National Institute for Health and Care Excellence

Final

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

[A2] Evidence review for risk factors associated with bacterial meningitis

NICE guideline NG240

Evidence review underpinning recommendation 1.1.8 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

Disclaimer

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Risk factors associated with bacterial meningitis

Review question

What factors are associated with an increased risk of bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group. Early recognition of the condition requires a high index of suspicion. The diagnosis of bacterial meningitis is frequently hindered by the non-specific nature of the early symptoms and signs, which may mimic those found in other serious conditions or milder viral illnesses.

The aim of this review is to evaluate the factors that are associated with an increased risk of bacterial meningitis, which healthcare professionals may take into consideration when initially assessing a patient.

Summary of the protocol

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

Table 1: Summary of the protocol

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis.
Prognostic factors	Any risk factors, alone or in combination
Comparator	Absence of risk factor(s)
Outcome	**Critical** • Risk ratios for diagnosis of bacterial meningitis* • Odds ratios** for diagnosis of bacterial meningitis* **Important** None * Diagnosis of bacterial meningitis must be made based on lumbar puncture ** adjusted odds ratios will be included where multivariate analyses are available

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.

Prognostic evidence

Included studies

Although there are population-level factors that may be associated with bacterial meningitis (for example, socioeconomic factors, age, winter season), this review focuses on risk factors that might be associated with an increased risk of bacterial meningitis at an individual level.

One cohort study was included for this review (Goldacre 2014). This study was retrospective and only reported univariate analyses but was included as no prospective studies or studies with multivariate analyses were identified.

The included study is summarised in Table 2.

The 1 eligible study included babies and children (Goldacre 2014).

All risk factors reported could be categorised as maternal and perinatal: maternal smoking during pregnancy; low birth weight; pre-term birth. The only comparison for which data was extractable was comparing these risk factors for bacterial meningitis (haemophilus or meningococcal meningitis) relative to viral meningitis.

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

Summary of the study that was included in this review is presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Risk factor	Outcomes	Comments
Goldacre 2014 Retrospective cohort study UK	N= 599 Babies and children admitted to hospital with a diagnosis of bacterial meningitis (haemophilus or meningococcal meningitis) or viral meningitis (study includes an 'all offspring' group but not eligible for inclusion in this review as includes BM and VM groups and unclear if other types of BM [other than meningococcal and haemophilus] included in this	• Maternal and perinatal risk factor: ○ Maternal smoking during pregnancy ○ Low birth weight (<2.5kg) ○ Pre-term delivery (gestational age <37 weeks)	Hospital admission for bacterial meningitis	Adjusted analyses cannot be extracted as based on the total population and the group of 'all offspring' do not meet inclusion criteria for this review. Only unadjusted data could be included. Diagnosis based on review of patients' hospital records. Data not extracted for population-level risk factors.

Study	Population	Risk factor	Outcomes	Comments
	group so cannot be categorised as absence of meningitis) Bacterial meningitis (n=287): Meningococcal meningitis (n=127); Haemophilus meningitis (n=160) Age: mean/median not reported; 29-364 days (n=124; 43%); 1-4 years (n=108; 38%); 5-9 years (n=12; 4%); 10-14 years (n=10; 3%); ≥15 years (n=33; 11%) Sex: male: 161 (56%); female 126 (44%) Viral meningitis (n=312): Age: mean/median not reported; 29-364 days (n=91; 29%); 1-4 years (n=57; 18%); 5-9 years (n=85; 27%); 10-14 years (n=40; 13%); ≥15 years (n=39; 13%) Sex: male: 194 (62%); female 118 (38%)			

BM: bacterial meningitis; CSF: cerebrospinal fluid; VM: viral meningitis.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no 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 very low quality due to a high risk of bias across multiple domains (for example, bias arising from the lack of clear specification of methods of measurement for any of the risk factors, study confounding as only unadjusted data could be included, missing data for some of the risk factors of interest, and outcome of hospital admission rather than diagnosis), and imprecision due to the very low numbers of events. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

There was no evidence of an increased risk of bacterial meningitis (relative to viral meningitis) in babies and children in the evidence reviewed, due to maternal smoking during pregnancy, low birth weight, or pre-term birth. However, as the findings were seriously imprecise for all outcomes, they should not be taken as definitive evidence of a lack of association.

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

As the objective of this review was to identify factors that are associated with an increased risk of bacterial meningitis to aid recognition, diagnosis of bacterial meningitis was the only outcome included for this review.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence for the outcome/prognostic factors identified in this review was very low quality and the reasons for downgrading the evidence was risk of bias (arising from measurement of the risk factor/outcomes, data unadjusted for confounding factors, and failure to adjust for missing data) and imprecision due to a low number of events.

Evidence was found for maternal and perinatal risk factors (maternal smoking during pregnancy, low birth weight, and pre-term birth).

Benefits and harms

The committee noted that the evidence was very limited with only 1 included study showing no significant associations between maternal smoking during pregnancy, low birth weight, or pre-term birth on the risk of receiving a diagnosis of bacterial meningitis (relative to viral meningitis) in babies and children.

The committee acknowledged that this evidence was very low quality, came from a single study, and was restricted to a comparison against viral meningitis only. The committee discussed the limited evidence base identified for this review and made recommendations based on their clinical knowledge and experience. The committee noted that although people with known immunodeficiencies were outside the scope of this guideline, there were some important risk factors for bacterial meningitis associated with immunodeficiency and the committee considered it important to include these in the recommendation in order to raise awareness and facilitate recognition.

The committee agreed that there are certain groups of people, particularly those that have congenital complement deficiency or acquired inhibition, or splenectomy or splenic dysfunction, who might be more at risk of developing bacterial meningitis. Similarly, the committee agreed that cerebrospinal fluid (CSF) leaks would also increase risk of bacterial meningitis. The committee discussed family history of meningococcal disease as a potential risk factor for bacterial meningitis (including meningococcal meningitis), as a potential indicator of immune deficiency given that most deficiency syndromes (including complement deficiency) are inherited. The committee also highlighted that a previous episode of bacterial meningitis or meningococcal disease, may suggest potential immunodeficiency and make people more susceptible to another episode of bacterial meningitis. Based on clinical consensus, the committee recommended that healthcare professionals should be on heightened alert to the possibility of bacterial meningitis in people with these risk factors.

The committee agreed that it was important to consider receipt of relevant immunisations, such as meningococcal, Haemophilus influenzae type b (Hib) or pneumococcal vaccines, as missing these immunisations would increase the risk of bacterial meningitis. The committee were also aware of evidence reviewed in Evidence review A4 (risk factors for meningococcal disease) showing that receiving the meningococcal serogroup C vaccine reduced the risk of a diagnosis of meningococcal disease in adolescents and noted that this population with meningococcal disease may also include those with meningococcal meningitis only.

The committee were aware of evidence showing that university students were at increased risk of a diagnosis of meningococcal disease (see Evidence review A4) and this population may include those with meningococcal meningitis only. Increased risk of meningococcal disease (including meningococcal meningitis only) was also associated with multiple kissing contacts, sharing a bedroom, and regular consumption of illicit drugs. The committee agreed that it was important that healthcare professionals be on heightened alert to the possibility of bacterial meningitis (including meningococcal meningitis) in people who are students in further or higher education particularly those in halls of residence or other large shared accommodations. The committee noted that risk would also be increased for those in close contact with people with meningococcal disease or Haemophilus influenzae type B (hib) outside of the educational setting, and included in the recommendation that healthcare professionals should ascertain whether close contact with someone with hib disease or meningococcal disease or presence in an area with an outbreak of meningococcal disease had occurred and be factored into the assessment for bacterial meningitis.

The committee were aware of evidence showing that people with cochlear implants may be at increased risk of contracting bacterial meningitis, and cochlear implant patients are included in the higher clinical risk group for developing pneumococcal meningitis and who should be immunised against pneumococcal infection in the Department of Health Green Book (Pneumococcal: the green book, chapter 25 - GOV.UK (www.gov.uk)). The committee agreed to include cochlear implants in the recommendations to raise awareness of this risk factor and aid recognition.

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 risk factors associated with bacterial meningitis rather than specific courses of action. The committee considered that their recommendations would assist the early and correct identification of bacterial meningitis which they considered 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 recommendation 1.1.8.

References – included studies

Prognostic

Goldacre 2014

Goldacre, M. J; Wotton, C. J; Maisonneuve, J. J; Maternal and perinatal factors associated with subsequent meningococcal, Haemophilus or enteroviral meningitis in children: database study; Epidemiology & Infection 142 (2): 371-8, 2014

Economic

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

Appendices

Appendix A Review protocols

Review protocol for review question: What factors are associated with an increased risk of bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021245980
Review title	Risk factors associated with bacterial meningitis
Review question	What factors are associated with an increased risk of bacterial meningitis?
Objective	This review aims to determine the risk factors (alone or in combination) that are associated bacterial meningitis
Searches	The following databases will be searched: Embase MEDLINE Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Searches will be restricted by: Date limitations: No date limit English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Bacterial meningitis

Field	Content
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Prognostic factors	Any risk factors, alone or in combination
Comparator/Reference standard/Confounding factors	Absence of risk factor(s)
Types of study to be included	• 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 analyses for a given risk factor 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.

Field	Content
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)	• Risk ratios for diagnosis of bacterial meningitis* • Odds ratios** for diagnosis of bacterial meningitis* * Diagnosis of bacterial meningitis must be made based on lumbar puncture **adjusted odds ratios will be included where multivariate analyses are available
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 risk factors, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklist: • ROBIS tool for systematic reviews • Quality in Prognostic Studies (QUIPS) tool for prognostic studies

Field	Content
	The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	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 (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/" **Minimally important differences** • 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:
	• -Population that do not receive a diagnosis of bacterial meningitis:
	  ○ Viral, tuberculous or fungal meningitis
	  ○ Absence of meningitis

Field	Content	
	• -Age: ○ Younger Infants: >28 days to ≤3 months of age ○ 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* *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	18/03/2021			
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.			
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines			

Field	Content	
	(including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=245980	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Prognostic, diagnostic, bacterial meningitis, signs and symptoms, risk factors, systematic review	
Details of existing review of same topic by same authors	None	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated

Field	Content	
	☐	Discontinued
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; N/A: not applicable; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PRESS: Peer Review of Electronic Search Strategies; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions; ROBIS: Risk of Bias in Systematic Reviews

Appendix B Literature search strategies

Literature search strategies for review question: What factors are associated with an increased risk of bacterial meningitis?

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

Clinical Search

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

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use medall
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis* or mening* encephalitis*).ti,ab.
9	Meningococcal Infections/ or exp Neisseria meningitidis/
10	9 use medall
11	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
12	11 use emczd
13	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
14	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
15	(Neisseria* mening* or n mening*).ti,ab.
16	or/2,4-8,10,12-15
17	"Signs and Symptoms"/ or Fever/ or Vomiting/ or Nausea/ or Diarrhea/ or Chills/ or Shivering/ or Sleepiness/ or Headache/ or Photophobia/ or Intracranial Pressure/ or exp Consciousness Disorders/ or *Coma/ or Seizures/ or Seizures, Febrile/ or Irritable Mood/ or Crying/ or Decerebrate State/ or Lethargy/ or Fatigue/ or Confusion/ or Malnutrition/ or exp Purpura/ or Muscle Hypotonia/ or exp Tachycardia/
18	17 use medall
19	*physical disease by body function/ or *fever/ or *vomiting/ or *nausea/ or *diarrhea/ or *chill/ or *shivering/ or *somnolence/ or *headache/ or *photophobia/ or *intracranial pressure/ or exp *consciousness disorder/ or *coma/ or *seizure/ or *febrile convulsion/ or *irritability/ or *crying/ or *decerebration/ or *lethargy/ or *fatigue/ or *confusion/ or *malnutrition/ or exp *purpura/ or *muscle hypotonia/ or exp *tachycardia/
20	19 use emczd
21	((head or cranial or intracranial) adj3 pain*).ti,ab.
22	((stiff* or rigid*) adj3 (neck* or nuchal or cervical or spine or spinal)).ti,ab.
23	(light adj3 (intoleran* or sensitiv*)).ti,ab.
24	((tense or bulge or bulging or full*) adj3 fontanelle?).ti,ab.
25	((raise? or rise or high or elevat*) adj3 intracranial pressure?).ti,ab.
26	((level? or decreas*) adj3 consciousness).ti,ab.
27	(irritab* or petulan* or bad mood or moody).ti,ab.
28	((symphyseal or cheek) adj3 sign?).ti,ab.
29	(abnormal adj3 postur*).ti,ab.
30	(muscle? adj3 (atonic or flaccid*)).ti,ab.
31	((decreas* or alter* or chang*) adj3 (conscious* or mental state?)).ti,ab.
32	((hemorrhagic or haemorrhagic) adj3 rash).ti,ab.
33	(capillar* adj2 refill*).ti,ab.
34	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.
35	((limb? or extremities or arms or legs) adj3 pain*).ti,ab.
36	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.
37	((elevated or rapid* or fast*) adj3 (heart?beat or heart rate)).ti,ab.

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

Database(s): Cochrane Library – Wiley interface

Cochrane Database of Systematic Reviews, Issue 11 of 12, November 2022, **Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2022
Date of last search: 08 November 2022

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	MeSH descriptor: [Neisseria meningitidis] explode all trees
#10	((bacter* or infect*) near/3 (mening* or leptomening* or subarachnoid space*)):ti,ab,kw
#11	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or (h next influenz*) or listeria* or pneumococc* or (gram next negativ* next bacill*) or streptococc* or GBS or (s next pneumon*)) near/3 (septic* or sepsis* or bacteraemi* or bacteremi* or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or (mening* next encephalitis*)).:ti,ab,kw
#13	((neisseria* next mening*) or (n next mening*)):ti,ab,kw
#14	MeSH descriptor: [Meningococcal Infections] this term only
#15	meningococc*:ti,ab,kw
#16	{or #1-#15}
#17	MeSH descriptor: [Signs and Symptoms] this term only
#18	MeSH descriptor: [Fever] this term only
#19	MeSH descriptor: [Vomiting] this term only
#20	MeSH descriptor: [Nausea] this term only
#21	MeSH descriptor: [Diarrhea] this term only
#22	MeSH descriptor: [Chills] this term only
#23	MeSH descriptor: [Shivering] this term only
#24	MeSH descriptor: [Sleepiness] this term only
#25	MeSH descriptor: [Headache] this term only
#26	MeSH descriptor: [Photophobia] this term only
#27	MeSH descriptor: [Intracranial Pressure] this term only
#28	MeSH descriptor: [Consciousness Disorders] explode all trees
#29	MeSH descriptor: [Coma] this term only
#30	MeSH descriptor: [Seizures] this term only
#31	MeSH descriptor: [Seizures, Febrile] this term only
#32	MeSH descriptor: [Irritable Mood] this term only
#33	MeSH descriptor: [Crying] this term only
#34	MeSH descriptor: [Decerebrate State] this term only
#35	MeSH descriptor: [Lethargy] this term only
#36	MeSH descriptor: [Fatigue] this term only
#37	MeSH descriptor: [Confusion] this term only
#38	MeSH descriptor: [Malnutrition] this term only
#39	MeSH descriptor: [Purpura] explode all trees
#40	MeSH descriptor: [Muscle Hypotonia] this term only
#41	MeSH descriptor: [Tachycardia] explode all trees
#42	((head or cranial or intracranial) near/3 pain*):ti,ab,kw
#43	((stiff* or rigid*) near/3 (neck* or nuchal or cervical or spine or spinal)):ti,ab,kw
#44	(light near/3 (intoleran* or sensitiv*)):ti,ab,kw
#45	((tense or bulge or bulging or full*) near/3 fontanelle*):ti,ab,kw
#46	((raise* or rise or high or elevat*) near/3 intracranial pressure*):ti,ab,kw
#47	((level* or decreas*) near/3 consciousness):ti,ab,kw
#48	(irritab* or petulan* or "bad mood" or moody):ti,ab,kw
#49	((symphyseal or cheek) near/3 sign*):ti,ab,kw
#50	(abnormal near/3 postur*):ti,ab,kw
#51	(muscle* near/3 (atonic or flaccid*)):ti,ab,kw
#52	((decreas* or alter* or chang*) near/3 (conscious* or "mental state" or "mental states")):ti,ab,kw
#53	((hemorrhagic or haemorrhagic) near/3 rash):ti,ab,kw
#54	(capillar* near/2 refill*):ti,ab,kw
#55	((cold or clammy or temperature) near/3 (hand* or feet or extremities)):ti,ab,kw
#56	((limb* or extremities or arms or legs) near/3 pain*):ti,ab,kw
#57	((mottled or mottling) near/3 (skin or epidermal)):ti,ab,kw
#58	((elevated or rapid* or fast*) near/3 (heartbeat or "heart beat" or "heart rate")):ti,ab,kw
#59	(sign? or symptom* or complain*):ti,ab,kw
#60	(clinical near/3 (manifest* or featur* or finding* or aspect*)):ti,ab,kw
#61	(present* near/3 (feature* or finding* or factor*)):ti,ab,kw or presentation*:ti
#62	(physical* near/3 (manifest* or characteristic* or featur* or finding*)):ti,ab,kw
#63	{or #17-#62}
#64	MeSH descriptor: [Sensitivity and Specificity] explode all trees
#65	MeSH descriptor: [Likelihood Functions] this term only

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

Economic Search

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

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

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

Database(s): Medline & Embase (Multifile) – OVID interface

Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022

Date of last search: 10 November 2022

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococ?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez

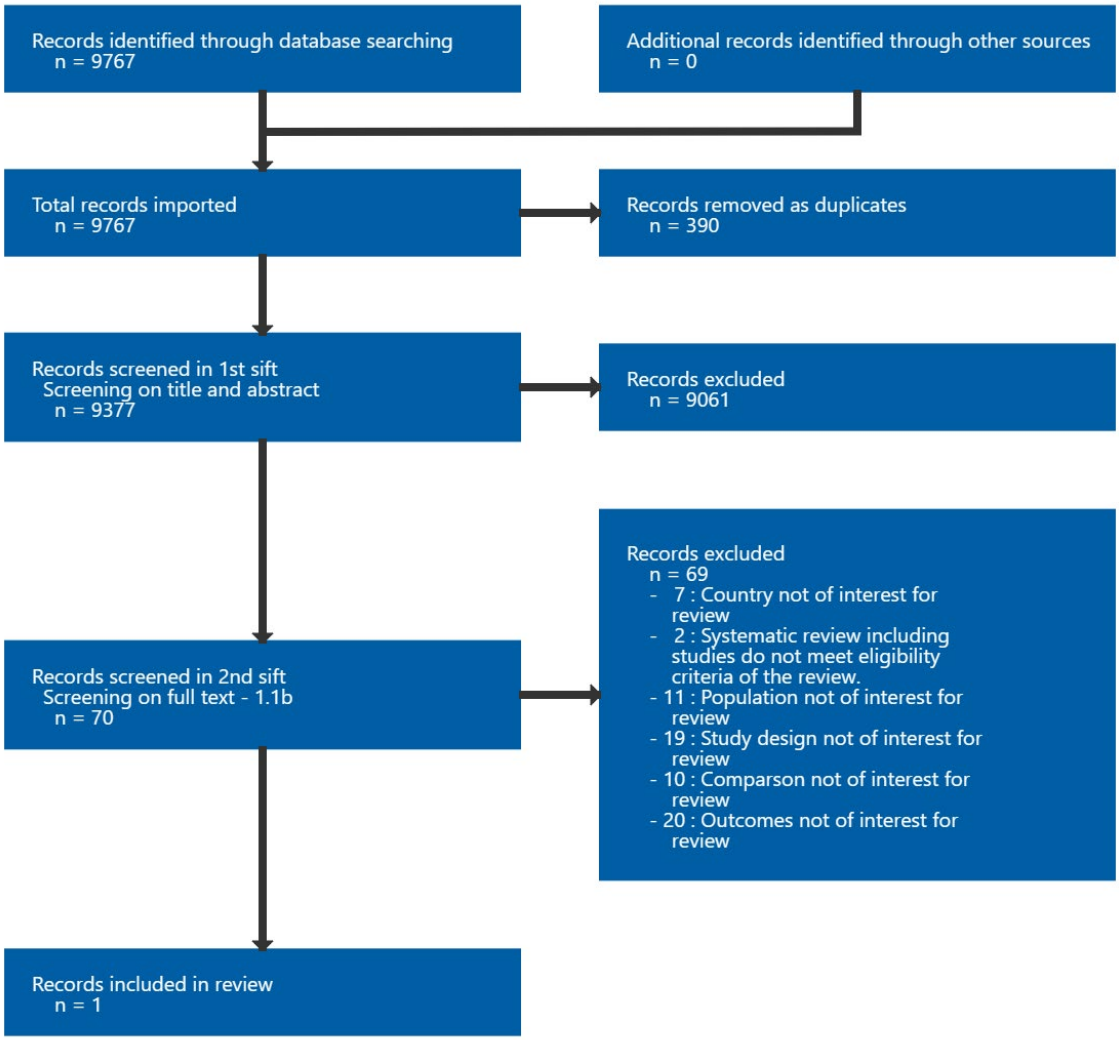
#	Searches
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/

#	Searches
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

Appendix C Prognostic evidence study selection

Study selection for: What factors are associated with an increased risk of bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What factors are associated with an increased risk of bacterial meningitis?

Table 4: Evidence tables

Goldacre, 2014

Bibliographic Reference Goldacre, M. J; Wotton, C. J; Maisonneuve, J. J.; Maternal and perinatal factors associated with subsequent meningococcal, Haemophilus or enteroviral meningitis in children: database study; Epidemiology & Infection; 2014; vol. 142 (no. 2); 371-8

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	1970 - 1989
Inclusion criteria	Babies and children who had been admitted to hospital with a diagnosis of meningococcal meningitis or haemophilus meningitis or viral meningitis were identified (using ICD criteria) and linked to the maternity dataset of the Oxford record linkage study (ORLS)
Exclusion criteria	Stillbirths, neonatal death cases (none were diagnosed with bacterial meningitis) and births where weight was recorded as <1000 g.
Patient characteristics	N=599 (study includes an 'all offspring' group but not eligible for inclusion in this review as includes meningitis groups and unclear if other types of bacterial meningitis [other than meningococcal and haemophilus] included in this group so cannot be categorised as absence of meningitis)

	Bacterial meningitis (n=287): Meningococcal meningitis (n=127); Haemophilus meningitis (n=160) Age: mean/median not reported; 29-364 days (n=124; 43%); 1-4 years (n=108; 38%); 5-9 years (n=12; 4%); 10-14 years (n=10; 3%); ≥15 years (n=33; 11%) Sex: male: 161 (56%); female 126 (44%) Viral meningitis (n=312): Age: mean/median not reported; 29-364 days (n=91; 29%); 1-4 years (n=57; 18%); 5-9 years (n=85; 27%); 10-14 years (n=40; 13%); ≥15 years (n=39; 13%) Sex: male: 194 (62%); female 118 (38%)
Risk factor(s) of interest	Maternal and perinatal factors: • Maternal smoking during pregnancy • Low birth weight (<2.5 kg) • Pre-term birth (gestational age <37 weeks)
Confounding factor(s) of interest	Adjusted analyses cannot be extracted as based on the total population and the group of 'all offspring' do not meet inclusion criteria for this review. Only unadjusted data could be included.
Duration of follow-up	Not reported
Setting	Secondary care (hospital)
Sources of funding	Not industry funded

Other information	Diagnosis based on review of patients' hospital records. Data not extracted for population-level risk factors.

CSF: cerebrospinal fluid; ICD: International Classification of Disease.

Outcomes

Maternal and perinatal risk factors for bacterial meningitis (comparison group: viral meningitis)

In those with a presence of a risk factor, the numbers refer to a total number with bacterial meningitis and with factor / total number with factor; in those with an absence of a risk factor, the numbers refer to a total number with bacterial meningitis and without factor / total number without factor.

Outcome	**N = 599**
Maternal smoking during pregnancy Data not available for whole sample (data only collected in the database on this variable post-1975). Data available for 56% of sample across those with and without risk factor Custom value	68/117
No maternal smoking during pregnancy Data not available for whole sample (data only collected in the database on this variable post-1975). Data available for 56% of sample across those with and without risk factor Custom value	116/218
Low birth weight (<2.5 kg) Custom value	17/46
Birth weight ≥2.5 kg Custom value	270/553
Pre-term birth (gestational age <37 weeks)	22/61

Outcome	N = 599
Data not available for whole sample. Data available for 85% of sample across those with and without risk factor Custom value	
Term birth (gestational age ≥38 weeks) Data not available for whole sample. Data available for 85% of sample across those with and without risk factor Custom value	217/448

Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias *(Study appears to have included all relevant children recorded in the dataset)*
Study Attrition	Study Attrition Summary	Low risk of bias *(No participants were lost to follow-up)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Birth weight and gestational age objective but maternal smoking during pregnancy based on self-report, and no clear specification of methods of measurement for any of the risk factors. Missing data for some of the risk factors of interest, 15% missing data for pre-term birth (gestational age) and 64% for maternal smoking, and reasons for missing data only provided for the latter risk factor)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Outcome is hospital admission rather than diagnosis per se. Paper does not confirm that diagnosis based on lumbar puncture)*
Study Confounding	Study Confounding Summary	High risk of bias *(Adjusted analyses cannot be extracted as based on the total population and the group of 'all offspring' do not meet inclusion criteria for this review. Only unadjusted data could be included.)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Statistical analysis used was adequate for the design of the study, however selective reporting of the results suspected. Logistic regression results reported only for selected variables.)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: What factors are associated with an increased risk of bacterial meningitis?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What factors are associated with an increased risk of bacterial meningitis?

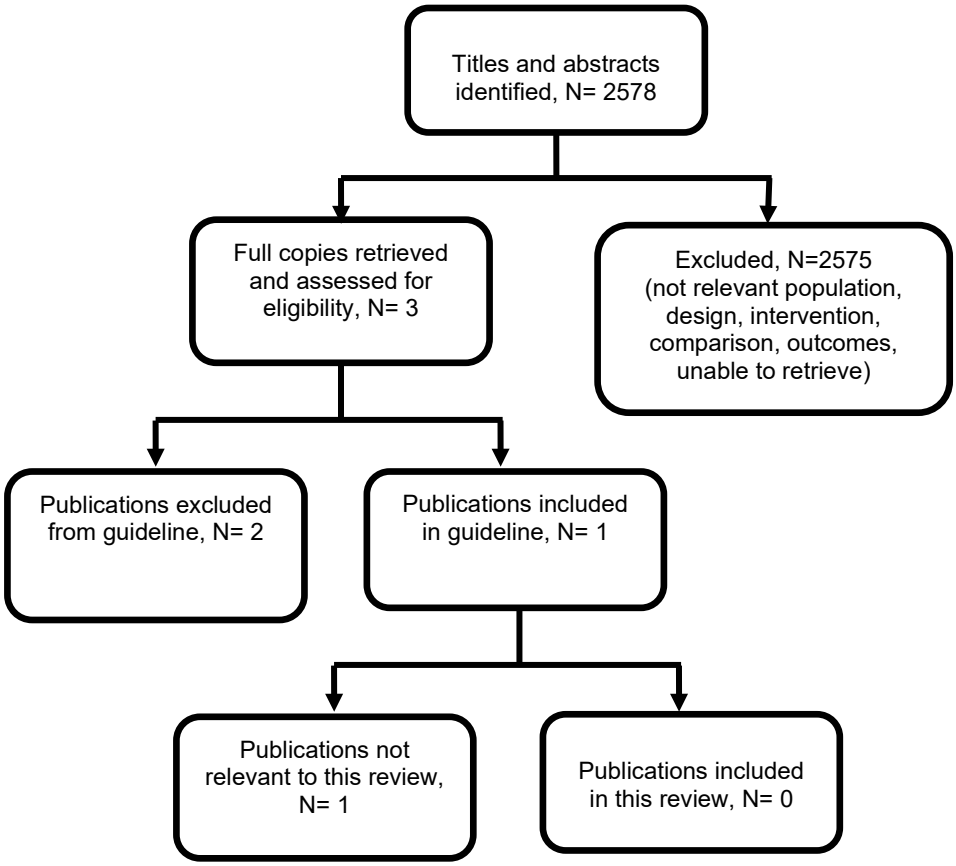
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of risk factor	Absence of risk factor	Relative (95% CI)	Absolute		
Maternal smoking during pregnancy (assessed with self-report)												
1 (Goldacre 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	68/117 (58.1%)	116/218 (53.2%)	RR 1.09 (0.9 to 1.33)	48 more per 1000 (from 53 fewer to 176 more)	VERY LOW	CRITICAL
Low birth weight (<2.5 kg)												
1 (Goldacre 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/46 (37%)	270/553 (48.8%)	RR 0.76 (0.51 to 1.11)	117 fewer per 1000 (from 239 fewer to 54 more)	VERY LOW	CRITICAL
Pre-term birth (gestational age <37 weeks)												
1 (Goldacre 2014)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/61 (36.1%)	217/448 (48.4%)	RR 0.74 (0.53 to 1.05)	126 fewer per 1000 (from 228 fewer to 24 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: relative risk; QUIPS: Quality in Prognosis Studies
1 Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
2 <300-≥150 events

Appendix G Economic evidence study selection

Study selection for: What factors are associated with an increased risk of bacterial meningitis?

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What factors are associated with an increased risk of bacterial meningitis?

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

Appendix I Economic model

Economic model for review question: What factors are associated with an increased risk of bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What factors are associated with an increased risk of bacterial meningitis?

Excluded prognostic studies

Table 5: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Arnold, C; Makintube, S; Istre, G.R. (1993) Day care attendance and other risk factors for invasive Haemophilus influenzae type b disease. American Journal of Epidemiology 138(5): 333-340	- Outcomes not of interest for review *Data only available for a sub-analysis of day care attendance*
Baker, C. J, Barrett, F. F, Gordon, R. C et al. (1973) Suppurative meningitis due to streptococci of Lancefield group B: A study of 33 infants. Journal of Pediatrics 82(4): 724-729	- Study design not of interest for review *Prevalence data on signs, symptoms & risk factors in early- and late-onset bacterial meningitis. No comparison with those without bacterial meningitis*
Bartlett, A. W, Smith, B, George, C. R. R et al. (2017) Epidemiology of Late and Very Late Onset Group B Streptococcal Disease: Fifteen-Year Experience from Two Australian Tertiary Pediatric Facilities. Pediatric infectious disease journal 36(1): 20-24	- Comparson not of interest for review *No non-meningitis comparison group*
Batra, P, Gupta, S, Gomber, S et al. (2011) Predictors of meningitis in children presenting with first febrile seizures. Pediatric Neurology 44(1): 35-39	- Country not of interest for review *Not a high-income OECD country*
Berg, A. T; Shapiro, E. D; Capobianco, L. A. (1991) Group day care and the risk of serious infectious illnesses. American Journal of Epidemiology 133(2): 154-163	- Outcomes not of interest for review *No relevant extractable data*
Bilavsky, E, Leibovitz, E, Elkon-Tamir, E et al. (2013) The diagnostic accuracy of the 'classic meningeal signs' in children with suspected bacterial meningitis. European Journal of Emergency Medicine 20(5): 361-363	- Outcomes not of interest for review *Data only available on age and sex (population-level risk factors)*
Bineshfar, Niloufar, Rezaei, Ali, Mirahmadi, Alireza et al. (2022) Evaluation of the epidemiologic, clinical, radiologic, and treatment methods of patients with subacute and chronic	- Comparson not of interest for review *No non-meningitis comparison arm*

Study	Code [Reason]
meningitis. BMC neurology 22(1): 340	
Cabellos, C, Verdaguer, R, Olmo, M et al. (2009) Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine 88(2): 115-119	- Study design not of interest for review *Prevalence study*
Casado-Flores, J, Aristegui, J, De Liria, C. R et al. (2006) Clinical data and factors associated with poor outcome in pneumococcal meningitis. European Journal of Pediatrics 165(5): 285-289	- Outcomes not of interest for review *Risk factors associated with poor outcome (rather than diagnosis)*
Chang, W. N, Huang, C. R, Lu, C. H et al. (2012) Adult Klebsiella pneumoniae meningitis in Taiwan: an overview. Acta Neurologica Taiwanica 21(2): 87-96	- Country not of interest for review *Not a high-income OECD country*
Cohen, N. L; Roland Jr, J. T; Marrinan, M. (2004) Meningitis in cochlear implant recipients: The North American experience. Otology and Neurotology 25(3): 275-281	- Study design not of interest for review *Survey study*
Dharmarajan, L; Salazar, L; Hasbun, R. (2016) Gender Differences in Community-acquired Meningitis in Adults: Clinical Presentations and Prognostic Factors. Journal of MeningitisJ 1(1)	- Population not of interest for review *5.6% of community-acquired meningitis population had bacterial meningitis*
Dias, S. P, Brouwer, M. C, Bijlsma, M. W et al. (2017) Sex-based differences in adults with community-acquired bacterial meningitis: a prospective cohort study. Clinical Microbiology & InfectionClin Microbiol Infect 23(2): 121.e9-121.e15	- Comparson not of interest for review *Sex-based differences in adults with bacterial meningitis. No comparison with those without bacterial meningitis.*
Doernberg, S, Schaaf, B, Dalhoff, K et al. (2011) Association of macrophage migration inhibitory factor (MIF) polymorphisms with risk of meningitis from Streptococcus pneumoniae. Cytokine 53(3): 292-294	- Study design not of interest for review *Prevalence data on signs and symptoms of bacterial meningitis. No comparison with those without bacterial meningitis.*
Fernandes, D, Goncalves-Pereira, J, Janeiro, S et al. (2014) Acute bacterial meningitis in the intensive care unit and risk factors for adverse clinical outcomes: Retrospective study. Journal of Critical Care 29(3): 347-350	- Outcomes not of interest for review *Risk factors for adverse clinical outcomes (not for diagnosis) of bacterial meningitis*
Flores-Cordero, J. M, Amaya-Villar, R, Rincon-Ferrari, M. D et al. (2003) Acute community-acquired bacterial meningitis in adults admitted to the intensive care unit: clinical manifestations, management and prognostic factors. Intensive	- Outcomes not of interest for review *Risk factors associated with poor clinical outcomes (not diagnosis) of bacterial meningitis*

Study	Code [Reason]
care medicine 29(11): 1967-73	
Fraser, D. W; Darby, C. P; Koehler, R. E. (1973) Risk factors in bacterial meningitis: Charleston County, South Carolina. Journal of Infectious Diseases 127(3): 271-277	- Outcomes not of interest for review *Data only available on ethnicity and causative organism (population-level risk factors)*
Fuentes-Antras, J, Ramirez-Torres, M, Osorio-Martinez, E et al. (2019) Acute Community-Acquired Bacterial Meningitis: Update on Clinical Presentation and Prognostic factors. The new microbiologica 41(4): 81-87	- Study design not of interest for review *Prevalence data on signs and symptoms of bacterial meningitis. No comparison with those without bacterial meningitis*
Geyik, M. F, Kokoglu, O. F, Hosoglu, S et al. (2002) Acute bacterial meningitis as a complication of otitis media and related mortality factors. Yonsei Medical JournalYonsei Med J 43(5): 573-8	- Country not of interest for review *Not a high-income OECD country*
Gomes, I, Melo, A, Lucena, R et al. (1996) Prognosis of bacterial meningitis in children. Arquivos de Neuro-Psiquiatria 54(3): 407-411	- Country not of interest for review *Not a high-income OECD country*
Haskins, R and Kotch, J. (1986) Day care and illness: evidence, cost, and public policy. PediatricsPediatrics 77(6pt2): 951-82	- Study design not of interest for review *Non-systematic review*
Hassink, S. G, Boucek Jr, R. J, Graham Jr, T. P et al. (1979) Transposition of the great arteries: Possible risk factor for Haemophilus influenzae type b meningitis. Journal of Pediatrics 94(5): 755-757	- Study design not of interest for review *No comparison group*
Henaff, F, Levy, C, Cohen, R et al. (2017) Risk factors in children older than 5 years with pneumococcal meningitis: Data from a national network. Pediatric Infectious Disease Journal 36(5): 457-461	- Study design not of interest for review *Prevalence data on risk factors for pneumococcal meningitis*
Howitz, M. F and Homoe, P. (2014) The risk of acquiring bacterial meningitis following surgery in Denmark, 1996-2009: a nationwide retrospective cohort study with emphasis on ear, nose and throat (ENT) and neurosurgery. Epidemiology & InfectionEpidemiol Infect 142(6): 1300-9	- Study design not of interest for review *All participants in study 1 had been exposed to potential risk factor (surgery) and study 2 included people with bacterial meningitis where the clinician suspected a surgical procedure to be the aetiology (and compared to average population in Denmark)*
Iles, K; Poplawski, N. K; Couper, R. T. (2001) Passive exposure to tobacco smoke and bacterial meningitis in children. Journal of Paediatrics & Child HealthJ Paediatr Child Health 37(4): 388-91	- Study design not of interest for review *Case-control study*

Study	Code [Reason]
Joffe, A; McCormick, M; DeAngelis, C. (1983) Which children with febrile seizures need lumbar puncture? A decision analysis approach. American Journal of Diseases of Children 137(12): 1153-1156	- Outcomes not of interest for review *Data only available on sex and ethnicity (population-level risk factors)*
Johansson Kostenniemi, U, Norman, D, Borgstrom, M et al. (2015) The clinical presentation of acute bacterial meningitis varies with age, sex and duration of illness. Acta PaediatricaActa Paediatr 104(11): 1117-24	- Comparson not of interest for review *Comparison between different age groups with bacterial meningitis. No comparison with those who did not have bacterial meningitis*
Kallio, M. J. T, Kilpi, T, Anttila, M et al. (1994) The effect of a recent previous visit to a physician on outcome after childhood bacterial meningitis. Journal of the American Medical Association 272(10): 787-791	- Study design not of interest for review *Prevalence data on signs and symptoms*
Karampatsas, Konstantinos, Davies, Hannah, Mynarek, Maren et al. (2022) Clinical Risk Factors Associated With Late-Onset Invasive Group B Streptococcal Disease: Systematic Review and Meta-Analyses. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 75(7): 1255-1264	- Systematic review including studies do not meet eligibility criteria of the review.
Kornelisse, R. F, Westerbeek, C. M. L, Spoor, A. B et al. (1995) Pneumococcal meningitis in children: Prognostic indicators and outcome. Clinical infectious diseases 21(6): 1390-1397	- Study design not of interest for review *Prevalence data on signs and symptoms or risk factors for pneumococcal meningitis*
Krishna, V; Liu, V; Singleton, A. F. (1983) Should lumbar puncture be routinely performed in patients with suspected bacteremia?. Journal of the National Medical Association 75(12): 1153-7	- Outcomes not of interest for review *Data only available on sex and ethnicity (population-level risk factors)*
Kronborg, G, tergaard, C, Weis, N et al. (2002) Serum level of YKL-40 is elevated in patients with Streptococcus pneumoniae bacteremia and is associated with the outcome of the disease. Scandinavian Journal of Infectious Diseases 34(5): 323-326	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Lalwani, A. K and Cohen, N. L. (2011) Longitudinal risk of meningitis after cochlear implantation associated with the use of the positioner. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 32(7): 1082-1085	- Study design not of interest for review *Participants recruited from the manufacturer's (cochlear implantation with the use of the positioner) clinical database*

Study	Code [Reason]
Levine, D. A, Platt, S. L, Dayan, P. S et al. (2004) Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics 113(6): 1728-34	- Population not of interest for review *Serious bacterial infection (defined as bacterial meningitis, bacteraemia, UTI, or bacterial enteritis)*
Levy, C, Taha, M. K, Weil Olivier, C et al. (2010) Association of meningococcal phenotypes and genotypes with clinical characteristics and mortality of meningitis in children. Pediatric Infectious Disease Journal 29(7): 618-623	- Comparson not of interest for review *Comparison between different age groups and causative organisms in bacterial meningitis. No comparison with those who did not have bacterial meningitis*
Liberalesso, P. B. N, Da Silva, I. C. B, Klagenberg, K. F et al. (2009) Incidence and risk factors for seizures in central nervous system infections in childhood. Journal of Epilepsy and Clinical Neurophysiology 15(2): 83-88	- Country not of interest for review *Not a high-income OECD country*
Lundbo, L. F and Benfield, T. (2017) Risk factors for community-acquired bacterial meningitis. Infectious DiseasesInfect Dis (Lond) 49(6): 433-444	- Study design not of interest for review *Non-systematic review. Studies included in this review were assessed for potential inclusion.*
Lyytikainen, O, Klemets, P, Ruutu, P et al. (2007) Defining the population-based burden of nosocomial pneumococcal bacteremia. Archives of Internal Medicine 167(15): 1635-1640	- Population not of interest for review *6% of nosocomial pneumococcal bacteraemia population had bacterial meningitis*
Magnussen, C. R. (1980) Meningitis in adults. Ten-year retrospective analysis at community hospital. New York State Journal of Medicine 80(6): 901-906	- Outcomes not of interest for review *Data only available on sex (population-level risk factor)*
Marrie, T. J, Tyrrell, G. J, Majumdar, S. R et al. (2018) Effect of Age on the Manifestations and Outcomes of Invasive Pneumococcal Disease in Adults. American Journal of Medicine 131(1): 100.e1-100.e7	- Population not of interest for review *4.9% of invasive pneumococcal disease population had bacterial meningitis*
Martinez, E, Mintegi, S, Vilar, B et al. (2015) Prevalence and predictors of bacterial meningitis in young infants with fever without a source. Pediatric Infectious Disease Journal 34(5): 494-498	- Population not of interest for review *82% of population with bacterial meningitis <=21 days old*
Najaf-Zadeh, A, Dubos, F, Hue, V et al. (2013) Risk of bacterial meningitis in young children with a first seizure in the context of fever: a systematic review and meta-analysis. PLoS ONE [Electronic Resource]PLoS ONE 8(1): e55270	- Systematic review including studies do not meet eligibility criteria of the review. *Studies included in this review were assessed for potential inclusion*

Study	Code [Reason]
Okike, I. O, Ladhani, S. N, Johnson, A. P et al. (2018) Clinical Characteristics and Risk Factors for Poor Outcome in Infants Less Than 90 Days of Age With Bacterial Meningitis in the United Kingdom and Ireland. The Pediatric infectious disease journal 37(9): 837-843	- Population not of interest for review *69% were <=28 days old*
Olcen, P; Barr, J; Kjellander, J. (1979) Meningitis and bacteremia due to Neisseria meningitidis: clinical and laboratory findings in 69 cases from Orebro county, 1965 to 1977. Scandinavian Journal of Infectious Diseases 11(2): 111-119	- Comparson not of interest for review *Compares signs and symptoms between those with meningococcal meningitis versus those with meningococcal meningitis and meningococcemia versus those with meningococcemia only*
Oostenbrink, R, Moons, K. G. M, Donders, A. R. T et al. (2001) Prediction of bacterial meningitis in children with meningeal signs: Reduction of lumbar punctures. Acta Paediatrica, International Journal of Paediatrics 90(6): 611-617	- Outcomes not of interest for review *Data only available on sex (population-level risk factor)*
Ostergaard, C; Konradsen, H.B; Samuelsson, S. (2005) Clinical presentation and prognostic factors of Streptococcus pneumoniae meningitis according to the focus of infection. BMC Infectious Diseases 5: 93	- Study design not of interest for review *Prevalence data on signs and symptoms of streptococcus pneumoniae meningitis*
Paciorek, M, Bednarska, A, Krogulec, D et al. (2019) Chronic alcohol abuse affects the clinical course and outcome of community-acquired bacterial meningitis. European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis 38(11): 2171-2176	- Outcomes not of interest for review *Risk factor for poor outcome (rather than diagnosis) of bacterial meningitis*
Rayanakorn, A, Goh, B. H, Lee, L. H et al. (2018) Risk factors for Streptococcus suis infection: A systematic review and meta-analysis. Scientific ReportsSci 8(1): 13358	- Country not of interest for review *Majority of studies not from a high-income OECD country. Studies included in this review were assessed for potential inclusion*
Reefhuis, J, Honein, M. A, Whitney, C. G et al. (2003) Risk of bacterial meningitis in children with cochlear implants. New England Journal of Medicine 349(5): 435-445	- Study design not of interest for review *All children had been exposed to the risk factor of interest (cochlear implant)*
Seminog, O. O and Goldacre, M. J. (2013) Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. Thorax 68(2): 171-176	- Population not of interest for review *Majority of population with pneumococcal disease had lobar pneumonia (no % distribution provided for lobar pneumonia, pneumococcal pneumonia, pneumococcal septicaemia and meningitis within the pneumococcal disease group)*

Study	Code [Reason]
Shahum, A, Holeckova, K, Lesnakova, M et al. (2007) Bacteremic meningitis is associated with inferior outcome in comparison to community acquired meningitis without bacteremia. Neuroendocrinology Letters 28(suppl3): 25-26	- Comparson not of interest for review *Risk factors in community acquired bacterial meningitis with bacteraemia vs community acquired bacterial meningitis alone.*
Shapiro, E. D; Aaron, N. H; Wald Chiponis, E. R. D. (1986) Risk factors for development of bacterial meningitis among children with occult bacteremia. Journal of Pediatrics 109(1): 15-19	- Comparson not of interest for review *Risk factors for the development of bacterial meningitis in children with occult bacteremia compared with children with occult bacteremia who did not subsequently develop bacterial meningitis*
Shinjoh, M, Yamaguchi, Y, Furuichi, M et al. (2020) Recent trends in pediatric bacterial meningitis in Japan, 2016-2018 - S. agalactiae has been the most common pathogen. Journal of Infection & ChemotherapyJ Infect Chemother 26(10): 1033-1041	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Shinjoh, M; Yamaguchi, Y; Iwata, S. (2017) Pediatric bacterial meningitis in Japan, 2013-2015 - 3-5 years after the wide use of Haemophilus influenzae type b and Streptococcus pneumoniae conjugated vaccines. Journal of Infection and Chemotherapy 23(7): 427-438	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Stefanelli, P, Fazio, C, Neri, A et al. (2003) Long-term predominance of a rare meningococcal phenotype in a small geographical area. European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis 22(9): 566-8	- Population not of interest for review *Meningococcal disease*
Summerfield, A. Q, Cirstea, S. E, Roberts, K. L et al. (2005) Incidence of meningitis and of death from all causes among users of cochlear implants in the United Kingdom. Journal of Public HealthJ Public Health (Oxf) 27(1): 55-61	- Population not of interest for review *None of the cohort contracted bacterial meningitis*
Tang, L. M, Chen, S. T, Hsu, W. C et al. (1999) Acute bacterial meningitis in adults: A hospital-based epidemiological study. QJM - Monthly Journal of the Association of Physicians 92(12): 719-725	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Taziarova, M, Holeckova, K, Lesnakova, A et al. (2007) Gram-negative bacillary community acquired meningitis is not a rare entity in last two decades. Neuroendocrinology Letters 28(suppl3): 18-19	- Comparson not of interest for review *Risk factors for gram-negative bacterial meningitis vs other types of bacterial meningitis*

Study	Code [Reason]
Theunisse, H. J, Pennings, R. J. E, Kunst, H. P. M et al. (2018) Risk factors for complications in cochlear implant surgery. European Archives of Oto-Rhino-Laryngology 275(4): 895-903	- Study design not of interest for review *All participants were exposed to the risk factor of interest (cochlear implant)*
Tubiana, S, Varon, E, Biron, C et al. (2020) Community-acquired bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort. Clinical Microbiology and Infection 26(9): 1192-1200	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Van Hoeck, K. J, Mahieu, L. M, Vaerenberg, M. H et al. (1997) A retrospective epidemiological study of bacterial meningitis in an urban area in Belgium. European Journal of Pediatrics 156(4): 288-291	- Outcomes not of interest for review *Data only available on sex, age, ethnicity, and winter-season (population-level risk factors)*
Vasilopoulou, V. A, Karanika, M, Theodoridou, K et al. (2011) Prognostic factors related to sequelae in childhood bacterial meningitis: Data from a Greek meningitis registry. BMC Infectious Diseases 11 (no pagination)	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Videholm, Samuel, Kostenniemi, Urban, Lind, Torbjorn et al. (2021) Perinatal factors and hospitalisations for severe childhood infections: a population-based cohort study in Sweden. BMJ open 11(10): e054083	- Comparson not of interest for review *Data cannot be extracted as comparison arms are sepsis and all participants (that includes bacterial meningitis and sepsis groups)*
Wasier, A. P, Chevret, L, Essouri, S et al. (2005) Pneumococcal meningitis in a pediatric intensive care unit: prognostic factors in a series of 49 children. Pediatric Critical Care Medicine 6(5): 568-72	- Outcomes not of interest for review *Risk factors for poor outcome (rather than diagnosis) of bacterial meningitis*
Wilson-Clark, S. D; Squires, S; Deeks, S. (2006) Bacterial meningitis among cochlear implant recipients--Canada, 2002. Mmwr morbidityandmortalityweeklyreport55suppl1: 20-24	- Study design not of interest for review *A survey*
Wooltorton, E. (2002) Cochlear implant recipients at risk for meningitis. CMAJ Canadian Medical Association JournalCmaj 167(6): 670	- Study design not of interest for review *Non-systematic review*
Yaniv, E and Pocock, R. (1988) Complications of ear disease. Clinical Otolaryngology and Allied Sciences 13(5): 357-361	- Country not of interest for review *Not a high-income OECD country*
Zhou, Qi, Ong, Melissa, Lan, Marie et al. (2022)	- Population not of interest for review

Study	Code [Reason]
Decreasing Trend in Incidence of Late Onset Culture Positive Bloodstream Infections but Not Late Onset Meningitis in Preterm Infants <33 Weeks Gestation in Canadian Neonatal Intensive Care Unit. Neonatology 119(1): 60-67	*Neonates*
Zipser, C. M, Deuel, J, Ernst, J et al. (2019) Predisposing and precipitating factors for delirium in neurology: a prospective cohort study of 1487 patients. Journal of Neurology 266(12): 3065-3075	- Population not of interest for review *Explores risk factors for delirium in neurological patients*

OECD: Organisation for Economic Co-operation and Development

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: What factors are associated with an increased risk of bacterial meningitis?

No research recommendations were made for this review question.