National Institute for Health and Care Excellence

Final

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

[A3] Evidence review for symptoms and signs associated with meningococcal disease

NICE guideline NG240

Evidence review underpinning recommendations 1.1.1 to 1.1.3, 1.1.9 to 1.1.13, 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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ISBN: 978-1-4731-5753-8

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Review question

What symptoms and signs, individually or in combination, are associated with meningococcal disease?

Introduction

Meningococcal disease (meningococcal sepsis with or without an associated meningitis) is a rare but serious infection, which can occur in any age group. Meningococcal disease is a life-threatening medical emergency, which may progress with devastating speed. Early recognition of the condition requires a high index of suspicion.

The diagnosis of meningococcal disease is difficult 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 meningococcal disease 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 or confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on 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 meningococcal disease* • Specificity for diagnosis of meningococcal disease* **Association data (if insufficient accuracy data)** • Risk ratios for diagnosis of meningococcal disease* • Odds ratios for diagnosis of bacterial meningococcal disease* * Diagnosis of meningococcal disease based on any diagnostic laboratory test for N. meningitidis **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

Seven studies were included for this review, 6 single-gate, cross-sectional, diagnostic test accuracy (DTA) studies (Baker 1989, Borchsenius 1991, Close 2011, Nielsen 2001, Waterfield 2021, Wells 2001), and 1 two-gate, cross-sectional, DTA study (Haj-Hassan 2011).

The included studies are summarised in Table 2.

Six studies included babies and children, and reported results for babies and children combined (Baker 1989, Close 2011, Haj-Hassan 2011, Nielsen 2001, Waterfield 2021, Wells 2001), 1 study (in addition to reporting results for babies and children) reported results for an adults-only (Close 2011), and 1 study had an undefined age range and reported results for the whole sample (Borchsenius 1991).

The signs and symptoms of meningococcal disease in babies and children reported by the studies can be categorised as follows: general signs of illness and duration of illness (Baker 1989, Haj-Hassan 2011, Waterfield 2021, Wells 2001); unusual, abnormal, or pale skin colour (Haj-Hassan 2011, Waterfield 2021); presence, and type and size, of rash (Close 2011, Haj-Hassan 2011, Nielsen 2001, Waterfield 2021, Wells 2001); distribution and duration of rash (Baker 1989, Nielsen 2001, Waterfield 2021, Wells 2001); signs or symptoms of meningism (Baker 1989, Haj-Hassan 2011, Nielsen 2001, Waterfield 2021); reduced consciousness (Close 2011, Waterfield 2021); signs of shock (Haj-Hassan 2011, Waterfield 2021, Wells 2001); limb or body pain (Haj-Hassan 2011, Waterfield 2021); cardiac

and respiratory symptoms (Haj-Hassan 2011, Nielsen 2001, Waterfield 2021); gastrointestinal symptoms and refusal of food and drink (Haj-Hassan 2011, Nielsen 2001, Waterfield 2021).

One study (Close 2011) reported presence of haemorrhagic rash and reduced consciousness as potential signs/symptoms of meningococcal disease in adults.

One study (Borchsenius 1991) reported the following signs and symptoms of meningococcal disease 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 used blood and/or cerebrospinal (CSF) culture detection for Neisseria meningitidis (Baker 1989) as the reference standard; 1 study used blood and/or CSF culture and/or CSF leukocyte count (Borchsenius 1991); 1 study used culture (from blood or CSF) and/or polymerase chain reaction (PCR) for Neisseria meningitides (Waterfield 2021); 1 study used bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in CSF, bacteria or viruses obtained from culture of CSF, and/or clinical/laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site (for example, blood, throat swab, skin or faeces) (Close 2011); 1 study used blood and/or CSF and/or skin culture for Neisseria meningitidis and/or gram negative diplococci in CSF and/or positive PCR for meningococcal DNA from blood or CSF (Wells 2001). Two studies included both confirmed (blood and/or CSF culture detection for Neisseria meningitides) and probable (clinical diagnosis without culture confirmation) cases, although the majority (79% and 74% respectively) were confirmed through microbiological techniques (Haj-Hassan 2011, Nielsen 2001).

For the 1 two-gate study the comparison group included children presenting in primary care with minor febrile infection (Haj-Hassan 2011). For 3 (of the 6 single-gate) studies, the comparison group were those negative for meningococcal disease (Borchsenius 1991, Waterfield 2021, Wells 2001). For 2 of these studies (Waterfield 2021, Wells 2001) no further details were provided about those negative for meningococcal disease; in the remaining study (Borchsenius 1991) the negative for meningococcal disease group included people with bacterial meningitis or septicaemia with causes other than Neisseria meningitidis, other bacterial infections and viral infections. One study compared those with documented invasive bacterial disease to those with nonbacteremic disease including those with viral meningitis (Baker 1989), and 1 study compared those with a confirmed or probable diagnosis of meningococcal disease with those with no invasive bacterial disease (Nielsen 2001). For 1 study, the comparison group was those with viral meningitis (Close 2011).

Signs and symptoms were identified or reported by healthcare professionals in 6 studies (Baker 1989, Borchsenius 1991, Close 2011, Nielsen 2001, Waterfield 2021, Wells 2001), and by a non-healthcare professional (a parent) in 1 study (Haj-Hassan 2011).

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
Baker 1989 Single-gate, cross-sectional DTA study US	N=54 People aged <21 years with fever >38°C and petechial rash Invasive bacterial disease group (n=15): Median age 41 months (range 6 months to 15 years). Nonbacteremic disease group (n=39): Median age 45 months (range 3 months to 11 years)	Signs and symptoms taken from medical records: • Ill appearance • Signs of meningeal irritation • Petechiae above the nipple line (including the head and upper extremities) • Petechiae on the trunk below the nipple line • Petechiae on the lower extremities	Meningococcal disease was diagnosed by detection of N. meningitidis on blood or CSF culture.	• Sensitivity • Specificity	40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes). Comparison group includes those with viral meningitis but only 5% of this group.
Borchsenius 1991 Single-gate, cross-sectional DTA study Norway	N=120 People admitted to hospital with suspected systemic meningococcal disease (those with meningococcal meningitis only (n=56) are included in the review on signs and symptoms of bacterial meningitis). Meningococcal disease (n=59): Age reported for whole MD group only (including those with meningitis alone): 50% aged < 12 years.	Signs and symptoms recorded by healthcare professional on the day of admission to hospital: • Petechiae (≤4mm) • Reduced general condition • Ecchymoses (cutaneous haemorrhages >4 mm • Reduced consciousness • Cold extremities • Cyanosis • Neck stiffness • Body pain	Method of diagnosing meningococcal disease was reported for the whole MD group only (including those with meningitis alone): Meningococcal disease confirmed with growth of meningococci in blood and/or CSF (for 62%), or the diagnosis of meningococcal disease was based on the clinical picture, meningococcal antigen in CSF, or growth of N. meningitidis in pharyngeal swab specimens (for	• Sensitivity • Specificity	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)

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	No meningococcal disease (n=61): 79% aged < 12 years.		38%)		
Close 2011 Single-gate, cross-sectional DTA study UK	N=385 Confirmed case of bacterial or viral meningitis, or meningococcal septicaemia Babies/children subgroup (aged 19 years or younger) n=230 Bacterial meningitis/meningococcal septicaemia (n=191): Age: Mean/median not reported Sex: male: 96 (50%); female: 95 (50%) Viral meningitis (n=39): Age: Mean/median not reported Sex: male: 23 (59%); female: 16 (41%) Adult subgroup (aged >19 years) n=155 Bacterial meningitis/meningococcal septicaemia (n=102): Age: Mean/median not reported Sex: male: 48 (47%); female:	Signs and symptoms, recorded by healthcare professionals on the study data collection forms: • Haemorrhagic rash • Level of consciousness (unresponsive)	Confirmed cases defined as those with any one of the following: bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in cerebrospinal fluid (CSF); bacteria or viruses obtained from culture of CSF; clinical and/or laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site for example, blood, throat swab, skin or faeces	• Sensitivity • Specificity	Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause)

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	54 (53%) Viral meningitis (n=53): Age: Mean/median not reported Sex: male: 22 (42%); female: 31 (58%)				
Haj-Hassan 2011 Two-gate, cross-sectional DTA study UK	N=752 Children aged <16 years with non-fatal MD compared with children with minor febrile infection (presenting in primary care with any acute infection where fever was present [based on parental report]) Non-fatal MD (n=345): Age in months: Mean/median not reported; 28% <1 year, 45% 1-4 years, 28% 5-14 years Sex: male 188 (55%); female: 157 (46%) Minor febrile infection (n=407): Age in months (median; interquartile range (IQR) in parentheses): 42 (22–79); 10% <1 year, 52% 1-4 years, 38% 5-14 years Sex: male: 209 (51%); female:	Signs and symptoms as indicated in parent-reported questionnaire (symptoms in questionnaire based on those included in the meningococcal disease dataset [Thompson 2006] and non-specific symptoms common to childhood illnesses): • Irritable or miserable • Pale colour • Rash or new spots on the skin • Cold hands or feet • Neck pain or stiffness • Photophobia • Headache • Nausea or vomiting • Diarrhoea • Tummy pain • Difficult or laboured breathing • Cough • Sore throat • Feeling drowsy or very sleepy	Confirmed and probable cases based on clinical record review (blind to final outcome) by an expert panel of consultants in paediatric emergency medicine, infectious disease, and intensive care. The majority of cases (79%) were confirmed through microbiological techniques	• Sensitivity • Specificity	N=103 fatal MD cases reported in previous dataset (Thompson 2006) but not included in the comparison with minor febrile infection. Data not extracted for fever or high temperature as this was an inclusion criterion.

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	198 (49%)	• Confusion • Refusing food or feeds • Leg pain • General aching			
Nielsen 2001 Single-gate, cross-sectional DTA study Denmark	N=208 analysed Babies and children aged 1 month to 16 years with skin haemorrhages detected at admission/during hospital stay and rectal temperature >38°C within the 24 hours before inclusion. Meningococcal disease (n=39): Confirmed case n=29 (median age 30 months); probable case n=10 (median age 14 months). No invasive bacterial disease (n=169): Enterovirus infection n=18 (median age 21 months); adenovirus infection n=11 (median age 22 months); no invasive bacterial disease (either no bacteria in cultures from blood or spinal fluid and no antibiotic	Signs and symptoms, recorded by healthcare professionals on pre-printed study forms and including information from the case history and a standardized physical examination: • Case history included coughing prior to inclusion • Case history included vomiting prior to inclusion • Nuchal rigidity • More than 20 skin haemorrhages • Skin haemorrhages with maximum diameter >1mm • Skin haemorrhages with maximum diameter >2mm • Universal distribution of skin haemorrhages	Confirmed case defined as clinical diagnosis of meningitis or septicaemia confirmed by culture of Neisseria meningitidis from blood and/or spinal fluid. Probable case defined as clinical diagnosis of meningitis or septicaemia without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by CIEP	• Sensitivity • Specificity	Excluded from analysis: N=6: invasive bacterial infection excluding meningococcal disease; N=50 insufficient information (received antibiotics prior to, or in the absence of, blood culture).

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	treatment prior to culture; or no blood culture, but spontaneous recovery) n=140 (median age 27 months).				
Waterfield 2021 Single-gate, cross-sectional DTA study UK	N=1329 Children (aged under 18 years) presenting to paediatric emergency department with fever (≥38°C), new-onset non-blanching rash or features suggestive of meningococcal infection. Meningococcal disease (n=19): Median age 37 months (IQR 9-58) No meningococcal disease (n=1310): Median age 24 months (IQR 12-48)	Signs and symptoms, identified by healthcare professionals and recorded prospectively on an electronic case report form: • Duration of illness (<24 hours) • Duration of rash (<4 hours) • Petechiae without purpura • Purpura • SVC distribution of rash • Spreading rash • Unwell appearance (based on an overall assessment of appearance) • Signs of shock (defined as clinician-diagnosed shock, a long capillary refill time of 4 seconds or more, or hypotension) • Tachycardia	Diagnosis based on a positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	• Sensitivity • Specificity	

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
		• Tachypnoea • Gastrointestinal symptoms (abdominal pain, abdominal distension, diarrhoea, or nausea or vomiting) • Shivers or chills • Pallor • Unusual skin colour • Cold hands or feet • Respiratory symptoms • Sore throat or coryza • Lethargy • Refusal of food and drink • Limb pain • Signs or symptoms of meningism (a positive Brudzinski's and Kernig's sign, a bulging fontanelle, irritability, photophobia, neck stiffness, and headache) • Reduced consciousness			
Wells 2001 Single-gate, cross-sectional DTA study UK	N=218 Children aged ≤15 years presenting to an A&E department with a non-blanching rash	Signs and symptoms data collected on standard proforma by the paediatric medical team at the time of presentation: • Illness	Meningococcal infection defined using a positive blood, CSF, or skin culture for N. meningitidis, Gram negative diplococci in	• Sensitivity • Specificity	Method of diagnosis used in confirmed cases: Positive blood culture alone (n=5; 21%); Positive PCR alone (n=9; 37.5%); Positive PCR

Study	Population	Index test(s)	Reference standard(s)	Outcomes	Comments
	Age in months (median): 24; 55% <3 years Meningococcal disease (n=24): Serogroup of N. meningitidis: B n=12 (50%); C n=11 (46%); unknown n=1 (4%) Negative for MD (n=194): No further details reported	categorisation (defined as toxic, irritable and crying inconsolably, or lethargic) • Purpuric rash (lesions >2 mm in diameter) • Rash distribution beyond the SVC • Fever >38.5°C • Fever >37.5°C • Hypotension (defined as 2 SD or more below the mean for age) • Delayed capillary refill (defined as >2 seconds)	CSF, or PCR for meningococcal DNA from blood or CSF		and blood culture (n=9; 37.5%); Positive PCR, blood culture, and CSF (n=1; 4%)

A&E: accident and emergency; CIEP: counterimmunoelectrophoresis; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; IQR: interquartile range; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction; SD: standard deviation; SVC: superior vena cava

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. Downgrading of the evidence was due to risk of bias, imprecision (95% confidence intervals crossing decision making thresholds), and indirectness. No meta-analyses were conducted for any of the index tests due to insufficient evidence after stratifying for age, person identifying the sign/symptom (healthcare professional or non-healthcare professional) and the comparison group. For the majority of 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.

None of the signs or symptoms examined were both very sensitive and very specific for a diagnosis of meningococcal disease.

Signs and symptoms of meningococcal disease in babies and children

General signs of illness and duration of illness

There was evidence that the following signs or symptoms were both moderately specific and moderately sensitive for a diagnosis of meningococcal disease in babies and children: duration of illness of less than 24 hours; a fever defined as a temperature over 38.5°C or 37.5°C; lethargy; drowsiness.

The evidence for illness categorisation or appearance was somewhat mixed, with studies that included a comparator group of undefined non-meningococcal disease showing moderate specificity and moderate sensitivity, and a study with a nonbacteremic disease comparator group (including those with viral meningitis) showing high specificity but non-significant sensitivity.

Shivers or chills, and confusion, were very specific, but not sensitive, for a diagnosis of meningococcal disease in babies and children.

Being considered irritable or miserable was a moderately sensitive symptom of meningococcal disease, however, was not specific.

Unusual, abnormal, or pale skin colour

There was some evidence that pale skin colour was a moderately to highly specific, but not sensitive, sign of meningococcal disease in babies and children. Unusual skin colour was also very specific, but not sensitive.

Presence, and type and size, of rash

There was some evidence that the presence of any rash, and the presence of a haemorrhagic rash, were both moderately specific and moderately sensitive for a diagnosis of meningococcal disease in babies and children. There was also some evidence that the presence of skin haemorrhages with a maximum diameter over 1mm was moderately specific and very sensitive.

The presence of purpura (lesions over 2mm) was a very specific and moderately sensitive sign of meningococcal disease in babies and children.

The presence of petechiae only (without purpura) was neither sensitive nor specific for a diagnosis of meningococcal disease in babies and children.

Distribution and duration of rash

There was evidence that the following signs associated with the distribution of the rash were both moderately specific and moderately sensitive for a diagnosis of meningococcal disease in babies and children: the presence of a spreading rash; petechiae on the trunk below the nipple line; petechiae on the lower extremities. Universal distribution of skin haemorrhages was also a moderately specific, but very sensitive, sign of meningococcal disease.

There was some evidence that rash distribution limited to the superior vena cava (SVC) was moderately specific, but not sensitive, for a diagnosis of meningococcal disease in babies and children. While, rash distribution beyond the SVC was very sensitive but not specific.

The presence of more than 20 skin haemorrhages, the presence of petechiae above the nipple line (including the head and upper extremities), and the duration from the onset of the rash of under 4 hours, were all moderately sensitive but not specific signs of a diagnosis of meningococcal disease in babies and children.

Signs or symptoms of meningism

There was some evidence that a composite clinical factor of signs or symptoms of meningism was moderately to highly specific, but not sensitive, for a diagnosis of meningococcal disease in babies and children.

Neck pain or stiffness, and photophobia, were both very specific but not sensitive symptoms of meningococcal disease in babies and children.

Headache was moderately specific, but also not sensitive.

Reduced consciousness

There was evidence for reduced consciousness as a very specific symptom of meningococcal disease in babies and children. Reduced consciousness was also moderately sensitive with a comparator group of undefined non-meningococcal disease, but was not sensitive with a viral meningitis comparator group.

Signs of shock

A composite factor of signs of shock (defined as clinician-diagnosed shock, a long capillary refill time of 4 seconds or more, or hypotension) was very specific and moderately sensitive for a diagnosis of meningococcal disease in babies and children. Hypotension (defined as 2 standard deviations or more below the mean for age) was also a very specific sign, but was not sensitive.

Delayed capillary refill (defined as over 2 seconds) was both moderately specific and moderately sensitive for a diagnosis of meningococcal disease in babies and children. Cold hands or feet was moderately to very specific, but not sensitive.

Limb or body pain

There was evidence for limb pain as a very specific, but not sensitive, symptom of meningococcal disease in babies and children. General aching was moderately specific, and also not sensitive, for a diagnosis of meningococcal disease.

Cardiac and respiratory symptoms

Tachycardia and tachypnoea were both moderately specific and moderately sensitive for a diagnosis of meningococcal disease in babies and children.

There was some evidence that respiratory symptoms, and difficult or laboured breathing, were moderately specific but not sensitive for a diagnosis of meningococcal disease in babies and children.

The evidence for sore throat and cough were somewhat mixed. Sore throat was moderately specific but not sensitive, however, a composite factor of sore throat or coryza was neither sensitive nor specific. There was some evidence for the presence of a cough as moderately specific but not sensitive in a study with healthcare professional identification of signs/symptoms. While another study that used non-healthcare (parental) identification of signs/symptoms showed the presence of a cough as neither sensitive nor specific for a diagnosis of meningococcal disease.

Gastrointestinal symptoms and food refusal

There was some evidence for nausea or vomiting as moderately specific for a diagnosis of meningococcal disease in babies and children. This symptom was also shown to be moderately sensitive with non-healthcare (parental) identification of signs/symptoms, but not sensitive with healthcare professional identification of signs/symptoms.

There was also some evidence for food refusal as a moderately specific symptom of meningococcal disease, although estimates of sensitivity ranged from moderate to not sensitive.

Gastrointestinal symptoms, diarrhoea, and tummy pain were all moderately specific but not sensitive for a diagnosis of meningococcal disease in babies and children.

Signs and symptoms of meningococcal disease in adults

There was some evidence for the presence of a haemorrhagic rash and reduced consciousness, as very specific but not sensitive for a diagnosis of meningococcal disease (compared to viral meningitis) in adults.

Signs and symptoms of meningococcal disease in an undefined age range

There was some evidence that the following symptoms were moderately specific but not sensitive for a diagnosis of meningococcal disease in an undefined age range: reduced general condition; neck stiffness; reduced consciousness; body pain.

Cyanosis and cold extremities were both very specific, but not sensitive, signs of meningococcal disease in an undefined age range.

The presence of petechiae (lesions with a maximum diameter up to 4 mm) was both moderately specific and moderately sensitive for a diagnosis of meningococcal disease in an undefined age range. Ecchymoses (over 4 mm) were also moderately specific, but were not sensitive.

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 meningococcal disease. The reference standard was a confirmed diagnosis of meningococcal disease based on diagnostic laboratory tests for N. meningitides. The

committee considered the impact of true positives (correctly identifying meningococcal disease and starting the appropriate management), true negatives (being able to provide reassurance that the person does not have meningococcal disease), false positives (potentially starting unnecessary treatments) and false negatives (failing to identify people that require further interventions and intensive management). The committee agreed that both sensitivity and specificity were important. Sensitivity was important as failing to identify meningococcal disease 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 meningococcal disease, as the misdiagnosis of meningococcal disease would result in the initiation of inappropriate treatment.

The quality of the evidence

The quality of the evidence ranged from high to very low and evidence was typically downgraded due to risk of bias (for example, due to the index tests being interpreted with knowledge of the results of the reference standard, and potential for risk of bias and/or concerns about applicability with regards to patient selection) and imprecision (95% confidence intervals crossing decision making thresholds).

Evidence was found for: general signs of illness and duration of illness; unusual, abnormal, or pale skin colour; presence of haemorrhagic rash; type and size of rash; distribution and duration of rash; signs or symptoms of meningism; reduced consciousness; signs of shock; limb or body pain; cardiac and respiratory symptoms; gastrointestinal symptoms and refusal of food and drink.

No meta-analyses were conducted for any of the index tests due to insufficient evidence after stratifying for age, person identifying the sign/symptom (healthcare professional or non-healthcare professional) 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 meningococcal disease. 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 expertise to define combinations of signs and symptoms that might increase suspicion that a person has meningococcal disease.

The committee emphasised that meningococcal disease is a life-threatening medical emergency but can be difficult to diagnose and drew on their clinical knowledge and experience to include recommendations to help reduce the chance that meningococcal disease will be missed, by raising awareness that meningococcal disease: is a rapidly evolving condition; can be difficult to distinguish from other infections with similar signs and symptoms; may be harder to detect in some age groups, for example teenagers or young adults may be less likely to appear unwell.

The committee considered evidence showing that the presence of a haemorrhagic, non-blanching rash with lesions larger than 2 mm (purpura) was moderately to highly specific and moderately sensitive, and the presence of a spreading rash was moderately specific and moderately sensitive, for a diagnosis of meningococcal disease. There was also evidence that a number of features of meningitis (including neck pain or stiffness, photophobia, and a composite clinical factor of signs or symptoms of meningism) were moderately or highly specific (but not sensitive) for a diagnosis of meningococcal disease, however, most of this evidence included a non-sepsis and non-meningitis comparison group. The committee agreed that in order to differentiate meningococcal disease from meningitis, signs or symptoms of meningism would need to be combined with a non-blanching rash to raise the

index of suspicion for meningococcal disease. Based on their clinical knowledge and experience, and the evidence for the individual signs and symptoms, the committee agreed that the presence of purpura, a rapidly progressive and/or spreading non-blanching petechial or purpuric rash, and any symptom or sign of bacterial meningitis when combined with a non-blanching petechial or purpuric rash, should be considered as red flag symptoms for meningococcal disease.

Based on their clinical experience, the committee noted that sometimes rashes can be difficult to detect and recommended that clinicians look all over the body to check for a rash (including nappy areas for babies). The committee also 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. The committee highlighted that rashes can be harder to detect on brown, black or tanned skin, and included this in the recommendation to raise awareness of the need to consider this during examination. The rapidly evolving nature of meningococcal disease also means that a rash can change from blanching to non-blanching, and based on their clinical knowledge and experience, the committee recommended that patients, parents and carers were made aware of this and asked to look out for any changes.

The committee highlighted that although non-blanching rashes are classically associated with meningococcal disease and the association is supported by the evidence in this review, not everyone with proven meningococcal disease has a rash. Based on their clinical knowledge and experience, the committee included a recommendation that absence of a rash should not be used to rule out a diagnosis of meningococcal disease.

The committee noted that while people with meningococcal disease may present in the community or to hospital with 1 or more of the red flag symptoms (presence of purpura, a rapidly spreading non-blanching petechial or purpuric rash, and/or any sign or symptom of bacterial meningitis when combined with a non-blanching petechial or purpuric rash), meningococcal disease can present in different ways (and with none of the red flag symptoms). The committee agreed to include a recommendation to raise awareness of this by highlighting that meningococcal disease can be strongly suspected based on clinical assessment even in people with none of the red flag symptoms. Based on their clinical knowledge and experience, the evidence in this review, and other relevant NICE guidance (Sepsis: recognition, diagnosis and early management and Fever in under 5s: assessment and initial management) the committee identified signs and symptoms associated with serious illness that might also be indicators of meningococcal disease and included these in a table. The committee agreed based on expert consensus opinion that meningococcal disease can present with any combination of the signs and symptoms included in the table, and outside of the red flags the evidence was not clear enough to rank other signs or symptoms in order of importance.

The committee took into account the rapidly evolving nature of meningococcal disease, 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.

The committee considered evidence for appearing ill, or being categorised as ill, and overall studies showed moderate specificity and moderate sensitivity for meningococcal disease. The committee agreed that appearing ill to a healthcare professional may support the diagnosis of meningococcal disease.

There was some evidence in this review that pale or unusual skin colour (including cyanosis) were moderately to highly specific, but not sensitive, signs of meningococcal disease. The committee agreed that these findings were consistent with their clinical experience that pale

or unusual skin colour (including cyanosis) can be associated with meningococcal disease and they agreed to include this sign in the table but to maintain consistent terminology with the NICE Fever in under 5s guideline (pale, mottled skin or cyanosis). As with detecting the presence of a rash, the committee noted that skin changes may be difficult to see on brown, black or tanned skin, and flagged this in the notes section of the table.

There was no specific evidence that quantified the diagnostic accuracy of parental or carer concern, although some studies included in the evidence review relied on parental report of signs and symptoms. The committee took into account the lack of any definitive 'index tests' for meningococcal disease (none of the signs or symptoms examined were both very sensitive and very specific) and the rapidly evolving nature of the condition and based on consensus added parent or carer concern to the table of features that may support a diagnosis of meningococcal disease. This was highlighted as particularly important as changes to appearance or general signs of illness can be subtle, particularly to people that are not familiar with the patient's usual state.

Another symptom that the committee agreed may support the diagnosis of meningococcal disease but that was also important to interpret in the context of a person's normal function was altered mental state. The evidence reviewed showed that reduced consciousness, confusion, lethargy and drowsiness were at least moderately specific for a diagnosis of meningococcal disease, although there was more variability in the sensitivity estimates. There was also some evidence that being considered irritable or miserable was a moderately sensitive (but not specific) symptom of meningococcal disease. There was some evidence that objective measures of new or altered mental state, including assessing the level of consciousness with the Alert, Voice, Pain, Unresponsive (AVPU) scale and/or Glasgow Coma Scale (GCS), was very specific for a diagnosis of meningococcal disease. However, in other studies the method of assessing altered mental state was unclear, and the committee highlighted based on their clinical experience that changes can be subtle. Drawing on their expertise and the evidence reviewed the committee agreed that lethargy, unusual behaviour (particularly being agitated, aggressive or subdued), or altered level of consciousness or altered cognition (including confusion or delirium) can be associated with meningococcal disease. The committee also highlighted that meningococcal disease 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 meningococcal disease) 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 meningococcal disease in babies.

The committee considered evidence showing that cold hands and/or feet was a moderately to highly specific, but not sensitive, sign of meningococcal disease. Based on their clinical knowledge and experience, the committee also noted that cold extremities may be present in the early stages of the illness and agreed that this clinical feature might support the diagnosis of meningococcal disease.

There was some evidence that tachycardia (raised heart rate) was both moderately specific and moderately sensitive for a diagnosis of meningococcal disease. Based on their clinical knowledge and experience, the committee were also aware that bradycardia (slow heart rate) could be an indicator of severe illness. The committee agreed that both high age-specific heart rate and low heart rate defined as less than 60 beats per minute for babies and children under 12 years should be included in the table as signs that may support a diagnosis of meningococcal disease.

There was some evidence that hypotension (low blood pressure) was very specific, but not sensitive, for a diagnosis of meningococcal disease. Based on this evidence, and their clinical knowledge and experience, the committee agreed that low age-specific blood pressure should be included in the table as a clinical feature that might support a diagnosis of meningococcal disease.

The committee considered evidence showing that delayed capillary refill time (defined as over 2 seconds) was both a moderately specific and moderately sensitive sign of meningococcal disease. There was also evidence showing that a composite factor of signs of shock (defined as clinician-diagnosed shock, a long capillary refill time of 4 seconds or more, or hypotension) was very specific and moderately sensitive for a diagnosis of meningococcal disease. The committee agreed that a capillary refill time of 3 seconds or longer should be included in the table as a sign that might support a diagnosis of meningococcal disease.

The committee highlighted that although prolonged capillary refill time may be a more specific individual sign of dehydration, reduced urine output is commonly reported as a marker of dehydration. No evidence specific to this review was identified. However, the committee considered the evidence and recommendations in the NICE Sepsis guideline that included reduced urine output as a high to moderate risk criterion, and agreed to include this in the table as a clinical feature that might support a diagnosis of meningococcal disease.

There was some evidence that tachypnoea (raised respiratory rate) was both moderately specific and moderately sensitive for a diagnosis of meningococcal disease. There was no evidence for specific rates for different age bands, but the recommendation highlighted that it was important to use an age-specific threshold for defining raised respiratory rate. There was also some evidence that respiratory symptoms, and difficult or laboured breathing, were moderately specific but not sensitive. The NICE Fever in under 5s guideline included grunting in their risk stratification and based on their clinical experience and consideration of the evidence in that guideline, the committee agreed to include grunting as a respiratory symptom that might support the diagnosis of meningococcal disease.

There was some evidence that presence of fever was both moderately specific and moderately sensitive for a diagnosis of meningococcal disease, when the threshold was defined as a temperature of over 37.5°C and with a threshold over 38.5°C. The evidence included was from children aged up to 15 years, however, the age range, mean or median age of included participants is not reported. Based on their clinical knowledge and experience, the committee reflected that very high temperature is unusual in young children and can often be indicative of bacterial infection. The committee considered the evidence and recommendations in the NICE Fever in under 5s guideline, and agreed to include consistent thresholds for fever, with a temperature of 39°C or higher potentially supporting a diagnosis of meningococcal disease in children aged 3 to 6 months, and a temperature of 38°C or higher raising the index of suspicion for children younger than 3 months. Drawing on their clinical knowledge and experience, the committee also recommended that receipt of antipyretic treatment should be checked as it may make fever harder to identify. Based on their clinical knowledge, the committee also highlighted that hypothermia can indicate infection, and included a temperature of less than 36°C as a feature that might support the diagnosis of meningococcal disease.

There was some evidence for gastrointestinal symptoms, diarrhoea, and tummy pain as moderately specific but not sensitive for a diagnosis of meningococcal disease, and the committee agreed to include abdominal pain and diarrhoea in the recommendation.

There was some evidence for limb pain as a very specific symptom of meningococcal disease, and some evidence showing general aching to be moderately specific, neither symptom was sensitive for a diagnosis of meningococcal disease. The committee considered the evidence and recommendations in the NICE Sepsis guideline that included leg pain to indicate high to moderate risk in children with suspected sepsis. The committee noted that leg pain may be an indicator of reduced perfusion (in addition to prolonged capillary refill time and cold extremities) and agreed that leg pain should be included as a potential symptom of meningococcal disease.

Given the potentially serious implications of a delay to treatment (including death), the committee agreed based on expert clinical consensus that people with suspected meningococcal disease 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 clinical assessment for meningococcal disease. Based on their clinical knowledge and experience and considering the rapidly evolving nature of meningococcal disease, 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 meningococcal disease, they may have another serious condition. The committee specifically wanted to highlight other forms of sepsis, 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 meningococcal disease 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 1.1.3, 1.1.9 to 1.1.13, 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 bacterial meningitis [A1].

References – included studies

Diagnostic

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Borchsenius, F., Bruun, J.N., Tonjum, T., Systemic meningococcal disease: the diagnosis on admission to hospital, NIPH Annals, 14, 11-22, 1991

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Close, R.M., Ejidokun, O.O., Verlander, N.Q., Fraser, G., Meltzer, M., Rehman, Y., Muir, P., Ninis, N., Stuart, J.M., Early diagnosis model for meningitis supports public health decision making, Journal of Infection, 63, 32-38, 2011

Haj-Hassan 2011

Haj-Hassan, T.A., Thompson, M.J., Mayon-White, R.T., Ninis, N., Harnden, A., Smith, L.F., Perera, R., Mant, D.C., Which early ‘red flag’symptoms identify children with meningococcal disease in primary care?, British Journal of General Practice, 61, e97-e104, 2011

Nielsen 2001

Nielsen, H.E., Andersen, E.A., Andersen, J., Böttiger, B., Christiansen, K.M., Daugbjerg, P., Larsen, S.O., Lind, I., Nir, M., Olofsson, K., Diagnostic assessment of haemorrhagic rash and fever, Archives of Disease in Childhood, 85, 160-165, 2001

Waterfield 2021

Waterfield, T., Maney, J.A., Fairley, D., Lyttle, M.D., McKenna, J.P., Roland, D., Corr, M., McFetridge, L., Mitchell, H., Woolfall, K., Lynn, F., Validating clinical practice guidelines for the management of children with non-blanching rashes in the UK (PiC): a prospective, multicentre cohort study, Lancet Infectious Diseases, 21, 569-577, 2021

Wells 2001

Wells, L.C., Smith, J.C., Weston, V.C., Collier, J., Rutter, N., The child with a non-blanching rash: how likely is meningococcal disease?, Archives of Disease in Childhood, 85, 218-222, 2001

Economic

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

Appendices

Appendix A Review protocols

Review protocol for review question: What symptoms and signs, individually or in combination, are associated with meningococcal disease?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021245982
Review title	Symptoms and signs associated with meningococcal disease
Review question	What symptoms and signs, individually or in combination, are associated with meningococcal disease?
Objective	To determine the signs and symptoms (individually or in combination) that are associated meningococcal disease.
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	Meningococcal disease
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days

Field	Content
	old and younger) with suspected or confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis). Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis.
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 • 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

Field	Content
	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 meningococcal disease* • Specificity for diagnosis of meningococcal disease* 2. Association data (if insufficient accuracy data) • Risk ratios for diagnosis of meningococcal disease* • Odds ratios for diagnosis of bacterial meningococcal disease* * Diagnosis of meningococcal disease based on any diagnostic laboratory test for N. meningitidis.
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 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-

Field	Content
	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 factor 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 an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation

Field	Content
	(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 meningococcal disease: ○ Non-meningococcal sepsis ○ Meningitis ○ Absence of sepsis and 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	CRD42021245982	
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, meningococcal disease, 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; QUIPS: Quality in Prognostic 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 meningococcal disease?

Clinical Search

This was a combined search to cover both this review and the reviews on risk factors associated with meningococcal disease and signs, symptoms and risk factors associated with bacterial meningitis.

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.
38	(sign? or symptom* or complain*).ti,ab.

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

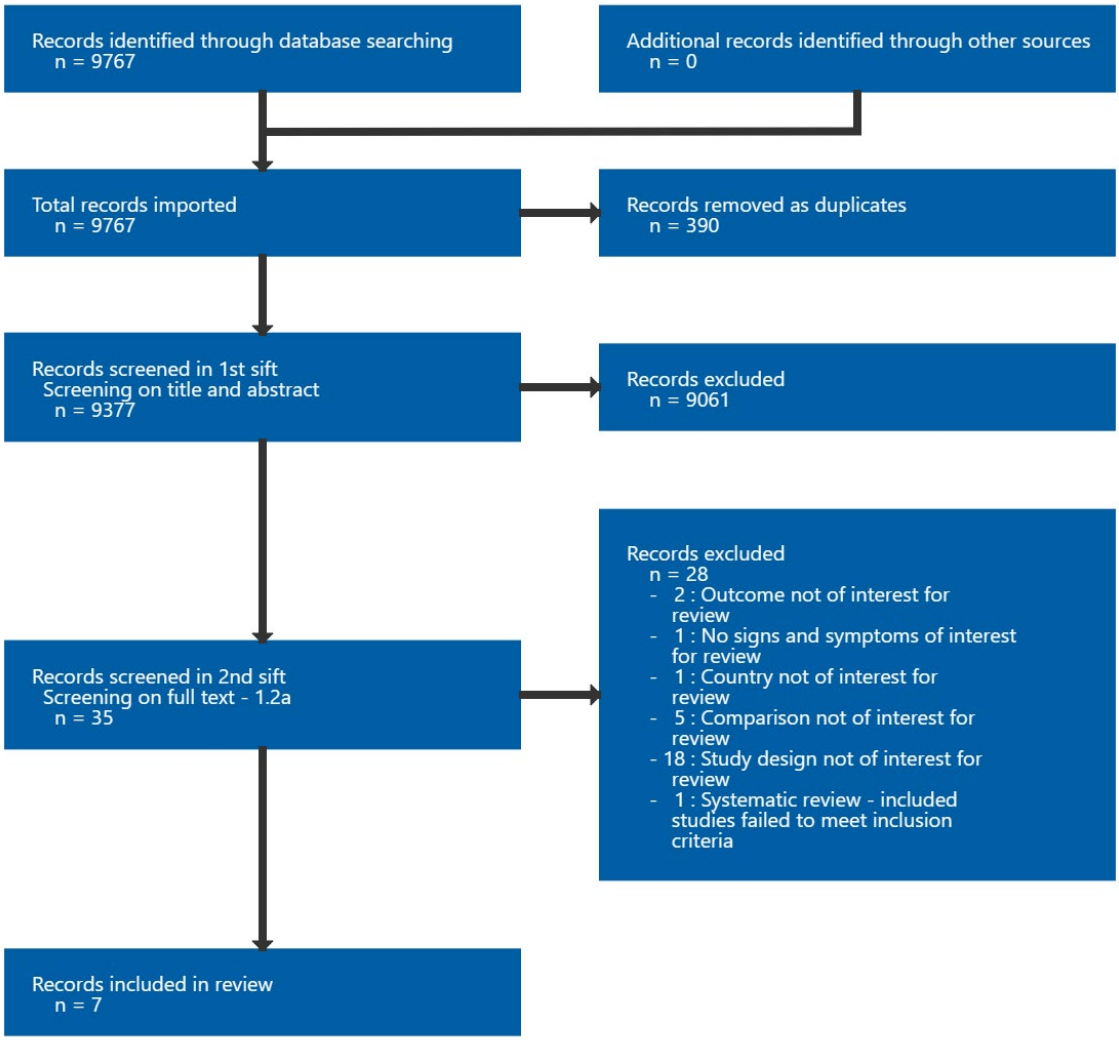
#	Searches
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.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

Figure 1: Study selection flow chart



Appendix D Evidence tables – Diagnostic evidence

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

Table 4: Evidence tables

Baker, 1989

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

Study details

Country/ies where study was carried out	US
Study type	Single-gate, cross-sectional DTA study
Study dates	November 1982 to October 1983
Inclusion criteria	People aged <21 years with fever >38°C and petechial rash
Exclusion criteria	Children with purpura fulminans; known bleeding diatheses; neonates
Patient characteristics	N=54: n=15 (8%) with documented invasive bacterial disease; n=39 (21%) nonbacteremic disease. Invasive bacterial disease group (n=15): Age in months (median; range in parentheses): 41 (6-180) n=4 (27%) meningococcal meningitis and bacteraemia; n=4 (27%) meningococcal meningitis without bacteraemia; and n=7 (47%) bacteraemia without meningitis (5 with N. meningitidis, 1 with H. influenzae type b, and 1 with S. pneumoniae)

	Nonbacteremic disease group (n=39): Age in months (median; range in parentheses): 45 (3-132) n=34 (87%) pharyngitis/upper respiratory tract infection; n=3 (8%) urinary tract infection/acute gastroentereitis; n=2 (5%) viral meningitis
Index test(s)	Signs and symptoms taken from medical records: (a) Ill appearance (b) Signs of meningeal irritation (c) Petechiae above the nipple line (including the head and upper extremities) (d) Petechiae on the trunk below the nipple line (e) Petechiae on the lower extremities
Reference standard(s)	Meningococcal disease was diagnosed by detection of N. meningitidis on blood or CSF culture.
Duration of follow-up	Not reported
Sources of funding	Not reported
Other information	40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes). Comparison group includes those with viral meningitis but only 5% of this group.

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/symptoms of invasive bacterial disease

Outcome	N = 54
Ill appearance Custom value	TP 7; FP 4; FN 8; TN 35
Signs of meningeal irritation Custom value	TP 5; FP 1; FN 10; TN 38
Petechiae above the nipple line (including the head and upper extremities) Custom value	TP 12; FP 35; FN 3; TN 4
Petechiae on the trunk below the nipple line Custom value	TP 11; FP 16; FN 4; TN 23
Petechiae on the lower extremities Custom value	TP 12; FP 11; FN 3; TN 28

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Only those with identified infective organisms were included in the analysis (excludes 85 patients where no organism was isolated))*

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled but only those with identified infective organisms included in the analysis (excludes 85 patients where no organism was isolated))*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes))*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No *(Index tests were not systematically quantified, and some were subjective (for example, ill appearance))*
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 were not systematically quantified, and some were 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	Is the reference standard likely to correctly classify the target condition?	Yes
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low *(No information about whether reference standards were interpreted without knowledge of the index tests; however, tests are objective so unlikely that knowledge of results would introduce bias)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Interval between index test and reference standard is not clear)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Unclear interval between index test and reference standard)*

Borchsenius, 1991

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

Study details

Country/ies where study was carried out	Norway

Study type	Single-gate, cross-sectional DTA study (a very small number of patients [5% of full sample that included those with meningitis only] included retrospectively)
Study dates	December 1981 to April 1982
Inclusion criteria	People admitted to hospital with suspected systemic meningococcal disease (those with meningococcal meningitis only (n=56) are included in the review on signs and symptoms of bacterial meningitis)
Exclusion criteria	Not reported
Patient characteristics	N=120 Meningococcal disease (n=59): Age: Reported for whole MD group only; Mean/median not reported; 50% aged < 12 years Septicaemia (arterial hypotension or cutaneous haemorrhages; n=21, 36%); meningitis and septicaemia (both meningitis and septicaemia; n=17, 29%); other (other systemic meningococcal infections; n=21, 36%). No meningococcal disease (n=61): Age: Mean/median not reported; 79% aged < 12 years. Bacterial meningitis or septicaemia, excluding those due to N. meningitidis (n=16, 26%); bacterial infection (with known bacterial aetiology; n=9, 15% [pneumonia, n=4; urinary tract infection, n=1; toxic shock syndrome, n=1; systemic bacterial infections, n=3); viral infections (positive viral isolation or serious meningitis; n=14, 23%); other diseases (n=22, 36%; includes n=15 with upper respiratory tract infections of unknown aetiology). n=2 who were difficult to categorize included in the control group as meningitis of unknown microbiological aetiology).
Index test(s)	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 diagnosing meningococcal disease was reported for the whole MD group only (including those with meningitis alone): Meningococcal disease confirmed with growth of meningococci in blood and/or CSF (for 62%), or the diagnosis of meningococcal disease was 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; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis

Outcomes

Signs and symptoms of meningococcal disease

Outcome	**N = 120**
Petechiae (<=4mm) Custom value	TP 48; FP 11; FN 11; TN 50

Outcome	N = 120
Reduced general condition Custom value	TP 28; FP 10; FN 31; TN 51
Ecchymoses (cutaneous haemorrhages >4 mm) Custom value	TP 27; FP 9; FN 32; TN 52
Reduced consciousness Custom value	TP 25; FP 11; FN 34; TN 50
Cold extremities Custom value	TP 20; FP 4; FN 39; TN 57
Cyanosis Custom value	TP 9; FP 0; FN 50; TN 61
Neck stiffness Custom value	TP 20; FP 26; FN 39; TN 35
Body pain Custom value	TP 17; FP 8; FN 42; TN 53

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient	Was a consecutive or random	Yes

Section	Question	Answer
selection: risk of bias	sample of patients enrolled?	
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not reported)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Generally a consecutive sample enrolled (5% included retrospectively), but exclusion criteria not reported. Inclusion criteria limited to patients hospitalized with suspected systemic meningococcal disease, but no further details reported.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No *(No detail on how clinical features measured, and many of these factors are subjective, for instance, reduced general condition, and reduced consciousness. Data not reported for non-significant signs and symptoms)*
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)*

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear *(The 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: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*
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	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Interval between index test and reference standard is not clear)*
Flow and timing: risk of bias	Did all patients receive a reference	Yes

Section	Question	Answer
	standard?	
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Unclear interval between index test and reference standard)*

Close, 2011

Bibliographic Reference	Close, R.M; Ejidokun, O.O; Verlander, N.Q; Fraser, G; Meltzer, M; Rehman, Y; Muir, P; Ninis, N; Stuart, J.M.; Early diagnosis model for meningitis supports public health decision making; Journal of Infection; 2011; vol. 63 (no. 1); 32-38

Study details

Country/ies where study was carried out	UK
Study type	Single-gate, cross-sectional DTA study
Study dates	July 2008 to June 2009
Inclusion criteria	Confirmed case of bacterial or viral meningitis, or meningococcal septicaemia. Suspected cases (those with a clinical diagnosis of bacterial or viral meningitis, or meningococcal septicaemia) were recruited, but only confirmed cases were included in the analysis.
Exclusion criteria	Neonates (aged <1 month).
Patient	N=719 suspected cases, of which 293 (41%) confirmed as bacterial meningitis or meningococcal septicaemia, and 92 (13%)

characteristics	as viral meningitis. N=385 confirmed cases (those included in analysis). Babies/children subgroup (aged 19 years or younger) n=230 Bacterial meningitis/meningococcal septicaemia (n=191): Age: Mean/median not reported Sex: male: 96 (50%); female: 95 (50%) Viral meningitis (n=39): Age: Mean/median not reported Sex: male: 23 (59%); female: 16 (41%) Adult subgroup (aged >19 years) n=155 Bacterial meningitis/meningococcal septicaemia (n=102): Age: Mean/median not reported Sex: male: 48 (47%); female: 54 (53%) Viral meningitis (n=53):

	Age: Mean/median not reported Sex: male: 22 (42%); female: 31 (58%) For whole sample (babies/children and adult subgroups combined): N. meningitidis n=234 (80%), S. pneumonia n=49 (17%), H. influenza n=3 (1%), other bacterial n=7 (2%) Of the 234 cases of meningococcal infection, 67 were reported as meningococcal septicaemia without meningitis. Proportion of those with meningitis only not reported. Viral meningitis (babies/children and adult subgroups combined): Enterovirus N=70 (76%), Herpes simplex virus N=7 (8%), Varicella zoster virus N=5 (5%), other viral N=10 (11%)
Index test(s)	Signs and symptoms, recorded by healthcare professionals on the study data collection forms: (a) Haemorrhagic rash (b) Level of consciousness (unresponsive)
Reference standard(s)	Confirmed cases defined as those with any one of the following: bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in CSF; bacteria or viruses obtained from culture of CSF; clinical and/or laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site, for example blood, throat swab, skin or faeces.
Duration of follow-up	Not reported
Sources of funding	Not industry funded
Other information	Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause)

Abbreviations: CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; DTA: diagnostic test accuracy; H. influenzae: Haemophilus influenzae; N. Meningitidis: Neisseria Meningitidis; RNA: ribonucleic acid; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Signs and symptoms of meningococcal disease

Outcome	**N = 385**
Babies/children Data available for 75% of subgroup Custom value	TP 107; FP 7; FN 48; TN 10
Adults Data available for 63% of subgroup Custom value	TP 22; FP 0; FN 50; TN 26
Babies/children Data available for 65% of subrgoup Custom value	TP 14; FP 0; FN 116; TN 19
Adults Data available for 61% of subgroup Custom value	TP 9; FP 0; FN 60; TN 26

Critical appraisal - QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
Patient	Was a case-control design avoided?	Yes

Section	Question	Answer
selection: risk of bias		
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Included only laboratory confirmed cases, and this may have biased results through the exclusion of bacterial meningitis cases where no organism could be identified (possibly because of antibiotics given prior to arrival at the hospital). Comparison limited to viral meningitis)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled, but included only laboratory confirmed cases, which may have biased results through the exclusion of bacterial meningitis cases where no organism could be identified (possibly because of antibiotics given prior to arrival at the hospital))*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause))*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No information about whether index tests were interpreted without knowledge of the reference standards; however, tests are objective (and standardized) so unlikely that knowledge of results would introduce bias)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*
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	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Interval between index test and reference standard is not clear)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	No *(Data is missing (for between 25% and 39% across variables and subgroups) and no attempts to collect information for those who dropped out is described. Reasons for loss to follow-up are not described. Patients with missing data are not adequately described)*

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Interval between index tests and reference standard is unclear. All patients not included in the analysis, data is missing (for between 25% and 39% across variables and subgroups) and no attempts to collect information for those who dropped out is described. Reasons for loss to follow-up are not described. Patients with missing data are not adequately described)*

Haj-Hassan, 2011

Bibliographic Reference	Haj-Hassan, T.A; Thompson, M.J; Mayon-White, R.T; Ninis, N; Harnden, A; Smith, L.F.P; Perera, R; Mant, D.C.; Which early 'red flag' symptoms identify children with meningococcal disease in primary care?; British Journal of General Practice; 2011; vol. 61 (no. 584); e97-e104

Study details

Country/ies where study was carried out	UK
Study type	Two-gate, cross-sectional DTA study Frequency of presenting symptoms in children attending primary care with acute febrile infections compared with previously reported frequencies in children with meningococcal disease (Thompson 2006)
Study dates	Non-fatal MD: December 1997 to February 1999. Minor febrile infection: June 2007 to July 2009 (children recruited at a similar seasonal rate to that found in the meningococcal disease study (Thompson 2006) in 20 sampling periods of 1-week's duration).
Inclusion criteria	Non-fatal MD: Children aged 0 to 16 years; non-fatal cases matched with children who had died from meningococcal disease (fatal cases reported in Thompson 2006 but not included in current study). Minor febrile infection: Children between 1 month and 16 years of age presenting in primary care with acute illness; accompanied by an adult caregiver who was able to provide informed consent; attending an acute appointment made within the previous 72 hours; minor febrile infection (defined as any acute infection in which the parent indicated on the symptoms

	questionnaire that fever was present in current illness).
Exclusion criteria	Non-fatal MD: Diagnoses did not meet criteria for inclusion; parental consent not given. Minor febrile infection: Final diagnosis not consistent with an acute infection (for example, minor trauma, atopic eczema, asthma, allergic rhinitis, infantile colic); insufficient information to determine a diagnosis; serious illness (defined as those referred acutely to hospital [emergency department or admission] within the subsequent 2 weeks); children in 15-16 year age group excluded from analysis as only N=12 recruited.
Patient characteristics	N=752 Non-fatal MD (n=345): Age in months: Mean/median not reported; 28% <1 year, 45% 1-4 years, 28% 5-14 years Sex: male 188 (55%); female: 157 (46%) n=103 fatal MD cases reported in previous dataset (Thompson 2006) but not included in the comparison with minor febrile infection. Further MD details not available for non-fatal MD alone. Data for combined fatal and non-fatal cases (n=448): 66% septicaemia; 22% meningitis; 12% both. For n=307 in whom meningococcal serogrouping data available (fatal and non-fatal cases combined): 50% serogroup B; 47% serogroup C; 3% W135 and Y serogroups collectively. Minor febrile infection (n=407): Age in months (median; interquartile range (IQR) in parentheses): 42 (22–79); 10% <1 year, 52% 1-4 years, 38% 5-14 years Sex: male: 209 (51%); female: 198 (49%) Duration of illness in days, reported by parents (median; IQR in parentheses): 4 (2-6)

	Diagnoses included: upper respiratory tract infections (33%); acute otitis media (15%); tonsillitis or pharyngitis (14%); non-specific viral illness (14%); LRTI or pneumonia (9%).
Index test(s)	Signs and symptoms as indicated in parent-reported questionnaire (symptoms in questionnaire based on those included in the meningococcal disease dataset [Thompson 2006] and non-specific symptoms common to childhood illnesses). Classic meningeal features: (a) Photophobia (b) Neck pain or stiffness (c) Headache Suggested red flags: (a) Leg pain (b) Cold hands and feet (c) Pale colour Other features: (a) Confusion (b) Drowsy or very sleepy (c) Rash or new spots on skin (defined as any type of rash. MD dataset included all rash types mentioned by the parent and/or GP; minor febrile infection dataset based on parental reports only)

	(d) Nausea or vomiting (e) Irritable or miserable (f) General aching (g) Refusing food or feeds (h) Difficult/laboured breathing (i) Diarrhoea (j) Sore throat (k) Tummy pain (l) Cough
Reference standard(s)	Clinical record review (blind to final outcome) by an expert panel of consultants in paediatric emergency medicine, infectious disease, and intensive care, although the majority of cases (79%) were confirmed through microbiological techniques. A case was categorised as meningitis if the child had neck stiffness, photophobia, or other CNS signs, and as septicaemia if the child had cardiovascular shock or multiorgan failure but no signs of meningitis. Some children had features of both meningitis and septicaemia.
Duration of follow-up	Not reported (MD study parents interviewed a median of 4 months after hospital admission; minor febrile infection data collected at point of care)
Sources of funding	Not industry funded
Other information	N=103 fatal MD cases reported in previous dataset (Thompson 2006) but not included in the comparison with minor febrile infection. Thompson 2006: Thompson, M.J., Ninis, N., Perera, R., Mayon-White, R., Phillips, C., Bailey, L., Harnden, A., Mant, D., Levin, M., Clinical

	recognition of meningococcal disease in children and adolescents, The Lancet, 367, 397-403, 2006 Data not extracted for fever or high temperature as this was an inclusion criterion

Abbreviations: CNS: central nervous system; DTA: diagnostic test accuracy; MD: meningococcal disease

Outcomes

Signs and symptoms for meningococcal disease

Outcome	**N = 752**
Photophobia Custom value	TP 73; FP 16; FN 272; TN 391
Neck pain or stiffness Custom value	TP 86; FP 23; FN 259; TN 384
Headache Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper) Custom value	TP 79; FP 130; FN 171; TN 236
Leg pain Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper) Custom value	TP 94; FP 21; FN 156; TN 345
Cold hands and feet Custom value	TP 139; FP 74; FN 206; TN 333
Pale colour Custom value	TP 65; FP 169; FN 280; TN 238
Confusion	TP 101; FP 7; FN 149; TN 359

Outcome	N = 752
Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper) Custom value	
Drowsy or very sleepy Custom value	TP 275; FP 142; FN 70; TN 265
Rash or new spots on skin Custom value	TP 267; FP 57; FN 78; TN 350
Nausea or vomiting Custom value	TP 250; FP 147; FN 95; TN 260
Irritable or miserable Custom value	TP 236; FP 213; FN 109; TN 194
General aching Custom value	TP 129; FP 94; FN 216; TN 313
Refusing food or feeds Custom value	TP 200; FP 181; FN 145; TN 226
Difficult/laboured breathing Custom value	TP 42; FP 54; FN 303; TN 353
Diarrhoea Custom value	TP 35; FP 80; FN 310; TN 327

Outcome	N = 752
Sore throat Custom value	TP 50; FP 198; FN 295; TN 209
Tummy pain Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper) Custom value	TP 12; FP 95; FN 238; TN 271
Cough Custom value	TP 6; FP 268; FN 339; TN 139

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Two-gate study design)*
Patient selection: risk of bias	Was a case-control design avoided?	No *(Children with confirmed MD compared with those presenting in primary care with minor febrile infection)*
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Those with serious illness excluded from the comparison group)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Two-gate study design comparing children with confirmed MD with those presenting in primary care with minor febrile infection, and those with serious illness excluded from the comparison group)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Only those with non-fatal MD included in analysis, and proportions of people with meningitis, septicaemia, or both, only reported for combined fatal and non-fatal cases (22% meningitis only in combined dataset))*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No *(Limited detail on how the index tests were measured and defined and many are subjective)*
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 subjective and poorly defined)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear *(Clinical record review (blind to final outcome) by an expert panel of consultants in paediatric emergency medicine, infectious disease, and intensive care, although the majority of cases (79%) were confirmed through microbiological techniques)*
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Clinical record review (blind to final outcome) by an expert panel of consultants in paediatric emergency medicine, infectious disease, and intensive care, although the majority of cases (79%) were confirmed through microbiological techniques)*

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	No *(There was not an appropriate interval between index test(s) and reference standard. For the MD group, parents were interviewed a median of 4 months after hospital admission about signs and symptoms)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes *(Some patients (21%) did not have diagnosis confirmed through microbiological techniques, but the results of the index test did not influence the decision on whether to perform the reference standard or which reference standard to use)*
Flow and timing: risk of bias	Were all patients included in the analysis?	No *(For some index tests, only children aged >1 year were included)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(There was not an appropriate interval between index test(s) and reference standard. For the MD group, parents were interviewed a median of 4 months after hospital admission about signs and symptoms)*

Nielsen, 2001

Bibliographic Reference	Nielsen, H.E; Andersen, E.A; Andersen, J; Bottiger, B; Christiansen, K.M; Daugbjerg, P; Larsen, S.O; Lind, I; Nir, M; Olofsson, K.; Diagnostic assessment of haemorrhagic rash and fever; Archives of Disease in Childhood; 2001; vol. 85 (no. 2); 160-165

Study details

Country/ies where study was carried out	Denmark

Study type	Single-gate, cross-sectional DTA study
Study dates	September 1993 to June 1996
Inclusion criteria	Babies and children aged 1 month to 16 years with skin haemorrhages detected at admission/during hospital stay and rectal temperature >38°C within the 24 hours before inclusion
Exclusion criteria	If a child was admitted twice during the study period and fulfilled the inclusion criteria on both occasions, only the first admission was included in the study.
Patient characteristics	N=264 included in the study and N=208 analysed (excluded from analysis were those with: invasive bacterial infection excluding meningococcal disease, n=6; insufficient information [either antibiotic treatment prior to blood culture, or no blood culture but treated with antibiotics], n=50). Meningococcal disease (n=39): Confirmed case n=29 (median age 30 months); probable case n=10 (median age 14 months). N=9 serogroup C cases. No invasive bacterial disease (n=169): Enterovirus infection n=18 (median age 21 months); adenovirus infection n=11 (median age 22 months); no invasive bacterial disease (either no bacteria in cultures from blood or spinal fluid and no antibiotic treatment prior to culture; or no blood culture, but spontaneous recovery) n=140 (median age 27 months).
Index test(s)	Signs and symptoms, recorded by healthcare professionals on preprinted study forms and including information from the case history and a standardized physical examination: (a) Case history included coughing prior to inclusion (b) Case history included vomiting prior to inclusion (c) Nuchal rigidity (d) More than 20 skin haemorrhages (e) Skin haemorrhages with maximum diameter >1mm (f) Skin haemorrhages with maximum diameter >2mm

	(g) Universal distribution of skin haemorrhages
Reference standard(s)	Confirmed case defined as clinical diagnosis of meningitis or septicaemia confirmed by culture of Neisseria meningitidis from blood and/or spinal fluid. Probable case defined as clinical diagnosis of meningitis or septicaemia without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.
Duration of follow-up	Not reported
Sources of funding	Not industry funded
Other information	Paper reports many outcomes as medians rather than dichotomised. Factors reported as percentages rather than numbers (converted to numbers based on assumption that data available for whole sample).

Abbreviations: DTA: diagnostic test accuracy

Outcomes

Signs and symptoms of meningococcal disease

Outcome	**N = 208**
Case history included coughing prior to inclusion Custom value	TP 6; FP 63; FN 33; TN 106
Case history included vomiting prior to inclusion Custom value	TP 17; FP 68; FN 22; TN 101
Nuchal rigidity Custom value	TP 16; FP 5; FN 23; TN 164
More than 20 skin haemorrhages	TP 29; FP 86; FN 10; TN 83

Outcome	N = 208
Custom value	
Skin haemorrhages with maximum diameter >1mm Custom value	TP 37; FP 37; FN 2; TN 132
Skin haemorrhages with maximum diameter >2mm Custom value	TP 29; FP 14; FN 10; TN 155
Universal distribution of skin haemorrhages Custom value	TP 36; FP 68; FN 3; TN 101

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes *(There was only one exclusion criterion: if a child was admitted twice during the study period and fulfilled the inclusion criteria on both occasions, only the first admission was included in the study)*
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	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Unclear *(Not all prognostic factors clearly described, although all with extractable data are objective. Non-standard thresholds used for size of skin haemorrhages.)*
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; not all prognostic factors clearly described, although all with extractable data are objective. Non-standard thresholds used for size of skin haemorrhages.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*
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	Was there an appropriate interval between index test(s) and reference standard?	Yes *(Index tests and reference standard conducted at the same time)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(Index tests and reference standard conducted at the same time, and all patients included in the analysis)*

Waterfield, 2021

Bibliographic Reference	Waterfield, T; Maney, J. A; Fairley, D; Lyttle, M. D; McKenna, J. P; Roland, D; Corr, M; McFetridge, L; Mitchell, H; Woolfall, K; Lynn, F; Patenall, B; Shields, M. D; Paediatric Emergency Research in the, U. K; Ireland, Group; Validating clinical practice guidelines for the management of children with non-blanching rashes in the UK (PiC): a prospective, multicentre cohort study; The Lancet Infectious Diseases; 2021; vol. 21 (no. 4); 569-577

Study details

Country/ies where study was carried out	UK
Study type	Single-gate, cross-sectional DTA study
Study dates	November 2017 to June 2019

Inclusion criteria	Children (aged under 18 years) presenting to paediatric emergency department with fever (≥38°C), new-onset non-blanching rash or features suggestive of meningococcal infection
Exclusion criteria	Pre-existing haematological condition (haematological malignancy, idiopathic thrombocytopenic purpura, or coagulopathy); existing diagnosis of Henoch-Schönlein purpura
Patient characteristics	N=1329 Meningococcal disease (n=19): Age in months (median; interquartile range (IQR) in parentheses): 37 (9-58) Sex: male: 16 (84%); female: 3 (16%) Serogroup of N. meningitidis: B n=17 (89%); C n=1 (5%); W n=1 (5%) No meningococcal disease (n=1310): Age in months (median; interquartile range (IQR) in parentheses): 24 (12-48) Sex: male: 765 (58%); female: 545 (42%) No further details provided for those negative for meningococcal disease
Index test(s)	Signs and symptoms, identified by healthcare professionals and recorded prospectively on an electronic case report form: (a) Duration of illness (<24 hours) (b) Duration of rash (<4 hours) (c) Petechiae only (without purpura)

	(d) Purpura (e) Superior vena cava distribution of rash (f) Spreading rash (g) Unwell appearance (based on an overall assessment of appearance) (h) Signs of shock (defined as clinician-diagnosed shock, a long capillary refill time of 4 seconds or more, or hypotension) (i) Tachycardia (j) Tachypnoea (k) Gastrointestinal symptoms (abdominal pain, abdominal distension, diarrhoea, or nausea or vomiting) (l) Shivers or chills (m) Pallor (n) Unusual skin colour (o) Cold hands or feet (p) Respiratory symptoms (q) Sore throat or coryza (r) Lethargy (s) Refusal of food and drink

	(t) Limb pain (u) Signs or symptoms of meningism (a positive Brudzinski's and Kernig's sign, a bulging fontanelle, irritability, photophobia, neck stiffness, and headache) (v) Reduced consciousness
Reference standard(s)	Diagnosis based on a positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)
Duration of follow-up	Not reported
Sources of funding	Not industry funded

Abbreviations: CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; N. Meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction

Outcomes

Signs and symptoms of meningococcal disease

Outcome	**N = 1329**
Duration of illness (<24 hours) Data available for 99% of sample Custom value	TP 10; FP 430; FN 9; TN 873
Duration of rash (<4 hours) Data available for 93% of sample Custom value	TP 12; FP 753; FN 7; TN 461
Petechiae only (without purpura) Custom value	TP 6; FP 1245; FN 13; TN 65
Purpura	TP 13; FP 65; FN 6; TN 1245

Outcome	N = 1329
Custom value	
Superior vena cava distribution of rash Custom value	TP 6; FP 482; FN 13; TN 828
Spreading rash Custom value	TP 12; FP 308; FN 7; TN 1002
Unwell appearance Custom value	TP 16; FP 362; FN 3; TN 948
Signs of shock Custom value	TP 13; FP 67; FN 6; TN 1243
Tachycardia Custom value	TP 15; FP 592; FN 4; TN 718
Tachypnoea Data available for 99% of sample Custom value	TP 12; FP 431; FN 7; TN 863
Gastrointestinal symptoms Custom value	TP 8; FP 557; FN 11; TN 753
Shivers or chills Custom value	TP 6; FP 106; FN 13; TN 1204
Pallor	TP 8; FP 95; FN 11; TN 1215

Outcome	N = 1329
Custom value	
Unusual skin colour Custom value	TP 9; FP 108; FN 10; TN 1202
Cold hands or feet Custom value	TP 9; FP 129; FN 10; TN 1181
Respiratory symptoms Custom value	TP 8; FP 400; FN 11; TN 910
Sore throat or coryza Custom value	TP 5; FP 673; FN 14; TN 637
Lethargy Custom value	TP 13; FP 307; FN 6; TN 1003
Refusal of food and drink Custom value	TP 8; FP 403; FN 11; TN 907
Limb pain Custom value	TP 6; FP 66; FN 13; TN 1244
Signs or symptoms of meningism Custom value	TP 7; FP 273; FN 12; TN 1037
Reduced consciousness Custom value	TP 10; FP 13; FN 9; TN 1297

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Unclear *(Children with clear alternative diagnoses were excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled, but excluded children with clear alternative diagnoses)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No *(Limited detail on how the index tests were measured and defined and many are subjective)*
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 subjective and poorly defined)*
Index tests: applicability	Are there concerns that the index test, its	Low

Section	Question	Answer
	conduct, or interpretation differ from the review question?	
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*
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	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Interval between index test and reference standard is not clear)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	No *(Some missing data but limited attrition (1-7%))*
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 (1-7%))*

Wells, 2001

Bibliographic Reference	Wells, L.C; Smith, J.C; Weston, V.C; Collier, J; Rutter, N.; The child with a non-blanching rash: how likely is meningococcal disease?; Archives of Disease in Childhood; 2001; vol. 85 (no. 3); 218-222
Study details	
Country/ies where study was carried out	UK
Study type	Single-gate, cross-sectional DTA study
Study dates	1 November 1998 to 31 October 1999
Inclusion criteria	Babies and children aged up to 15 years; presenting to an accident and emergency department with a non-blanching rash.
Exclusion criteria	Not explicitly reported, but excluded those with a clear alternative diagnosis (11 with Henoch–Schonlein purpura, 1 with idiopathic thrombocytopenic purpura, 1 with haemolytic uraemic syndrome, 1 with acute leukaemia, and 1 with a previously recognised clotting disorder)
Patient characteristics	N=218 Age in months (median): 24; 55% <3 years Meningococcal disease (n=24) Serogroup of N. meningitidis: B n=12 (50%); C n=11 (46%); unknown n=1 (4%). No further details provided for those negative for meningococcal disease
Index test(s)	Signs and symptoms data collected on standard proforma by the paediatric medical team at the time of presentation. Clinical features: (a) Illness categorisation (defined as toxic, irritable and crying inconsolably, or lethargic)

	(b) Purpura (lesions >2 mm in diameter) (c) Rash beyond superior vena cava (SVC) (d) Fever >38.5°C (e) Fever >37.5°C (f) Hypotension (defined as 2 SD or more below the mean for age) (g) Capillary refill >2 seconds
Reference standard(s)	Meningococcal infection defined using a positive blood, CSF, or skin culture for N. meningitidis, Gram negative diplococci in CSF, or PCR for meningococcal DNA from blood or CSF. Method of diagnosis used in confirmed cases: Positive blood culture alone (n=5; 21%); Positive PCR alone (n=9; 37.5%); Positive PCR and blood culture (n=9; 37.5%); Positive PCR, blood culture, and CSF (n=1; 4%).
Duration of follow-up	Not reported
Sources of funding	Not reported

Abbreviations: CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; DTA: diagnostic test accuracy; N. Meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction; SD: standard deviation

Outcomes

Signs and symptoms for meningococcal disease

Outcome	**N = 218**
Illness categorisation Custom value	TP 19; FP 36; FN 5; TN 158
Purpura	TP 20; FP 23; FN 4; TN 171

Outcome	N = 218
Lesions >2 mm in diameter Custom value	
Rash beyond superior vena cava (SVC) Custom value	TP 24; FP 120; FN 0; TN 74
Fever >38.5°C Custom value	TP 14; FP 37; FN 10; TN 157
Fever >37.5°C Custom value	TP 19; FP 88; FN 5; TN 106
hypotension Custom value	TP 5; FP 2; FN 13; TN 66
Capillary refill >2 seconds Custom value	TP 20; FP 28; FN 4; TN 165

Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes

Section	Question	Answer
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Unclear *(Children with clear alternative diagnoses were excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Consecutive sample enrolled but excluded children with clear alternative diagnoses)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(No information about whether index tests were interpreted without knowledge of the reference standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Unclear *(Most index tests were systematically quantified and thresholds defined, although thresholds for the categorisation of 'ill' are unclear)*
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 standards. Most index tests were systematically quantified and thresholds defined, although thresholds for the categorisation of 'ill' are unclear)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes

Section	Question	Answer
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(No information about whether reference standards were interpreted without knowledge of the index tests)*
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	Was there an appropriate interval between index test(s) and reference standard?	Yes *(Index tests and reference standard conducted at the same time)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(Index tests and reference standard conducted at the same time, and all patients included in the analysis)*

Appendix E Forest plots

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

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: Illness categorisation or appearance for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Comparison group	Identification	Sensitivity (95% CI)	Specificity (95% CI)
Baker 1989	7	4	8	35	Mixed (includes M/S)	HCP	0.47 [0.21, 0.73]	0.90 [0.76, 0.97]
Waterfield 2021	16	362	3	948	Undefined	HCP	0.84 [0.60, 0.97]	0.72 [0.70, 0.75]
Wells 2001	19	36	5	158	Undefined	HCP	0.79 [0.58, 0.93]	0.81 [0.75, 0.87]

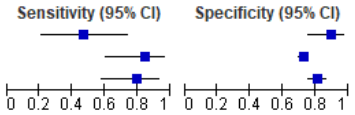


Figure 3: Pale skin colour for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Comparison group	Identification	Sensitivity (95% CI)	Specificity (95% CI)
Haj-Hassan 2011	65	169	280	238	Absence of M/S	Non-HCP	0.19 [0.15, 0.23]	0.58 [0.54, 0.63]
Waterfield 2021	8	95	11	1215	Undefined	HCP	0.42 [0.20, 0.67]	0.93 [0.91, 0.94]

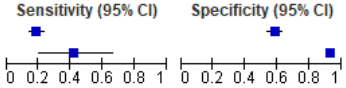


Figure 4: Purpura (lesions >2 mm in diameter) for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Comparison group	Identification	Sensitivity (95% CI)	Specificity (95% CI)
Nielsen 2001	29	14	10	155	Absence of M/S	HCP	0.74 [0.58, 0.87]	0.92 [0.86, 0.95]
Waterfield 2021	13	65	6	1245	Undefined	HCP	0.68 [0.43, 0.87]	0.95 [0.94, 0.96]
Wells 2001	20	23	4	171	Undefined	HCP	0.83 [0.63, 0.95]	0.88 [0.83, 0.92]

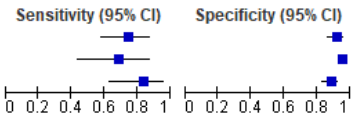


Figure 5: Signs of meningism for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Comparison group	Identification	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Baker 1989	5	1	10	38	Mixed (includes M/S)	HCP	0.33 [0.12, 0.62]	0.97 [0.87, 1.00]		
Waterfield 2021	7	273	12	1037	Undefined	HCP	0.37 [0.16, 0.62]	0.79 [0.77, 0.81]		

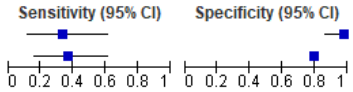


Figure 6: Neck pain or stiffness for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Comparison group	Identification	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Haj-Hassan 2011	86	23	259	384	Absence of M/S	Non-HCP	0.25 [0.20, 0.30]	0.94 [0.92, 0.96]		
Nielsen 2001	16	5	23	164	Absence of M/S	HCP	0.41 [0.26, 0.58]	0.97 [0.93, 0.99]		

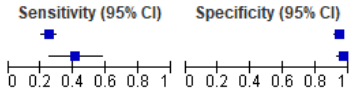
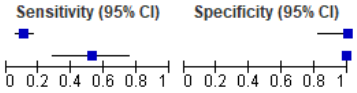


Figure 7: Reduced consciousness for diagnosis of meningococcal disease in babies and children

Study	TP	FP	FN	TN	Comparison group	Identification	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Close 2011	14	0	116	19	VM	HCP	0.11 [0.06, 0.17]	1.00 [0.82, 1.00]		
Waterfield 2021	10	13	9	1297	Undefined	HCP	0.53 [0.29, 0.76]	0.99 [0.98, 0.99]		



Appendix F GRADE table

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

Table 5: Illness categorisation or appearance for diagnosis of meningococcal disease in babies and children. Comparison group: nonbacteremic disease (includes viral meningitis)/negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Baker 1989)	Population: Invasive bacterial disease compared to nonbacteremic disease (includes VM) (People aged <21 years with fever >38°C and petechial rash) Reference standard: Detection of N. meningitidis on blood or CSF culture	54	Sensitivity: 0.47 (0.21 to 0.73)	Serious[1]	No serious	Serious[2]	Serious[3]	VERY LOW	0.64	0.81
			Specificity: 0.90 (0.76 to 0.97)	Serious[1]	No serious	Serious[2]	Serious[3]	VERY LOW		

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.84 (0.60 to 0.97)	Serious[1]	No serious	No serious	Serious[3]	LOW	0.04	1.00
			Specificity: 0.72 (0.70 to 0.75)	Serious[1]	No serious	No serious	No serious	MODERATE		
1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash) Reference standard: Blood, CSF or skin culture, gram staining, blood or CSF PCR	218	Sensitivity: 0.79 (0.58 to 0.93)	No serious	No serious	No serious	Serious[3]	MODERATE	0.35	0.97
			Specificity: 0.81 (0.75 to 0.87)	No serious	No serious	No serious	No serious	HIGH		

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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] 40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes)

[3] 95% CI crosses 1 decision making threshold

Table 6: Irritable or miserable for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.68 (0.63 to 0.73)	Very serious[1]	No serious	No serious	No serious	LOW	0.53	0.64
			Specificity: 0.48 (0.43 to 0.53)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; MD: meningococcal disease; 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 7: Duration of illness (<24 hours) for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1322	Sensitivity: 0.53 (0.29 to 0.76)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.02	0.99
			Specificity: 0.67 (0.64 to 0.70)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 8: Fever >37.5°C for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash)	218	Sensitivity: 0.79 (0.58 to 0.93)	No serious	No serious	No serious	Serious[1]	MODERATE	0.18	0.96

	Reference standard: Blood, CSF or skin culture, gram staining, blood or CSF PCR		Specificity: 0.55 (0.47 to 0.62)	No serious	No serious	No serious	Serious[1]	MODERATE		

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value
[1] 95% CI crosses 1 decision making threshold

Table 9: Fever >38.5°C for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash)	218	Sensitivity: 0.58 (0.37 to 0.78)	No serious	No serious	No serious	Serious[1]	MODERATE	0.27	0.94
	Reference standard: Blood, CSF or skin culture, gram staining, blood or CSF PCR		Specificity: 0.81 (0.75 to 0.86)	No serious	No serious	No serious	No serious	HIGH		

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value
[1] 95% CI crosses 1 decision making threshold

Table 10: Shivers or chills for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.32 (0.13 to 0.57)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.05	0.99
			Specificity: 0.92 (0.90 to 0.93)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 11: Lethargy for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.68 (0.43 to 0.87)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.04	0.99
			Specificity: 0.77 (0.74 to 0.79)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 12: Drowsiness for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD)	752	Sensitivity: 0.80 (0.75 to 0.84)	Very serious[1]	No serious	No serious	No serious	LOW	0.66	0.79

	Reference standard: Clinical record review (79% confirmed through microbiological techniques)		Specificity: 0.65 (0.60 to 0.70)	Very serious[1]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; 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

Table 13: Confusion for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD)	616[1]	Sensitivity: 0.40 (0.34 to 0.47)	Very serious[2]	No serious	No serious	No serious	LOW	0.94	0.71
	Reference standard: Clinical record review (79% confirmed through microbiological techniques)		Specificity: 0.98 (0.96 to 0.99)	Very serious[2]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; PPV: positive predictive value
[1] Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper)
[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 14: Pale skin colour for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis/negative for MD (no further detail). Non-healthcare professional (parental)/healthcare professional identification

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

1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.19 (0.15 to 0.23)	Very serious[1]	No serious	No serious	No serious	LOW	0.28	0.46
			Specificity: 0.58 (0.54 to 0.63)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.42 (0.20 to 0.67)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.08	0.99
			Specificity: 0.93 (0.91 to 0.94)	Serious[2]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value

[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 15: Unusual skin colour for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.47 (0.24 to 0.71)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.08	0.99
			Specificity: 0.92 (0.90 to 0.93)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 16: Presence of any rash for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.77 (0.73 to 0.82)	Very serious[1]	No serious	No serious	No serious	LOW	0.82	0.82
			Specificity: 0.86 (0.82 to 0.89)	Very serious[1]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; 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

Table 17: Presence of haemorrhagic rash for diagnosis of meningococcal disease in babies and children. Comparison group: viral meningitis. Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Close 2011)	Population: bacterial meningitis or meningococcal septicaemia compared to viral meningitis (Children aged ≤19 years with a confirmed case of bacterial or viral meningitis, or meningococcal septicaemia) Reference standard: Any 1 of: bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in CSF; bacteria or viruses obtained from culture of CSF; clinical and/or laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site, for example blood, throat swab, skin or faeces	172[1]	Sensitivity: 0.69 (0.61 to 0.76)	Serious[2]	No serious	Serious[3]	No serious	LOW	0.94	0.17
			Specificity: 0.59 (0.33 to 0.82)	Serious[2]	No serious	Serious[3]	Serious[4]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PPV: positive predictive value
[1] Data available for 75% of sample
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause)
[4] 95% CI crosses 1 decision making threshold

Table 18: Skin haemorrhages with maximum diameter >1mm for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Healthcare professional identification

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 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease (Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion) Reference standard: Confirmed case: Culture of N. Meningitidis from	208	Sensitivity: 0.95 (0.83 to 0.99)	No serious	No serious	No serious	Serious[1]	MODERATE	0.50	0.99

	blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.		Specificity: 0.78 (0.71 to 0.84)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PPV: positive predictive value

[1] *95% CI crosses 1 decision making threshold*

Table 19: Purpura (lesions >2 mm in diameter) for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis/negative for MD (no further detail). Healthcare professional identification

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 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease (Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion) Reference standard: Confirmed case: Culture of N. Meningitidis from	208	Sensitivity: 0.74 (0.58 to 0.87)	No serious	No serious	No serious	No serious	HIGH	0.67	0.94

	blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.		Specificity: 0.92 (0.86 to 0.95)	No serious	No serious	No serious	Serious[1]	MODERATE		
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of	1329	Sensitivity: 0.68 (0.43 to 0.87)	Serious[2]	No serious	No serious	Serious[1]	LOW	0.17	1.00

	meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)		Specificity: 0.95 (0.94 to 0.96)	Serious[2]	No serious	No serious	No serious	MODERATE		
1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash) Reference standard: Blood, CSF or skin culture, gram staining, blood or CSF PCR	218	Sensitivity: 0.83 (0.63 to 0.95)	No serious	No serious	No serious	Serious[1]	MODERATE	0.47	0.98
			Specificity: 0.88 (0.83 to 0.92)	No serious	No serious	No serious	Serious[1]	MODERATE		

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive; PCR: positive polymerase chain reaction; PPV: positive predictive value

[1] 95% CI crosses 1 decision making threshold

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

Table 20: Petechiae only (without purpura) for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.32 (0.13 to 0.57)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.00	0.83
			Specificity: 0.05 (0.04 to 0.06)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 21: More than 20 skin haemorrhages for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Healthcare professional identification

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 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease (Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion) Reference standard: Confirmed case: Culture of N. Meningitidis from	208	Sensitivity: 0.74 (0.58 to 0.87)	No serious	No serious	No serious	No serious	HIGH	0.25	0.89

	blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.		Specificity: 0.49 (0.41 to 0.57)	No serious	No serious	No serious	Serious[1]	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PPV: positive predictive value

[1] 95% CI crosses 1 decision making threshold

Table 22: Universal distribution of skin haemorrhages for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Healthcare professional identification

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 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease (Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion) Reference standard: Confirmed case: Culture of N. Meningitidis from	208	Sensitivity: 0.92 (0.79 to 0.98)	No serious	No serious	No serious	Serious[1]	MODERATE	0.35	0.97

	blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.		Specificity: 0.60 (0.52 to 0.67)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PPV: positive predictive value

[1] *95% CI crosses 1 decision making threshold*

Table 23: Spreading rash for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.63 (0.38 to 0.84)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.04	0.99
			Specificity: 0.76 (0.74 to 0.79)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 24: Rash beyond superior vena cava (SVC) for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash) Reference standard: Blood, CSF or skin culture, gram staining, blood or CSF PCR	218	Sensitivity: 1.00 (0.86 to 1.00)	No serious	No serious	No serious	Serious[1]	MODERATE	0.17	1.00
			Specificity 0.38 (0.31 to 0.45)	No serious	No serious	No serious	No serious	HIGH		

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value; SVC: superior vena cava
[1] 95% CI crosses 1 decision making threshold

Table 25: Petechiae on the trunk below the nipple line for diagnosis of meningococcal disease in babies and children. Comparison group: nonbacteremic disease (includes viral meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Baker 1989)	Population: Invasive bacterial disease compared to nonbacteremic disease (includes VM) (People aged <21 years with fever >38°C and petechial rash) Reference standard: Detection of N. meningitidis on blood or CSF culture	54	Sensitivity: 0.73 (0.45 to 0.92)	Serious[1]	No serious	Serious[2]	Very serious[3]	VERY LOW	0.41	0.85
			Specificity: 0.59 (0.42 to 0.74)	Serious[1]	No serious	Serious[2]	Serious[4]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; N. Meningitidis: Neisseria Meningitidis; 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] 40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes)
[3] 95% CI crosses 2 decision making thresholds
[4] 95% CI crosses 1 decision making threshold

Table 26: Petechiae on the lower extremities for diagnosis of meningococcal disease in babies and children. Comparison group: nonbacteremic disease (includes viral meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Baker 1989)	Population: Invasive bacterial disease compared to nonbacteremic disease (includes VM) (People aged <21 years with fever >38°C and petechial rash) Reference standard: Detection of N. meningitidis on blood or CSF culture	54	Sensitivity: 0.80 (0.52 to 0.96)	Serious[1]	No serious	Serious[2]	Serious[3]	VERY LOW	0.52	0.90
			Specificity: 0.72 (0.55 to 0.85)	Serious[1]	No serious	Serious[2]	No serious	LOW		

CI: confidence interval; CSF: cerebrospinal fluid; N. Meningitidis: Neisseria Meningitidis; 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] 40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes)
[3] 95% CI crosses 1 decision making threshold

Table 27: Petechiae above the nipple line for diagnosis of meningococcal disease in babies and children. Comparison group: nonbacteremic disease (includes viral meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Baker 1989)	Population: Invasive bacterial disease compared to nonbacteremic disease (includes VM) (People aged <21 years with fever >38°C and petechial rash) Reference standard: Detection of N. meningitidis on blood or CSF culture	54	Sensitivity: 0.80 (0.52 to 0.96)	Serious[1]	No serious	Serious[2]	Very serious[3]	VERY LOW	0.26	0.57
			Specificity: 0.10 (0.03 to 0.24)	Serious[1]	No serious	Serious[2]	No serious	LOW		

CI: confidence interval; CSF: cerebrospinal fluid; N. Meningitidis: Neisseria Meningitidis; 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] 40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes)
[3] 95% CI crosses 2 decision making thresholds

Table 28: Superior vena cava (SVC) distribution of rash for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.32 (0.13 to 0.57)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.01	0.98
			Specificity: 0.63 (0.61 to 0.66)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 29: Duration of rash (<4 hours) for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1233[1]	Sensitivity: 0.63 (0.38 to 0.84)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.02	0.99
			Specificity: 0.38 (0.35 to 0.41)	Serious[2]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value

[1] Data available for 99% of sample

[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 30: Signs of meningism for diagnosis of meningococcal disease in babies and children. Comparison group: nonbacteremic disease (includes viral meningitis)/negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Baker 1989)	Population: Invasive bacterial disease compared to nonbacteremic disease (includes VM) (People aged <21 years with fever >38°C and petechial rash) Reference standard: Detection of N. meningitidis on blood or CSF culture	54	Sensitivity: 0.33 (0.12 to 0.62)	Serious[1]	No serious	Serious[2]	Serious[3]	VERY LOW	0.83	0.79
			Specificity: 0.97 (0.87 to 1.00)	Serious[1]	No serious	Serious[2]	Serious[3]	VERY LOW		
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of	1329	Sensitivity: 0.37 (0.16 to 0.62)	Serious[1]	No serious	No serious	Serious[3]	LOW	0.03	0.99

	meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)		Specificity: 0.79 (0.77 to 0.81)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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] 40% of MD population is indirect (27% with meningococcal meningitis alone and 13% with meningitis with other causes)

[3] 95% CI crosses 1 decision making threshold

Table 31: Neck pain or stiffness for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental)/healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed	752	Sensitivity: 0.25 (0.20 to 0.30)	Very serious[1]	No serious	No serious	No serious	LOW	0.79	0.60

	through microbiological techniques)		Specificity: 0.94 (0.92 to 0.96)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Nielsen 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease (Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion) Reference standard: Confirmed case: Culture of N. Meningitidis from blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a	208	Sensitivity: 0.41 (0.26 to 0.58)	No serious	No serious	No serious	Serious[2]	MODERATE	0.76	0.88
			Specificity: 0.97 (0.93 to 0.99)	No serious	No serious	No serious	No serious	HIGH		

	significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoel ectrophoresis.									

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive; 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 32: Photophobia for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.21 (0.17 to 0.26)	Very serious[1]	No serious	No serious	No serious	LOW	0.82	0.59
			Specificity: 0.96 (0.94 to 0.98)	Very serious[1]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; 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

Table 33: Headache for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	616[1]	Sensitivity: 0.32 (0.26 to 0.38)	Very serious[2]	No serious	No serious	No serious	LOW	0.38	0.58
			Specificity: 0.64 (0.59 to 0.69)	Very serious[2]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; PPV: positive predictive value
[1] Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper)
[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 34: Reduced consciousness for diagnosis of meningococcal disease in babies and children. Comparison group: viral meningitis/negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Close 2011)	Population: bacterial meningitis or meningococcal septicaemia compared to viral meningitis (Children aged ≤19 years with a confirmed case of bacterial or viral meningitis, or meningococcal septicaemia) Reference standard: Any 1 of: bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in CSF; bacteria or viruses obtained from culture of CSF; clinical and/or laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site, for example blood, throat swab, skin or faeces	149[1]	Sensitivity: 0.11 (0.06 to 0.17)	Serious[2]	No serious	Serious[3]	No serious	LOW	1.00	0.14
			Specificity: 1.00 (0.82 to 1.00)	Serious[2]	No serious	Serious[3]	Serious[4]	VERY LOW		

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.53 (0.29 to 0.76)	Serious[2]	No serious	No serious	Serious[4]	LOW	0.43	0.99
			Specificity: 0.99 (0.98 to 0.99)	Serious[2]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value; VM: viral meningitis

[1] Data available for 65% of sample

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

[3] Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause)

[4] 95% CI crosses 1 decision making threshold

Table 35: Signs of shock for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.68 (0.43 to 0.87)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.16	1.00
			Specificity: 0.95 (0.94 to 0.96)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 36: Hypotension for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash) Reference standard: Blood, CSF or skin culture, gram staining, blood or CSF PCR	86[1]	Sensitivity: 0.28 (0.10 to 0.53)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.71	0.84
			Specificity 0.97 (0.90 to 1.00)	Serious[2]	No serious	No serious	No serious	MODERATE		

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value
[1] Data only available for 39% of sample
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2 (due to the proportion of missing data for this factor)
[3] 95% CI crosses 1 decision making threshold

Table 37: Delayed capillary refill for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Wells 2001)	Population: MD compared to non-MD (undefined) (Children ≤15 years presenting to A&E with non-blanching rash) Reference standard: Blood,	217	Sensitivity: 0.83 (0.63 to 0.95)	No serious	No serious	No serious	Serious[1]	MODERATE	0.42	0.98
			Specificity 0.85 (0.80 to 0.90)	No serious	No serious	No serious	Serious[1]	MODERATE		

	CSF or skin culture, gram staining, blood or CSF PCR									

A&E: accident and emergency; CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value
[1] 95% CI crosses 1 decision making threshold

Table 38: Cold hands or feet for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis/negative for MD (no further detail). Non-healthcare professional (parental)/healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.40 (0.35 to 0.46)	Very serious[1]	No serious	No serious	No serious	LOW	0.65	0.62
			Specificity: 0.82 (0.78 to 0.85)	Very serious[1]	No serious	No serious	No serious	LOW		

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.47 (0.24 to 0.71)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.07	0.99
			Specificity: 0.90 (0.88 to 0.92)	Serious[2]	No serious	No serious	Serious[3]	LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value
[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 39: Limb pain for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis/negative for MD (no further detail). Non-healthcare professional (parental)/healthcare professional identification

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

1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	616[1]	Sensitivity: 0.38 (0.32 to 0.44)	Very serious[2]	No serious	No serious	No serious	LOW	0.82	0.69
			Specificity: 0.94 (0.91 to 0.96)	Very serious[2]	No serious	No serious	No serious	LOW		
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.32 (0.13 to 0.57)	Serious[3]	No serious	No serious	Serious[4]	LOW	0.08	0.99
			Specificity: 0.95 (0.94 to 0.96)	Serious[3]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value

[1] Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper)
[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[4] 95% CI crosses 1 decision making threshold

Table 40: General aching for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.37 (0.32 to 0.43)	Very serious[1]	No serious	No serious	No serious	LOW	0.58	0.59
			Specificity: 0.77 (0.72 to 0.81)	Very serious[1]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; 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

Table 41: Tachycardia for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.79 (0.54 to 0.94)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.02	0.99
			Specificity: 0.55 (0.52 to 0.58)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 42: Respiratory symptoms for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.42 (0.20 to 0.67)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.02	0.99
			Specificity: 0.69 (0.67 to 0.72)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 43: Tachypnoea for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

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

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1313[1]	Sensitivity: 0.63 (0.38 to 0.84)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.03	0.99
			Specificity: 0.67 (0.64 to 0.69)	Serious[2]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value

[1] Data available for 99% of the sample

[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 44: Difficult/laboured breathing for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.12 (0.09 to 0.16)	Very serious[1]	No serious	No serious	No serious	LOW	0.44	0.54
			Specificity: 0.87 (0.83 to 0.90)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; MD: meningococcal disease; 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 45: Cough for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental)/healthcare professional identification

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

1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.02 (0.01 to 0.04)	Very serious[1]	No serious	No serious	No serious	LOW	0.02	0.29
			Specificity: 0.34 (0.30 to 0.39)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Nielsen 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease (Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion)	208	Sensitivity: 0.15 (0.06 to 0.31)	No serious	No serious	No serious	No serious	HIGH	0.09	0.76
			Specificity: 0.63 (0.55 to 0.70)	No serious	No serious	No serious	No serious	HIGH		

	Reference standard: Confirmed case: Culture of N. Meningitidis from blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoel ectrophoresis.									

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive; PPV: positive predictive value
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 46: Sore throat for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

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

1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.14 (0.11 to 0.19)	Very serious[1]	No serious	No serious	No serious	LOW	0.20	0.41
			Specificity: 0.51 (0.46 to 0.56)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; MD: meningococcal disease; 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 47: Sore throat or coryza for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of	1329	Sensitivity: 0.26 (0.09 to 0.51)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.01	0.98

	meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)		Specificity: 0.49 (0.46 to 0.51)	Serious[1]	No serious	No serious	Serious[2]	LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 48: Gastrointestinal symptoms for diagnosis of meningococcal disease in babies and children. Comparison group: negative for MD (no further detail). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of	1329	Sensitivity: 0.42 (0.20 to 0.67)	Serious[1]	No serious	No serious	Serious[2]	LOW	0.01	0.99

	meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)		Specificity: 0.57 (0.55 to 0.60)	Serious[1]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; MD: meningococcal disease; 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 49: Nausea or vomiting for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental)/healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.72 (0.67 to 0.77)	Very serious[1]	No serious	No serious	No serious	LOW	0.63	0.73
			Specificity: 0.64 (0.59 to 0.69)	Very serious[1]	No serious	No serious	No serious	LOW		
1 (Nielsen 2001)	Population: MD (confirmed or probable case) compared to no invasive bacterial disease	208	Sensitivity: 0.44 (0.28 to 0.60)	No serious	No serious	No serious	Serious[2]	MODERATE	0.20	0.82

	(Babies/children aged 1 month-16 years, with haemorrhages in the skin of any size detected at admission or during the stay in hospital, and a rectal temperature >38°C within the 24 hours before inclusion) Reference standard: Confirmed case: Culture of N. Meningitidis from blood and/or CSF. Probable case: clinical diagnosis without culture confirmation, but defined by a significant increase in meningococcal antibody titres, or a high antibody titre in a single serum sample drawn during the 2nd or 3rd week after onset of disease, and/or demonstration of serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.		Specificity: 0.60 (0.52 to 0.67)	No serious	No serious	No serious	No serious	HIGH		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive; 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 50: Diarrhoea for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.10 (0.07 to 0.14)	Very serious[1]	No serious	No serious	No serious	LOW	0.30	0.51
			Specificity: 0.80 (0.76 to 0.84)	Very serious[1]	No serious	No serious	No serious	LOW		

CI: confidence interval; MD: meningococcal disease; 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

Table 51: Tummy pain for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis. Non-healthcare professional (parental) identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD)	616[1]	Sensitivity: 0.05 (0.03 to 0.08)	Very serious[1]	No serious	No serious	No serious	LOW	0.11	0.53
			Specificity 0.74	Very	No serious	No serious	No serious	LOW		

	Reference standard: Clinical record review (79% confirmed through microbiological techniques)		(0.69 to 0.78)	serious[1]						

CI: confidence interval; MD: meningococcal disease; NPV: negative predictive value; PPV: positive predictive value
[1] Analysed in children >1 year (as considered age-specific by authors of the meningococcal paper)
[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 52: Food refusal for diagnosis of meningococcal disease in babies and children. Comparison group: absence of sepsis and meningitis/negative for MD (no further detail). Non-heathcare professional (parental)/healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Haj-Hassan 2011)	Population: MD compared to minor febrile infection (Children aged <16 years with non-fatal MD) Reference standard: Clinical record review (79% confirmed through microbiological techniques)	752	Sensitivity: 0.58 (0.53 to 0.63)	Very serious[1]	No serious	No serious	No serious	LOW	0.52	0.61
			Specificity: 0.56 (0.51 to 0.60)	Very serious[1]	No serious	No serious	No serious	LOW		

1 (Waterfield 2021)	Population: MD compared to non-MD (undefined) (Children <18 years presenting to paediatric emergency department with fever ≥38°C, new-onset non-blanching rash or features suggestive of meningococcal infection) Reference standard: Positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF)	1329	Sensitivity: 0.42 (0.20 to 0.67)	Serious[2]	No serious	No serious	Serious[3]	LOW	0.02	0.99
			Specificity: 0.69 (0.67 to 0.72)	Serious[2]	No serious	No serious	No serious	MODERATE		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PCR: positive polymerase chain reaction; PPV: positive predictive value
[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 53: Presence of haemorrhagic rash for diagnosis of meningococcal disease in adults. Comparison group: viral meningitis. Healthcare professional identification

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

1 (Close 2011)	Population: bacterial meningitis or meningococcal septicaemia compared to viral meningitis (Adults aged >19 years with a confirmed case of bacterial or viral meningitis, or meningococcal septicaemia) Reference standard: Any 1 of: bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in CSF; bacteria or viruses obtained from culture of CSF; clinical and/or laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site, for example blood, throat swab, skin or faeces	98[1]	Sensitivity: 0.31 (0.20 to 0.43)	Serious[2]	No serious	Serious[3]	No serious	LOW	1.00	0.34
			Specificity: 1.00 (0.87 to 1.00)	Serious[2]	No serious	Serious[3]	Serious[4]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PPV: positive predictive value

[1] Data available for 63% of sample

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

[3] Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause)

[4] 95% CI crosses 1 decision making threshold

Table 54: Reduced consciousness for diagnosis of meningococcal disease in adults. Comparison group: viral meningitis. Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Close 2011)	Population: bacterial meningitis or meningococcal septicaemia compared to viral meningitis (Adults aged >19 years with a confirmed case of bacterial or viral meningitis, or meningococcal septicaemia) Reference standard: Any 1 of: bacteria, bacterial antigen, bacterial or viral DNA or RNA identified in CSF; bacteria or viruses obtained from culture of CSF; clinical and/or laboratory diagnosis of meningitis accompanied by microbiological evidence of pathogen from another site, for example blood, throat swab, skin or faeces	95[1]	Sensitivity: 0.13 (0.06 to 0.23)	Serious[2]	No serious	Serious[3]	No serious	LOW	1.00	0.30
			Specificity: 1.00 (0.87 to 1.00)	Serious[2]	No serious	Serious[3]	Serious[4]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; NPV: negative predictive value; PPV: positive predictive value
[1] Data available for 61% of sample
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
[3] Population may be indirect. Unclear how many people have meningitis only (however, only 80% had N. meningitidis as the cause)
[4] 95% CI crosses 1 decision making threshold

Table 55: Reduced general condition for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.47 (0.34 to 0.61)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.74	0.62

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.84 (0.72 to 0.92)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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 56: Cyanosis for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.15 (0.07 to 0.27)	Very serious[1]	No serious	No serious	No serious	LOW	1.00	0.55

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 1.00 (0.94 to 1.00)	Very serious[1]	No serious	No serious	No serious	LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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

Table 57: Petechiae (≤4 mm) for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.81 (0.69 to 0.90)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.81	0.82

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.82 (0.70 to 0.91)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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 58: Ecchymoses (>4 mm) for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.46 (0.33 to 0.59)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.75	0.62

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.85 (0.74 to 0.93)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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 59: Neck stiffness for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.34 (0.22 to 0.47)	Very serious[1]	No serious	No serious	No serious	LOW	0.43	0.47

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.57 (0.44 to 0.70)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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 60: Reduced consciousness for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.42 (0.30 to 0.56)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW	0.69	0.60

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.82 (0.70 to 0.91)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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 61: Cold extremities for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.34 (0.22 to 0.47)	Very serious[1]	No serious	No serious	No serious	LOW	0.83	0.59

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.93 (0.84 to 0.98)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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 62: Body pain for diagnosis of meningococcal disease in undefined age range. Comparison group: negative for MD (includes non-meningococcal sepsis and meningitis). Healthcare professional identification

No of studies	Study details	No of participants	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality of evidence	PPV	NPV
1 (Borchsenius 1991)	Population: MD compared to non-MD (includes those with bacterial meningitis/septicaemia with causes other than N. meningitidis, other bacterial infections and viral infections). (Patients with suspected systemic meningococcal disease admitted to hospital. Those with meningitis only are included in the review on signs and symptoms of bacterial	120	Sensitivity: 0.29 (0.18 to 0.42)	Very serious[1]	No serious	No serious	No serious	LOW	0.68	0.56

	meningitis) Reference standard: Method of diagnosis reported for the whole MD group (including those with meningitis alone): MD confirmed with 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%)		Specificity: 0.87 (0.76 to 0.94)	Very serious[1]	No serious	No serious	Serious[2]	VERY LOW		

CI: confidence interval; CSF: cerebrospinal fluid; MD: meningococcal disease; N. Meningitidis: Neisseria Meningitidis; 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

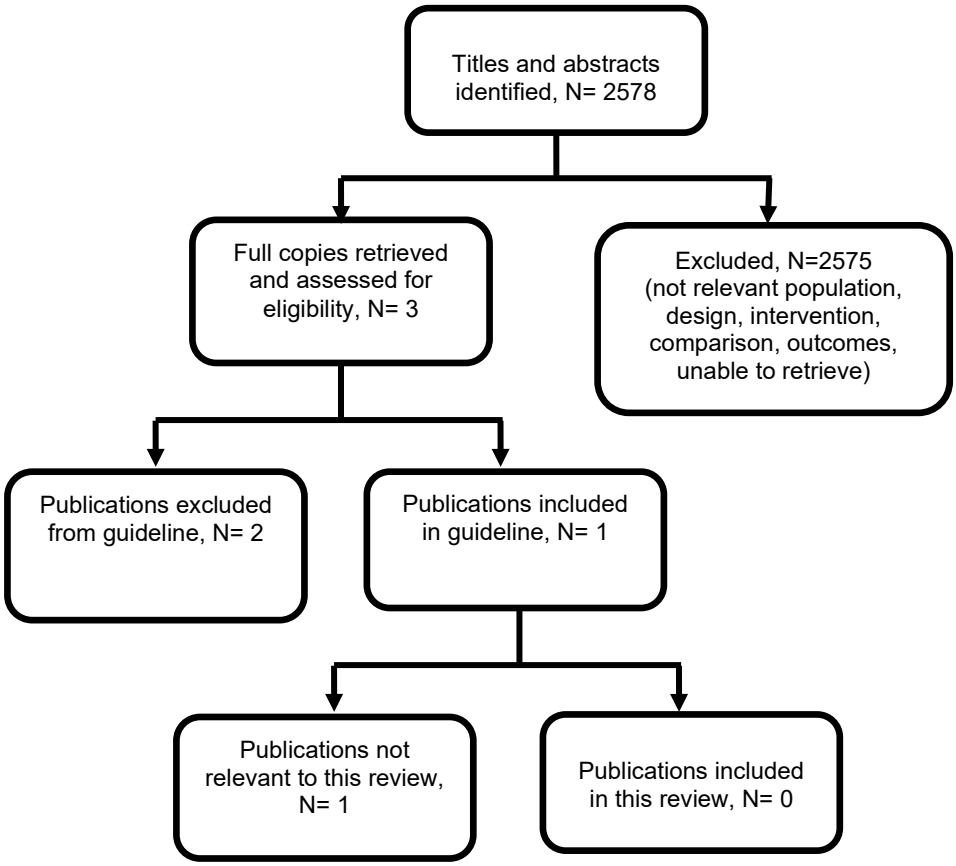
[2] 95% CI crosses 1 decision making threshold

Appendix F Economic evidence study selection

Study selection for: What symptoms and signs, individually or in combination, are associated with meningococcal disease?

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 8).

Figure 8: Study selection flow chart



Appendix G Economic evidence tables

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

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

Appendix H Economic model

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

No economic analysis was conducted for this review question.

Appendix I Excluded studies

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

Excluded diagnostic and prognostic studies

Table 63: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Ali, S., Hovenden, J.L., Symon, D.N.K., Review of meningococcal infection in children at a United Kingdom hospital, Acta Microbiologica et Immunologica Hungarica, 56, 81-87, 2009	Study design not of interest for review [Case series]
Aponso, D., Bullen, C., Presenting features of meningococcal disease, public health messages and media publicity: are they consistent?, New Zealand Medical Journal, 114, 83-85, 2001	Study design not of interest for review [Prevalence study on signs and symptoms of meningococcal disease. No comparison with those without meningococcal disease.]
Burman, L.A., Norrby, R., Trollfors, B., Invasive pneumococcal infections: incidence, predisposing factors, and prognosis, Reviews of Infectious Diseases, 7, 133-142, 1985	Study design not of interest for review [Case series]
Campbell, H., Andrews, N., Parikh, S., Ribeiro, S., Gray, S., Lucidarme, J., Ramsay, M.E., Borrow, R., Ladhani, S.N., Variable clinical presentation by the main capsular groups causing invasive meningococcal disease in England, Journal of Infection, 80, 182-189, 2020	Comparison not of interest for review [Comparison between different serogroups of meningococcal disease. Serogroups B, Y, and W]
De Greeff, S.C., De Melker, H.E., Schouls, L.M., Spanjaard, L., Van Deuren, M., Pre-admission clinical course of meningococcal disease and opportunities for the earlier start of appropriate intervention: a prospective epidemiological study on 752 patients in the Netherlands, 2003-2005, European Journal of Clinical Microbiology and Infectious Diseases, 27, 985-992, 2008	Study design not of interest for review [Prevalence data for signs and symptoms in meningococcal disease. No comparison with those without meningococcal disease]
Dubey, Himanshu, Oster, Philipp, Fazeli, Mir Sohail et al. (2022) Risk Factors for Contracting Invasive Meningococcal Disease and Related Mortality: A Systematic Literature Review and Meta-analysis. International journal of infectious diseases: IJID : official publication of the International Society for Infectious Diseases 119: 1-9	Systematic review - included studies failed to meet inclusion criteria
Evans-Jones, L.G., Whittle, H.C., Onyewotu, I.I., Egler, L.J., Greenwood, B.M., Comparative study of group A and group C meningococcal infection, Archives of Disease in Childhood, 52, 320-323, 1977	Country not of interest for review [Not a high-income OECD country (Nigeria)]
Fijnvandraat, K., Derkx, B., Peters, M., Bijlmer, R., Sturk, A., Prins, M.H., van Deventer, S.J. and ten Cate, J.W., Coagulation activation and tissue necrosis in meningococcal septic shock: severely reduced protein C levels predict a high mortality, Thrombosis and Haemostasis, 73, 15-	Outcome not of interest for review [Risk factors associated with adverse outcomes in meningococcal disease]

Study	Reason for exclusion
20, 1995	
Geishofer, G., Binder, A., Müller, M., Zöhrer, B., Resch, B., Müller, W., Faber, J., Finn, A., Endler, G., Mannhalter, C. and Zenz, W., 4G/5G promoter polymorphism in the plasminogen-activator-inhibitor-1 gene in children with systemic meningococcaemia, European Journal of Pediatrics, 164, 486-90, 2005	Study design not of interest for review [Case-control study]
Granier, S., Owen, P., Stott, N.C.H., Recognizing meningococcal disease: the case for further research in primary care, British Journal of General Practice, 48, 1167-1171, 1998	Study design not of interest for review [Systematic review doesn't include individual study quality assessment. Studies included in this review were assessed for potential inclusion]
Guiddir, T., Gros, M., Hong, E., Terrade, A., Denizon, M., Deghmane, A.E. and Taha, M.K., Unusual initial abdominal presentations of invasive meningococcal disease, Clinical Infectious Diseases, 67, 1220-1227, 2018	Outcome not of interest for review [Fatality rate with abdominal pain vs no abdominal pain in invasive meningococcal disease]
Healy, C.M., Butler, K.M., Smith, E.O.B., Hensey, O.P., Terence, B., Moloney, A.C., MacMahon, P., Cosgrove, J. and Cafferkey, M.T., Influence of serogroup on the presentation, course, and outcome of invasive meningococcal disease in children in the Republic of Ireland, 1995-2000, Clinical Infectious Diseases, 34, 1323-1330, 2002	Comparison not of interest for review [Comparison between different serogroups of meningococcal disease. Serogroup b vs c meningococcal disease]
Inkelis, S.H., O'Leary, D., Wang, V.J., Malley, R., Nicholson, M.K., Kuppermann, N., Extremity pain and refusal to walk in children with invasive meningococcal disease, Pediatrics, 110(1), e3, 2002	Study design not of interest for review [Prevalence data on signs and symptoms of meningococcal disease. No comparison with those without meningococcal disease]
Kuppermann, N., Malley, R., Inkelis, S.H. and Fleisher, G.R., Clinical and hematologic features do not reliably identify children with unsuspected meningococcal disease, Pediatrics, 103(2), e20, 1999	No signs and symptoms of interest for review [Mean temperature as continuous outcome as opposed to presence or absence of fever]
Leonard, P.A., Beattie, T.F., Presenting features of paediatric meningococcal disease-a five year experience from a paediatric accident and emergency department, Health Bulletin, 58, 148-151, 2000	Study design not of interest for review [Prevalence data on signs and symptoms of meningococcal disease. No comparison with those without meningococcal disease]
Loenenbach, A.D., van der Ende, A., de Melker, H.E., Sanders, E.A., Knol, M.J., The clinical picture and severity of invasive meningococcal disease serogroup W compared with other serogroups in the Netherlands, 2015–2018, Clinical Infectious Diseases, 70, 2036-2044, 2020	Comparison not of interest for review [Comparison between different serogroups of meningococcal disease]
Marzouk, O., Thomson, A.P., Sills, J.A., Hart, C.A., Harris, F., Features and outcome in meningococcal disease presenting with maculopapular rash, Archives of disease in childhood, 66, 485-487, 1991	Study design not of interest for review [Prevalence data on different types of rash in meningococcal disease. No comparison with those without meningococcal disease]
Parikh, S.R., Campbell, H., Gray, S.J., Beebeejaun, K., Ribeiro, S., Borrow, R., Ramsay, M.E., Ladhani, S.N., Epidemiology, clinical presentation, risk factors, intensive care	Study design not of interest for review [Prevalence data on signs and symptoms of meningococcal disease. No comparison with those without meningococcal disease]

Study	Reason for exclusion
admission and outcomes of invasive meningococcal disease in England, 2010–2015, Vaccine, 36, 3876-3881, 2018	
Paul, V.K., Verma, I.C., Deorari, A.K., Clinical aspects of meningococcal infections, Indian Journal of Pediatrics, 55, 207-217, 1988	Study design not of interest for review [Case series]
Schildkamp, R.L., Lodder, M.C., Bijlmer, H.A., Dankert, J., Scholten, R.J., Clinical manifestations and course of meningococcal disease in 562 patients, Scandinavian Journal of Infectious Diseases, 28, 47-51, 1996	Comparison not of interest for review [Compares signs and symptoms in meningococcal meningitis vs meningococcal disease vs meningococcal sepsis. No comparison with those without meningococcal meningitis/disease]
Sørensen, H.T., Møller-Petersen, J., Krarup, H.B., Pedersen, H., Hansen, H., Hamburger, H., Diagnostic problems with meningococcal disease in general practice, Journal of Clinical Epidemiology, 45, 1289-1293, 1992	Comparison not of interest for review [Compares signs and symptoms in those with a correct referral diagnosis from GP of meningococcal disease (meningitis/sepsis) or CNS infection vs those that the referring GP thought did not have MD /CNS infection (incorrect diagnosis). No comparison with those without meningococcal meningitis/disease]
Stinson, C., Burman, C., Presa, J., Abalos, M., Atypical presentation of invasive meningococcal disease caused by serogroup W meningococci, Epidemiology & Infection, 148, e12, 2020	Study design not of interest for review [Literature review. Studies included in this review were assessed for potential inclusion]
Stovall, S.H., Schutze, G.E., 2002, Meningococcal infections in children from Arkansas, Pediatric Infectious Disease Journal, 21, 366-370, 2002	Study design not of interest for review [Prevalence data on signs and symptoms of meningococcal infections. No comparison with those without meningococcal disease]
Thompson, M.J., Ninis, N., Perera, R., Mayon-White, R., Phillips, C., Bailey, L., Harnden, A., Mant, D., Levin, M., Clinical recognition of meningococcal disease in children and adolescents, Lancet, 367, 397-403, 2006	Study design not of interest for review [Prevalence data on signs and symptoms of meningococcal disease. No comparison with those without meningococcal disease]
Toejum, T., Nilsson, F., Bruun, J.N., Haneberg, B., The early phase of meningococcal disease, NIPH Annals, 6, 175-181, 1983	Study design not of interest for review [Case control study]
Voss, L., Lennon, D., Sinclair, J., The clinical features of paediatric meningococcal disease Auckland, 1985-87, New Zealand Medical Journal, 102, 243-245, 1989	Study design not of interest for review [Prevalence data for signs and symptoms of meningococcal disease. No comparison with those without meningococcal disease]
Wang, V.J., Kuppermann, N., Malley, R., Barnett, E.D., Meissner, H.C., Schmidt, E.V., Fleisher, G.R., Meningococcal disease among children who live in a large metropolitan area, 1981–1996, Clinical Infectious Diseases, 32, 1004-1009, 2001	Study design not of interest for review [Epidemiological study (no details on signs and symptoms or risk factors with meningococcal disease)]
Wong, V.K., Hitchcock, W., Mason, W.H., Meningococcal infections in children: a review of 100 cases, Pediatric Infectious Disease Journal, 8, 224-227, 1989	Study design not of interest for review [Prevalence data for signs and symptoms of meningococcal infections. No comparison with those without meningococcal disease]

Excluded economic studies

No economic evidence was identified for this review.

Appendix J Research recommendations – full details

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

No research recommendations were made for this review question.