR positive for N. meningitidis (n=1; 1.1%). Patients were considered to have viral meningitis if they fulfilled the following: (a) a pleocytosis in the CSF of at least 7 WBC/mm3 (b) absence of any bacterial growth on culture of the CSF

	(c) rapid and benign clinical course (d) no aetiology other than viral infection.
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	20/90 of those with bacterial meningitis received antibiotics before referral. 10/90 of those with bacterial meningitis (and none of those with viral meningitis) were immunocompromised (defined by history of splenectomy, use of immunosuppressive drugs, or infection by HIV).

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; HIV: human immunodeficiency virus; N. Meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; S. pneumoniae: Streptococcus pneumoniae; WBC: white blood count

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 144**
Presence of a least 1 sign of severity at presentation (altered mental status; focal neurological deficits; seizures at or before presentation; or shock) Custom value	TP 89; FN 1; FP 1; TN 53
Altered mental status Custom value	TP 81; FN 9; FP 1; TN 53
Focal neurological deficits Custom value	TP 32; FN 58; FP 0; TN 54
Seizures at or before presentation Custom value	TP 21; FN 69; FP 0; TN 54
Shock	TP 46; FN 44; FP 0; TN 54

Outcome	N = 144
Custom value	

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Two-gate retrospective study design comparing patients with confirmed bacterial meningitis to those with confirmed viral meningitis, and excluded patients with culture-negative meningoencephalitis, herpes virus encephalitis, mycobacterial, and fungal 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?	High *(No information about whether index tests were interpreted without knowledge of the reference standard, and index tests not systematically quantified)*
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?	High *(No information about interval between index tests and reference standard. Missing data for some signs and symptoms and data cannot be extracted for these index tests as N per arm is unclear)*

De Cauwer, 2007

Bibliographic Reference	De Cauwer, H. G.; Eykens, L.; Hellinckx, J.; Mortelmans, L. J.; Differential diagnosis between viral and bacterial meningitis in children; Eur J Emerg Med; 2007; vol. 14 (no. 6); 343-7

Study details

Country/ies where study was carried out	Belgium
Study type	Single-gate, cross-sectional (retrospective) DTA study.
Study dates	1997 to 2005
Inclusion criteria	Children (0-15 years old) admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of viral or bacterial meningitis
Exclusion criteria	Patients with Lyme's disease
Patient characteristics	N=92 Bacterial meningitis (n=21): Age in years (mean; range in parentheses): 3.9 (0-13) Sex: male 12 (57%); female: 9 (43%)

	Bacterial aetiology: Meningococcal meningitis (n=16; 76%); pneumococcal meningitis (n=5; 24%) Viral meningitis (n=71): Age in years (mean; range in parentheses): 6.1 (0-15) Sex: male 46 (65%); female: 25 (35%)
Index test(s)	Signs and symptoms (reported by the paediatrician): (a) Headache (b) Neck strain (c) Photophobia (d) Fever (e) Neck stiffness (f) Nausea (g) Vomiting (h) Sick for >2 days (i) Convulsions (j) Petechiae
Reference standard(s)	Bacterial meningitis defined by either a positive culture from CSF or a pleocytosis ≥ 10 white blood cells in the CSF and a positive blood culture for a bacterial disease. Haemocultures were positive in 18/21, negative in 2/21 and not performed in 1/21. In the same group, CSF cultures were

	positive in 14/21 and negative in 7/21.
Duration of follow-up	Not reported
Sources of funding	Not reported

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 92**
Headache Data available for 95% of sample Custom value	TP 2; FP 53; FN 17; TN 15
Neck strain Data available for 97% of sample Custom value	TP 8; FP 3; FN 60; TN 18
Photophobia Data available for 97% of sample Custom value	TP 19; FP 1; FN 49; TN 20
Fever Data available for 97% of sample Custom value	TP 56; FP 19; FN 12; TN 2
Neck stiffness Data available for 97% of sample Custom value	TP 60; FP 13; FN 8; FP 8
Nausea	TP 54; FP 10; FN 14; TN 11

Outcome	N = 92
Data available for 97% of sample Custom value	
Vomiting Data available for 97% of sample Custom value	TP 55; FP 11; FN 13; TN 10
Sick for >2 days Data available for 92% of sample Custom value	TP 14; FP 5; FN 51; TN 15
Convulsions Data available for 97% of sample Custom value	TP 2; FP 4; FN 66; TN 17
Petechiae Data available for 98% of sample Custom value	TP 5; FP 13; FN 64; TN 8

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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

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(No information about whether index tests were interpreted without knowledge of the reference standard, and index tests not systematically quantified)*
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?	High *(Reference standard defined as positive CSF culture and/or CSF pleocytosis and a positive blood culture. 14/21 in bacterial meningitis group had positive CSF culture)*
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 *(Unclear interval between index test and reference standard, and some missing data but limited attrition (2-8%))*

Fretzayas, 2010

Bibliographic Reference	Fretzayas, A; Moustaki, M; Stefos, E; Markoulatos, P; Choreuti, E; Constantopoulos, A.; Differential diagnosis of meningococcal meningitis based on common clinical and laboratory findings: Are there criterion standards?; Infectious Diseases in Clinical Practice; 2010; vol. 18 (no. 4); 253-257

Study details

Country/ies where study was carried out	Greece

Study type	Single-gate, cross-sectional DTA study
Study dates	December 2000 to December 2001
Inclusion criteria	Children aged 1 month to 14 years who underwent diagnostic lumbar puncture for infectious meningitis during the study period after being admitted to the participating hospital (2nd Department of Pediatrics of Athens Medical School)
Exclusion criteria	Patients who were administered antibiotics within 72 hours before evaluation; those who underwent a neurosurgical procedure or lumbar puncture for reasons other than the diagnosis of infectious meningitis; those with known immunodeficiency
Patient characteristics	N=145 Meningococcal meningitis (n=40): Age in months (mean; standard deviation in parentheses): 75.3 (39.7) Sex: male: 25 (62.5%); female: 15 (37.5%) Viral meningitis/no meningitis (n=105): Viral meningitis (n=32); No meningitis (n=73) Age in months (mean; standard deviation in parentheses): 50.3 (53.3) Sex: male: 54 (51%); female: 51 (49%)
Index test(s)	Signs and symptoms (recorded in a pre-coded questionnaire on admission): (a) Respiratory symptoms (b) Gastrointestinal symptoms (c) Vomiting

	(d) Neck stiffness (e) Kernig's sign (f) Brudzinski's sign (g) Hemorrhagic rash (i) Headache
Reference standard(s)	Bacterial meningitis, which was in all cases meningococcal, was confirmed by blood or CSF culture and/or Gram stain, or by PCR for meningococcus
Duration of follow-up	Not reported
Sources of funding	Not reported (authors declared no conflicts of interest)

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; PCR: positive polymerase chain reaction

Outcomes

Signs and symptoms of meningococcal meningitis

Outcome	**N = 145**
Respiratory symptoms Custom value	TP 5; FP 22; FN 35; TN 83
Gastrointestinal symptoms Custom value	TP 27; FP 50; FN 13; TN 55
Vomiting Custom value	TP 24; FP 35; FN 16; TN 70
Neck stiffness Custom value	TP 36; FP 54; FN 4; TN 51

Outcome	N = 145
Kernig's sign Custom value	TP 4; FP 8; FN 36; TN 97
Brudzinski's sign Custom value	TP 7; FP 8; FN 33; TN 97
Hemorrhagic rash Custom value	TP 4; FP 10; FN 36; TN 95
Headache Only reported for children aged >1 year Custom value	TP 30; FP 45; FN 5; TN 27

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled, but excluded children treated with antibiotics within 72 hours before evaluation (may not reflect clinical practice))*
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 tests were interpreted without knowledge of the reference standard (data on signs/symptoms collected at admission, prior to lumbar puncture). However, limited detail provided on how signs and symptoms were defined and measured.)*
Index tests:	Are there concerns that the index test, its	Low

Section	Question	Answer
applicability	conduct, or interpretation differ from the review question?	
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Reference standard defined as CSF culture, blood culture, Gram stain, or PCR. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard, and some missing data but limited attrition (3%))*

Gowin, 2017

Bibliographic Reference	Gowin, E; Januszkiewicz-Lewandowska, D; Slowinski, R; Blaszczynski, J; Michalak, M; Wysocki, J.; With a little help from a computer: Discriminating between bacterial and viral meningitis based on dominance-based rough set approach analysis; Medicine; 2017; vol. 96 (no. 32)

Study details

Country/ies where study was carried out	Poland
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	Not reported
Inclusion criteria	Children hospitalised with meningitis at the participating hospital (Infectious Diseases Department, St. Joseph Children's Hospital, Poznan)
Exclusion criteria	Not reported

Patient characteristics	N=148 Bacterial meningitis (n=84): Age in months (mean; standard deviation in parentheses): 61.6 (64.9) Viral meningitis (n=64): Age in months (mean; standard deviation in parentheses): 117.7 (57.2) Total sample (N=148): Sex: male: 78 (53%); female: 70 (47%)
Index test(s)	Signs and symptoms present on admission taken from medical records: (a) Headache (b) Rash (c) Vomiting (d) Seizures
Reference standard(s)	Bacterial meningitis diagnosed based on positive CSF culture (or detection of bacterial genetic material by PCR) along with typical clinical symptoms: fever, headache, and existing meningeal signs. The gold standard for bacterial meningitis was positive culture. For rapid diagnosis, fast latex tests and direct examination of Gram stain were performed.
Duration of follow-up	Not reported
Sources of funding	Not industry funded
Other information	No breakdown of bacterial or viral pathogens isolated

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; PCR: positive polymerase chain reaction

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 148**
Headache Custom value	TP 38; FP 56; FN 46; TN 8
Rash Custom value	TP 33; FP 4; FN 51; TN 60
Vomiting Custom value	TP 6; FP 49; FN 78; TN 15
Seizures Custom value	TP 17; FP 6; FN 67; TN 58

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Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Unclear if consecutive or random sample of patients enrolled and study dates not reported. Only children diagnosed with bacterial meningitis or viral meningitis were included (and no further detail reported on exclusion criteria))*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index tests were interpreted without knowledge of the reference standard (data on signs/symptoms collected at admission, and taken from medical records). However, limited detail provided on how signs and symptoms were defined and measured.)*
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?	High *(Reference standard defined as CSF culture, Gram stain, or PCR. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard)*

Joffe, 1983

Bibliographic Reference	Joffe, A; McCormick, M; DeAngelis, C.; Which children with febrile seizures need lumbar puncture? A decision analysis approach; American Journal of Diseases of Children; 1983; vol. 137 (no. 12); 1153-1156

Study details

Country/ies where study was carried out	US
Study type	Single-gate, cross-sectional (retrospective) DTA study

Study dates	January 1978 - October 1979
Inclusion criteria	Children aged 6 months to 6 years, presenting at the emergency room with a first episode of seizure and fever.
Exclusion criteria	Children who did not undergo lumbar puncture and insufficient follow-up data available (telephone follow-up or chart review did not document the outcome of the acute illness); children with a predisposition to meningitis (for example, those who had a CNS shunt).
Patient characteristics	N=241 Meningitis (n=13) Age in months: Mean 22 (SD not reported) Sex: male 6 (46%); female: 7 (54%) No meningitis/febrile seizures (n=228) Age in months: Mean 23 (SD not reported) Sex: male 144 (63%); female: 84 (37%)
Index test(s)	Signs and symptoms (taken from medical records): (a) Visit to a physician in the 48 hours prior to the seizure (b) Seizure at presentation (c) Type of seizure (focal versus generalized) (d) Presence of rash/petechiae, cyanosis, hypotension, or grunting respirations (e) Abnormal neurologic findings (defined as stiff neck, increased tone, deviated eyes, ataxia, no response to voice, inability to fix and follow, no response to painful stimuli, positive doll's eye sign, floppy muscle tone, nystagmus, and bulging or tense

	fontanelle) (f) Presence of at least 1 factor (visit to physician within 48 hours or focal type of seizure) (g) Presence of at least 1 factor (visit to physician within 48 hours or abnormal neurologic finding) (h) Presence of at least 1 factor (visit to physician within 48 hours or seizure at presentation) (i) Presence of at least 1 factor (focal type of seizure or presence of abnormal physical finding [rash/petechiae, cyanosis, hypotension, or grunting respirations]) (j) Presence of at least 1 factor (focal type of seizure or abnormal neurologic findings) (k) Presence of at least 1 factor (visit to physician within 48 hours; seizure at presentation; focal type of seizure; presence of abnormal physical finding [rash/petechiae, cyanosis, hypotension, or grunting respirations]; abnormal neurologic findings)
Reference standard(s)	CSF pleocytosis (11/13 of children with CSF pleocytosis had positive CSF bacterial cultures)
Duration of follow-up	Not reported
Sources of funding	Not industry funded
Other information	Very small number of participants with bacterial meningitis enrolled in the study

Abbreviations: CSF: cerebrospinal fluid; CNS: central nervous system; DTA: diagnostic test accuracy; SD: standard deviation

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 241**
Visit to a physician in the 48 hours prior to the seizure Custom value	TP 6; FN 7; FP 37; TN 191

Outcome	N = 241
Seizure at presentation Custom value	TP 3; FN 10; FP 9; TN 219
Type of seizure (focal) Custom value	TP 5; FN 8; FN 20; TN 208
Presence of rash/petechiae, cyanosis, hypotension, or grunting respirations Custom value	TP 3; FN 10; FP 10; TN 218
Abnormal neurologic findings Custom value	TP 12; FN 1; FP 37; TN 191
Presence of at least 1 factor (visit to physician within 48 hours or focal type of seizure) Custom value	TP 9; FN 4; FP 50; TN 178
Presence of at least 1 factor (visit to physician within 48 hours or abnormal neurologic finding) Custom value	TP 13; FN 0; FP 66; TN 162
Presence of at least 1 factor (visit to physician within 48 hours or seizure at presentation) Custom value	TP 7; FN 6; FP 41; TN 187
Presence of at least 1 factor (focal type of seizure or presence of abnormal physical finding [rash/petechiae, cyanosis, hypotension, or grunting respirations]) Custom value	TP 6; FN 7; FP 25; TN 203
Presence of at least 1 factor (focal type of seizure or abnormal neurologic findings) Custom value	TP 12; FN 1; FP 41; TN 187
Presence of at least 1 factor (visit to physician within 48 hours; seizure at presentation; focal type of seizure; presence of	TP 13; FN 0;

Outcome	N = 241
abnormal physical finding [rash/petechiae, cyanosis, hypotension, or grunting respirations]; abnormal neurologic findings) Custom value	FP 87; TN 141

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Consecutive sample enrolled and the study avoided inappropriate exclusions)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index tests were interpreted without knowledge of the reference standard (data signs/symptoms collected at emergency room presentation and taken from medical records). However, limited detail provided on how signs and symptoms were defined and measured.)*
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 *(CSF pleocytosis used to identify meningitis (study not restricted to bacterial meningitis), although 85% of those diagnosed with meningitis had positive CSF bacterial cultures)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard	Low

Section	Question	Answer
	does not match the review question?	
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Unclear interval between index test and reference standard)*

Krishna, 1983

Bibliographic Reference	Krishna, V; Liu, V; Singleton, A. F.; Should lumbar puncture be routinely performed in patients with suspected bacteremia?; Journal of the National Medical Association; 1983; vol. 75 (no. 12); 1153-7

Study details

Country/ies where study was carried out	US
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	June 1979 to June 1980
Inclusion criteria	Paediatric patients (under 18 years of age) who had undergone a lumbar puncture
Exclusion criteria	Not reported
Patient characteristics	N=168 Bacterial meningitis (n=10): Age in months (mean; range in parentheses): 7.8 (9 days to 18 months) Sex: male: 6 (60%); female: 4 (40%) Positive CSF culture (n=9): H. influenzae B (n=3); H. influenzae nontypeable (n=1); S. pneumoniae meningitis (n=2); N.

	meningitidis C (n=1); group D streptococcus (n=1); Listeria monocytogenes (n=1) Other type of meningitis/no meningitis (n=158): Bacteremia only (positive blood cultures and normal CSF [no bacterial or aseptic meningitis]), n=3; Aseptic meningitis (abnormal CSF but negative CSF culture results), n=10; No meningitis (negative CSF cultures, normal CSF findings by judges, and no bacteremia), n=145 Age in months (mean; range in parentheses): 7.3 (4 days to 9 years) Sex: male: 93 (59%); female: 65 (41%)
Index test(s)	Signs and symptoms taken from medical records: (a) Fever (b) Upper respiratory symptoms (c) Diarrhoea (d) Loss of appetite (e) Vomiting (d) Seizures (e) Constipation (f) Reduced consciousness, defined as non-alert appearance (converted data for 'alert') (g) Irritable

	(h) Lethargic (i) Toxic or ill (j) Petechiae
Reference standard(s)	Bacterial meningitis diagnosed based on positive bacterial cultures of the CSF, regardless of blood culture results. For 1/10 of this group, CSF culture was negative, but the patient developed a subdural effusion and a mild communicating hydrocephalus. Blood culture yielded H. influenzae B, and CSF was interpreted as abnormal by two independently working expert judges.
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	Very small number of participants with bacterial meningitis enrolled in the study

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; H. influenzae type B: Haemophilus influenzae type b (Hib); H. influenzae nontypeable: Haemophilus influenzae nontypeable; N. Meningitidis: Neisseria Meningitidis; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 168**
Fever Custom value	TP 10; FP 128; FN 0; TN 30
Upper respiratory symptoms Custom value	TP 5; FP 8; FN 5; TN 150
Diarrhoea Custom value	TP 3; FP 58; FN 7; TN 100

Outcome	N = 168
Loss of appetite Custom value	TP 2; FP 42; FN 8; TN 116
Vomiting Custom value	TP 2; FP 43; FN 8; TN 115
Seizures Custom value	TP 2; FP 26; FN 8; TN 132
Constipation Custom value	TP 0; FP 7; FN 10; TN 151
Reduced consciousness Custom value	TP 10; FP 123; FN 0; TN 35
Irritable Custom value	TP 3; FP 30; FN 7; TN 128
Lethargic Custom value	TP 5; FP 11; FN 5; TN 147
Toxic or ill Custom value	TP 0; FP 10; FN 10; TN 148
Petechiae Custom value	TP 2; FP 0; FN 8; TN 158

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Study appears to have included all relevant cases admitted to the hospital, but 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?	High *(No information about whether index tests were interpreted without knowledge of the reference standard, and index tests not systematically quantified and many are subjective)*
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 *(Unclear interval between index test and reference standard)*

Lembo, 1991

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

Study details

Country/ies where study was carried out	US
Study type	Single-gate, cross-sectional DTA study
Study dates	February 1984 - August 1985
Inclusion criteria	Children presenting to hospital for evaluation of an acute febrile episode
Exclusion criteria	History of malignancy, immunodeficiency, or intracranial surgery or were receiving immunosuppressive therapy
Patient characteristics	N=160 Bacterial meningitis (n=10): Causative organisms: H. influenzae type B (5/10; 50%); S. pneumoniae (3/10; 30%); group A streptococci (1/10; 10%); Listeria monocytogenes (1/10; 10%) Other illnesses (n=150): Aseptic meningitis (n=14); other bacterial infections (n=10); other illnesses (n=126) Total sample (N=160): Age in months (median): 6 Sex: male 84 (52.5%); female: 76 (47.5%)
Index test(s)	Signs and symptoms recorded at presentation: (a) Signs and symptoms of meningism, defined as any sign of meningeal irritation (for example, nuchal rigidity, Kernig's sign, or Brudzinski's sign) or increased intracranial pressure (full/bulging anterior fontanelle) (b) Any symptom of CNS infection, defined as irritability, lethargy, headache, or stiff neck
Reference standard(s)	BM was defined on the basis of the recovery of a bacterial pathogen from CSF by standard culture techniques or by the identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive

	culture
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	Very small number of participants with bacterial meningitis enrolled in the study

Abbreviations: CSF: cerebrospinal fluid; CNS: central nervous system; DTA: diagnostic test accuracy; H. influenzae type B: Haemophilus influenzae type b (Hib); S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 160**
Signs or symptoms of meningism Custom value	TP 7; FN 3; FP 28; TN 122
Any symptom of CNS infection Custom value	TP 3; FN 0; FP 99; TN 23

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Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Consecutive sample enrolled and the study avoided inappropriate exclusions)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index tests were interpreted without knowledge of the reference standard (signs/symptoms recorded at presentation to emergency room or acute care clinic). However, limited detail provided on how signs and symptoms were defined and measured.)*
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 *(BM defined on the basis of the recovery of a bacterial pathogen from CSF by standard culture techniques or by the identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive culture. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard, and some missing data but limited attrition (2%))*

Levy, 1990

Bibliographic Reference Levy, M; Wong, E; Fried, D.; Diseases that mimic meningitis. Analysis of 650 lumbar punctures; Clinical Pediatrics; 1990; vol. 29 (no. 5); 254-261

Study details

Country/ies where study was carried out	Israel
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	1977 to 1982
Inclusion criteria	Children undergoing lumbar puncture for presumed diagnosis of meningitis. Lumbar puncture was performed in all children presenting with a first episode of seizure and fever.
Exclusion criteria	Not reported
Patient characteristics	N=650; Data analysed for N=630 Bacterial meningitis (n=50) Other type of meningitis/no meningitis (n=580): Viral meningitis (n=212); normal CSF findings (n=368) Age: Mean/median not reported; 0-8 weeks (n=58; 9%); 8 weeks to 24 months (n=213; 34%); 2 years to 5 years (n=217; 34%); 5 years to 12 years (n=142; 23%)
Index test(s)	Signs and symptoms (recorded at presentation, and taken from medical records): (a) Fever (b) Convulsion with fever (c) Convulsion without fever (d) Irritability (e) Lethargy

	(f) Headache (g) Vomiting (h) Nuchal rigidity (i) Budzinski sign (j) Kernig sign (k) Bulging fontanelle
Reference standard(s)	Bacterial meningitis diagnosed based on high cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein. Paper reports that 'in most such instances bacteria were recovered from the CSF culture' but proportion not reported
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	All of the children with bacterial meningitis were treated with antibiotics. No details on bacterial aetiology of patients diagnosed with bacterial meningitis

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; PMN: polymorphonuclear

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 630**
Fever Custom value	TP 46; FP 432; FN 4; TN 148
Convulsion with fever	TP 1; FP 92; FN 49; TN 488

Outcome	N = 630
Custom value	
Convulsion without fever Custom value	TP 0; FP 6; FN 50; TN 574
Irritability Custom value	TP 9; FP 54; FN 41; TN 526
Lethargy Custom value	TP 23; FP 151; FN 27; TN 429
Headache Custom value	TP 9; FP 182; FN 41; TN 398
Vomiting Custom value	TP 31; FP 354; FN 19; TN 226
Nuchal rigidity Custom value	TP 18; FP 170; FN 32; TN 410
Budzinski sign Custom value	TP 31; FP 278; FN 19; TN 302
Kernig sign Custom value	TP 7; FP 46; FN 43; TN 534
Bulging fontanelle In babies/children aged up to 2 years (N=271) Custom value	TP 7; FP 22; FN 26; TN 216

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled, but 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?	High *(No information about whether index tests were interpreted without knowledge of the reference standard, and index tests not systematically quantified)*
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?	High *(Paper reports that 'in most such instances bacteria were recovered from the CSF culture.' but proportion not reported)*
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 *(Unclear interval between index test and reference standard, and some missing data but limited attrition (3%))*

Magazzini, 2012

Bibliographic Magazzini, S; Nazerian, P; Vanni, S; Paladini, B; Pepe, G; Casanova, B; Crugnola, C; Grifoni, S.; Clinical picture of meningitis

Reference in the adult patient and its relationship with age; Internal and Emergency Medicine; 2012; vol. 7 (no. 4); 359-364

Study details

Country/ies where study was carried out	Italy
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	January 2002 to December 2006
Inclusion criteria	Adults presenting to the emergency department and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial (including meningoencephalitis)
Exclusion criteria	Glasgow Coma Scale (GCS) not clearly recorded; comorbidities, such as vascular or essential brain chronic disease (dementia); medications that could impact the GCS evaluation; workup could not be completed (including lumbar puncture could not be performed) because of contraindications
Patient characteristics	N=202 Bacterial meningitis (n=40): Age in years (mean; standard deviation in parentheses): 55.7 (18.2) Immunocompromised n=6 (15%) Viral meningitis (n=162): Age in years (mean; standard deviation in parentheses): 39.5 (17.4) Immunocompromised n=10 (6%)

	Whole sample (N=202): Sex: male: 105 (52%); female: 97 (48%)
Index test(s)	Signs and symptoms (recorded from physical examination performed by the emergency physicians in the emergency department, and taken from medical record): (a) Reduced consciousness, defined as GCS score <15 (b) Kernig or Brudzinski signs (c) Neck stiffness (d) Kernig or Brudzinski signs or neck stiffness (e) Neurological complaints, including seizure and focal neurological deficits (f) Severe sepsis or shock (Severe sepsis was defined as the presence of sepsis and one or more organ dysfunctions, or hypoperfusion with lactic acidosis. Septic shock was defined as the presence of sepsis and refractory hypotension)
Reference standard(s)	Lumbar puncture performed on all participants. The diagnosis of meningitis and its aetiology were established by the infectious disease specialist or the intensitivist based on all laboratory and instrumental investigations performed during the hospital stay, and on the basis of hospital course.
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	No details on bacterial aetiology of patients diagnosed with bacterial meningitis

Abbreviations: DTA: diagnostic test accuracy; GCS: Glasgow Coma Scale

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 202**

Outcome	N = 202
Reduced consciousness Custom value	TP 27; FP 36; FN 13; TN 126
Kernig or Brudzinski signs Custom value	TP 19; FP 51; FN 21; TN 111
Neck stiffness Custom value	TP 28; FP 89; FN 12; TN 73
Kernig or Brudzinski signs or neck stiffness Custom value	TP 28; FP 99; FN 12; TN 63
Neurological complaints Custom value	TP 10; FP 25; FN 30; TN 137
Severe sepsis or shock Custom value	TP 24; FP 0; FN 16; TN 162

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled but only adults diagnosed with bacterial meningitis or viral meningitis were included)*
Patient selection:	Are there concerns that included	Low *(Some patients were immunocompromised (15% of bacterial meningitis group and 6% of*

Section	Question	Answer
applicability	patients do not match the review question?	*viral meningitis group) but not downgraded for indirectness as below threshold (25%))*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(Index tests were interpreted without knowledge of the reference standard, and sufficient detail provided on how signs and symptoms were defined and measured)*
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?	High *(Lumbar puncture performed on all participants. The diagnosis of meningitis and its etiology were established by the infectious disease specialist or the intensitivist based on all laboratory and instrumental investigations performed during the hospital stay, and on the basis of hospital course. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard)*

Magnussen, 1980

Bibliographic Reference Magnussen, C. R.; Meningitis in adults. Ten-year retrospective analysis at community hospital; New York State Journal of Medicine; 1980; vol. 80 (no. 6); 901-906

Study details

Country/ies where study was carried out	US
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	1969 to 1978
Inclusion criteria	Older children and adults discharged from the participating hospital with a diagnosis of acute meningitis. Data only analysed for those with bacterial or aseptic meningitis.
Exclusion criteria	Children aged less than 12 years
Patient characteristics	N=59 Bacterial meningitis (n=25): Age in years (mean): 53.6 Sex: male: 13 (52%); female: 12 (48%) Bacterial aetiology: Pneumococcal (n=9; 36%); meningococcal (n=2; 8%); Pseudomonas species (n=1; 4%); S. epidermidis (n=1; 4%); Gamma-streptococcus (n=1; 4%); Alpha-streptococcus (n=1; 4%); H. influenzae (n=1; 4%); unknown (n=9; 36%). Aseptic meningitis (n=34): Age in years (mean): 28.6 Sex: male: 13 (38%); female: 21 (62%)

Index test(s)	Signs and symptoms (recorded at presentation, and taken from medical records): (a) Fever (defined as temperature >38.9°C) (b) Headache (c) Nuchal rigidity (d) Moderate or severe mentation changes (e) Focal neurologic signs
Reference standard(s)	Bacterial meningitis: Known aetiology - positive result on CSF gram stain or a CSF culture and/or blood culture positive for pathogenic bacterial species. Unknown aetiology - negative CSF gram stain and negative CSF culture or blood cultures, but had CSF lab results showing a total WBC of more than 1,000 per cubic mm with more than 50% PMN's, plus total protein greater or equal to 80mg/100ml and/or glucose less than or equal to 40mg/100ml.
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	Study includes 9/25 diagnoses made without positive culture Papilledema also reported as an outcome but no events in either arm

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; H. influenzae: Haemophilus influenzae; PMN: polymorphonuclear; S. epidermidis: Staphylococcus epidermidis; WBC: white blood count

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	N = 59
Fever Custom value	TP 17; FP 8; FN 8; TN 26
Headache Custom value	TP 12; FP 34; FN 13; TN 0
Nuchal rigidity Custom value	TP 22; FP 26; FN 3; TN 8
Moderate or severe mentation changes Custom value	TP 11; FP 1; FN 14; TN 33
Focal neurologic signs Custom value	TP 5; FP 1; FN 20; TN 33

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled but excluded children aged under 12 years, and those with meningitis types other than bacterial or aseptic (tuberculosis, fungal, and unknown) were not included in the analysis)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Index tests were interpreted without knowledge of the reference standard (data on signs/symptoms recorded at presentation). However, limited detail provided on how signs and symptoms were defined and measured, and retrospective study over 10 years with various investigators assessing signs and symptoms without clear definitions)*
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?	High *(Study includes 9/25 diagnoses made without positive culture)*
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 *(Unclear interval between index test and reference standard)*

Nielsen, 1988

Bibliographic Reference	Nielsen, B; Sorensen, H. T; Ostergaard Nielsen, J.; Children admitted for observation for suspected meningitis. Problems in diagnosis in general practice; Scandinavian Journal of Primary Health Care; 1988; vol. 6 (no. 4); 229-232

Study details

Country/ies where study was carried	Denmark

out	
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	May 1980 to April 1987
Inclusion criteria	Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward.
Exclusion criteria	Not reported
Patient characteristics	N=160 Purulent meningitis (n=17): Bacterial aetiology: H. influenzae (n=2; 12%); N. meningitidis (n=8; 47%); S. pneumoniae (n=2; 12%); unknown organisms (n=2; 12%); n=3 (18%) with PM due to N. meningitidis were admitted with a different diagnosis Other types of meningitis/non-meningitis (n=143): Aseptic meningitis (n=5; 3%); aseptic meningitis with parotitis (n=10; 7%); parotitis (uncomplicated; n=2; 1%); encephalitis/radiculomyelitis (n=5; 3%); upper respiratory tract infections (n=45; 31%); fever of unknown origin (n=42; 29%); pneumonia (n=21; 15%); gastroenteritis (n=4; 3%); measles (n=4; 3%); urinary tract infection (n=2; 1%); other (n=3; 2%) Total sample (N=160): Age in years (median; lower and upper quartiles parentheses): 5 (2-9) Sex: male: 111 (69%); female: 49 (31%) 78/160 (49%) underwent lumbar puncture

Index test(s)	Signs and symptoms (taken from referral letters from GPs and hospital discharge letters): (a) Duration of symptoms of 24 hours or less (b) Fever (c) Neck stiffness (d) Kernig's sign (e) Rash (f) Petechiae (g) Nausea/vomiting (h) Impaired consciousness (i) Convulsions
Reference standard(s)	Criteria for diagnosis not reported. All those with purulent meningitis underwent a lumbar puncture (and N=61, 43%, of those in the control group underwent LP)
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	Very small number of participants with purulent meningitis enrolled in the study

Abbreviations: DTA: diagnostic test accuracy; GP: general practitioner; H. influenzae type B: Haemophilus influenzae type b (Hib); LP: lumbar puncture; N. Meningitidis: Neisseria Meningitidis; PM: Purulent meningitis; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of purulent meningitis

Outcome	**N = 160**

Outcome	N = 160
Duration of symptoms of 24 hours or less Custom value	TP 11; FP 56; FN 6; TN 87
Fever Custom value	TP 17; FP 137; FN 0; TN 6
Neck stiffness Custom value	TP 13; FP 58; FN 4; TN 85
Kernig's sign Custom value	TP 12; FP 24; FN 5; TN 119
Rash Custom value	TP 5; FP 14; FN 12; TN 129
Petechiae Custom value	TP 4; FP 2; FN 13; TN 141
Nausea/vomiting Custom value	TP 12; FP 75; FN 5; TN 68
Impaired consciousness Custom value	TP 10; FP 18; FN 7; TN 125
Convulsions Custom value	TP 2; FP 6; FN 15; TN 137

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled but 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?	High *(Index tests may have been interpreted with knowledge of the reference standard as signs and symptoms taken from hospital discharge letters (as well as from GP referral letters), limited detail provided on how signs and symptoms were defined and measured, and retrospective study over 7 years with various investigators assessing signs and symptoms without clear definitions)*
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?	High *(Criteria for diagnosis not reported)*
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 *(Unclear interval between index test and reference standard)*

Oostenbrink, 2001

Bibliographic Reference	Oostenbrink, R; Moons, K. G. M; Donders, A. R. T; Grobbee, D. E; Moll, H. A.; Prediction of bacterial meningitis in children with meningeal signs: Reduction of lumbar punctures; Acta Paediatrica, International Journal of Paediatrics; 2001; vol. 90 (no. 6); 611-617

Study details

Country/ies where study was carried out	Netherlands
Study type	Single-gate, cross-sectional (retrospective) DTA study
Study dates	1988 to 1995 (data collected on patients between 1996 and 1998 used to create a validation set but signs and symptoms not reported for these later patients)
Inclusion criteria	Babies and children aged from 1 month to 15 years visiting the emergency department of the participating hospital during the study dates; who were retrospectively coded as having meningeal signs
Exclusion criteria	Patients with a history of severe neurological disease; ventricular drain; those referred from other hospitals
Patient characteristics	N=286 Bacterial meningitis (n=84): Age in years (mean; 95% confidence interval in parentheses): 3.6 (2.8–4.3) Sex: male: 42 (50%); female: 42 (50%) Other types of meningitis/non-meningitis (n=202): Age in years (mean; 95% confidence interval in parentheses): 3.5 (3.0–4.0)

	Sex: male: 133 (66%); female: 69 (34%) Viral/aseptic meningitis (n=34; 17%); pneumonia (n=20; 10%); other bacterial infections, including septicaemia, urinary tract infections and gastroenteritis (n=8; 4%); self-limiting diseases, upper respiratory tract infections, non-specified viral infection and myogenic torticollis (n=140; 69%)
Index test(s)	Signs and symptoms taken from medical records (based on clinical history and physical examination): (a) Complex convulsions (b) Disturbed consciousness (defined as reaction to pain only or no reaction at all) (c) Cyanosis (d) Petechiae or ecchymoses (e) Meningeal irritation (defined as presence of Brudzinski sign I or II, Kernig sign, tripod phenomenon or neck stiffness in children aged over 1 year, and in children aged 1 year or under one of the previous signs or irritability during manipulation of the head or legs by the paediatrician, or a bulging fontanelle) (f) Focal neurological disorders
Reference standard(s)	Bacterial meningitis defined as leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood.
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	Data could not be extracted for signs/symptoms with missing data as only overall percentage of sample reported and n's per group unclear

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	N = 286
Complex convulsions Custom value	TP 5; FP 2; FN 79; TN 200
Disturbed consciousness Custom value	TP 53; FP 12; FN 31; TN 190
Cyanosis Custom value	TP 10; FP 0; FN 74; TN 202
Petechiae or ecchymoses Custom value	TP 18; FP 6; FN 66; TN 196
Meningeal irritation Custom value	TP 84; FP 123; FN 0; TN 79
Focal neurological disorders Custom value	TP 19; FP 20; FN 65; TN 182

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Consecutive sample enrolled, and study avoided inappropriate exclusions)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard. Some detail provided on how signs and symptoms defined, however, retrospective study over 7 years and definitions not systematically quantified)*
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?	High *(Bacterial meningitis defined as leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard)*

Walsh-Kelly, 1992

Bibliographic Reference	Walsh-Kelly, C; Nelson, D.B; Smith, D.S; Losek, J.D; Melzer-Lange, M; Hennes, H.M; Glaeser, P.W.; Clinical predictors of bacterial versus aseptic meningitis in childhood; Annals of Emergency Medicine,Ann.Emerg.Med.; 1992; vol. 21 (no. 8); 910-914

Study details

Country/ies where study was carried	US

out	
Study type	Single-gate, cross-sectional DTA study
Study dates	August 1985 to February 1988
Inclusion criteria	Children undergoing lumbar puncture, after examination by 1/6 pediatric emergency attending physicians in the emergency department of the participating hospital during the study period
Exclusion criteria	Not reported
Patient characteristics	N=172 Bacterial meningitis (n=53): Age in months (mean; range in parentheses): 30 (3 weeks to 16 years) Bacterial aetiology: H. influenzae (n=35; 66%); S. pneumoniae (n=12; 23%); N. meningitidis (n=3; 6%); Group B Streptococcus (n=2; 4%); Escherichia coli (n=1; 2%) Aseptic meningitis (n=119): Age in months (mean; range in parentheses): 31 (1 week to 17 years)
Index test(s)	Signs and symptoms (recorded by paediatric emergency attending physicians in the emergency department): (a) Bulging fontanelle (b) Nuchal rigidity, defined as neck stiffness with active and/or passive neck flexion (c) Kernig's sign, defined as complete extension of the leg was not possible or produced significant discomfort (d) Brudzinski's sign, defined as passive neck flexion resulted in flexion of the legs (hips and knees) (e) Nuchal rigidity or Kernig's sign or Brudzinski's sign

	(f) Toxic/moribund. Toxic defined as lethargic, inconsolable, and lack of interest in environment and significant alterations in respiratory or heart rates or decreased peripheral perfusion. Moribund defined as unarousable with poor peripheral perfusion and unstable vital signs (g) Lethargic/comatose (h) Shock
Reference standard(s)	CSF culture, CSF latex agglutination or Gram stain
Duration of follow-up	Not reported
Sources of funding	Not reported

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; H. influenzae type B: Haemophilus influenzae type b (Hib); N. Meningitidis: Neisseria Meningitidis; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of bacterial meningitis

Outcome	**N = 172**
Bulging fontanelle Only reported for babies aged under 1 year Custom value	TP 11; FP 9; FN 14; TN 64
Nuchal rigidity Custom value	TP 39; FP 38; FN 14; TN 81
Kernig's sign Custom value	TP 28; FP 18; FN 25; TN 101
Brudzinski's sign	TP 32; FP 31; FN 21; TN 88

Outcome	N = 172
Custom value	
Nuchal rigidity or Kernig's sign or Brudzinski's sign Custom value	TP 44; FP 51; FN 9; TN 68
Toxic/moribund Custom value	TP 26; FP 11; FN 27; TN 108
Lethargic/comatose Custom value	TP 46; FP 53; FN 7; TN 66
Shock Custom value	TP 9; FP 6; FN 44; TN 113

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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 aseptic meningitis were included (and no further detail reported 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 *(Index tests were interpreted without knowledge of the reference standard (clinical information collected prior to lumbar puncture), and detailed definitions of signs/symptoms provided)*

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?	High *(Reference standard defined as CSF culture, CSF latex agglutination or Gram stain. No details on proportion of population diagnosed with CSF culture)*
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 *(Unclear interval between index test and reference standard)*

Appendix E Forest plots

Forest plots for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

This section includes forest plots only for outcomes that include more than one study. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Toxic or ill appearance for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Krishna 1983	0	10	10	148	Other men./non-meningitis (mixed)	0.00 [0.00, 0.31]	0.94 [0.89, 0.97]
Walsh-Kelly 1992	26	11	27	108	VM	0.49 [0.35, 0.63]	0.91 [0.84, 0.95]

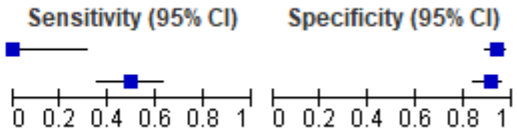


Figure 3: Fever (threshold undefined) for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
De Cauwer 2007	56	19	12	2	VM	0.82 [0.71, 0.91]	0.10 [0.01, 0.30]
Krishna 1983	10	128	0	30	Other men./non-meningitis (mixed)	1.00 [0.69, 1.00]	0.19 [0.13, 0.26]
Levy 1990	46	432	4	148	Other men./non-meningitis (mixed)	0.92 [0.81, 0.98]	0.26 [0.22, 0.29]
Nielsen 1988	17	137	0	6	Other men./non-meningitis (mixed)	1.00 [0.80, 1.00]	0.04 [0.02, 0.09]

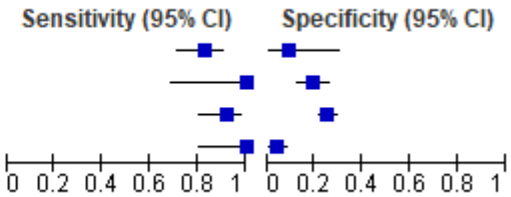


Figure 4: Lethargy for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Krishna 1983	5	11	5	147	Other men./non-meningitis (mixed)	0.50 [0.19, 0.81]	0.93 [0.88, 0.96]
Levy 1990	23	151	27	429	Other men./non-meningitis (mixed)	0.46 [0.32, 0.61]	0.74 [0.70, 0.77]
Walsh-Kelly 1992	46	53	7	66	VM	0.87 [0.75, 0.95]	0.55 [0.46, 0.65]

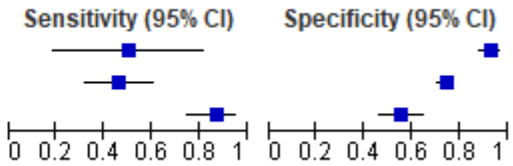


Figure 5: Irritability for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Krishna 1983	3	30	7	128	Other men./non-meningitis (mixed)	0.30 [0.07, 0.65]	0.81 [0.74, 0.87]
Levy 1990	9	54	41	526	Other men./non-meningitis (mixed)	0.18 [0.09, 0.31]	0.91 [0.88, 0.93]

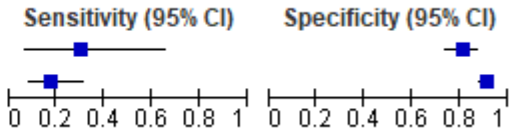


Figure 6: Presence of rash for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Gowin 2017	33	4	51	60	VM	0.39 [0.29, 0.51]	0.94 [0.85, 0.98]
Nielsen 1988	5	14	12	129	Other men./non-meningitis (mixed)	0.29 [0.10, 0.56]	0.90 [0.84, 0.95]

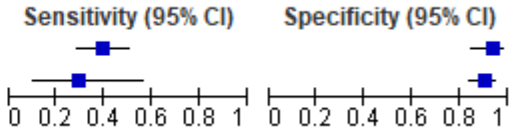


Figure 7: Haemorrhagic rash for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Fretzayas 2010	4	10	36	95	Other men./non-meningitis (mixed)	0.10 [0.03, 0.24]	0.90 [0.83, 0.95]
Oostenbrink 2001	18	6	66	196	Other men./non-meningitis (mixed)	0.21 [0.13, 0.32]	0.97 [0.94, 0.99]

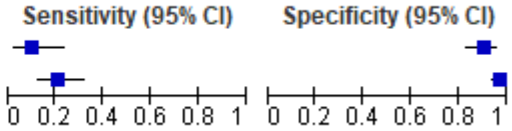


Figure 8: Petechiae for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
De Cauwer 2007	5	13	64	8	VM	0.07 [0.02, 0.16]	0.38 [0.18, 0.62]
Krishna 1983	2	0	8	158	Other men./non-meningitis (mixed)	0.20 [0.03, 0.56]	1.00 [0.98, 1.00]
Nielsen 1988	4	2	13	141	Other men./non-meningitis (mixed)	0.24 [0.07, 0.50]	0.99 [0.95, 1.00]

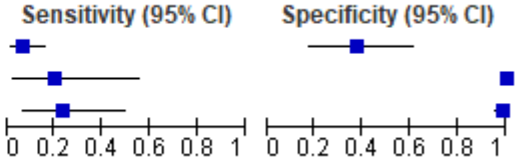


Figure 9: Signs or symptoms of meningism for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Lembo 1991	7	28	3	122	Other men./non-meningitis (mixed)	0.70 [0.35, 0.93]	0.81 [0.74, 0.87]
Oostenbrink 2001	84	123	0	79	Other men./non-meningitis (mixed)	1.00 [0.96, 1.00]	0.39 [0.32, 0.46]

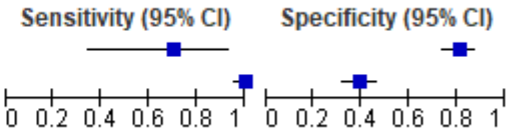


Figure 10: Brudzinski's sign for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2013	21	10	19	36	Absence of meningitis	0.53 [0.36, 0.68]	0.78 [0.64, 0.89]
Fretzayas 2010	7	8	33	97	Other men./non-meningitis (mixed)	0.17 [0.07, 0.33]	0.92 [0.86, 0.97]
Levy 1990	31	278	19	302	Other men./non-meningitis (mixed)	0.62 [0.47, 0.75]	0.52 [0.48, 0.56]
Walsh-Kelly 1992	32	31	21	88	VM	0.60 [0.46, 0.74]	0.74 [0.65, 0.82]

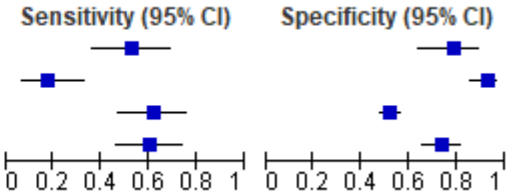


Figure 11: Kernig's sign for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2013	21	2	19	44	Absence of meningitis	0.53 [0.36, 0.68]	0.96 [0.85, 0.99]
Fretzayas 2010	4	8	36	97	Other men./non-meningitis (mixed)	0.10 [0.03, 0.24]	0.92 [0.86, 0.97]
Levy 1990	7	46	43	534	Other men./non-meningitis (mixed)	0.14 [0.06, 0.27]	0.92 [0.90, 0.94]
Nielsen 1988	12	24	5	119	Other men./non-meningitis (mixed)	0.71 [0.44, 0.90]	0.83 [0.76, 0.89]
Walsh-Kelly 1992	28	18	25	101	VM	0.53 [0.39, 0.67]	0.85 [0.77, 0.91]

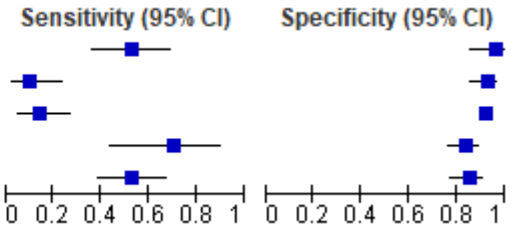


Figure 12: Neck stiffness for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2013	26	21	14	25	Absence of meningitis	0.65 [0.48, 0.79]	0.54 [0.39, 0.69]
Levy 1990	18	170	32	410	Other men./non-meningitis (mixed)	0.36 [0.23, 0.51]	0.71 [0.67, 0.74]
Fretzayas 2010	36	54	4	51	Other men./non-meningitis (mixed)	0.90 [0.76, 0.97]	0.49 [0.39, 0.59]
Nielsen 1988	13	58	4	85	Other men./non-meningitis (mixed)	0.76 [0.50, 0.93]	0.59 [0.51, 0.68]
De Cauwer 2007	60	13	8	8	VM	0.88 [0.78, 0.95]	0.38 [0.18, 0.62]
Walsh-Kelly 1992	39	38	14	81	VM	0.74 [0.60, 0.85]	0.68 [0.59, 0.76]

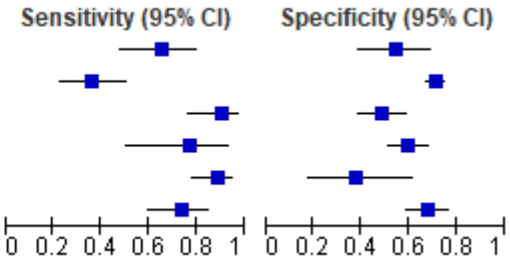


Figure 13: Bulging fontanelle for diagnosis of bacterial meningitis in babies

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Levy 1990	7	22	26	216	Other men./non-meningitis (mixed)	0.21 [0.09, 0.39]	0.91 [0.86, 0.94]
Walsh-Kelly 1992	11	9	14	64	VM	0.44 [0.24, 0.65]	0.88 [0.78, 0.94]

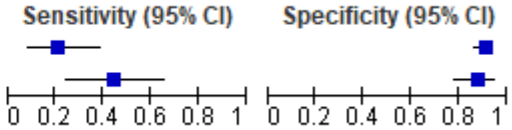


Figure 14: Headache for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2013	10	12	30	34	Absence of meningitis	0.25 [0.13, 0.41]	0.74 [0.59, 0.86]
Fretzayas 2010	30	45	5	27	Other men./non-meningitis (mixed)	0.86 [0.70, 0.95]	0.38 [0.26, 0.50]
Levy 1990	9	182	41	398	Other men./non-meningitis (mixed)	0.18 [0.09, 0.31]	0.69 [0.65, 0.72]
De Cauwer 2007	2	53	17	15	VM	0.11 [0.01, 0.33]	0.22 [0.13, 0.34]
Gowin 2017	38	56	46	8	VM	0.45 [0.34, 0.56]	0.13 [0.06, 0.23]

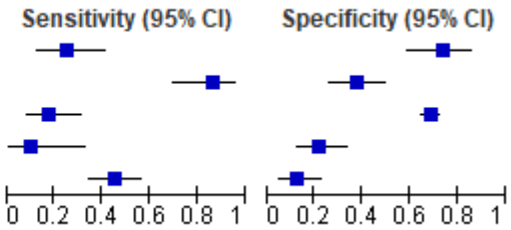


Figure 15: Seizure for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Gowin 2017	17	6	67	58	VM	0.20 [0.12, 0.30]	0.91 [0.81, 0.96]
Joffe 1983	3	9	10	219	Absence of meningitis	0.23 [0.05, 0.54]	0.96 [0.93, 0.98]
Krishna 1983	2	26	8	132	Other men./non-meningitis (mixed)	0.20 [0.03, 0.56]	0.84 [0.77, 0.89]

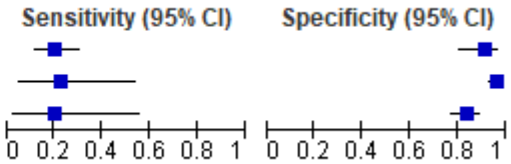


Figure 16: Convulsions for a diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2013	12	6	28	40	Absence of meningitis	0.30 [0.17, 0.47]	0.87 [0.74, 0.95]
De Cauwer 2007	2	4	66	17	VM	0.03 [0.00, 0.10]	0.81 [0.58, 0.95]
Nielsen 1988	2	6	15	137	Other men./non-meningitis (mixed)	0.12 [0.01, 0.36]	0.96 [0.91, 0.98]

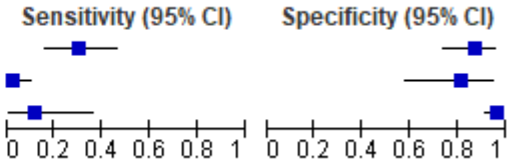


Figure 17: Reduced consciousness for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Krishna 1983	10	123	0	35	Other men./non-meningitis (mixed)	1.00 [0.69, 1.00]	0.22 [0.16, 0.29]
Nielsen 1988	10	18	7	125	Other men./non-meningitis (mixed)	0.59 [0.33, 0.82]	0.87 [0.81, 0.92]
Oostenbrink 2001	53	12	31	190	Other men./non-meningitis (mixed)	0.63 [0.52, 0.73]	0.94 [0.90, 0.97]

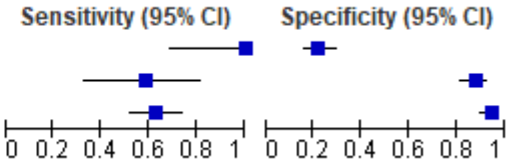


Figure 18: Respiratory symptoms for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Fretzayas 2010	5	22	35	83	Other men./non-meningitis (mixed)	0.13 [0.04, 0.27]	0.79 [0.70, 0.86]
Krishna 1983	5	8	5	150	Other men./non-meningitis (mixed)	0.50 [0.19, 0.81]	0.95 [0.90, 0.98]

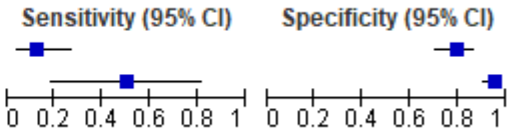


Figure 19: Vomiting for diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Krishna 1983	2	43	8	115	Other men./non-meningitis (mixed)	0.20 [0.03, 0.56]	0.73 [0.65, 0.80]
Levy 1990	31	354	19	226	Other men./non-meningitis (mixed)	0.62 [0.47, 0.75]	0.39 [0.35, 0.43]
Fretzayas 2010	24	35	16	70	Other men./non-meningitis (mixed)	0.60 [0.43, 0.75]	0.67 [0.57, 0.76]
Gowin 2017	6	49	78	15	VM	0.07 [0.03, 0.15]	0.23 [0.14, 0.36]
De Cauwer 2007	55	11	13	10	VM	0.81 [0.70, 0.89]	0.48 [0.26, 0.70]

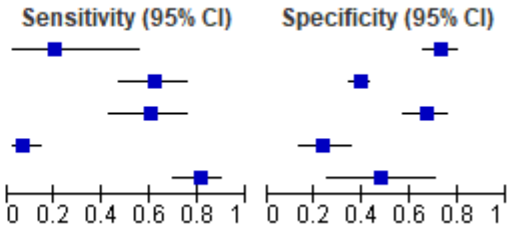


Figure 20: Nausea or vomiting for a diagnosis of bacterial meningitis in babies and children

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Bilavsky 2013	28	4	12	42	Absence of meningitis	0.70 [0.53, 0.83]	0.91 [0.79, 0.98]
Nielsen 1988	12	75	5	68	Other men./non-meningitis (mixed)	0.71 [0.44, 0.90]	0.48 [0.39, 0.56]

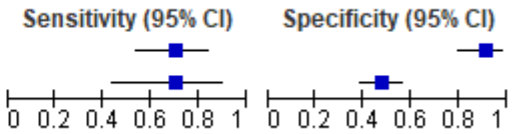


Figure 21: Focal neurological deficits for diagnosis of bacterial meningitis in adults

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Behrman 1989	13	7	17	13	Other meningitis (mixed)	0.43 [0.25, 0.63]	0.65 [0.41, 0.85]
Brivet 2005	32	0	58	54	VM	0.36 [0.26, 0.46]	1.00 [0.93, 1.00]

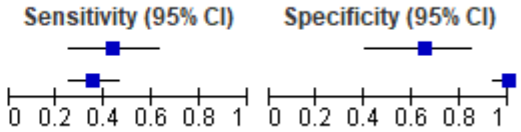
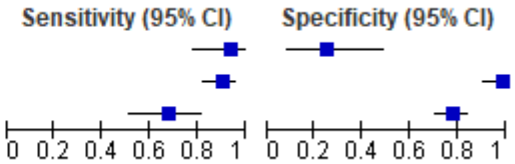


Figure 22: Altered mental state for diagnosis of bacterial meningitis in adults

Study	TP	FP	FN	TN	Comparison	Sensitivity (95% CI)	Specificity (95% CI)
Behrman 1989	28	15	2	5	Other meningitis (mixed)	0.93 [0.78, 0.99]	0.25 [0.09, 0.49]
Brivet 2005	83	1	9	53	VM	0.90 [0.82, 0.95]	0.98 [0.90, 1.00]
Magazzini 2012	27	36	13	126	VM	0.68 [0.51, 0.81]	0.78 [0.71, 0.84]



Appendix F GRADE table

GRADE tables for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

Table 5: Toxic or ill appearance for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.00 (0.00 to 0.31)	Serious[1]	No serious	No serious	No serious	MODERATE	0.00	0.94
			Specificity: 0.94 (0.89 to 0.97)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.49 (0.35 to 0.63)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.70	0.80

			Specificity: 0.91 (0.84 to 0.95)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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 6: Clinical history included fever (≥38°C) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.97 (0.87 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.51	0.89
			Specificity: 0.17 (0.08 to 0.31)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 7: Fever (38°C to 39°C) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.63 (0.46 to 0.77)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.47	0.55
			Specificity: 0.39 (0.25 to 0.55)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 8: Fever (≥ 39.1°C) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM	86	Sensitivity: 0.10 (0.03 to 0.24)	Very serious[1]	No serious	No serious	No serious	LOW	0.29	0.50

	compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture		Specificity: 0.78 (0.64 to 0.89)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 9: Fever (threshold undefined) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	89	Sensitivity: 0.82 (0.71 to 0.91)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.75	0.14
			Specificity: 0.10 (0.01 to 0.30)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had	168	Sensitivity: 1.00 (0.69 to 1.00)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.07	1.00

	undergone LP) Reference standard: Positive bacterial CSF culture		Specificity: 0.19 (0.13 to 0.26)	Serious[3]	No serious	No serious	No serious	MODERATE		
1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.92 (0.81 to 0.98)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.10	0.97
			Specificity: 0.26 (0.22 to 0.29)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward)	160	Sensitivity: 1.00 (0.80 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.11	1.00

	Reference standard: Criteria for diagnosis not reported (LP performed)		Specificity: 0.04 (0.02 to 0.09)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; 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 10: Lethargy for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.50 (0.19 to 0.81)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.31	0.97
			Specificity: 0.93 (0.88 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW		

1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.46 (0.32 to 0.61)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW	0.13	0.94
			Specificity: 0.74 (0.70 to 0.77)	Very serious[3]	No serious	No serious	No serious	LOW		
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.87 (0.75 to 0.95)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.46	0.90
			Specificity: 0.55 (0.46 to 0.65)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PMN: polymorphonuclear; PPV: positive predictive value; VM: viral meningitis
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 11: Irritability for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.30 (0.07 to 0.65)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.09	0.95
			Specificity: 0.81 (0.74 to 0.87)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis)	630	Sensitivity: 0.18 (0.09 to 0.31)	Very serious[3]	No serious	No serious	No serious	LOW	0.14	0.93

	Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein		Specificity: 0.91 (0.88 to 0.93)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PMN: polymorphonuclear; 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
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 12: Visit to a physician within 48 hours for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.46 (0.19 to 0.75)	No serious	No serious	No serious	Serious[1]	MODERATE	0.14	0.96
			Specificity: 0.84 (0.78 to 0.88)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 13: Duration of symptoms of 24 hours or less for a diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward) Reference standard: Criteria for diagnosis not reported (LP performed)	160	Sensitivity: 0.65 (0.38 to 0.86)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.16	0.94
			Specificity: 0.61 (0.52 to 0.69)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; LP: lumbar puncture; NPV: negative predictive value; PPV: positive predictive value
[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 14: Duration of illness of over 2 days for diagnosis of bacterial meningitis in babies and children

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

1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	85	Sensitivity: 0.22 (0.12 to 0.33)	Very serious[1]	No serious	No serious	No serious	LOW	0.74	0.23
			Specificity: 0.75 (0.51 to 0.91)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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

Table 15: Cyanosis for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Oostenbrink 2001)	Population: BM compared to other types of meningitis and no meningitis (Babies and children aged from 1 month to 15 years visiting the ED, who were retrospectively	286	Sensitivity: 0.12 (0.06 to 0.21)	Serious[1]	No serious	No serious	No serious	MODERATE	1.00	0.73

	coded as having meningeal signs) Reference standard: Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood		Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; ED: emergency department; 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 16: Presence of rash for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Gowin 2017)	Population: BM compared to VM (Children hospitalised with meningitis at the participating hospital) Reference standard: CSF culture, CSF latex agglutination, Gram stain, and/or PCR	148	Sensitivity: 0.39 (0.29 to 0.51)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.89	0.54
			Specificity: 0.94 (0.85 to 0.98)	Serious[1]	No serious	No serious	Serious[2]	LOW		

1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward) Reference standard: Criteria for diagnosis not reported (LP performed)	160	Sensitivity: 0.29 (0.10 to 0.56)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW	0.26	0.91
			Specificity: 0.90 (0.84 to 0.95)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value; VM: viral meningitis
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 17: Haemorrhagic rash for diagnosis of bacterial meningitis in babies and children

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

1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus	145	Sensitivity: 0.10 (0.03 to 0.24)	Serious[1]	No serious	No serious	No serious	MODERATE	0.29	0.73
			Specificity: 0.90 (0.83 to 0.95)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Oostenbrink 2001)	Population: BM compared to other types of meningitis and no meningitis (Babies and children aged from 1 month to 15 years visiting the ED, who were retrospectively coded as having meningeal signs) Reference standard: Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood	286	Sensitivity: 0.21 (0.13 to 0.32)	Serious[1]	No serious	No serious	No serious	MODERATE	0.75	0.75
			Specificity: 0.97 (0.94 to 0.99)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; ED: emergency department; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value

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

[2] 95% CI crosses 1 decision making threshold

Table 18: Petechiae for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	90	Sensitivity: 0.07 (0.02 to 0.16)	Very serious[1]	No serious	No serious	No serious	LOW	0.28	0.11
			Specificity: 0.38 (0.18 to 0.62)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.20 (0.03 to 0.56)	Serious[3]	No serious	No serious	Serious[2]	LOW	1.00	0.95
			Specificity: 1.00 (0.98 to 1.00)	Serious[3]	No serious	No serious	No serious	MODERATE		

1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward) Reference standard: Criteria for diagnosis not reported (LP performed)	160	Sensitivity: 0.24 (0.07 to 0.50)	Very serious[1]	No serious	No serious	No serious	LOW	0.67	0.92
			Specificity: 0.99 (0.95 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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 19: Signs or symptoms of meningism for diagnosis of bacterial meningitis in babies and children

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

1 (Lembo 1991)	Population: BM compared to other types of meningitis and no meningitis (Children presenting to hospital for evaluation of an acute febrile episode) Reference standard: CSF culture, or identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive culture	160	Sensitivity: 0.70 (0.35 to 0.93)	No serious	No serious	No serious	Very serious[1]	LOW	0.20	0.98
			Specificity: 0.81 (0.74 to 0.87)	No serious	No serious	No serious	No serious	HIGH		
1 (Oostenbrink 2001)	Population: BM compared to other types of meningitis and no meningitis (Babies and children aged from 1 month to 15 years visiting the ED, who were retrospectively coded as having meningeal signs) Reference standard: Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood	286	Sensitivity: 1.00 (0.96 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE	0.41	1.00
			Specificity: 0.39 (0.32 to 0.46)	Serious[2]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; ED: emergency department; NPV: negative predictive value; PPV: positive predictive value
[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 20: Brudzinski's sign for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.53 (0.36 to 0.68)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.68	0.65
			Specificity: 0.78 (0.64 to 0.89)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus	145	Sensitivity: 0.17 (0.07 to 0.33)	Serious[3]	No serious	No serious	No serious	MODERATE	0.47	0.75
			Specificity: 0.92 (0.86 to 0.97)	Serious[3]	No serious	No serious	Serious[2]	LOW		

1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.62 (0.47 to 0.75)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.10	0.94
			Specificity: 0.52 (0.48 to 0.56)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.60 (0.46 to 0.74)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.51	0.81
			Specificity: 0.74 (0.65 to 0.82)	Serious[3]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; 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 21: Kernig's sign for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.53 (0.36 to 0.68)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.91	0.70
			Specificity: 0.96 (0.85 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent	145	Sensitivity: 0.10 (0.03 to 0.24)	Serious[3]	No serious	No serious	No serious	MODERATE	0.33	0.73

	diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus		Specificity: 0.92 (0.86 to 0.97)	Serious[3]	No serious	No serious	Serious[2]	LOW		
1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.14 (0.06 to 0.27)	Very serious[1]	No serious	No serious	No serious	LOW	0.13	0.93
			Specificity: 0.92 (0.90 to 0.94)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward)	160	Sensitivity: 0.71 (0.44 to 0.90)	Very serious[1]	No serious	No serious	Very serious[4]	VERY LOW	0.33	0.96

	Reference standard: Criteria for diagnosis not reported (LP performed)		Specificity: 0.83 (0.76 to 0.89)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.53 (0.39 to 0.67)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.61	0.80
			Specificity: 0.85 (0.77 to 0.91)	Serious[3]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; 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 22: Brudzinski's sign and Kernig's sign for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.45 (0.29 to 0.62)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.90	0.67
			Specificity: 0.96 (0.85 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 23: Neck stiffness for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM	86	Sensitivity: 0.65 (0.48 to 0.79)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.55	0.64

	compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture		Specificity: 0.54 (0.39 to 0.69)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	89	Sensitivity: 0.88 (0.78 to 0.95)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.82	0.50
			Specificity: 0.38 (0.18 to 0.62)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus	145	Sensitivity: 0.90 (0.76 to 0.97)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.40	0.93
			Specificity: 0.49 (0.39 to 0.59)	Serious[3]	No serious	No serious	Serious[2]	LOW		

1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.36 (0.23 to 0.51)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.10	0.93
			Specificity: 0.71 (0.67 to 0.74)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward) Reference standard: Criteria for diagnosis not reported (LP performed)	160	Sensitivity: 0.76 (0.50 to 0.93)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.18	0.96
			Specificity: 0.59 (0.51 to 0.68)	Very serious[1]	No serious	No serious	No serious	LOW		

1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.74 (0.60 to 0.85)	Serious[3]	No serious	No serious	No serious	MODERATE	0.51	0.85
			Specificity: 0.68 (0.59 to 0.76)	Serious[3]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; 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 24: Neck strain for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of	89	Sensitivity: 0.12 (0.05 to 0.22)	Very serious[1]	No serious	No serious	No serious	LOW	0.73	0.23

	meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR		Specificity: 0.86 (0.64 to 0.97)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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

Table 25: Photophobia for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	89	Sensitivity: 0.28 (0.18 to 0.40)	Very serious[1]	No serious	No serious	No serious	LOW	0.95	0.29
			Specificity: 0.95 (0.76 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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

Table 26: Bulging fontanelle for diagnosis of bacterial meningitis in babies

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

		participants								
1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	271	Sensitivity: 0.21 (0.09 to 0.39)	Very serious[1]	No serious	No serious	No serious	LOW	0.24	0.89
			Specificity: 0.91 (0.86 to 0.94)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	98	Sensitivity: 0.44 (0.24 to 0.65)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.55	0.82

			Specificity: 0.88 (0.78 to 0.94)	Serious[3]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PMN: polymorphonuclear; 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 27: Neck stiffness and Brudzinski's sign for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.50 (0.34 to 0.66)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.67	0.64
			Specificity: 0.78 (0.64 to 0.89)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 28: Neck stiffness and Kernig's sign for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.53 (0.36 to 0.68)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.91	0.70
			Specificity: 0.96 (0.85 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 29: Brudzinski's sign, Kernig's sign, and neck stiffness for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM	86	Sensitivity: 0.45 (0.29 to 0.62)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.90	0.67

	compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture		Specificity: 0.96 (0.85 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 30: Brudzinski's sign, or Kernig's sign, or neck stiffness for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.83 (0.70 to 0.92)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.46	0.88
			Specificity: 0.57 (0.48 to 0.66)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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 31: Headache for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture	86	Sensitivity: 0.25 (0.13 to 0.41)	Very serious[1]	No serious	No serious	No serious	LOW	0.45	0.53
			Specificity: 0.74 (0.59 to 0.86)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	87	Sensitivity: 0.11 (0.01 to 0.33)	Very serious[1]	No serious	No serious	No serious	LOW	0.04	0.47
			Specificity: 0.22 (0.13 to 0.34)	Very serious[1]	No serious	No serious	No serious	LOW		

1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus	107	Sensitivity: 0.86 (0.70 to 0.95)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.40	0.84
			Specificity: 0.38 (0.26 to 0.50)	Serious[2]	No serious	No serious	Serious[3]	LOW		
1 (Gowin 2017)	Population: BM compared to VM (Children hospitalised with meningitis at the participating hospital) Reference standard: CSF culture, CSF latex agglutination, Gram stain, and/or PCR	148	Sensitivity: 0.45 (0.34 to 0.56)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.40	0.15
			Specificity: 0.13 (0.06 to 0.23)	Serious[2]	No serious	No serious	No serious	MODERATE		

1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.18 (0.09 to 0.31)	Very serious[1]	No serious	No serious	No serious	LOW	0.05	0.91
			Specificity: 0.69 (0.65 to 0.72)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; 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] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] 95% CI crosses 1 decision making threshold

Table 32: Any symptom of CNS infection (irritability, lethargy, headache, or stiff neck) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Lembo 1991)	Population: BM compared to other types of meningitis and no meningitis (Children presenting to hospital for evaluation of an acute febrile	125	Sensitivity: 1.00 (0.29 to 1.00)	No serious	No serious	No serious	Very serious[1]	LOW	0.03	1.00

	episode) Reference standard: CSF culture, or identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive culture		Specificity: 0.19 (0.12 to 0.27)	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
[1] 95% CI crosses 2 decision making thresholds

Table 33: Focal neurological deficits for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Oostenbrink 2001)	Population: BM compared to other types of meningitis and no meningitis (Babies and children aged from 1 month to 15 years visiting the ED, who were retrospectively coded as having meningeal signs) Reference standard: Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood	286	Sensitivity: 0.23 (0.14 to 0.33)	Serious[1]	No serious	No serious	No serious	MODERATE	0.49	0.74
			Specificity: 0.90 (0.85 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; ED: emergency department; 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 34: Any abnormal neurologic findings for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.92 (0.64 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.24	0.99
			Specificity: 0.84 (0.78 to 0.88)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 35: Seizure for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Gowin 2017)	Population: BM compared to VM (Children hospitalised with meningitis at the participating hospital)	148	Sensitivity: 0.20 (0.12 to 0.30)	Serious[1]	No serious	No serious	No serious	MODERATE	0.74	0.46

	Reference standard: CSF culture, CSF latex agglutination, Gram stain, and/or PCR		Specificity: 0.91 (0.81 to 0.96)	Serious[1]	No serious	No serious	Serious[2]	LOW		
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.23 (0.05 to 0.54)	No serious	No serious	No serious	Serious[2]	MODERATE	0.25	0.96
			Specificity: 0.96 (0.93 to 0.98)	No serious	No serious	No serious	No serious	HIGH		
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.20 (0.03 to 0.56)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.07	0.94
			Specificity: 0.84 (0.77 to 0.89)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; ER: emergency room; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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 36: Focal seizure for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.38 (0.14 to 0.68)	No serious	No serious	No serious	Serious[1]	MODERATE	0.20	0.96
			Specificity: 0.91 (0.87 to 0.95)	No serious	No serious	No serious	Serious[1]	MODERATE		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 37: Convulsions for a diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM	86	Sensitivity: 0.30 (0.17 to 0.47)	Very serious[1]	No serious	No serious	No serious	LOW	0.67	0.59

	compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture		Specificity: 0.87 (0.74 to 0.95)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	89	Sensitivity: 0.03 (0.00 to 0.10)	Very serious[1]	No serious	No serious	No serious	LOW	0.33	0.20
			Specificity: 0.81 (0.58 to 0.95)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward)	160	Sensitivity: 0.12 (0.01 to 0.36)	Very serious[1]	No serious	No serious	No serious	LOW	0.25	0.90

	Reference standard: Criteria for diagnosis not reported (LP performed)		Specificity: 0.96 (0.91 to 0.98)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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

Table 38: Complex convulsions for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Oostenbrink 2001)	Population: BM compared to other types of meningitis and no meningitis (Babies and children aged from 1 month to 15 years visiting the ED, who were retrospectively coded as having meningeal signs) Reference standard: Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood	286	Sensitivity: 0.06 (0.02 to 0.13)	Serious[1]	No serious	No serious	No serious	MODERATE	0.71	0.72
			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; ED: emergency department; 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 39: Convulsion with fever for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.02 (0.00 to 0.11)	Very serious[1]	No serious	No serious	No serious	LOW	0.01	0.91
			Specificity: 0.84 (0.81 to 0.87)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; LP: lumbar puncture; NPV: negative predictive value; PMN: polymorphonuclear; PPV: positive predictive value
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 40: Convulsion without fever for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis)	630	Sensitivity: 0.00 (0.00 to 0.07)	Very serious[1]	No serious	No serious	No serious	LOW	0.00	0.92

	Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein		Specificity: 0.99 (0.98 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; LP: lumbar puncture; NPV: negative predictive value; PMN: polymorphonuclear; PPV: positive predictive value
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 41: Reduced consciousness for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 1.00 (0.69 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.08	1.00
			Specificity: 0.22 (0.16 to 0.29)	Serious[1]	No serious	No serious	No serious	MODERATE		

1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward) Reference standard: Criteria for diagnosis not reported (LP performed)	160	Sensitivity: 0.59 (0.33 to 0.82)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW	0.36	0.95
			Specificity: 0.87 (0.81 to 0.92)	Very serious[3]	No serious	No serious	Serious[2]	VERY LOW		
1 (Oostenbrink 2001)	Population: BM compared to other types of meningitis and no meningitis (Babies and children aged from 1 month to 15 years visiting the ED, who were retrospectively coded as having	286	Sensitivity: 0.63 (0.52 to 0.73)	Serious[1]	No serious	No serious	No serious	MODERATE	0.82	0.86

	meningeal signs) Reference standard: Leucocyte count of >5 cells ul-1 in the CSF, with positive bacterial cultures of CSF or blood		Specificity: 0.94 (0.90 to 0.97)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; ED: emergency department; LP: lumbar puncture; 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
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 42: Shock for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Walsh-Kelly 1992)	Population: BM compared to VM (Children undergoing LP) Reference standard: CSF culture, CSF latex agglutination or Gram stain	172	Sensitivity: 0.17 (0.08 to 0.30)	Serious[1]	No serious	No serious	No serious	MODERATE	0.60	0.72

			Specificity: 0.95 (0.89 to 0.98)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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 43: Respiratory symptoms for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus	145	Sensitivity: 0.13 (0.04 to 0.27)	Serious[1]	No serious	No serious	No serious	MODERATE	0.19	0.70
			Specificity: 0.79 (0.70 to 0.86)	Serious[1]	No serious	No serious	No serious	MODERATE		

1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.50 (0.19 to 0.81)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.38	0.97
			Specificity: 0.95 (0.90 to 0.98)	Serious[1]	No serious	No serious	No serious	MODERATE		

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

Table 44: Gastrointestinal symptoms for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious	145	Sensitivity: 0.68 (0.51 to 0.81)	Serious[1]	No serious	No serious	No serious	MODERATE	0.35	0.81

	meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus		Specificity: 0.52 (0.42 to 0.62)	Serious[1]	No serious	No serious	Serious[2]	LOW		

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

Table 45: Nausea for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	89	Sensitivity: 0.79 (0.68 to 0.88)	Very serious[1]	No serious	No serious	No serious	LOW	0.84	0.44
			Specificity: 0.52 (0.30 to 0.74)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; NPV: negative predictive value; PCR: positive polymerase chain reaction; 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

Table 46: Vomiting for diagnosis of bacterial meningitis in babies and children

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

		participants								
1 (De Cauwer 2007)	Population: BM compared to VM (Children aged 0 to 15 years old admitted to the paediatric ward for clinical observations of meningitis, and final diagnosis of VM or BM) Reference standard: CSF culture, blood culture, Gram stain, or PCR	89	Sensitivity: 0.81 (0.70 to 0.89)	Very serious[1]	No serious	No serious	No serious	LOW	0.83	0.43
			Specificity: 0.48 (0.26 to 0.70)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Fretzayas 2010)	Population: BM compared to other types of meningitis and no meningitis (Children aged 1 month to 14 years who underwent diagnostic LP for infectious meningitis) Reference standard: Blood or CSF culture and/or Gram stain, or by PCR for meningococcus	145	Sensitivity: 0.60 (0.43 to 0.75)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.41	0.81
			Specificity: 0.67 (0.57 to 0.76)	Serious[3]	No serious	No serious	No serious	MODERATE		

1 (Gowin 2017)	Population: BM compared to VM (Children hospitalised with meningitis at the participating hospital) Reference standard: CSF culture, CSF latex agglutination, Gram stain, and/or PCR	148	Sensitivity: 0.07 (0.03 to 0.15)	Serious[3]	No serious	No serious	No serious	MODERATE	0.11	0.16
			Specificity: 0.23 (0.14 to 0.36)	Serious[3]	No serious	No serious	No serious	MODERATE		
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.20 (0.03 to 0.56)	Serious[3]	No serious	No serious	Serious[2]	LOW	0.04	0.94
			Specificity: 0.73 (0.65 to 0.80)	Serious[3]	No serious	No serious	No serious	MODERATE		

1 (Levy 1990)	Population: BM compared to other types of meningitis and no meningitis (Children undergoing LP for presumed diagnosis of meningitis) Reference standard: High cell counts (predominantly PMN cells), low or normal sugar levels, and elevated protein	630	Sensitivity: 0.62 (0.47 to 0.75)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.08	0.92
			Specificity: 0.39 (0.35 to 0.43)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; NPV: negative predictive value; PCR: positive polymerase chain reaction; PMN: polymorphonuclear; 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 47: Nausea or vomiting for a diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Bilavsky 2013)	Population: BM compared to no meningitis (Babies and children aged 3 months to 17 years with a confirmed diagnosis of BM	86	Sensitivity: 0.70 (0.53 to 0.83)	Very serious[1]	No serious	No serious	No serious	LOW	0.88	0.78

	compared with matched controls without BM or VM) Reference standard: Presence of a positive bacterial CSF culture		Specificity: 0.91 (0.79 to 0.98)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		
1 (Nielsen 1988)	Population: BM compared to other types of meningitis and no meningitis (Children, aged under 16 years, admitted for observation for suspected meningitis to the paediatric ward) Reference standard: Criteria for diagnosis not reported (LP performed)	160	Sensitivity: 0.71 (0.44 to 0.90)	Very serious[1]	No serious	No serious	Very serious[3]	VERY LOW	0.14	0.93
			Specificity: 0.48 (0.39 to 0.56)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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] 95% CI crosses 2 decision making thresholds

Table 48: Diarrhoea for diagnosis of bacterial meningitis in babies and children

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

1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.30 (0.07 to 0.65)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.05	0.93
			Specificity: 0.63 (0.55 to 0.71)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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: Constipation for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.00 (0.00 to 0.31)	Serious[1]	No serious	No serious	No serious	MODERATE	0.00	0.94
			Specificity: 0.96 (0.91 to 0.98)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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 50: Loss of appetite for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Krishna 1983)	Population: BM compared to other types of meningitis and no meningitis (Paediatric patients aged <18 years who had undergone LP) Reference standard: Positive bacterial CSF culture	168	Sensitivity: 0.20 (0.03 to 0.56)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.05	0.94
			Specificity: 0.73 (0.66 to 0.80)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CI: confidence interval; CSF: cerebrospinal fluid; LP: lumbar puncture; 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 51: Presence of abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and	241	Sensitivity: 0.23 (0.05 to 0.54)	No serious	No serious	No serious	Serious[1]	MODERATE	0.23	0.96

	fever) Reference standard: CSF pleocytosis		Specificity: 0.96 (0.92 to 0.98)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 52: Presence of at least 1 of: visit to physician within 48 hours or focal type of seizure, for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.69 (0.39 to 0.91)	No serious	No serious	No serious	Very serious[1]	LOW	0.15	0.98
			Specificity: 0.78 (0.72 to 0.83)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 2 decision making thresholds

Table 53: Presence of at least 1 of: visit to physician within 48 hours or abnormal neurologic finding, for diagnosis of bacterial meningitis in babies and children

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

1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 1.00 (0.75 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.16	1.00
			Specificity: 0.71 (0.65 to 0.77)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 54: Presence of at least 1 of: visit to physician within 48 hours or seizure at presentation, for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.54 (0.25 to 0.81)	No serious	No serious	No serious	Serious[1]	MODERATE	0.15	0.97
			Specificity: 0.82 (0.76 to 0.87)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room

[1] 95% CI crosses 1 decision making threshold

Table 55: Presence of at least 1 of: focal seizure or abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations) for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 0.46 (0.19 to 0.75)	No serious	No serious	No serious	Serious[1]	MODERATE	0.19	0.97
			Specificity: 0.89 (0.84 to 0.93)	No serious	No serious	No serious	Serious[1]	MODERATE		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 56: Presence of at least 1 of: focal seizure or abnormal neurologic findings, for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and	241	Sensitivity: 0.92 (0.64 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.23	0.99

	fever) Reference standard: CSF pleocytosis		Specificity: 0.82 (0.76 to 0.87)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 57: Presence of at least 1 of: visit to physician within 48 hours, seizure, focal seizure, abnormal physical finding (rash/petechiae, cyanosis, hypotension, or grunting respirations), or abnormal neurologic findings, for diagnosis of bacterial meningitis in babies and children

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Joffe 1983)	Population: BM compared to no meningitis (Children aged 6 months to 6 years, presenting at the ER with a first episode of seizure and fever) Reference standard: CSF pleocytosis	241	Sensitivity: 1.00 (0.75 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.13	1.00
			Specificity: 0.62 (0.55 to 0.68)	No serious	No serious	No serious	No serious	HIGH		

BM: bacterial meningitis; CSF: cerebrospinal fluid; ER: emergency room
[1] 95% CI crosses 1 decision making threshold

Table 58: Fever for diagnosis of bacterial meningitis in adults

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

1 (Behrman 1989)	Population: BM compared to other types of meningitis (mixed) (Older adults, aged ≥65 years admitted to the participating hospital, with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess) Reference standard: CSF culture, other CSF findings and/or blood culture	50	Sensitivity: 1.00 (0.88 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.65	1.00
			Specificity: 0.20 (0.06 to 0.44)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 59: Signs or symptoms of meningism for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Behrman 1989)	Population: BM compared to other types of meningitis (mixed) (Older adults, aged ≥65 years admitted to the participating	50	Sensitivity: 0.57 (0.37 to 0.75)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.61	0.41

	hospital, with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess) Reference standard: CSF culture, other CSF findings and/or blood culture		Specificity: 0.45 (0.23 to 0.68)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 60: Brudzinski's sign or Kernig's sign for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magazzini 2012)	Population: BM compared to VM (Adults presenting to the ED and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial, including meningoencephalitis) Reference standard: Criteria for diagnosis not reported (LP performed)	202	Sensitivity: 0.47 (0.32 to 0.64)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.27	0.84
			Specificity: 0.69 (0.61 to 0.76)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; ED: emergency department; LP: lumbar puncture; 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 61: Neck stiffness for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magazzini 2012)	Population: BM compared to VM (Adults presenting to the ED and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial, including meningoencephalitis) Reference standard: Criteria for diagnosis not reported (LP performed)	202	Sensitivity: 0.70 (0.53 to 0.83)	Serious[1]	No serious	No serious	No serious	MODERATE	0.24	0.86
			Specificity: 0.45 (0.37 to 0.53)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; ED: emergency department; LP: lumbar puncture; 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 62: Brudzinski's sign, or Kernig's sign, or neck stiffness for diagnosis of bacterial meningitis in adults

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

1 (Magazzini 2012)	Population: BM compared to VM (Adults presenting to the ED and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial, including meningoencephalitis) Reference standard: Criteria for diagnosis not reported (LP performed)	202	Sensitivity: 0.70 (0.53 to 0.83)	Serious[1]	No serious	No serious	No serious	MODERATE	0.22	0.84
			Specificity: 0.39 (0.31 to 0.47)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; ED: emergency department; LP: lumbar puncture; VM: viral meningitis
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 63: Headache for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Behrman 1989)	Population: BM compared to other types of meningitis (mixed) (Older adults, aged ≥65 years admitted to the participating	50	Sensitivity: 0.27 (0.12 to 0.46)	Very serious[1]	No serious	No serious	No serious	LOW	0.44	0.31

	hospital, with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess) Reference standard: CSF culture, other CSF findings and/or blood culture		Specificity: 0.50 (0.27 to 0.73)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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: Focal neurological deficits for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Behrman 1989)	Population: BM compared to other types of meningitis (mixed) (Older adults, aged ≥65 years admitted to the participating hospital, with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess) Reference standard: CSF culture, other CSF findings and/or blood culture	50	Sensitivity: 0.43 (0.25 to 0.63)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.65	0.43
			Specificity: 0.65 (0.41 to 0.85)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

1 (Brivet 2005)	Population: BM compared to VM (Adults aged over 16 years hospitalized at the participating hospital with a diagnosis of community-acquired BM or VM recorded in the hospital discharge diagnostic database) Reference standard: Bacterial pathogens identified in both CSF and blood cultures, CSF culture alone, or blood culture alone	144	Sensitivity: 0.36 (0.26 to 0.46)	Very serious[1]	No serious	No serious	No serious	LOW	1.00	0.48
			Specificity: 1.00 (0.93 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 65: Neurological complaints for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magazzini 2012)	Population: BM compared to VM (Adults presenting to the ED and admitted to the infectious disease department or intensive care	202	Sensitivity: 0.25 (0.13 to 0.41)	Serious[1]	No serious	No serious	No serious	MODERATE	0.29	0.82

	unit with a discharge diagnosis of meningitis, viral or bacterial, including meningoencephalitis) Reference standard: Criteria for diagnosis not reported (LP performed)		Specificity: 0.85 (0.78 to 0.90)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; ED: emergency department; LP: lumbar puncture; 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: Seizures for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Brivet 2005)	Population: BM compared to VM (Adults aged over 16 years hospitalized at the participating hospital with a diagnosis of community-acquired BM or VM recorded in the hospital discharge diagnostic database) Reference standard: Bacterial pathogens identified in both CSF and blood cultures, CSF culture alone, or	144	Sensitivity: 0.23 (0.15 to 0.33)	Very serious[1]	No serious	No serious	No serious	LOW	1.00	0.44
			Specificity: 1.00 (0.93 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

	blood culture alone									

BM: bacterial meningitis; CSF: cerebrospinal fluid; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 67: Altered mental state for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Behrman 1989)	Population: BM compared to other types of meningitis (mixed) (Older adults, aged ≥65 years admitted to the participating hospital, with the discharge diagnosis of meningitis, subdural empyema, brain abscess, or epidural abscess) Reference standard: CSF culture, other CSF findings and/or blood culture	50	Sensitivity: 0.93 (0.78 to 0.99)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.65	0.71
			Specificity: 0.25 (0.09 to 0.49)	Very serious[1]	No serious	No serious	No serious	LOW		

1 (Brivet 2005)	Population: BM compared to VM (Adults aged over 16 years hospitalized at the participating hospital with a diagnosis of community-acquired BM or VM recorded in the hospital discharge diagnostic database) Reference standard: Bacterial pathogens identified in both CSF and blood cultures, CSF culture alone, or blood culture alone	144	Sensitivity: 0.90 (0.82 to 0.95)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.99	0.85
			Specificity: 0.98 (0.90 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Magazzini 2012)	Population: BM compared to VM (Adults presenting to the ED and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial, including meningoencephalitis) Reference standard: Criteria for diagnosis not reported (LP	202	Sensitivity: 0.68 (0.51 to 0.81)	Serious[3]	No serious	No serious	No serious	MODERATE	0.43	0.91
			Specificity: 0.78 (0.71 to 0.84)	Serious[3]	No serious	No serious	No serious	MODERATE		

	performed)									

BM: bacterial meningitis; CSF: cerebrospinal fluid; ED: emergency department; LP: lumbar puncture; 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 68: Shock for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Brivet 2005)	Population: BM compared to VM (Adults aged over 16 years hospitalized at the participating hospital with a diagnosis of community-acquired BM or VM recorded in the hospital discharge diagnostic database) Reference standard: Bacterial pathogens identified in both CSF and blood cultures, CSF culture alone, or blood culture alone	144	Sensitivity: 0.51 (0.40 to 0.62)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	1.00	0.55
			Specificity: 1.00 (0.93 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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

Table 69: Severe sepsis or shock for diagnosis of bacterial meningitis in adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magazzini 2012)	Population: BM compared to VM (Adults presenting to the ED and admitted to the infectious disease department or intensive care unit with a discharge diagnosis of meningitis, viral or bacterial, including meningoencephalitis) Reference standard: Criteria for diagnosis not reported (LP performed)	202	Sensitivity: 0.60 (0.43 to 0.75)	Serious[1]	No serious	No serious	Serious[2]	LOW	1.00	0.91
			Specificity: 1.00 (0.98 to 1.00)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; ED: emergency department; LP: lumbar puncture; 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 70: Presence of at least 1 of: altered mental status, focal neurological deficits, seizures, or shock, for diagnosis of bacterial meningitis in adults

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

1 (Brivet 2005)	Population: BM compared to VM (Adults aged over 16 years hospitalized at the participating hospital with a diagnosis of community-acquired BM or VM recorded in the hospital discharge diagnostic database) Reference standard: Bacterial pathogens identified in both CSF and blood cultures, CSF culture alone, or blood culture alone	144	Sensitivity: 0.99 (0.94 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW	0.99	0.98
			Specificity: 0.98 (0.90 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; VM: viral meningitis
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 71: Fever for diagnosis of bacterial meningitis in older children and adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magnussen 1980)	Population: BM compared to VM (Older children aged ≥12 years, and adults with a discharge diagnosis of acute meningitis)	59	Sensitivity: 0.68 (0.46 to 0.85)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.68	0.76

	Reference standard: CSF Gram stain, CSF culture, other CSF findings, or blood culture		Specificity: 0.76 (0.59 to 0.89)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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 72: Neck stiffness for diagnosis of bacterial meningitis in older children and adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magnussen 1980)	Population: BM compared to VM (Older children aged ≥12 years, and adults with a discharge diagnosis of acute meningitis)	59	Sensitivity: 0.88 (0.69 to 0.97)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.46	0.73
	Reference standard: CSF Gram stain, CSF culture, other CSF findings, or blood culture		Specificity: 0.24 (0.11 to 0.41)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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 73: Headache for diagnosis of bacterial meningitis in older children and adults

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

1 (Magnussen 1980)	Population: BM compared to VM (Older children aged ≥12 years, and adults with a discharge diagnosis of acute meningitis) Reference standard: CSF Gram stain, CSF culture, other CSF findings, or blood culture	59	Sensitivity: 0.48 (0.28 to 0.69)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.26	0.00
			Specificity: 0.00 (0.00 to 0.10)	Serious[1]	No serious	No serious	No serious	MODERATE		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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 74: Focal neurological deficits for diagnosis of bacterial meningitis in older children and adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magnussen 1980)	Population: BM compared to VM (Older children aged ≥12 years, and adults with a discharge diagnosis of acute meningitis) Reference standard: CSF Gram stain, CSF culture, other CSF findings, or blood culture	59	Sensitivity: 0.20 (0.07 to 0.41)	Serious[1]	No serious	No serious	No serious	MODERATE	0.83	0.62
			Specificity: 0.97 (0.85 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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 75: Altered mental state for diagnosis of bacterial meningitis in older children and adults

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Magnussen 1980)	Population: BM compared to VM (Older children aged ≥12 years, and adults with a discharge diagnosis of acute meningitis) Reference standard: CSF Gram stain, CSF culture, other CSF findings, or blood culture	59	Sensitivity: 0.44 (0.24 to 0.65)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.92	0.70
			Specificity: 0.97 (0.85 to 1.00)	Serious[1]	No serious	No serious	Serious[2]	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid; 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 76: Reduced general condition for diagnosis of bacterial meningitis in undefined age range

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those	92	Sensitivity: 0.63 (0.49 to 0.75)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	1.00	0.63

	with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count		Specificity: 1.00 (0.90 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 77: Cyanosis for diagnosis of bacterial meningitis in undefined age range

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count	92	Sensitivity: 0.05 (0.01 to 0.15)	Very serious[1]	No serious	No serious	No serious	LOW	1.00	0.40
			Specificity: 1.00 (0.90 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 78: Petechiae (≤4mm) for diagnosis of bacterial meningitis in undefined age range

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

1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count	92	Sensitivity: 0.52 (0.38 to 0.65)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.76	0.50
			Specificity: 0.75 (0.58 to 0.88)	Very serious[1]	No serious	No serious	No serious	LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 79: Ecchymoses (>4 mm) for diagnosis of bacterial meningitis in undefined age range

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count	92	Sensitivity: 0.11 (0.04 to 0.22)	Very serious[1]	No serious	No serious	No serious	LOW	0.25	0.26
			Specificity: 0.50 (0.33 to 0.67)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid

[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 80: Neck stiffness for diagnosis of bacterial meningitis in undefined age range

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count	92	Sensitivity: 0.89 (0.78 to 0.96)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.79	0.79
			Specificity: 0.64 (0.46 to 0.79)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 81: Reduced consciousness for diagnosis of bacterial meningitis in undefined age range

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those	92	Sensitivity: 0.54 (0.40 to 0.67)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.97	0.57

	with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count		Specificity: 0.97 (0.85 to 1.00)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 82: Cold extremities for diagnosis of bacterial meningitis in undefined age range

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count	92	Sensitivity: 0.16 (0.08 to 0.28)	Very serious[1]	No serious	No serious	No serious	LOW	0.75	0.41
			Specificity: 0.92 (0.78 to 0.98)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

BM: bacterial meningitis; CSF: cerebrospinal fluid
[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 83: Body pain for diagnosis of bacterial meningitis in undefined age range

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

1 (Borchsenius 1991)	Population: BM compared to no meningitis (Patients with suspected systemic meningococcal disease admitted to hospital, those with meningitis only are included in this review) Reference standard: CSF culture, blood culture, and/or CSF leukocyte count	92	Sensitivity: 0.27 (0.16 to 0.40)	Very serious[1]	No serious	No serious	No serious	LOW	0.71	0.42
			Specificity: 0.83 (0.67 to 0.94)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

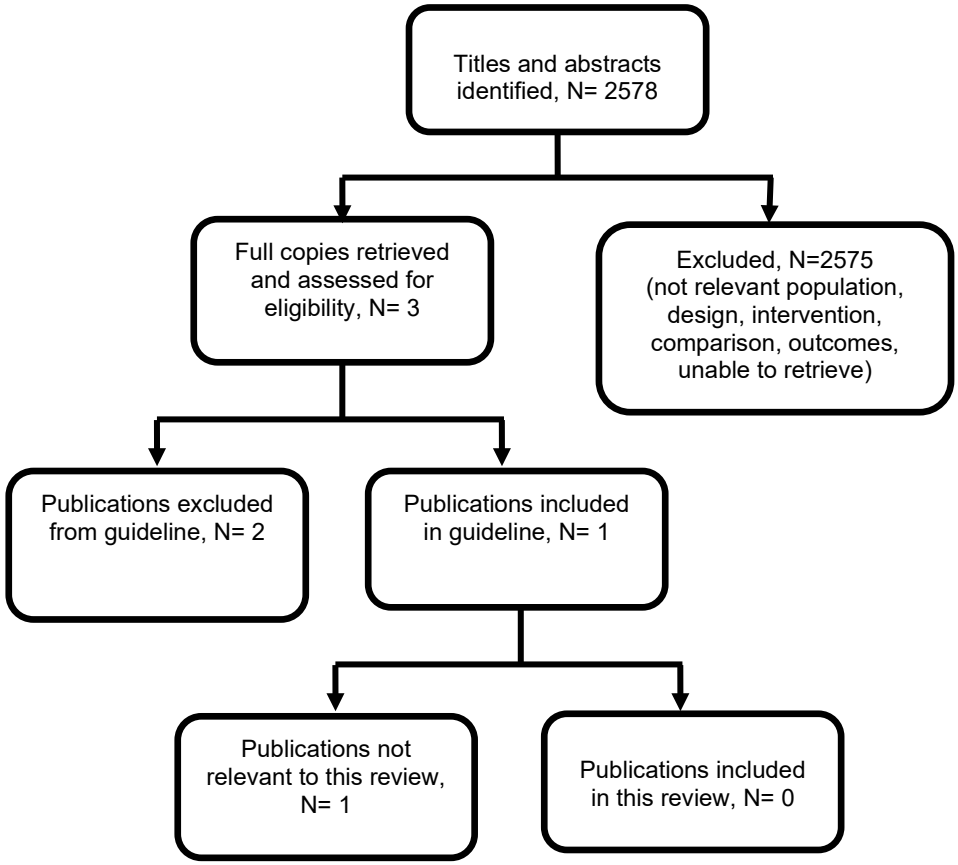
BM: bacterial meningitis; CSF: cerebrospinal fluid
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[2] 95% CI crosses 1 decision making threshold

Appendix G Economic evidence study selection

Study selection for: What symptoms and signs, individually or in combination, are associated with 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 23).

Figure 23: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

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

Appendix I Economic model

Economic model for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

Table 84: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Abdelmaguid, N, Seleem, W. S, Soliman, A. T et al. (2019) Clinical presentations, laboratory analysis and linear growth in 50 neonates and young infants with acute meningitis: One year experience of a single center in Qatar. Mediterranean Journal of Hematology and Infectious Diseases 11 (1)	- Population not of interest for review *Population combination of neonates and young babies*
Akaishi, T, Kobayashi, J, Abe, M et al. (2019) Sensitivity and specificity of meningeal signs in patients with meningitis. Journal of General and Family MedicineJ Gen Fam Med 20(5): 193-198	- Population not of interest for review *Meningitis (all causes, not sub-grouped by cause). Individual studies included in this review were assessed for potential inclusion*
Akpede, G.O, Abiodun, P.O, Ambe, J.P et al. (1994) Presenting features of bacterial meningitis in young infants. Annals of Tropical Paediatrics 14(3): 245-252	- Country not of interest for review *Non OECD high income country*
Akpede, G.O; Jalo, I; Dawodu, S.O. (2002) A revised clinical method for assessment of severity of acute bacterial meningitis. Annals of Tropical Paediatrics 22(1): 33-44	- Country not of interest for review *Non OECD high income country*
Al-Mazrou, Y.Y, Musa, E.K, Abdalla, M.N et al. (2003) Disease burden and case management of bacterial meningitis among children under 5 years of age in Saudi Arabia. Saudi Medical Journal 24(12): 1300-1307	- No outcomes of interest for review
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)	- Country not of interest for review *Non OECD high income country*
Amarilyo, G, Alper, A, Ben-Tov, A et al. (2011) Diagnostic accuracy of clinical symptoms and signs in children with meningitis. Pediatric Emergency Care 27(3): 196-199	- Population not of interest for review *89% Aseptic meningitis*
Amaya-Villar, R, Garcia-Cabrera, E, Sulleiro-Igual, E et al. (2010) Three-year multicenter	- Comparison not of interest for review

Study	Code [Reason]
surveillance of community-acquired listeria monocytogenes meningitis in adults. BMC Infectious Diseases 10 (no pagination)	*Bacterial meningitis caused by listeria monocytogenes vs. bacterial meningitis with other causes*
Aminzadeh, Z and Roudgari, A. (2010) Jolt accentuation of headache in diagnosis of acute meningitis. Iranian Journal of Clinical Infectious Diseases 5(2): 106-109	- Country not of interest for review *Non-OECD high income country*
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(2): 115-122	- Population not of interest for review *Acute meningitis of unknown aetiology*
Andersen, J, Backer, V, Voldsgaard, P et al. (1997) Acute meningococcal meningitis: analysis of features of the disease according to the age of 255 patients. Copenhagen Meningitis Study Group. Journal of Infection 34(3): 227-235	- Study design not of interest for review *Prevalence study*
Anttila, M; Himberg, J. J; Peltola, H. (1992) Precise quantification of fever in childhood bacterial meningitis. Clinical PediatricsClin Pediatr (Phila) 31(4): 221-7	- No outcomes of interest for review *Quantification of fever*
Attia, J, Hatala, R, Cook, D.J et al. (1999) The rational clinical examination. Does this adult patient have acute meningitis?. JAMA 282(2): 175-181	- Population not of interest for review *Acute meningitis (all causes). Individual studies included in this review were assessed for potential inclusion*
Baraff, L. J, Oslund, S. A, Schriger, D. L et al. (1992) Probability of bacterial infections in febrile infants less than three months of age: A meta-analysis. Pediatric infectious disease journal 11(3): 257-265	- Population not of interest for review *<50% of babies with bacterial infections diagnosed with bacterial meningitis*
Baumgartner, E. T; Augustine, R. A; Steele, R. W. (1983) Bacterial meningitis in older neonates. American Journal of Diseases of Children 137(11): 1052-1054	- Population not of interest for review *75% of population are neonates <28 days*
Beg, M, Ali, S, Ahmad, S et al. (2007) A study of computed tomography of head before lumbar puncture in patients with suspected meningitis. Journal, Indian Academy of Clinical Medicine 8(4): 355-359	- Population not of interest for review *75% of population with tuberculous meningitis*
Best, J and Hughes, S. (2008) Evidence behind the WHO guidelines: Hospital care for children - What are the useful clinical features of bacterial	- Study design not of interest for review *clinical review*

Study	Code [Reason]
meningitis found in infants and children?. Journal of Tropical Pediatrics 54(2): 83-86	
Bhat, B.V, Verma, I.C, Puri, R.K et al. (1991) A profile of pyogenic meningitis in children. Journal of the Indian Medical Association 89(8): 224-227	- Country not of interest for review *Non-OECD high income country*
Bineshfar, Niloufar, Rezaei, Ali, Mirahmadi, Alireza et al. (2022) Evaluation of the epidemiologic, clinical, radiologic, and treatment methods of patients with subacute and chronic meningitis. BMC neurology 22(1): 340	- Comparison not of interest for review *No non-meningitis comparison arm*
Bingen, E, Levy, C, Varon, E et al. (2008) Pneumococcal meningitis in the era of pneumococcal conjugate vaccine implementation. European Journal of Clinical Microbiology and Infectious Diseases 27(3): 191-199	- Study design not of interest for review *Prevalence study*
Bodilsen, J, Brouwer, M. C, Kjaergaard, N et al. (2018) Community-acquired meningitis in adults caused by Escherichia coli in Denmark and The Netherlands. Journal of Infection 77(1): 25-29	- Study design not of interest for review *Prevalence study*
Bonadio, W. A; Mannenbach, M; Krippendorf, R. (1990) Bacterial meningitis in older children. American Journal of Diseases of Children 144(4): 463-465	- Study design not of interest for review *Case series*
Brady, J.P, Awan, F.B, Wafula, E.M et al. (1993) Recognition of illness in very young infants by inexperienced health workers. Annals of Tropical Paediatrics 13(4): 401-407	- Country not of interest for review *Non-OECD high income country*
Bredfeldt, R. C, Cain, S. R, Schutze, G. E et al. (1995) Relation between passive tobacco smoke exposure and the development of bacterial meningitis in children. Journal of the American Board of Family PracticeJ Am Board Fam Pract 8(2): 95-8	- Study design not of interest for review *Case-control study*
Brent, A.J, Lakhanpaul, M, Ninis, N et al. (2011) Evaluation of temperature-pulse centile charts in identifying serious bacterial illness: observational cohort study. Archives of Disease in Childhood 96(4): 368-373	- Population not of interest for review *Emergency department dataset didn't include bacterial meningitis or meningococcal disease in their serious bacterial infection population*
Bruyn, G. A, Kremer, H. P, de Marie, S et al. (1989) Clinical evaluation of pneumococcal meningitis in adults over a twelve-year period. European Journal of Clinical Microbiology &	- Study design not of interest for review *Prevalence study*

Study	Code [Reason]
Infectious DiseasesEur J Clin Microbiol Infect Dis 8(8): 695-700	
Cabellos, C, Verdaguer, R, Olmo, M et al. (2009) Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine 88(2): 115-119	- Study design not of interest for review *Prevalence study*
Carrie, C, Walewski, V, Levy, C et al. (2019) Klebsiella pneumoniae and Klebsiella oxytoca meningitis in infants. Epidemiological and clinical features. Archives de Pediatrie 26(1): Dec-15	- Study design not of interest for review *Case report*
Casu, S, Blau, J, Schempf, B et al. (2019) If you don't take a temperature, you can't find a fever: Awareness in out-of-hospital vital signs in cases of suspected sepsis. Notfall und Rettungsmedizin 22(6): 509-513	- Comparison not of interest for review *Compares mean values in vital signs across different disease groups (pneumonia, meningitis, septic shock)*
Chadwick, D. R and Lever, A. M. L. (2002) The impact of new diagnostic methodologies in the management of meningitis in adults at a teaching hospital. QJM - Monthly Journal of the Association of Physicians 95(10): 663-670	- Population not of interest for review *33% of population had bacterial meningitis or meningococcal disease*
Chan, Y. C, Wilder-Smith, A, Ong, B. K et al. (2002) Adult community acquired bacterial meningitis in a Singaporean teaching hospital. A seven-year overview (1993-2000). Singapore Medical Journal 43(12): 632-6	- Study design not of interest for review *Case report*
Chang, C. J, Chang, W. N, Huang, L. T et al. (2004) Bacterial meningitis in infants: The epidemiology, clinical features, and prognostic factors. Brain and Development 26(3): 168-175	- Study design not of interest for review *Prevalence data on signs and symptoms*
Chang, W. N, Huang, C. R, Lu, C. H et al. (2012) Adult Klebsiella pneumoniae meningitis in Taiwan: an overview. Acta Neurologica Taiwanica 21(2): 87-96	- Country not of interest for review *Non OECD high income country*
Chang, W. N, Lu, C. H, Huang, C. R et al. (2007) Epidemiology of adult staphylococcal meningitis in Southern Taiwan: A clinical comparison of Staphylococcus aureus infection and coagulase-negative staphylococcal infection. Japanese Journal of Infectious Diseases 60(5): 262-266	- Study design not of interest for review *Narrative review and case series*
Chao, Y.N; Chiu, N.C; Huang, F.Y. (2008) Clinical features and prognostic factors in childhood pneumococcal meningitis. Journal of	- Country not of interest for review *Non OECD high income country*

Study	Code [Reason]
Microbiology, Immunology and Infection 41(1): 48-53	
Chen, S. Y, Lee, J. J, Chien, C. C et al. (2020) High incidence of severe neurological manifestations and high mortality rate for adult Listeria monocytogenes meningitis in Taiwan. Journal of Clinical Neuroscience 71: 177-185	- Study design not of interest for review *Case series*
Chen, S.H, Yen, M.H, Chiu, C.H et al. (2006) Clinical observation of meningitis caused by penicilin-susceptible and -non-susceptible Streptococcus pneumoniae in Taiwanese children. Annals of Tropical Paediatrics 26(3): 181-185	- Study design not of interest for review *Prevalence data for signs and symptoms*
Cheng, B. C, Chang, W. N, Lu, C. H et al. (2004) Bacterial meningitis in hemodialyzed patients. Journal of Nephrology 17(2): 236-241	- Country not of interest for review *Non OECD high income country*
Cleland, G, Leung, C, Wan Sai Cheong, J et al. (2018) Paediatric invasive Haemophilus influenzae in Queensland, Australia, 2002-2011: Young Indigenous children remain at highest risk. Journal of Paediatrics & Child HealthJ Paediatr Child Health 54(1): 36-41	- Population not of interest for review *13% of population had meningitis*
Cohen, J, Cristofaro, P, Carlet, J et al. (2004) New method of classifying infections in critically ill patients. Critical Care MedicineCrit Care Med 32(7): 1510-26	- No outcomes of interest for review *Mortality*
Coll, M.T, Uriz, M.S, Pineda, V et al. (1994) Meningococcal meningitis with 'normal' cerebrospinal fluid. Journal of Infection 29(3): 289-294	- Study design not of interest for review *Case series*
Curtis, S, Stobart, K, Vandermeer, B et al. (2010) Clinical features suggestive of meningitis in children: a systematic review of prospective data. Pediatrics 126(5): 952-960	- Country not of interest for review
Davey, P. G; Cruikshank, J. K; McManus, I. C. (1982) Bacterial meningitis - ten years experience. Journal of Hygiene 88(3): 383-401	- Study design not of interest for review *Case series*
de la Torre, Mercedes, Gomez, Borja, Velasco, Roberto et al. (2022) Value of Temperature for Predicting Invasive Bacterial Infection in Febrile Infants: A Spanish Pediatric Emergency Research Group (RISeuP-SPERG) Study.	- Insufficient data to include in review

Study	Code [Reason]
Pediatric emergency care 38(6): e1294-e1297	
Deivanayagam, N, Ashok, T. P, Nedunchelian, K et al. (1993) Bacterial meningitis: diagnosis by latex agglutination test and clinical features. Indian pediatrics 30(4): 495-500	- Country not of interest for review *Non-OECD high income country*
Delerme, S, Castro, S, Viallon, A et al. (2009) Meningitis in elderly patients. European Journal of Emergency Medicine 16(5): 273-6	- Comparison not of interest for review *Younger vs older patients presenting with acute meningitis*
Domingo, P, Pomar, V, de Benito, N et al. (2013) The spectrum of acute bacterial meningitis in elderly patients. BMC Infectious Diseases 13: 108	- Comparison not of interest for review *Comparison between different age groups*
Dubos, F, Martinot, A, Gendrel, D et al. (2009) Clinical decision rules for evaluating meningitis in children. Current Opinion in NeurologyCurr Opin Neurol 22(3): 288-93	- Study design not of interest for review *Review of the performance and level of validation of decision rules*
Dunbar, M, Shah, H, Shinde, S et al. (2018) Stroke in Pediatric Bacterial Meningitis: Population-Based Epidemiology. Pediatric Neurology 89: Nov-18	- Comparison not of interest for review *stroke vs. no stroke*
Duramaz, B. B, Kihtir, H. S, Petmezci, M. T et al. (2020) Analysis of meningitis cases in pediatric intensive care unit: 8-year single center experience. Medical Journal of Bakirkoy 16(1): 26-32	- Country not of interest for review *Non-OECD high income country*
Durand, M. L, Calderwood, S. B, Weber, D. J et al. (1993) Acute bacterial meningitis in adults - A review of 493 episodes. New England Journal of Medicine 328(1): 21-28	- Study design not of interest for review *Case series*
Ellis, J, Luintel, A, Chandna, A et al. (2019) Community-acquired acute bacterial meningitis in adults: A clinical update. British Medical Bulletin 131(1): 57-70	- Study design not of interest for review *Narrative review*
Elmore, J.G. (1996) Acute meningitis with a negative gram's stain: Clinical and management outcomes in 171 episodes. American Journal of Medicine 100(1): 78-84	- Population not of interest for review *Aseptic meningitis*
Elsaid, M.F, Alsoub, H, Bessisso, M.S et al. (2002) Clinical presentation of acute bacterial meningitis in Qatar. Neurosciences 7(4): 266-271	- Study design not of interest for review *Case series*

Study	Code [Reason]
Elsaid, M.F, Flamerzi, A.A, Bessisso, M.S et al. (2006) Acute bacterial meningitis in Qatar. Saudi Medical Journal 27(2): 198-204	- Study design not of interest for review *Case series*
Esposito, S, Rinaldi, V. E, Argentiero, A et al. (2018) Approach to Neonates and Young Infants with Fever without a Source Who Are at Risk for Severe Bacterial Infection. Mediators of InflammationMediators Inflamm 2018: 4869329	- Study design not of interest for review *Narrative review*
Estal, P. L. D, Lledo-Ibanez, G. M, Rios-Garces, R et al. (2013) Meningitis due to Listeria monocytogenes in adults. Revista de Neurologia 56(1): 13-18	- Non-English language article *Article in Spanish*
Farley, M.M, Harvey, R.C, Stull, T et al. (1993) A population-based assessment of invasive disease due to group B Streptococcus in nonpregnant adults. New England Journal of Medicine 328(25): 1807-1811	- Population not of interest for review *4% of population had meningitis*
Fellner, A, Goldstein, L, Lotan, I et al. (2020) Meningitis without meningeal irritation signs: What are the alerting clinical markers?. Journal of the Neurological Sciences 410 (no pagination)	- Population not of interest for review *Acute meningitis (no proportion of bacterial meningitis)*
Fleming, S, Gill, P, Jones, C et al. (2015) The Diagnostic Value of Capillary Refill Time for Detecting Serious Illness in Children: A Systematic Review and Meta-Analysis. PLoS ONE [Electronic Resource] 10(9): e0138155	- Population not of interest for review *Serious illness (various aetiology) Individual studies included in this review were assessed for potential inclusion*
Fletcher, E. M and Sharieff, G. (2013) Necessity of lumbar puncture in patients presenting with new onset complex febrile seizures. Western Journal of Emergency Medicine 14(3): 206-211	- Population not of interest for review *0.5% of population had bacterial meningitis*
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)	- Country not of interest for review *Non-OECD high income countr*
Garshin, M. I. (1957) Basic elements of diagnosis of otogenous meningitis. Vrachebnoe Delo 9: 937-942	- Non-English language article *Article in Russian*
Gehlbach, S. H. (1988) Fever in children younger than three months of age. A pooled analysis. Journal of Family PracticeJ 27(3): 305-12	- Population not of interest for review *1.3% of population had bacterial meningitis*

Study	Code [Reason]
Geiseler, P. J; Nelson, K. E; Levin, S. (1981) Community-acquired purulent meningitis of unknown etiology. A continuing problem. Archives of Neurology 38(12): 749-53	- Comparison not of interest for review *Purulent meningitis vs. bacterial meningitis*
Geiseler, P.J and Nelson, K.E. (1982) Bacterial meningitis without clinical signs of meningeal irritation. Southern Medical Journal 75(4): 448-450	- Study design not of interest for review *Case series*
Ghotbi, F and Shiva, F. (2009) An assessment of the necessity of lumbar puncture in children with seizure and fever. JPMA - Journal of the Pakistan Medical Association 59(5): 292-295	- Country not of interest for review *Non-OECD high income country*
Gossage, J. D. (1964) Acute puruleni meningitis in children: experience at the hospital for sick children, Toronto. Canadian Medical Association Journal 90(10): 615-617	- Study design not of interest for review *Case series*
Green, S.M, Rothrock, S.G, Clem, K.J et al. (1993) Can seizures be the sole manifestation of meningitis in febrile children?. Pediatrics 92(4): 527-534	- Study design not of interest for review *Case series*
Groover, R. V; Sutherland, J. M; Landing, B. H. (1961) PURULENT MENINGITIS of NEWBORN INFANTS. ELEVEN-YEAR EXPERIENCE in THE ANTIBIOTIC ERA. New England journal of medicine (Print) 264(22): 1115-1121	- Population not of interest for review *Neonates <28 days*
Guilbert, J, Levy, C, Cohen, R et al. (2010) Late and ultra late onset Streptococcus B meningitis: clinical and bacteriological data over 6 years in France. Acta PaediatricaActa Paediatr 99(1): 47-51	- Comparison not of interest for review *Comparison between late and ultra late onset Streptococcus B meningitis*
Hagedoorn, N. N, Borensztajn, D, Nijman, R. G et al. (2021) Development and validation of a prediction model for invasive bacterial infections in febrile children at European Emergency Departments: MOFICHE, a prospective observational study. Archives of Disease in Childhood 106(7): 641-647	- Population not of interest for review *11% of population had bacterial meningitis*
Heckenberg, S. G. B, De Gans, J, Brouwer, M. C et al. (2008) Clinical features, outcome, and meningococcal genotype in 258 adults with meningococcal meningitis: A prospective cohort study. Medicine 87(4): 185-192	- Study design not of interest for review *Prevalence data on signs and symptoms of meningococcal meningitis*

Study	Code [Reason]
Horenstein, S and Schreiber, D. J. (1974) Clinical features of bacterial meningitis. Advances in neurology 6: 141-159	- Study design not of interest for review *Clinical discussion*
Hu, F, Shi, X, Fan, Y et al. (2021) Cerebrospinal fluid changes and clinical features of aseptic meningitis in patients with Kawasaki disease. Journal of International Medical Research 49(2)	- Country not of interest for review *Non-OECD high income country*
Iguchi, M, Noguchi, Y, Yamamoto, S et al. (2020) Diagnostic test accuracy of jolt accentuation for headache in acute meningitis in the emergency setting. Cochrane Database of Systematic Reviews	- Population not of interest for review *Acute meningitis (all types). Studies included in this review were assessed for potential inclusion*
Isenberg, H. (1992) Bacterial meningitis: signs and symptoms. Antibiotics and chemotherapy 45: 79-95	- Study design not of interest for review *Narrative review about signs and symptoms*
Jacob, M. S, Gunasekaran, K, Miraclin, A. T et al. (2020) Clinical profile and outcome of patients with cerebral venous thrombosis secondary to bacterial infections. Annals of Indian Academy of Neurology 23(4): 477-481	- Country not of interest for review *Non-OECD high income country*
Juganariu, G, Miftode, E, Teodor, D et al. (2012) Clinical features and course of bacterial meningitis in children. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 116(3): 722-726	- Country not of interest for review *Non OECD high income country*
Kapoor, R. K, Kumar, R, Misra, P. K et al. (1996) Brainstem auditory evoked response (BAER) in childhood bacterial meningitis. Indian Journal of PediatricsIndian J Pediatr 63(2): 217-25	- Country not of interest for review *Non-OECD high income country*
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(7): e6426	- Comparison not of interest for review *Comparison between different causes of bacterial meningitis*
Khan, F. Y, Abu-Khattab, M, Almaslamani, E. A et al. (2017) Acute Bacterial Meningitis in Qatar: A Hospital-Based Study from 2009 to 2013. BioMed Research International 2017 (no pagination)	- Population not of interest for review *72% of population had neurosurgery, head injury and immunosuppression*
Khatib, U, van de Beek, D, Lees, J. A et al. (2017) Adults with suspected central nervous system infection: A prospective study of diagnostic accuracy. Journal of infection 74(1): 01-Sep	- Population not of interest for review *>50% population without bacterial meningitis or meningococcal disease*

Study	Code [Reason]
Kilpi, T, Anttila, M, Kallio, M. J. T et al. (1993) Length of prediagnostic history related to the course and sequelae of childhood bacterial meningitis. Pediatric Infectious Disease Journal 12(3): 184-188	- Comparison not of interest for review *Duration of illness <24hrs vs 24-48hrs vs >48hrs*
Kimia, A, Ben-Joseph, E.P, Rudloe, T et al. (2010) Yield of lumbar puncture among children who present with their first complex febrile seizure. Pediatrics 126(1): 62-69	- Population not of interest for review *>50% population without bacterial meningitis or meningococcal disease*
Kirkpatrick, B; Reeves, D.S; Macgowan, A.P. (1994) A review of the clinical presentation, laboratory features, antimicrobial therapy and outcome of 77 episodes of pneumococcal meningitis occurring in children and adults. Journal of Infection 29(2): 171-182	- Study design not of interest for review *Prevalence data on signs and symptoms or risk factors for pneumococcal meningiti*
Kjaergaard, N, Bodilsen, J, Justesen, U. S et al. (2019) Community-acquired meningitis caused by beta-haemolytic streptococci in adults: a nationwide population-based cohort study. European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis 38(12): 2305-2310	- Study design not of interest for review *Prevalence data on signs and symptoms*
Klouda, Timothy M; Wang, Hongyue; Yaeger, Jeffrey P (2020) Association of Cough Status With Bacterial Infections in Febrile Infants. Hospital pediatrics 10(2): 185-189	- Insufficient data to include in review
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(4): 508-19	- Index test not of interest for review *Clinical prediction rules for bacterial meningitis. Studies included in this review were assessed for potential inclusion*
Kyaw, M.H, Clarke, S, Jones, I.G et al. (2002) Incidence of invasive pneumococcal disease in Scotland, 1988-99. Epidemiology and Infection 128(2): 139-147	- No outcomes of interest for review *Incidence of invasive pneumococcal disease*
Laher, A. E, Etlouba, Y, Moolla, M et al. (2018) First-presentation with psychotic behavior to the Emergency Department: Meningitis or not, that is the question. American journal of emergency medicine 36(11): 2068-2075	- Country not of interest for review *Non-OECD high income country*
Lai, P. C; Huang, Y. T; Wang, P. J. (2006) A seasonal outbreak of pediatric aseptic meningitis in Eastern Taiwan: Clinical presentations and	- Population not of interest for review *Aseptic meningitis*

Study	Code [Reason]
laboratory analyses. Tzu Chi Medical Journal 18(6): 423-426	
Lai, W. A, Chen, S. F, Tsai, N. W et al. (2011) Clinical characteristics and prognosis of acute bacterial meningitis in elderly patients over 65: a hospital-based study. BMC geriatrics 11: 91	- Population not of interest for review *52% of population were immunocompromised*
Lamonte, M; Silberstein, S. D; Marcelis, J. F. (1995) Headache associated with aseptic meningitis. Headache 35(9): 520-526	- Population not of interest for review *Aseptic or viral meningitis*
Lee, B.E, Chawla, R, Langley, J.M et al. (2006) Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of aseptic meningitis. BMC Infectious Diseases 62006articlenumber	- Population not of interest for review *Aseptic or viral meningitis*
Leonard, P.A and Beattie, T.F. (2004) Is measurement of capillary refill time useful as part of the initial assessment of children?. European Journal of Emergency Medicine 11(3): 158-163	- No outcomes of interest for review *No association data to support relationship between CRT and meningococcal disease (narrative text only)*
Lepur, D and Barsic, B. (2007) Community-acquired bacterial meningitis in adults: Antibiotic timing in disease course and outcome. Infection 35(4): 225-231	- No outcomes of interest for review *Regression analysis explores the association between antibiotic timing and unfavourable outcome in those with bacterial meningitis*
Levi, S, Grant, J. R, Westphal, M. C et al. (1976) Development of a decision guide; optimal discriminators for meningitis as determined by statistical analysis. Methods of Information in Medicine 15(2): 87-90	- Population not of interest for review *Bacterial and viral meningitis with no stratified analysis by meningitis type*
Lien, C. Y, Lee, J. J, Tsai, W. C et al. (2019) The clinical characteristics of spontaneous Gram-negative bacterial meningitis in adults: A hospital-based study. Journal of Clinical Neuroscience 64: 101-105	- Population not of interest for review *60% of population were immunocompromised*
Lorber, J and Sunderland, R. (1980) Lumbar puncture in children with convulsions associated with fever. Lancet 1(8172): 785-786	- Population not of interest for review *80% viral meningitis*
Luaces Cubells, C, Garcia Garcia, J. J, Roca Martinez, J et al. (1997) Clinical data in children with meningococcal meningitis in a Spanish hospital. Acta paediatrica 86(1): 26-Sep	- No outcomes of interest for review

Study	Code [Reason]
Lund, W. S. (1978) A review of 50 cases of intracranial complications from otogenic infection between 1961 and 1977. Clinical Otolaryngology & Allied SciencesClin Otolaryngol Allied Sci 3(4): 495-501	- Study design not of interest for review *Case-series*
Marom, T, Shemesh, S, Habashi, N et al. (2020) Adult otogenic meningitis in the pneumococcal conjugated vaccines era. International Archives of Otorhinolaryngology 24(2): E175-E181	- Study design not of interest for review *Prevalence data for signs and symptoms for otogenic meningitis*
Matulyte, E, Kiveryte, S, Paulauskiene, R et al. (2020) Retrospective analysis of the etiology, clinical characteristics and outcomes of community-acquired bacterial meningitis in the University Infectious Diseases Centre in Lithuania. BMC Infectious Diseases 20(1): 733	- Comparison not of interest for review *Unfavourable vs favourable outcomes in different subtypes of bacterial meningitis*
Metersky, M. L; Williams, A; Rafanan, A. L. (1997) Retrospective analysis: Are fever and altered mental status indications for lumbar puncture in a hospitalized patient who has not undergone neurosurgery?. Clinical Infectious Diseases 25(2): 285-291	- Population not of interest for review *15% of population had bacterial meningitis*
Michael, B. D, Sidhu, M, Stoeter, D et al. (2010) Acute central nervous system infections in adults--a retrospective cohort study in the NHS North West region. Qjm 103(10): 749-58	- Population not of interest for review *29.5% of population had purulent meningitis*
Michelson, Kenneth A, Neuman, Mark I, Pruitt, Christopher M et al. (2021) Height of fever and invasive bacterial infection. Archives of disease in childhood 106(6): 594-596	- Insufficient data to include in review
Miner, J.R, Heegaard, W, Mapes, A et al. (2001) Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. Journal of Emergency Medicine 21(4): 387-392	- Study design not of interest for review *Prevalence study*
Mishal, J, Embon, A, Darawshe, A et al. (2008) Community acquired acute bacterial meningitis in children and adults: An 11-year survey in a community hospital in Israel. European Journal of Internal Medicine 19(6): 421-426	- Comparison not of interest for review *Comparison between different age groups of bacterial meningitis*
Mofidi, M, Negaresh, N, Farsi, D et al. (2017) Jolt accentuation and its value as a sign in diagnosis of meningitis in patients with fever and headache. Turkish Journal of Emergency Medicine 17(1):	- Country not of interest for review *Non-OECD high income country*

Study	Code [Reason]
29-31	
Molyneux, E.; Riordan, F. A.; Walsh, A. (2006) Acute bacterial meningitis in children presenting to the Royal Liverpool Children's Hospital, Liverpool, UK and the Queen Elizabeth Central Hospital in Blantyre, Malawi: a world of difference. Ann Trop Paediatr 26(1): 29-37	- Population not of interest for review *Prevalence study*
Muli, J. M, Seckova, S, Sladeckova, V et al. (2007) Meningococcal meningitis is still the commonest neuroinfection in the community in tropics: Overview of 62 cases. Neuroendocrinology Letters 28(suppl3): 23-24	- Country not of interest for review *Non-OECD high income country*
Nademi, Z, Clark, J, Richards, C.G.M et al. (2001) The causes of fever in children attending hospital in the North of England. Journal of Infection 43(4): 221-225	- Population not of interest for review *8% of population with microbiologically or radiologically proven disease had meningitis or sepsis*
Nakao, J. H, Jafri, F. N, Shah, K et al. (2014) Jolt accentuation of headache and other clinical signs: Poor predictors of meningitis in adults. American journal of emergency medicine 32(1): 24-28	- Population not of interest for review *Acute meningitis (all causes) defined as pleocytosis on CSF*
Nigrovic, L. E; Malley, R; Kuppermann, N. (2012) Meta-analysis of bacterial meningitis score validation studies. Archives of Disease in ChildhoodArch Dis Child 97(9): 799-805	- Index test not of interest for review *Bacterial meningitis score clinical decision rule, no details on signs and symptoms. Studies included in this review were assessed for potential inclusion.*
Offringa, M, Beishuizen, A, Derksen-Lubsen, G et al. (1992) Seizures and fever: can we rule out meningitis on clinical grounds alone?. Clinical pediatrics 31(9): 514-22	- Population not of interest for review *Meningitis population mixture of bacterial and viral, without breakdown into 2 groups*
Okike, I. O, Johnson, A. P, Henderson, K. L et al. (2014) Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Clinical Infectious Diseases 59(10): e150-7	- Index test not of interest for review *No details on signs and symptoms or risk factors for bacterial meningitis*
Okike, I. O, Ladhani, S. N, Anthony, M et al. (2017) Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants: An observational study. BMJ open 7 (8)	- Comparison not of interest for review *Compares the risk factors in young babies with bacterial meningitis admitted from home versus those who were in hospital prior to disease onset*

Study	Code [Reason]
Oostenbrink, R, Moons, K. G. M, Theunissen, C. C. W et al. (2001) Signs of meningeal irritation at the emergency department: How often bacterial meningitis?. Pediatric Emergency Care 17(3): 161-164	- Population not of interest for review *30% of the population had bacterial meningitis*
Orfanos, Ioannis, Sotoca Fernandez, Jorge, Elfving, Kristina et al. (2022) Paediatric emergency departments should manage young febrile and afebrile infants the same if they have a fever before presenting. Acta paediatrica (Oslo, Norway : 1992) 111(10): 2004-2009	- Insufficient data to include in review
Ostergaard, C, Hoiby, N, Konradsen, H.B et al. (2006) Prehospital diagnostic and therapeutic management of otogenic Streptococcus pneumoniae meningitis. Scandinavian Journal of Infectious Diseases 38(3): 172-180	- Comparison not of interest for review *Compares those with otogenic pneumococcal meningitis versus those with pneumococcal meningitis*
Paciorek, M, Bienkowski, C, Bednarska, A et al. (2019) The clinical course and outcome of Listeria monocytogenes meningitis: A retrospective single center study. Neuroendocrinology Letters 40(2): 79-84	- Comparison not of interest for review *Comparison between Listeria monocytogenes meningitis vs. other bacterial meningitis*
Pagliano, P, Fusco, U, Attanasio, V et al. (2007) Pneumococcal meningitis in childhood: a longitudinal prospective study. FEMS Immunology and Medical Microbiology 51(3): 488-495	- No outcomes of interest for review *Meningitis- related death or evidence of neurological sequelae in survivors.*
Pantell, R. H, Naber, M, Lamar, R et al. (1980) Fever in the first six months of life. Risks of underlying serious infection. Clinical Pediatrics 19(2): 77-82	- No outcomes of interest for review *No association data: only narrative text*
Parkinson, M. S. (1972) Early recognition of symptoms in childhood meningitis. The Practitioner 209(250): 191-195	- Insufficient data to include in review *Data presented as bar charts and precise data unavailable*
Parner, E.T, Reefhuis, J, Schendel, D et al. (2007) Hearing loss diagnosis followed by meningitis in Danish children, 1995-2004. Otolaryngology - Head and Neck Surgery 136(3): 428-433	- Population not of interest for review *Meningitis (includes bacterial meningitis, meningococcal meningitis, viral meningitis, and other meningitis) with no stratified analysis by meningitis type*
Patel, M. S, Merianos, A, Hanna, J. N et al. (1993) Epidemic meningococcal meningitis in central Australia, 1987-1991. Medical Journal of Australia 158(5): 336-40	- Index test not of interest for review *No signs and symptoms or risk factors for meningococcal meningitis*

Study	Code [Reason]
Petersen, R, Hannerz, H, Tuchsen, F et al. (2011) Meningitis, sepsis and endocarditis among workers occupationally exposed to pigs. Occupational Medicine (Oxford)Occup Med (Oxf) 61(6): 437-9	- Population not of interest for review *18% of population had bacterial meningitis*
Petrovici, C. G, Leca, D, Teodor, A et al. (2013) Bacterial meningitis during sepsis in diabetic patient. Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din IasiRev Med Chir Soc Med Nat Iasi 117(4): 901-7	- Country not of interest for review *Non-OECD high income country*
Plouffe, J. F; Breiman, R. F; Facklam, R. R. (1996) Bacteremia with Streptococcus pneumoniae. Implications for therapy and prevention. Franklin County Pneumonia Study Group. JAMAJama 275(3): 194-8	- Population not of interest for review *Pneumonia*
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(211): 331-40	- Study design not of interest for review *Case series*
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(1): 60-65	- Country not of interest for review *Non-OECD high income country*
Ragunathan, L, Ramsay, M, Borrow, R et al. (2000) Clinical features, laboratory findings and management of meningococcal meningitis in England and Wales: report of a 1997 survey. Meningococcal meningitis: 1997 survey report. Journal of infection 40(1): 74-9	- Study design not of interest for review *Prevalence data on signs and symptoms of meningococcal meningitis*
Ramezani, A, Nagga, K, Hansson, O et al. (2015) Hepatocyte growth factor in cerebrospinal fluid differentiates community-acquired or nosocomial septic meningitis from other causes of pleocytosis. Fluids and Barriers of the CNS 12 (1)	- No outcomes of interest for review *Biological results (hepatocyte growth factor in CSF)*
Rapp, C, Aoun, O, Ficko, C et al. (2010) Travel-related cerebro-meningeal infections: the 8-year experience of a French infectious diseases unit. Journal of Travel MedicineJ Travel Med 17(1): 01-Jul	- Population not of interest for review *viral meningitis*
Rasmussen, H. H, Sorensen, H. T, Moller-Petersen, J et al. (1992) Bacterial meningitis in elderly patients: Clinical picture and course. Age	- Study design not of interest for review *Prevalence study*

Study	Code [Reason]
and Ageing 21(3): 216-220	
Richardson, M. P, Reid, A, Williamson, T. J et al. (1997) Acute otitis media and otitis media with effusion in children with bacterial meningitis. Journal of Laryngology and Otology 111(10): 913-916	- Study design not of interest for review *Case-control study*
Riordan, F.A.I, Thomson, A.P.J, Sills, J.A et al. (1995) Bacterial meningitis in the first three months of life. Postgraduate Medical Journal 71(831): 36-38	- Comparison not of interest for review *Signs and symptoms of meningitis in 2 series (1949-1952 vs 1982-1991) of babies with bacterial meningitis*
Rosenberg, N. M and Bobowski, T. (1988) Clinical indicators for lumbar puncture. Pediatric Emergency Care 4(1): 05-Aug	- Study design not of interest for review *Prevalence study*
Rosenberg, N. M, Meert, K, Marino, D et al. (1992) Seizures associated with meningitis. Pediatric Emergency Care 8(2): 67-69	- Study design not of interest for review *Prevalence data on signs and symptoms*
Rosman, N. P, Peterson, D. B, Kaye, E. M et al. (1985) Seizures in bacterial meningitis: prevalence, patterns, pathogenesis, and prognosis. Pediatric Neurology 1(5): 278-85	- Study design not of interest for review *Prevalence data on signs and symptoms*
Ross, M. (2011) Towards evidence based emergency medicine: PRIVATE Best BETs from the Manchester Royal Infirmary. BET 4: Are meningeal irritation signs reliable in diagnosing meningitis in children?. Emergency Medicine Journal 28(9): 813-4	- Study design not of interest for review *Topic report*
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(3): 292-4	- Population not of interest for review *19% of the population had bacterial meningitis and 31% of those were 0-28 days old*
Saeed, M; Nadeem, T; Al-Nufiee, S.M. (2011) Is lumbar puncture necessary among children with first febrile seizure?. Pakistan Paediatric Journal 35(3): 145-148	- No outcomes of interest for review
Sato, R; Kuriyama, A; Luthe, S. K. (2017) Can We Rule Out Meningitis from Negative Jolt Accentuation? A Retrospective Cohort Study. Headache 57(4): 586-592	- Population not of interest for review *Acute meningitis (all causes, 3.4% defined as bacterial)defined as pleocytosis on CSF*
Scarfone, R, Murray, A, Gala, P et al. (2017) Lumbar Puncture for All Febrile Infants 29-56	- No outcomes of interest for review

Study	Code [Reason]
Days Old: A Retrospective Cohort Reassessment Study. Journal of PediatricsJ Pediatr 187: 200-205.e1	
Schaap, T. P, Schutte, J. M, Zwart, J. J et al. Fatal meningitis during pregnancy in the Netherlands: A nationwide confidential enquiry. BJOG: An International Journal of Obstetrics and Gynaecology 119(13): 1558-1563	- No outcomes of interest for review
Schlesinger, L.S; Ross, S.C; Schaberg, D.R. (1987) Staphylococcus aureus meningitis: A broad-based epidemiologic study. Medicine 66(2): 148-156	- Population not of interest for review *55% had some sort of central nervous system disorder*
Scott, L. A, Tintinalli, J. E, Brewer, K. L et al. (2008) Lumbar punctures for suspected meningitis in adults. Infectious Diseases in Clinical Practice 16(5): 298-302	- Population not of interest for review *73% of population had viral, fungal or parasitic infections*
See, K.C; Tay, S.K; Low, P.S. (2001) Diagnosing and prognosticating acute meningitis in young infants within 24 hours of admission. Annals of the Academy of Medicine, Singapore 30(5): 503-509	- Population not of interest for review *27.3% had acute bacterial meningitis*
Serrano, L; Patel, K. R; Silverberg, J. I. (2019) Association between atopic dermatitis and extracutaneous bacterial and mycobacterial infections: A systematic review and meta-analysis. Journal of the American Academy of DermatologyJ Am Acad Dermatol 80(4): 904-912	- Population not of interest for review *Extracutaneous infections (includes endocarditis, meningitis, encephalitis, bone and joint infections, and sepsis). Studies included in this review were assessed for potential inclusion*
Shapiro, E. D; Aaron, N. H; Wald Chiponis, E. R. D. (1986) Risk factors for development of bacterial meningitis among children with occult bacteremia. Journal of Pediatrics 109(1): 15-19	- No outcomes of interest for review
Sigurdardottir, B, Bjornsson, O. M, Jonsdottir, K. E et al. (1997) Acute bacterial meningitis in adults: A 20-year overview. Archives of Internal Medicine 157(4): 425-430	- Study design not of interest for review *Prevalence study*
Smitherman, H.F; Caviness, A.C; Macias, C.G. (2005) Retrospective review of serious bacterial infections in infants who are 0 to 36 months of age and have influenza A infection. Pediatrics 115(3): 710-718	- No outcomes of interest for review
Snaebjarnardottir, K, Erlendsdottir, H, Reynisson, I. K et al. (2013) Bacterial meningitis in children in	- No outcomes of interest for review

Study	Code [Reason]
Iceland, 1975-2010: A nationwide epidemiological study. Scandinavian Journal of Infectious Diseases 45(11): 819-824	
Sulaiman, T, Medi, S, Erdem, H et al. (2020) The diagnostic utility of the Thwaites' system and lancet consensus scoring system in tuberculous vs. non-tuberculous subacute and chronic meningitis: multicenter analysis of 395 adult patients. BMC Infectious Diseases 20 (1)	- Comparison not of interest for review *Explores the diagnostic utility of the "Thwaites' system" and "Lancet consensus scoring system" in differentiating tuberculous meningitis from the other aetiologies of subacute meningitis and chronic meningitis*
Takagi, D, Oren-Ziv, A, Shles, A et al. (2021) Bulging fontanelle in febrile infants as a predictor of bacterial meningitis. European Journal of Pediatrics 180(4): 1243-1248	- Population not of interest for review *10% of meningitis cohort was bacterial*
Tamune, H, Kuki, T, Kashiyama, T et al. (2018) Does This Adult Patient With Jolt Accentuation of Headache Have Acute Meningitis?. HeadacheHeadache 58(10): 1503-1510	- Population not of interest for review *Acute meningitis (all causes) Studies included in this review were assessed for potential inclusion*
Tamune, H, Takeya, H, Suzuki, W et al. (2013) Absence of jolt accentuation of headache cannot accurately rule out meningitis in adults. American Journal of Emergency Medicine 31(11): 1601-1604	- Population not of interest for review *Acute meningitis (all causes, only 1.6% defined as bacterial) defined as pleocytosis on CSF*
Tang, L. M, Chen, S. T, Hsu, W. C et al. (1997) Klebsiella meningitis in Taiwan: An overview. Epidemiology and Infection 119(2): 135-142	- Comparison not of interest for review *Comparison between Klebsiella meningitis and other bacterial meningitis*
Thomas, K. E, Hasbun, R, Jekel, J et al. (2002) The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. Clinical Infectious Diseases 35(1): 46-52	- Population not of interest for review *Acute meningitis (all causes) defined as pleocytosis on CSF*
Thompson, M, Van den Bruel, A, Verbakel, J et al. (2012) Systematic review and validation of prediction rules for identifying children with serious infections in emergency departments and urgent-access primary care. Health Technology Assessment (Winchester, England)Health Technol Assess 16(15): 1-100	- Population not of interest for review *Serious infection (9% meningitis; 6% meningococcal infection). Studies included in this review were assessed for potential inclusion*
Tichy, S. (1967) Contemporaneous problems of the diagnostics and therapy of otogenic cerebral and cerabellar abscesses. Plzensky Lek sborn(s19): 95-99	- Study design not of interest for review *Case series*

Study	Code [Reason]
Trainor, J. L, Hampers, L. C, Krug, S. E et al. (2001) Children with first-time simple febrile seizures are at low risk of serious bacterial illness. Academic Emergency Medicine 8(8): 781-787	- Population not of interest for review *Serious bacterial infection (of those with bacterial meningitis 68% with ventriculoperitoneal shunt or recent cranial surgery)*
Tsai, M. H, Lu, C. H, Huang, C. R et al. (2006) Bacterial meningitis in young adults in Southern Taiwan: clinical characteristics and therapeutic outcomes. Infection 34(1): 02-Aug	- Population not of interest for review *74% of population had post-neurosurgical meningitis*
Tubiana, S, Lemaignen, A, Cazanave, C et al. (2016) NEURO-06 - Adult pneumococcal meningitis: Presentation, management and prognosis within the COMBAT cohort. Medecine et Maladies Infectieuses 46(4): 86	- Non-English language article *Article in French*
Tucci, M, Lebel, M.H, Gauthier, M et al. (1995) Admission to a pediatric intensive care unit for bacterial meningitis: Review of 168 cases. Journal of Intensive Care Medicine 10(5): 253-260	- Study design not of interest for review *Case series*
Uchihara, T and Tsukagoshi, H. (1991) Jolt accentuation of headache: The most sensitive sign of CSF pleocytosis. Headache 31(3): 167-171	- Population not of interest for review *Acute meningitis (all causes, only 3.3% defined as bacterial) defined as pleocytosis on CSF*
Unhanand, M, Mustafa, M.M, McCracken, G.H et al. (1993) Gram-negative enteric bacillary meningitis: a twenty-one-year experience. Journal of Pediatrics 122(1): 15-21	- Population not of interest for review *73% of population are neonates <28 days*
Vadher, P. J, Vaidya, N. S, Soni, P et al. (1991) Bacteriological study of meningococcal meningitis. Journal of Postgraduate Medicine 37(2): 76-78	- Country not of interest for review *Non OECD high income country*
Valmari, P, Peltola, H, Ruuskanen, O et al. (1987) Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician. European Journal of Pediatrics 146(5): 515-518	- Comparison not of interest for review *Comparisons between different age groups*
Van De Beek, D, De Gans, J, Spanjaard, L et al. (2004) Clinical features and prognostic factors in adults with bacterial meningitis. New England journal of medicine 351(18): 1849-1859+1923	- No outcomes of interest for review *Favourable and unfavourable outcomes associated with bacterial meningitis*
Van den Bruel, A, Aertgeerts, B, Bruyninckx, R et al. (2007) Signs and symptoms for diagnosis of	- Population not of interest for review

Study	Code [Reason]
serious infections in children: a prospective study in primary care. British Journal of General Practice 57(540): 538-546	*Includes a mix of those with viral and bacterial meningitis, and sepsis (29% had sepsis/meningitis*
Van Den Bruel, A, Thompson, M. J, Haj-Hassan, T et al. (2011) Diagnostic value of laboratory tests in identifying serious infections in febrile children: Systematic review. BMJ 342(7810): d3082	- Population not of interest for review *Serious infection (9% meningitis; 6% meningococcal infection) Studies included in this review were assessed for potential inclusion*
van Samkar, A, Brouwer, M. C, Schultsz, C et al. (2015) Streptococcus suis Meningitis: A Systematic Review and Meta-analysis. PLoS Neglected Tropical Diseases [electronic resource]PLoS Negl Trop Dis 9(10): e0004191	- Study design not of interest for review *Studies included only report prevalence data on signs and symptoms*
Verbakel, J. Y, Macfaul, R, Aertgeerts, B et al. (2014) Sepsis and meningitis in hospitalized children: Performance of clinical signs and their prediction rules in a case-control study. Pediatric Emergency Care 30(6): 373-380	- Study design not of interest for review *Case-control study*
Verbakel, J. Y, Van den Bruel, A, Thompson, M et al. (2013) How well do clinical prediction rules perform in identifying serious infections in acutely ill children across an international network of ambulatory care datasets?. BMC Medicine 11 (1)	- Population not of interest for review *Serious infection Studies included in this review were assessed for potential inclusion*
Vibha, D, Bhatia, R, Prasad, K et al. (2010) Clinical features and independent prognostic factors for acute bacterial meningitis in adults. Neurocritical Care 13(2): 199-204	- Country not of interest for review *Non-OECD high income country*
Vincent, J. (1994) Meningeal signs in pediatric practice. Indian Journal of Pediatrics 61(5): 463-468	- Study design not of interest for review *Narrative review*
Voss, L; Lennon, D; Gillies, M. (1989) Haemophilus influenzae type b disease in Auckland children 1981-87. New Zealand Medical Journal 102(865): 149-151	- No outcomes of interest for review
Waghdhare, S, Kalantri, A, Joshi, R et al. (2010) Accuracy of physical signs for detecting meningitis: A hospital-based diagnostic accuracy study. Clinical Neurology and Neurosurgery 112(9): 752-757	- Country not of interest for review *Non-OECD high income country*
Wang, A. Y, Machicado, J. D, Khoury, N. T et al. (2014) Community-acquired meningitis in older adults: clinical features, etiology, and prognostic	- Population not of interest for review *7.4% of population had bacterial meningitis*

Study	Code [Reason]
factors. Journal of the American Geriatrics Society 62(11): 2064-70	
Ware, S. J and McLaughlin, S. (1978) Haemophilus meningitis in Portsmouth. LancetLancet 2(8082): 197-9	- Study design not of interest for review *Case reports*
Weinstein, L. (1985) Bacterial meningitis. Specific etiologic diagnosis on the basis of distinctive epidemiologic, pathogenetic, and clinical features. Medical Clinics of North America 69(2): 219-29	- Study design not of interest for review *Narrative review*
Weisfelt, M, Van De Beek, D, Spanjaard, L et al. (2006) Community-acquired bacterial meningitis in older people. Journal of the American Geriatrics Society 54(10): 1500-1507	- No outcomes of interest for review *Factors associated with an unfavourable outcome in bacterial meningitis*
Yang, Y.J; Liu, C.C; Wang, S.M. (1998) Group B streptococcal infections in children: the changing spectrum of infections in infants. Journal of Microbiology, Immunology and Infection 31(2): 107-112	- Population not of interest for review *Non OECD high income country*
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)	- Population not of interest for review *Non OECD high income country*
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	- Population not of interest for review *Non OECD high income country*
Youssef, F. G, Afifi, S. A, Azab, A. M et al. (2006) Differentiation of tuberculous meningitis from acute bacterial meningitis using simple clinical and laboratory parameters. Diagnostic microbiology and infectious disease 55(4): 275-278	- Country not of interest for review *Non OECD high income country*
Zacho, J, Benfield, T, Tybjaerg-Hansen, A et al. (2016) Increased baseline C-Reactive protein concentrations are associated with increased risk of infections: Results from 2 large danish population cohorts. Clinical Chemistry 62(2): 335-342	- Population not of interest for review *Infections (viral, bacterial, and other infections, no specific details on meningitis)*
Zoons, E, Weisfelt, M, de Gans, J et al. (2008)	- Comparison not of interest for review

Study	Code [Reason]
Seizures in adults with bacterial meningitis. Neurology 70(22pt2): 2109-2115	*Clinical/ laboratory features and outcomes in adults with bacterial meningitis with seizures with those without seizures*

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: What symptoms and signs, individually or in combination, are associated with bacterial meningitis?

No research recommendations were made for this review question.