National Institute for Health and Care Excellence

Final

Neonatal infection: antibiotics for prevention and treatment

[N] Evidence review for factors associated with recurrent bacterial meningitis

NICE guideline NG195

Evidence review underpinning recommendations 1.14.9 to 1.14.11 and 1.14.29 to 1.14.34 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

Update information

March 2024: This evidence review was originally produced for the NICE guideline on bacterial meningitis and meningococcal disease. This guideline made new recommendations for newborn babies with meningitis. We have moved these recommendations into the neonatal infection guideline, so that all the recommendations for newborn babies are in one place. See the NICE website for the guideline recommendations.

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Contents

Factors associated with an increased risk of recurrent bacterial meningitis

Review question

What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group. Recurrent meningitis is exceptionally rare but may indicate an underlying disorder predisposing to infection.

The aim of this review is to determine what additional investigations should be performed in people who develop recurrent bacterial meningitis.

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 (including neonates defined as aged 28 days old and younger) with recurrent bacterial meningitis
Prognostic factors	Any risk factors, alone or in combination
Comparison	Absence of risk factor(s)
Outcome	**Critical** • Risk ratios for recurrence of bacterial meningitis • Odds ratios* for recurrence of bacterial meningitis *adjusted odds ratios will be included where multivariate analyses are available **Important** None

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 for the NICE guideline on bacterial meningitis and meningococcal disease.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Prognostic evidence

Included studies

Three studies were included for this review (Carpenter 1962, Durand 1993, Henaff 2017); all retrospective studies mainly based on hospital charts reviews.

All 3 studies reported on at least 1 anatomic factor (including head trauma, CSF leak, neurosurgery, CSF breach or fistula). One study (Henaff 2017) also included immunological factors, material factors and combination factors.

Studies with univariate analyses were included as no studies with multivariate analyses were identified.

One study included children (Henaff 2017); 1 included predominantly adults, aged 16 years and over (Durand 1993), and 1 included an undefined age range (Carpenter 1962).

The included studies are summarised in Table 2.

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	Prognostic factor	Outcomes	Comments
Carpenter 1962 Retrospective cohort study USA	N=209 n=8 with recurrent bacterial meningitis Participants who presented with bacterial meningitis Age and other socio-demographics: NR	Anatomic factor: • head trauma (old and recent combined)	• recurrence of bacterial meningitis	No sociodemographic characteristics of the population reported No multivariate analysis
Durand 1993 Retrospective cohort study USA	N=440 n=36 with recurrent bacterial meningitis Patients 16 years of age or older with acute (less than 7 days of	Anatomic factors: • CSF leak • remote head injury or neurosurgery (more than 1 month before the onset of meningitis)	• recurrence of bacterial meningitis	No multivariate analysis

Study	Population	Prognostic factor	Outcomes	Comments
	symptoms) bacterial meningitis and a definite or probable bacterial cause Age (mean [range]): 56% of the episodes in the community-acquired meningitis group were in those 50 years or older [16-88]; age of those in the nosocomial meningitis group not reported	• recent neurosurgery (within 1 month of the onset of meningitis		
Henaff 2017 Retrospective cohort study France	N=315 n=34 with recurrent pneumococcal meningitis Children aged 5 to 15 years with a diagnosis of pneumococcal meningitis Age (years, median [IQR]): 9 [7-12] for the period 2001-2009 and 10 [7-13] for the period 2010-2013	Anatomic factors: • CSF breach or fistula Immunologic factors: • unspecified primary immunodeficiency • complement C3 deficiency • HIV infection • leukaemia • Myelodysplastic disease • unspecified secondary immunodeficiency • sickle cell disease • congenital adrenal hyperplasia • Williams-Beuren syndrome • congenital encephalopathy • Down's syndrome • prematurity • congenital heart disease • autoimmune	• recurrence of pneumococcal meningitis	No multivariate analysis

Study	Population	Prognostic factor	Outcomes	Comments
		hepatitis • asplenia (without sickle cell disease) • sickle cell disease and autoimmune hepatitis • congenital heart defect and asplenia • congenital heart defect and William-Beuren syndrome Combination of factors: • CSF breach and born premature • CSF breach and immunodeficiency • valve and undefined immunolodeficiency • CSF breach, cochlear implant and born premature Material factors: • cochlear implant • derivation valve		

CSF: cerebrospinal fluid; IQR: interquartile range; NR: not reported

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 high or moderate risk of bias in some of the domains of the QUIPs checklist (potential bias arising from study participation, subjective measurement of the outcome, and failure to adjust for confounding factors) and because of imprecision due to a very low number of events.

Evidence was stratified by age (children, adults, and undefined age range) but no meta-analyses were possible as the studies did not report on comparable prognostic factors.

Prognostic factors for recurrent pneumococcal meningitis in children

Anatomical factors

The evidence showed that presence of cerebrospinal fluid (CSF) breach or fistula was strongly associated with an increased risk of recurrent pneumococcal meningitis in children.

Immunological factors

The evidence showed that presence of congenital adrenal hyperplasia was strongly associated with an increased risk of recurrent pneumococcal meningitis in children.

There was no evidence of an increased risk of recurrent pneumococcal meningitis in the evidence reviewed for children with unspecified primary or complement C3 immunodeficiency, HIV infection, leukaemia, myelodysplastic disease, unspecified immunodeficiency, sickle cell disease, Williams-Beuren syndrome, congenital encephalopathy, Down's syndrome, prematurity, congenital heart disease, autoimmune hepatitis, or asplenia (without sickle cell disease). There was no evidence of an increased risk of recurrent pneumococcal meningitis in the evidence reviewed for children with the following combinations of immunological prognostic factors: Sickle cell disease and autoimmune hepatitis; congenital heart defect and asplenia; or congenital heart disease and William-Beuren syndrome.

Material factors

There was no evidence of an increased risk of recurrent pneumococcal meningitis in the evidence reviewed for children with cochlear implant or derivation valve.

Combination of different types of factors

The evidence showed that presence of CSF breach and being born premature as well as CSF breach and unspecified immunodeficiency were strongly associated with an increased risk of recurrent pneumococcal meningitis in children.

There was no evidence of an increased risk of recurrent pneumococcal meningitis in the evidence reviewed for children with the following combinations of prognostic factors: valve and undefined immunodeficiency; and CSF breach, cochlear implant and prematurity. The quality of the evidence for all the above prognostic factors was very low.

Prognostic factors for recurrent bacterial meningitis in adults

Anatomical factors

The evidence showed that presence of CSF leak, remote head injury or neurosurgery (more than 1 month before the onset of meningitis) and recent neurosurgery (within 1 month of the onset of meningitis) were strongly associated with an increased risk of recurrent bacterial meningitis in adults.

Prognostic factors for recurrent bacterial meningitis in an undefined age range

Anatomical factors

The evidence showed that presence of head trauma (old and recent combined) was strongly associated with an increased risk of recurrent bacterial meningitis in a population where age was not reported; however, the quality of the evidence was very low.

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

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 topic was an epidemiological review which does not involve a comparison of competing courses of action.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

This review aimed to identify risk factors for recurrent bacterial meningitis; therefore, risk ratios and odds ratios for recurrence of bacterial meningitis were selected as the critical outcomes. No other outcomes were included.

The quality of the evidence

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

Evidence was found for anatomic prognostic factors (head trauma/injury, neurosurgery and CSF leak, breach or fistula), immunologic prognostic factors (unspecified primary/secondary/complement C3 deficiency, HIV infection, leukaemia, myelodysplastic disease, sickle cell disease, congenital adrenal hyperplasia, Williams-Beuren syndrome, congenital encephalopathy, Down's syndrome, prematurity, congenital heart disease, autoimmune hepatitis, asplenia (without sickle cell disease), sickle cell disease and autoimmune hepatitis, congenital heart defect and asplenia, congenital heart defect and William-Beuren syndrome), combination of prognostic factors (CSF breach and prematurity, CSF breach and immunodeficiency, valve and undefined immunolodeficiency, CSF breach, cochlear implant and prematurity) and material prognostic factors (cochlear implant, derivation valve).

Benefits and harms

The committee were concerned that the number of people with some of the prognostic factors of interest and the number of people with recurrent bacterial meningitis (in both those with and without the prognostic factors) was very small. Therefore, in some instances the associations, or lack thereof, found in the evidence are based on only 1 person having the prognostic factor of interest. The committee agreed that the prognostic factors and recurrent bacterial meningitis are both sufficiently rare that the sample sizes of the included studies were not large enough to give reliable results, and it was likely that estimated effects would be different even if there were only very small changes in the number of events. This led to the evidence being downgraded, as discussed above. The committee also discussed that recurrent bacterial meningitis due to immunological factors is rarely reported in the literature

as people with known immunodeficiency will receive interventions to prevent recurrent infections, including bacterial meningitis, such that future episodes rarely occur. This may provide some explanation of the low number of events and few included studies reported in the literature. As a result, the committee did not have confidence in the findings of the evidence reviewed and made recommendations based on their knowledge and experience. They also agreed it was important to consider the factors that increase susceptibility to infection more broadly than just those that are associated with recurrent bacterial meningitis.

For the majority of the immunological factors, there was no evidence of an increased risk of recurrent bacterial meningitis in the evidence reviewed. However, the estimated effects were very seriously imprecise due to the small number of events so this should not be taken as definitive evidence that there was no association between these factors and recurrent bacterial meningitis. As discussed above, the committee did not have confidence in these findings and, in their experience, primary or secondary immunodeficiency (for example due to HIV, congenital complement deficiency or acquired inhibition, splenectomy or splenic dysfunction, or hypogammaglobulinaemia) would increase risk of infections, including bacterial meningitis and, therefore, would be associated with an increased risk of recurrent bacterial meningitis in the absence of interventions to prevent future recurrence. Similarly, the committee agreed that communication between the cerebrospinal fluid (CSF) and external surface, for example caused by prior trauma or surgery or a congenital abnormality, would also increase risk of recurrent bacterial meningitis, which was supported by the current evidence showing a strong association between all the anatomical factors reported in the evidence (CSF leak, breach or fistula, head injury and neurosurgery) and recurrent bacterial meningitis. The committee agreed it was important to highlight that these factors are associated with recurrent bacterial meningitis to help identify people who may require intervention (such as prophylactic antibiotics and vaccination against pathogens that can cause bacterial meningitis) to prevent the occurrence of future episodes of bacterial meningitis.

The committee agreed it was important to also make recommendations about the actions that should be taken following both a first episode and a recurrent episode of bacterial meningitis to identify the factors presented above. The committee agreed that it was necessary to recommend actions that should be taken after a first episode to identify people at risk of a future episode so that interventions can be initiated early with the aim of preventing future episodes, rather than waiting for a second, potentially preventable, episode to occur. However, there were some differences in the actions recommended following first and recurrent episodes, as they agreed that the likelihood of factors that increase susceptibility to infection being present would be greater in those that have already had a recurrent episode compared with those who have had a single episode.

People with a first episode of bacterial meningitis

The committee were aware, based on their knowledge and experience that the risk of infections is higher in people with HIV. For example, they were aware of evidence that the risk of pneumococcal infections (Brouwer 2010) is higher in people with HIV compared with people who are HIV negative. The committee discussed that it is common practice to offer a HIV test to adults with a serious infection, such as bacterial meningitis, so recommended this should be done following a first episode of bacterial meningitis. However, they agreed they would be less likely to suspect HIV in babies and children with meningitis due, in part, to behaviours that increase risk of HIV being uncommon in these age groups. Therefore, routine HIV testing in babies and children with a first episode of bacterial meningitis was not recommended, but the committee agreed it should be considered where there are signs of immunodeficiency and risk factors for HIV, such as being from a country with a high rate of HIV infection (NICE 2016). The committee agreed that signs of immunodeficiency alone would be more likely to indicate primary immunodeficiency than presence of HIV in babies and children. The committee did not include neonates in this recommendation as they were not aware of any link between HIV and neonatal meningitis.

In the committee's view, rates of immunodeficiency in babies and children presenting with a first episode of pneumococcal meningitis are likely to be higher than in the general population because it would suggest a lack of immune response to routine pneumococcal vaccination, assuming they had the vaccination as recommended by the UK immunisation schedule (UK Health Security Agency 2022) and the meningitis was caused by a serotype covered by the vaccine. This was supported by some evidence that the committee were aware of that primary immunodeficiency is present in 8 to 26% of children with invasive pneumococcal disease (Bijker 2022; Gaschignard 2014). Therefore, they recommended that neonates, babies and children with a first episode of pneumococcal meningitis should be referred to a paediatric immunology and infectious disease specialist to consider the possibility of primary immunodeficiency. The committee did not extend this recommendation to cover adults, as they were not aware of any evidence of higher rates of primary immunodeficiency in adults with single episodes of invasive pneumococcal disease.

Based on their experience, the committee agreed that clinicians should examine the scalp and spine of neonates, babies, and young children with bacterial meningitis to check for the presence of an anatomical defect, such as a sinus tract. The committee recommended that this should be done after a single episode of bacterial meningitis as it can be done relatively easily and would not be resource intensive. The committee did not recommend this action in older children or adults, despite the evidence of an increased risk of recurrent bacterial meningitis associated with anatomical factors discussed above being present in all age groups, because they agreed it would be unusual for anomalies of this type to go undetected for that length of time. The committee also recommended taking a history of head trauma, surgery, or CSF leak in all age groups to help identify anatomical risk factors.

Finally, the committee recommended that a detailed immunisation and drug history should be taken. They agreed taking an immunisation history was important to identify both people who have not had routine vaccinations for pathogens associated with bacterial meningitis (Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis), in which vaccination uptake may help prevent future occurrences, and people who may have not responded to vaccination, indicating possible immunodeficiency as discussed above. Similarly, taking a drug history is important because there are several immunomodulatory drugs that may suppress the immune system increasing susceptibility to infections in general, such as high dose steroids, and infections caused by Neisseria meningitidis specifically, in the case of eculizumab (Joint Formulary Committee 2022).

People with a recurrent episode of bacterial meningitis

The committee agreed that people with recurrent meningitis should be reviewed by appropriate immunology and infection specialists (paediatric immunology and infectious disease specialist for neonates, babies, and children, and adult infection specialist or immunologist for adults) to seek advice on treating the current episode and to identify what action is needed to reduce the risk of further recurrence. They could not make recommendations about what further investigations or interventions would be needed as the accuracy of investigations for identifying immunodeficiency, or the effectiveness of interventions to reduce recurrence, were not reviewed as part of this guideline. However, they discussed that the further action would be guided by the specialist and would likely involve investigations for primary and secondary immunodeficiency, and consideration of vaccinations and other interventions to manage the risk associated with any identified immunodeficiency. They agreed it was necessary to specify the roles involved based on their experience that sometimes people are incorrectly referred to immunological laboratories which can cause delays.

Several of the recommendations the committee made regarding recurrent bacterial meningitis were the same as or similar to those made following a single episode of meningitis. The committee agreed that a detailed immunisation and drug history should be taken, and neonates, babies, and young children should be examined for anatomical defects,

as per the recommendations above. However, they agreed that if there has been a recurrent episode of bacterial meningitis, it would be important to take further action to investigate for a CSF leak, as opposed to just taking a history. As the evidence regarding the accuracy of investigations for identifying CSF leaks was not reviewed as part of this guideline, the committee could not recommend specific investigations that should be done. Therefore, they recommended that specialist radiological advice about investigations for a CSF leak should be sought. They discussed that, ideally, advice would come from a neuroradiologist, but they did not think it was appropriate to specify this as they may not be available at all hospitals, so specifying this role could cause delays and difficulty in implementing the recommendation. Similarly, they recommended that adults with recurrent bacterial meningitis are offered a HIV test. However, they agreed that this should also be offered to babies and children with recurrent bacterial meningitis, in the absence of additional risk factors for HIV due to the increased likelihood of there being an underlying immunodeficiency in people with recurrent bacterial meningitis discussed above.

The committee were aware that there are other recurrent conditions that may be mistaken for bacterial meningitis, such as Mollaret's lymphocytic meningitis. The committee agreed it was important to flag that there may be non-bacterial aetiologies where a bacterial cause is suspected but not confirmed to both facilitate a diagnosis to prevent further episodes recurring and to minimise the use of investigations or interventions, including antibiotics, for the wrong condition.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee noted that the number of episodes of recurrent bacterial meningitis was small relative to all episodes of bacterial meningitis. Further, the recommendations do not fundamentally change current practice and no significant resource impact to the NHS is anticipated.

The committee considered that highlighting risk factors associated with recurrent bacterial meningitis would promote awareness which in turn would facilitate more timely, appropriate, and cost-effective management. The committee considered that their management recommendations for recurrent bacterial meningitis were generally low cost and likely to be cost-effective given the anticipated benefits of such measures.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.14.9 to 1.14.11 and 1.14.29 to 1.14.34. Other evidence supporting these recommendations can be found in the evidence review on factors associated with recurrent meningococcal disease.

References – included studies

Prognostic

Carpenter 1962

Carpenter, R. R and Petersdorf, R. G. The clinical spectrum of bacterial meningitis. American Journal of Medicine 33(2): 262-275, 1962

Durand 1993

Durand, M. L, Calderwood, S. B, Weber, D. J et al. Acute bacterial meningitis in adults. A review of 493 episodes. New England journal of medicine 328(1): 21-Aug, 1993

Henaff 2017

Henaff, F, Levy, C, Cohen, R et al. Risk factors in children older than 5 years with pneumococcal meningitis: Data from a national network. Pediatric Infectious Disease Journal 36(5): 457-461, 2017

Economic

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

Other

Bijker 2022

Bijker, E. M., Bateman, E. A. L., Trück, J., Patel, P., Kelly, D. F., Screening for Immunodeficiencies in Children With Invasive Pneumococcal Disease: Six-year Experience From a UK Children's Hospital, The Pediatric Infection Disease Journal, 41(7), 575-578, 2022

Gaschignard 2014

Gaschignard, J., Levy, C., Chrabieh, M., Boisson, B., Bost-Bru, C., Dauger, S., Dubos, F., Durand, P., Gaudelus, J., Gendrel, G., Gras Le Guen, C., Grimpel, E., Guyon, G., Jeudy, C., Jeziorski, E., Leclerc, F., Léger, P. L., Lesage, F., Lorrot, M., Pellier, I., Pinquier, D., de Pontual, L., Sachs, P., Thomas, C., Tissières, P., Valla, F. V., Desprez, P., Frémeaux-Bacchi, V., Varon, E., Bossuyt, X., Cohen, R., Abel, L., Casanova, J. L., Puel, A., Picard, C., Invasive Pneumococcal Disease in Children Can Reveal a Primary Immunodeficiency, Clinical Infectious Diseases, 59, 244-251, 2014

Joint Formulary Committee 2022

Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Available at: http://www.medicinescomplete.com [Accessed 04/04/2022]

NICE 2016

National Institute for Health and Care Excellence (2016). HIV testing: increasing uptake among people who may have undiagnosed HIV. Available at: https://www.nice.org.uk/guidance/ng60 [Accessed 08/08/2022]

Reefhuis 2003

Reefhuis, J., Honein, M. A., Whitney, C. G., Chamany, S., Mann, E. A., Biernath, K., R., Broder, K., Manning, S., Avashia, S., Victor, M., Costa, P., Devine, O., Risk of Bacterial Meningitis in Children with Cochlear Implants, New England Journal of Medicine, 349, 435-445, 2003

UK Health Security Agency 2022

UK Health Security Agency (2022). UK immunisation schedule: the green book, chapter 11. Available at: https://www.gov.uk/government/publications/immunisation-schedule-the-green-book-chapter-11 [Accessed 08/08/22]

Wall 2014

Wall, C. E., Everett, D. B., Mukaka, M., Bar-Zeev, N., Feasey, N., Jahn, A., Moore, M., van Oosterhout, J. J., Pensalo, P., Baguimira, K., Gordon, S. B., Molyneux, E. M., Carrol, E. D., French, N., Molyneux, M. E., Heyderman, R. S., Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and *Haemophilus influenzae* type b vaccination, 2000–2012, Clinical Infectious Diseases, 58, e137-45, 2014

Appendices

Appendix A Review protocol

Review protocol for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021279506
Review title	Risk factors associated with recurrent bacterial meningitis
Review question	What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?
Objective	To determine the risk factors (individually or in combination) that are associated with recurrent bacterial meningitis
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Human studies • Date limitations: No date limitation • English language 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	Recurrent bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (including neonates defined as aged 28 days old and younger) with recurrent bacterial meningitis.

Field	Content
	Exclusion: People: • 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	Absence of risk factor(s)
Types of study to be included	Include published full-texts: • Systematic reviews of cohort studies • 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. 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)	• Risk ratios for recurrence of bacterial meningitis • Odds ratios* for recurrence of bacterial meningitis *adjusted odds ratios will be included where multivariate analyses are available
Secondary outcomes (important	N/A

Field	Content
outcomes)	
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 checklists: • ROBIS tool for systematic reviews • 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	Quantitative findings will be formally summarised in the review. Where multiple studies report on the 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:**

Field	Content
	• 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: • Age: o Neonates: ≤28 days - Extremely or very preterm: <32 weeks - Preterm: ≥32 weeks to <37 weeks - Term: ≥37 weeks o Younger Infants: >28 days to ≤3 months of age o Older infants: >3 months to <1 year of age o Children: ≥1 year to <18* years of age o Adults: ≥18* years of age • Infective organism: o Neisseria meningitidis o Streptococcus pneumoniae o Haemophilus influenzae o Group B streptococcus o Gram-negative bacilli o Listeria monocytogenes *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: o Young and middle aged adults o Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be

Field	Content			
	guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☐	Intervention		
	☐	Diagnostic		
	☒	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	17/11/2021			
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		☑	☑

Field	Content		
	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 (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=279506		
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		

Field	Content	
	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, recurrent, 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
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; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PRESS: Peer Review of Electronic Search Strategies; QUIPS: Quality in Prognosis Studies; ROBIS: Risk of Bias in Systematic Reviews

Appendix B Literature search strategies

Literature search strategies for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Clinical Search

This was a combined search to cover both this review and evidence review J2 on risk factors for recurrent meningococcal disease.

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

Embase Classic+Embase 1947 to 2021 July 28, **Ovid MEDLINE(R) ALL** 1946 to July 28, 2021

Date of last search: 29 July 2021

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	exp Recurrence/ use medall
18	exp recurrent disease/ or recurrent infection/ or reinfection/ or relapse/
19	18 use emczd
20	(recurren* adj2 (infect* or episode*)).ti,ab.
21	or/17,19-20
22	16 and 21
23	((recurren* or relaps* or flare* or survivor* or surviving or repeat or repeating or repeated or following) adj5 (meningitis* or meningo?encephalitis* or mening* encephalitis* or meningitides* or meningitidis* or meningococc*)).ti,ab.
24	((recurren* or relaps* or flare* or reinfect*) and (meningitis* or meningo?encephalitis* or mening* encephalitis* or meningitides* or meningitidis* or meningococc*)).ti.
25	22 or 23 or 24
26	Ventriculoperitoneal Shunt/ae use medall
27	brain ventricle peritoneum shunt/am, ae use emczd
28	(shunt* adj2 (associat* or relat*)).ti,ab.
29	((recurren* or relaps* or flare* or survivor* or surviving or repeat or repeating or repeated or following) adj5 shunt*).ti,ab.
30	or/26-29
31	16 and 30
32	Ventriculoperitoneal Shunt/ use medall
33	brain ventricle peritoneum shunt/ use emczd
34	shunt*.mp.
35	or/32-34
36	Risk/ or Risk Factors/
37	36 use medall
38	*risk/ or *risk factor/
39	38 use emczd

#	Searches
40	risk?.ti.
41	risk factor?.ab.
42	or/37,39-41
43	16 and 35 and 42
44	25 or 31 or 43
45	((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.)) or (ANIMALS not HUMANS).sh. or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.
46	45 use medall
47	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
48	47 use emczd
49	46 or 48
50	44 not 49
51	limit 50 to English language
52	limit 51 to yr="1960 -Current"
53	limit 52 to (conference abstract or conference paper or conference review or conference proceeding) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
54	53 use emczd
55	52 not 54

Database(s): Cochrane Library – Wiley interface

Cochrane Database of Systematic Reviews, Issue 7 of 12, July 2021, **Cochrane Central Register of Controlled Trials**, Issue 7 of 12, July 2021

Date of last search: 29 July 2021

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	(((bacter* or infect*) NEAR/3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))):ti,ab,kw
#10	((meningit* NEAR/3 (“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or “gram negativ* bacill*” or streptococc* or “group B streptococc*” or GBS or “streptococcus pneumon*” or “s pneumon*” or septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#11	((((“e coli” or “escherichia coli” or haemophilus or hemophilus or hib or “haemophilus influenz*” or “hemophilus influenz*” or “h influenz*” or listeria* or meningococc* or pneumococc* or “gram-negativ* bacill*” or “gram negativ* bacill*” or streptococc* or “group B streptococc*” or GBS or “streptococcus pneumon*” or “s pneumon*”) NEAR/3 (septic* or sepsis* or bacteraemia* or bacteremia*))):ti,ab,kw
#12	((meningit* or mening?encephalitis* or "mening* encephalitis*")):ti,ab,kw
#13	MeSH descriptor: [Meningococcal Infections] this term only
#14	MeSH descriptor: [Neisseria meningitidis] explode all trees
#15	((meningococc* NEAR/3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))):ti,ab,kw
#16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)):ti,ab,kw
#17	((Neisseria* NEXT mening*)):ti,ab,kw
#18	{or #1-#17}
#19	MeSH descriptor: [Recurrence] explode all trees
#20	(recurren* NEAR/2 (infect* or episode*)):ti,ab,kw
#21	#19 OR #20
#22	#18 AND #21
#23	(((recurren* or relaps* or flare* or survivor* or surviving or repeat or repeating or repeated or following) NEAR/5 (meningitis* or meningo?encephalitis* or "mening* encephalitis*" or meningitides* or meningitidis* or meningococc*))):ti,ab,kw
#24	(((recurren* or relaps* or flare* or reinfect*) and (meningitis* or meningo?encephalitis* or "mening* encephalitis*" or meningitides* or meningitidis* or meningococc*))):ti
#25	{or #22-#24}
#26	MeSH descriptor: [Ventriculoperitoneal Shunt] this term only and with qualifier(s): [adverse effects - AE]
#27	((shunt* NEAR/2 (associat* or relat*))):ti,ab,kw
#28	(((recurren* or relaps* or flare* or survivor* or surviving or repeat or repeating or repeated or following) NEAR/5 shunt*)):ti,ab,kw
#29	{or #26-#28}

#	Searches
#30	#18 AND #29
#31	MeSH descriptor: [Ventriculoperitoneal Shunt] this term only
#32	(shunt*):ti,ab,kw
#33	#31 OR #32
#34	MeSH descriptor: [Risk] this term only
#35	MeSH descriptor: [Risk Factors] this term only
#36	(risk*):ti
#37	(("risk factor*")):ab
#38	{or #34-#37}
#39	#18 AND #33 AND #38
#40	#25 OR #30 OR #39

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

Date of last search: 29 July 2021

#	Searches
1	MeSH DESCRIPTOR Meningitis IN DARE,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))) IN DARE, HTA
10	((meningencephalitis* or meningoencephalitis* or meningit*)) IN DARE, HTA
11	MeSH DESCRIPTOR Meningococcal Infections IN DARE,HTA
12	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN DARE,HTA
13	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))) IN DARE, HTA
14	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN DARE, HTA
15	((Neisseria* NEXT mening*)) IN DARE, HTA
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Recurrence EXPLODE ALL TREES IN DARE,HTA
18	((recurren* NEAR2 (infect* or episode*))) IN DARE, HTA
19	#17 OR #18
20	#16 AND #19
21	(((recurren* or relaps* or flare* or survivor* or surviving or repeat or repeating or repeated or following) NEAR5 (meningitis* or meningo?encephalitis* or "mening* encephalitis*" or meningitides* or meningitidis* or meningococc*))) IN DARE, HTA
22	(((recurren* or relaps* or flare* or reinfect*) AND (meningitis* or meningo?encephalitis* or "mening* encephalitis*" or meningitides* or meningitidis* or meningococc*))):TI IN DARE, HTA
23	#20 OR #21 OR #22
24	MeSH DESCRIPTOR Ventriculoperitoneal Shunt WITH QUALIFIER AE IN DARE,HTA
25	((shunt* NEAR2 (associat* or relat*))) IN DARE, HTA
26	(((recurren* or relaps* or flare* or survivor* or surviving or repeat or repeating or repeated or following) NEAR5 shunt*)) IN DARE, HTA
27	#24 OR #25 OR #26
28	#16 AND #27
29	MeSH DESCRIPTOR Ventriculoperitoneal Shunt IN DARE,HTA
30	(shunt*) IN DARE, HTA
31	#29 OR #30
32	MeSH DESCRIPTOR Risk IN DARE,HTA
33	MeSH DESCRIPTOR Risk Factors IN DARE,HTA
34	(risk*):TI IN DARE, HTA
35	(risk factor*) IN DARE, HTA
36	#32 OR #33 OR #34 OR #35
37	#16 AND #31 AND #36
38	#23 OR #28 OR #37

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 2021 March 10, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to March 09, 2021

Date of last search: 11 March 2021

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

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.

#	Searches
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez

#	Searches
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

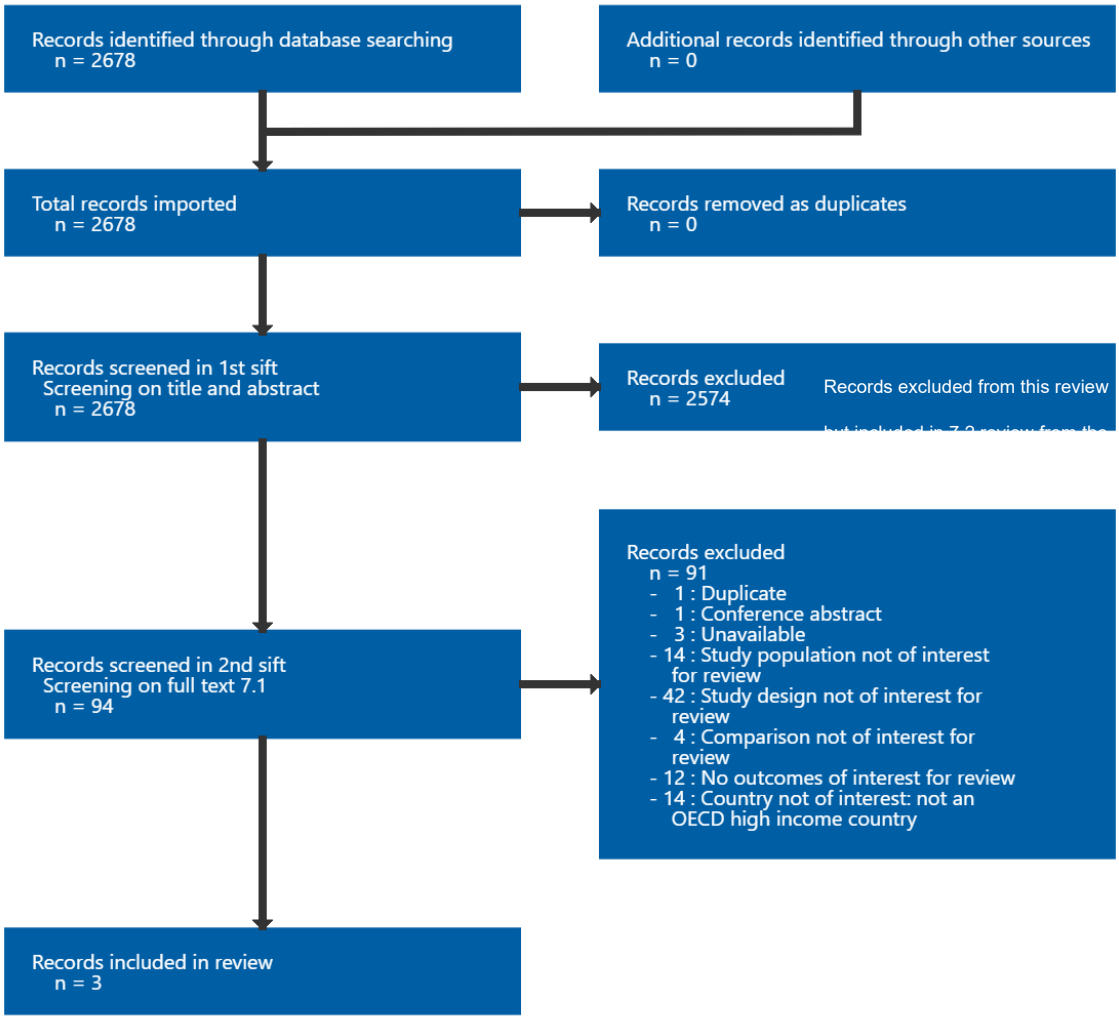
#	Searches
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez

#	Searches
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 (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Table 4: Evidence tables

Study details	Results and risk of bias assessment using the QUIPs checklist
Full citation Carpenter, R. R; Petersdorf, R. G.; The clinical spectrum of bacterial meningitis; American Journal of Medicine; 1962; vol. 33 (no. 2); 262-275 **Ref Id** 8558333 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Study dates** 1950 to 1960 **Inclusion criteria** Patients who presented with bacterial meningitis. The etiologic diagnosis was established by: n=173 culture of the CSF n=8 the causative organism grew in blood cultures and was seen in the gram stain of the CSF sediment n=6 the diagnosis of meningococcal meningitis was made in those with a purpuric rash and sterile CSF containing typical gram-negative diplococci n=22 the etiologic agent was unknown	**Results** **Prognostic factor: head trauma (old and recent combined); outcome: recurrent bacterial meningitis in babies, children and adults combined** | | recurrent meningitis | no recurrent meningitis | total | | --- | --- | --- | --- | | head trauma | 8 | 17 | 25 | | no head trauma | 0 | 184 | 184 | | total | 8 | 201 | 209 | **1. Risk of bias: Study participation (High/Moderate/Low)** Moderate: no exclusion criteria reported; no sociodemographic characteristics of the study population provided **2. Risk of bias: Study attrition (High/Moderate/Low)** Low: a retrospective review of hospital charts **3. Risk of bias: Prognostic factor measurement (High/Moderate/Low)** Low: based on hospital data **4. Risk of bias: Outcome measurement (High/Moderate/Low)** Moderate: no definition of recurrent meningitis provided **5. Risk of bias: Study confounding (High/Moderate/Low)** High: no attempts were made to identify or control for potential confounders

Study details	Results and risk of bias assessment using the QUIPs checklist
Exclusion criteria None reported **Patient characteristics** N=209, n=8 with recurrent meningitis No sociodemographic characteristics of the population reported. Causative pathogens in bacterial meningitis (cases/positive CSF culture, n): • Meningococcus: 53/46 • Pneumococcus: 63/59 • Haemophilus influenza: 35/34 Other: • unknown agent: 22/0 • mixed infections: 9/9 • Escherichia coli: 9/9 • Staphylococcus: 8/6 • Streptococcus: 3/3 • Paracolon: 2//2 • Diphteroid: 2/2 **Risk factor(s) of interest** Anatomic prognostic factor: • head trauma (old and recent combined) **Confounding factor(s)** No confounding factors were explicitly identified and controlled for by the authors because the study's aim was not to assess the prognostic factors. Not clear if there were any substantial baseline differences between the groups of interest as no data stratified by the presence and absence of prognostic factors reported	**6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)** High: not clear if there were any substantial baseline differences between the groups with and without the prognostic factor as no such data reported. There was no evidence of selective reporting of the results **Source of funding** No sources of funding reported **Other information**

Study details	Results and risk of bias assessment using the QUIPs checklist
Setting Hospital	
Full citation Durand, M. L; Calderwood, S. B; Weber, D. J; Miller, S. I; Southwick, F. S; Caviness, V. S; Jr; Swartz, M. N.; Acute bacterial meningitis in adults. A review of 493 episodes; New England journal of medicine; 1993; vol. 328 (no. 1); 21-Aug **Ref Id** 8555789 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Study dates** 1962 to 1988 **Inclusion criteria** Patients 16 years of age or older with acute (less than 7 days of symptoms) bacterial meningitis and a definite or probable bacterial cause. The diagnosis of meningitis caused by a specific bacterial pathogen was based on a compatible clinical picture and 1 of the following: • a positive cerebrospinal fluid (CSF) culture • confirmation at autopsy • negative CSF culture with a finding of neutrophilic pleocytosis and 1 of the following: a positive CSF antigen test or quellung test, a positive blood culture, identification of gram-negative diplococci on Gram's staining of CSF, or sputum or throat cultures positive for Neisseria meningitidis in those with a petechial or purpuric rash and a fulminant course.	**Results** **Prognostic factor: CSF leak; outcome: recurrent bacterial meningitis in adults*** | | recurrent meningitis | no recurrent meningitis | total | |---|---|---|---| | CSF leak | 22 | 40 | 62 | | no CSF leak | 14 | 364 | 378 | | total | 36 | 404 | 440 | **Prognostic factor: remote head injury or neurosurgery (more than 1 month before the onset of meningitis); outcome: recurrent bacterial meningitis in adults*** | | recurrent meningitis | no recurrent meningitis | total | |---|---|---|---| | remote head injury or neurosurgery | 8 | 10 | 18 | | no remote head injury or neurosurgery | 28 | 394 | 422 | | total | 36 | 404 | 440 | **Prognostic factor: recent neurosurgery (within 1 month of the onset of meningitis); outcome: recurrent bacterial meningitis in adults*** | | recurrent meningitis | no recurrent meningitis | total | |---|---|---|---| | recent neurosurgery | 19 | 103 | 122 | | no recent neurosurgery | 17 | 301 | 318 | | total | 36 | 404 | 440 |

Study details	Results and risk of bias assessment using the QUIPs checklist
A second episode of meningitis was considered to be recurrent if it was due to a different organism from the first or if it was due to the same organism but occurred more than 3 weeks after the completion of therapy for the initial episode. **Exclusion criteria** None reported **Patient characteristics** N=440 (n=404 with 1 episode of meningitis, n=36 with more than 1 episode of meningitis (89 episodes in total, including the 30 initial episodes). In 56% of the episodes in those with community-acquired meningitis were in patients 50 years of age or older (range 16 to 88). No other characteristics reported 72 episodes of "culture negative" bacterial meningitis were also included in the analysis diagnosed on the basis of a compatible clinical picture and pleocytosis of at least 100 neutrophils per cubic mm despite negative blood and CSF cultures and results of CSF Gram's staining that were negative (n=52), positive for organisms other than gram-negative diplococci (n=10) or not available (n=10). Causative organisms in single episodes of meningitis (n=404): • *Strep. pneumoniae* (n/%): 105/26 • Gram-negative bacilli (n/%): 66/16 • *N. meningitidis* (n/%): 36/9 • Streptococci (n/%): 30/7.4 • Enterococcus (n/%): 4/24.8 • *Staph. aureus* (n/%): 26/6.4 • *L. monocytogenes* (n/%): 34/8.4 • *H. influenzae* (n/%): 15/3.7	*calculated by the technical team **1. Risk of bias: Study participation (High/Moderate/Low)** Moderate: no exclusion criteria reported and very scarce information regarding baseline characteristics of the study population provided **2. Risk of bias: Study attrition (High/Moderate/Low)** Low: a retrospective review of hospital charts **3. Risk of bias: Prognostic factor measurement (High/Moderate/Low)** Low: based on hospital data **4. Risk of bias: Outcome measurement (High/Moderate/Low)** Low: definition of recurrent bacterial meningitis is provided **5. Risk of bias: Study confounding (High/Moderate/Low)** High: no attempts were made to identify and control for potential confounders **6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)** High: not clear if there were any substantial baseline differences between the groups with and without the prognostic factor as no such data reported. There was no evidence of selective reporting of the results **Source of funding** No sources of funding reported **Other information**

Study details	Results and risk of bias assessment using the QUIPs checklist
• Mixed bacterial species (n/%): 16/4 • Coagulase-negative staph. (n/%): 13/3.2 • Others [anaerobes, diphtheroids, micrococci, Neisseria species, propionbacteria] (n/%): 7/1.7 • Culture negative (n/%): 50/12.4 Causative organisms in recurrent meningitis (n=79) • *Strep. pneumoniae* (n/%): 14/17.7 • Gram-negative bacilli (n/%): 19/24 • *N. meningitidis* (n/%): 3/3.8 • Streptococci (n/%): 5/6.3 • *Staph. aureus* (n/%): 7/8.9 • *H. influenzae* (n/%): 4/5.1 • Mixed bacterial species (n/%): 2/2.5 • Coagulase-negative staph. (n/%): 3/3.8 • Others [anaerobes, diphtheroids, micrococci, Neisseria species, propionbacteria] (n/%): 3/3.8 • Culture negative (n/%): 19/24.1 *data is pooled across community-acquired and nosocomial meningitis groups; however, the study reports data stratified by the above groups **Risk factor(s) of interest** Anatomic prognostic factors: • CSF leak • remote head injury or neurosurgery (more than 1 month before the onset of meningitis) • recent neurosurgery (within 1 month of the onset of meningitis) **Confounding factor(s)** No confounding factors were explicitly identified and controlled for by the authors because the study's aim was not to assess the prognostic factors. Not clear if there were any substantial baseline differences	

Study details	Results and risk of bias assessment using the QUIPs checklist
between the groups of interest as no data stratified by the presence and absence of prognostic actors reported **Setting** General hospital	
Full citation Henaff, F; Levy, C; Cohen, R; Picard, C; Varon, E; Le Guen, C. G; Launay, E.; Risk factors in children older than 5 years with pneumococcal meningitis: Data from a national network; Pediatric Infectious Disease Journal; 2017; vol. 36 (no. 5); 457-461 **Ref Id** 8557501 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Study dates** 2001 to 2013 **Inclusion criteria** Children aged 5 to 15 years with a diagnosis of pneumococcal meningitis Diagnostic criteria: clinical signs associated with positive CSF culture and/or positive CSF antigen test results, and/or positive CSF PCR findings and/or positive culture for a normally sterile body site associated with CSF pleocytosis. **Exclusion criteria**	**Results** **Anatomic prognostic factors** **Prognostic factor: CSF breach or fistula; outcome: recurrent pneumococcal meningitis in children** | | recurrent meningitis | no recurrent meningitis | total | |---|---|---|---| | CSF breach or fistula | 18 | 45 | 63 | | no CSF breach or fistula | 16 | 229 | 245 | | total | 34 | 274 | 308 | **Immunologic prognostic factors** **Prognostic factor: unspecified primary immunodeficiency; outcome: recurrent pneumococcal meningitis in children** | | recurrent meningitis | no recurrent meningitis | total | |---|---|---|---| | unspecified primary immunodeficiency | 2 | 8 | 10 | | no unspecified primary immunodeficiency | 32 | 273 | 305 | | total | 34 | 281 | 315 | **Prognostic factor: complement C3 deficiency; outcome: recurrent pneumococcal meningitis in children** | | recurrent | no recurrent | total | |---|---|---|---|

Study details	Results and risk of bias assessment using the QUIPs checklist
None reported **Patient characteristics** Before PCV13 (13-valent pneumococcal conjugate vaccine) during 2001-2009 and after PCV13 during 2010-2013, there were 7 (3.3%) out of n=216 and 10 (12.8) out of n=99 children with pneumococcal meningitis who had the PCV13 vaccine, respectively. Other characteristics (N=315): • male sex (n/%): 198/63 • age (median (IQR)): 9 years (7-12) for the period 2001-2009 and 10 (7-13) for the period 2010-2013 • vaccination (not specified, n/%): 52/16.5 • PCV7 (n/%): 0 • PCV13 (n/%): 17/5.4 • case fatality rate (n/%): 30/9.5 • complications (n/%): 73/23.2 • recurrent otitis (n/%): 13/4.1 • recurrent meningitis (n/%): 34/10.8 *data is pooled across the groups with and without the PCV13 vaccine; however, the study reports data stratified by the above groups **Risk factor(s) of interest** Anatomic prognostic factors: • CSF breach or fistula Immunologic prognostic factors: • unspecified primary immunodeficiency • complement C3 deficiency • HIV infection • leukaemia • myelodysplastic disease	<table><tr><td></td><td>meningitis</td><td>meningitis</td><td></td></tr><tr><td>complement C3 deficiency</td><td>0</td><td>1</td><td>1</td></tr><tr><td>no complement C3 deficiency</td><td>34</td><td>280</td><td>314</td></tr><tr><td>total</td><td>34</td><td>281</td><td>315</td></tr></table> **Prognostic factor: HIV infection; outcome: recurrent pneumococcal meningitis in children** <table><tr><td></td><td>recurrent meningitis</td><td>no recurrent meningitis</td><td>total</td></tr><tr><td>HIV infection</td><td>0</td><td>4</td><td>4</td></tr><tr><td>no HIV infection</td><td>34</td><td>277</td><td>311</td></tr><tr><td>total</td><td>34</td><td>281</td><td>315</td></tr></table> **Prognostic factor: leukaemia; outcome: recurrent pneumococcal meningitis in children** <table><tr><td></td><td>recurrent meningitis</td><td>no recurrent meningitis</td><td>total</td></tr><tr><td>leukaemia</td><td>0</td><td>1</td><td>1</td></tr><tr><td>no leukaemia</td><td>34</td><td>280</td><td>314</td></tr><tr><td>total</td><td>34</td><td>281</td><td>315</td></tr></table> **Prognostic factor: myelodysplastic disease; outcome: recurrent pneumococcal meningitis in children** <table><tr><td></td><td>recurrent meningitis</td><td>no recurrent meningitis</td><td>total</td></tr><tr><td>myelodysplastic disease</td><td>0</td><td>1</td><td>1</td></tr></table>

Study details	Results and risk of bias assessment using the QUIPs checklist

- unspecified secondary immunodeficiency
- sickle cell disease
- congenital adrenal hyperplasia
- Williams-Beuren syndrome
- congenital encephalopathy
- Down's syndrome
- born premature
- congenital heart disease
- autoimmune hepatitis
- asplenia (without sickle cell disease)
- sickle cell disease and autoimmune hepatitis
- congenital heart defect and asplenia
- congenital heart defect and William-Beuren syndrome

Combination of prognostic factors:

- CSF breach and born premature
- CSF breach and immunodeficiency (not clear what type of deficiency it refers to)
- valve and undefined immunodeficiency
- CSF breach, cochlear implant and born premature

Material prognostic factors:

- cochlear implant
- derivation valve

Confounding factor(s)

No confounding factors were explicitly identified and controlled for by the authors because the study's aim was not to assess the prognostic factors. Not clear if there were any substantial baseline differences between the groups of interest as no data stratified by the presence and absence of prognostic factors reported

no myelodysplastic disease	34	280	314
total	34	281	315

Prognostic factor: unspecified secondary immunodeficiency; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
unspecified secondary immunodeficiency	0	5	5
no unspecified secondary immunodeficiency	34	276	310
total	34	281	315

Prognostic factor: sickle cell disease; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
sickle cell disease	0	3	3
no sickle cell disease	34	278	312
total	34	281	315

Prognostic factor: congenital adrenal hyperplasia; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
congenital adrenal hyperplasia	1	0	1
no congenital adrenal hyperplasia	33	281	314
total	34	281	315

Study details	Results and risk of bias assessment using the QUIPs checklist
Setting Hospital-based active surveillance (paediatric wards working with microbiology departments throughout France reported all cases of bacterial meningitis).	**Prognostic factor: Williams-Beuren syndrome; outcome: recurrent pneumococcal meningitis in children** | | recurrent meningitis | no recurrent meningitis | total | | Williams-Beuren syndrome | 0 | 1 | 1 | | no Williams-Beuren syndrome | 34 | 280 | 314 | | total | 34 | 281 | 315 | **Prognostic factor: congenital encephalopathy; outcome: recurrent pneumococcal meningitis in children** | | recurrent meningitis | no recurrent meningitis | total | | congenital encephalopathy | 0 | 1 | 1 | | no congenital encephalopathy | 34 | 280 | 314 | | total | 34 | 281 | 315 | **Prognostic factor: Down's syndrome; outcome: recurrent pneumococcal meningitis in children** | | recurrent meningitis | no recurrent meningitis | total | | Down's syndrome | 0 | 2 | 2 | | no Down's syndrome | 34 | 279 | 313 | | total | 34 | 281 | 315 | **Prognostic factor: born premature; outcome: recurrent pneumococcal meningitis in children**

Study details	Results and risk of bias assessment using the QUIPs checklist

	recurrent meningitis	no recurrent meningitis	total
born premature	2	6	8
not born premature	32	275	307
total	34	281	315

Prognostic factor: congenital heart disease; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
congenital heart disease	0	6	6
no congenital heart disease	34	275	309
total	34	281	315

Prognostic factor: autoimmune hepatitis; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
autoimmune hepatitis	0	1	1
no autoimmune hepatitis	34	280	314
total	34	281	315

Prognostic factor: asplenia (without sickle cell disease); outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total

Study details	Results and risk of bias assessment using the QUIPs checklist

asplenia (without sickle cell disease)	0	2	2
no asplenia (without sickle cell disease)	34	279	313
total	34	281	315

Prognostic factor: sickle cell disease and autoimmune hepatitis; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
sickle cell disease and autoimmune hepatitis	0	1	1
no sickle cell disease and autoimmune hepatitis	34	280	314
total	34	281	315

Prognostic factor: congenital heart defect and asplenia; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
congenital heart defect and asplenia	0	1	1
no congenital heart defect and asplenia	34	280	314
total	34	281	315

Prognostic factor: congenital heart defect and William-Beuren syndrome; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total

Study details	Results and risk of bias assessment using the QUIPs checklist

congenital heart defect and William-Beuren syndrome	0	1	1
no congenital heart defect and William-Beuren syndrome	34	280	
total	34	281	315

Combination of prognostic factors

Prognostic factor: CSF breach and born premature; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
CSF breach and born premature	2	3	5
no CSF breach and not born premature	32	278	310
total	34	281	315

Prognostic factor: CSF breach and immunodeficiency*; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
CSF breach and immunodeficiency	1	1	2
no CSF breach and immunodeficiency	33	280	313
total	34	281	315

*not clear what type of deficiency it refers to

Prognostic factor: valve and undefined immunodeficiency; outcome: recurrent pneumococcal meningitis in children

	recurrent	no recurrent	total

Study details	Results and risk of bias assessment using the QUIPs checklist

	meningitis	meningitis	
valve and undefined immunodeficiency	0	1	1
no valve and undefined immunodeficiency	34	280	314
total	34	281	315

Prognostic factor: CSF breach, cochlear implant and born premature; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
CSF breach, cochlear implant and born premature	0	1	1
no CSF breach, cochlear implant and born premature	34	280	314
total	34	281	315

Material prognostic factors

Prognostic factor: cochlear implant; outcome: recurrent pneumococcal meningitis in children

	recurrent meningitis	no recurrent meningitis	total
cochlear implant	0	4	4
no cochlear implant	34	277	311
total	34	281	315

Prognostic factor: derivation valve; outcome: recurrent pneumococcal meningitis in children

Study details	Results and risk of bias assessment using the QUIPs checklist

	recurrent meningitis	no recurrent meningitis	total
derivation valve	0	4	4
no derivation valve	34	277	311
total	34	281	315

1. Risk of bias: Study participation (High/Moderate/Low)
Moderate: no exclusion criteria reported

2. Risk of bias: Study attrition (High/Moderate/Low)
Low: a retrospective review of hospital charts

3. Risk of bias: Prognostic factor measurement (High/Moderate/Low)
Low: based on hospital data

4. Risk of bias: Outcome measurement (High/Moderate/Low)
Moderate: no definition of recurrent bacterial meningitis provided

5. Risk of bias: Study confounding (High/Moderate/Low)
High: no attempts were made to identify and control for potential confounders

6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)
High: not clear if there were any substantial baseline differences between the groups with and without the prognostic factor as no such data reported. There was no evidence of selective reporting of the results

Source of funding
No sources of funding reported

Other information

Study details	Results and risk of bias assessment using the QUIPs checklist

CSF: cerebrospinal fluid; IQR: interquartile range; QUIPS: quality in prognostic studies

Appendix E Forest plots

Forest plots for review question: What factors (individually or in combination) are associated with an increased risk of recurrent 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 (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Table 5: Evidence profile for anatomical prognostic factors for recurrent pneumococcal meningitis in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic factor	Relative (95% CI)	Absolute		
Prognostic factor: CSF breach or fistula												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	18/63 (28.6%)	16/245 (6.5%)	RR 4.38 (2.37 to 8.08)	221 more per 1000 (from 89 more to 462 more)	VERY LOW	CRITICAL

CSF: cerebrospinal fluid; 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] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events <150

Table 6: Evidence profile for immunological prognostic factors for recurrent pneumococcal meningitis in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic facto	Relative (95% CI)	Absolute		
Prognostic factor: Unspecified primary immunodeficiency												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	2/10 (20%)	32/305 (10.5%)	RR 1.91 (0.53 to 6.87)	95 more per 1000 (from 49 fewer to 616 more)	VERY LOW	CRITICAL

Prognostic factor: Complement C3 deficiency												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: HIV infection												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/4 (0%)	34/311 (10.9%)	POR 0.32 (0.01 to 7.70)	74 fewer per 1000 (from 108 fewer to 732 more)	VERY LOW	CRITICAL
Prognostic factor: Leukaemia												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Myelodysplastic disease												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Unspecified immunodeficiency												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/5 (0%)	34/310 (11%)	POR 0.32 (0.02 to 5.51)	75 fewer per 1000 (from 107 fewer to 495 more)	VERY LOW	CRITICAL
Prognostic factor: Sickle cell disease												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/3 (0%)	34/312 (10.9%)	POR 0.32 (0.01 to 12.56)	74 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Congenital adrenal hyperplasia												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	1/1 (100%)	33/314 (10.5%)	RR 7.05 (2.98 to 16.7)	636 more per 1000 (from 208 more to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Williams-Beuren syndrome												
1 (Henaff	observational	very	no serious	no serious	very serious	none	0/1	34/314	POR 0.33	73 fewer per 1000	VERY	CRITICAL

2017)	studies	serious[1]	inconsistency	indirectness	imprecision[2]		(0%)	(10.8%)	(0.00 to 180.43)	(from 108 fewer to 1000 more)	LOW	
Prognostic factor: Congenital encephalopathy												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Down's syndrome												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/2 (0%)	34/313 (10.9%)	POR 0.32 (0.00 to 28.47)	74 fewer per 1000 (from 109 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Prematurity												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	2/8 (25%)	32/307 (10.4%)	RR 2.4 (0.69 to 8.32)	146 more per 1000 (from 32 fewer to 763 more)	VERY LOW	CRITICAL
Prognostic factor: Congenital heart disease												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/6 (0%)	34/309 (11%)	POR 0.32 (0.02 to 4.31)	75 fewer per 1000 (from 108 fewer to 364 more)	VERY LOW	CRITICAL
Prognostic factor: Autoimmune hepatitis												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Asplenia (without sickle cell disease)												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/2 (0%)	34/313 (10.9%)	POR 0.32 (0.00 to 28.47)	74 fewer per 1000 (from 109 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Sickle cell disease and autoimmune hepatitis												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Congenital heart defect and asplenia												

1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Congenital heart disease and William-Beuren syndrome												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL

CI: confidence interval; POR: Peto odds ratio; 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] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events < 150

Table 7: Evidence profile for material prognostic factors for recurrent pneumococcal meningitis in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Presence of prognostic factor**	**Absence of prognostic factor**	**Relative (95% CI)**	**Absolute**		
Prognostic factor: Cochlear implant												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/4 (0%)	34/311 (10.9%)	POR 0.32 (0.01 to 7.70)	74 fewer per 1000 (from 108 fewer to 664 more)	VERY LOW	CRITICAL
Prognostic factor: Derivation valve												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/4 (0%)	34/311 (10.9%)	POR 0.32 (0.01 to 7.70)	74 fewer per 1000 (from 108 fewer to 664 more)	VERY LOW	CRITICAL

CI: confidence interval; POR: Peto odds ratios; QUIPS: Quality in Prognosis Studies
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events < 150

Table 8: Evidence profile for combination of prognostic factors for recurrent pneumococcal meningitis in children

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic factor	Relative (95% CI)	Absolute		
Prognostic factor: CSF breach and born premature												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	2/5 (40%)	32/310 (10.3%)	RR 3.88 (1.26 to 11.91)	297 more per 1000 (from 27 more to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: CSF breach and immunodeficiency[2]												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	1/2 (50%)	33/314 (10.5%)	RR 4.76 (1.15 to 19.74)	395 more per 1000 (from 16 more to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: Valve and undefined immunodeficiency												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL
Prognostic factor: CSF breach, cochlear implant and born premature												
1 (Henaff 2017)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	0/1 (0%)	34/314 (10.8%)	POR 0.33 (0.00 to 180.43)	73 fewer per 1000 (from 108 fewer to 1000 more)	VERY LOW	CRITICAL

CSF: cerebrospinal fluid; CI: confidence interval; POR: Peto odds ratio; 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] Not clear what type of immunodeficiency it refers to
[3] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events < 150

Table 9: Evidence profile for anatomical prognostic factors for recurrent bacterial meningitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic	Absence of prognostic	Relative (95% CI)	Absolute		

							factor	factor				
Prognostic factor: CSF leak												
1 (Durand 1993)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	22/62 (35.5%)	14/378 (3.7%)	RR 9.58 (5.19 to 17.7)	318 more per 1000 (from 155 more to 619 more)	VERY LOW	CRITICAL
Prognostic factor: Remote head injury or neurosurgery (more than 1 month before the onset of meningitis)												
1 (Durand 1993)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	8/18 (44.4%)	28/422 (6.6%)	RR 6.7 (3.57 to 12.56)	378 more per 1000 (from 171 more to 767 more)	VERY LOW	CRITICAL
Prognostic factor: Recent neurosurgery (within 1 month of the onset of meningitis)												
1 (Durand 1993)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	19/122 (15.6%)	17/318 (5.3%)	RR 2.91 (1.57 to 5.42)	102 more per 1000 (from 30 more to 236 more)	VERY LOW	CRITICAL

CSF: cerebrospinal fluid; 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] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events <150

Table 10: Evidence profile for anatomical prognostic factors for recurrent bacterial meningitis in undefined age

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Presence of prognostic factor**	**Absence of prognostic factor**	**Relative (95% CI)**	**Absolute**		
Prognostic factor: Head trauma (old and recent combined)												
1 (Carpenter 1962)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	8/25 (32%)	0/184 (0%)	POR 5716.68 [651.27 to 50179.70]	320 more per 1000 (from 140 more to 500 more)[3]	VERY LOW	CRITICAL

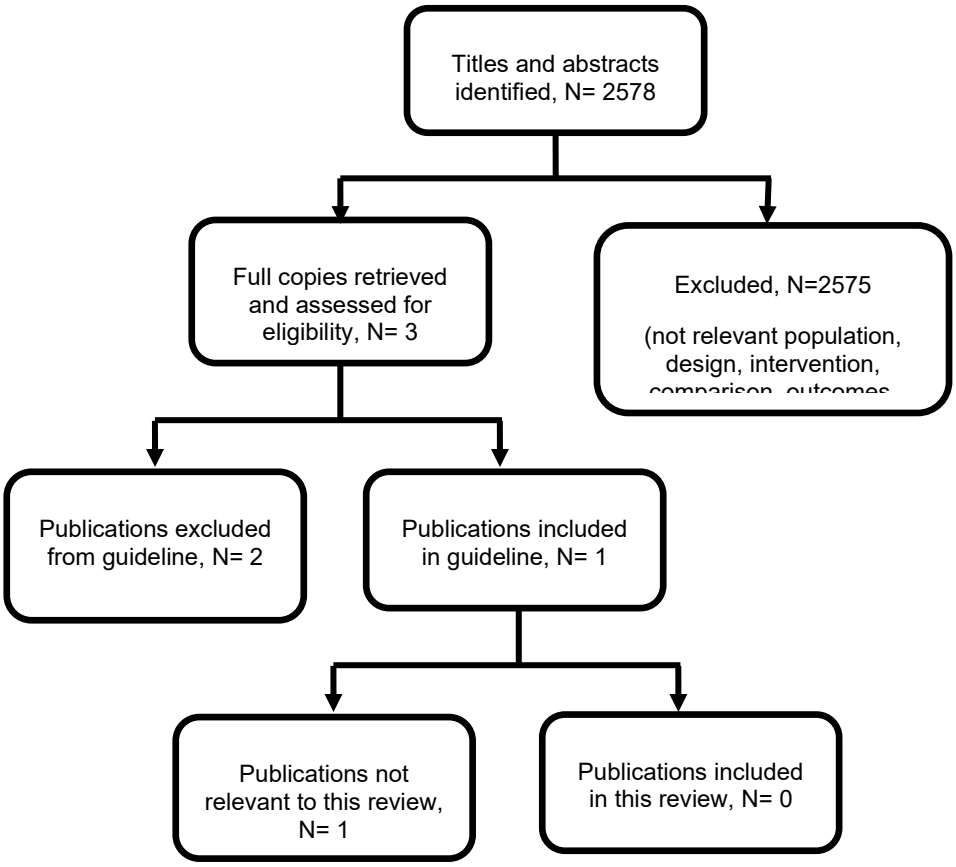
CI: confidence interval; POR: Peto odds ratio; QUIPS: Quality in Prognosis Studies
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events <150
[3] Calculated in Review Manager using the risk difference

Appendix G Economic evidence study selection

Study selection for: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 2).

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

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

Appendix I Economic model

Economic model for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

Excluded prognostic studies

Table 11: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Adriani, K. S, van de Beek, D, Brouwer, M. C et al. (2007) Community-acquired recurrent bacterial meningitis in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 45(5): e46-51	No outcomes of interest for review
Alsina, L, Basteiro, M. G, De Paz, H. D et al. (2015) Recurrent invasive pneumococcal disease in children: Underlying clinical conditions, and immunological and microbiological characteristics. PloS one 10 (3)	Study population not of interest for review [less than 50% of the population with meningitis]
Anderson, J. P. (1969) Recurrent virus meningitis. British Medical Journal 4(5686): 786	Study design not of interest for review [case report]
Anonymous (1966) Recurrent meningitis. Lancet 2(7459): 379	Study design not of interest for review [an annotation]
Anonymous (2018) Erratum: Utility of magnetic resonance cisternography with intrathecal gadolinium in detection of cerebrospinal fluid fistula associated with Mondini dysplasia in a patient with recurrent meningitis: Case report and literature review (Surgical Neurology International (2018) 9 (92) DOI: 10.4103/sni.sni_449_17). Surgical Neurology International 9 (1)	Study design not of interest for review [erratum]
Barrett Connor, E. (1971) Bacterial infection and sickle cell anemia. An analysis of 250 infections in 166 patients and a review of the literature. Medicine 50(2): 97-112	Study population not of interest for review [less than 50% of the population with meningitis]
Bloom, A. (1964) Recurrent Meningitis. Proceedings of the Royal Society of Medicine 57: 592	Study design not of interest for review [case report]
Butters, C, Phuong, L. K, Cole, T et al. (2019) Prevalence of Immunodeficiency in Children with Invasive Pneumococcal Disease in the Pneumococcal Vaccine Era: A Systematic Review. JAMA Pediatrics 173(11): 1084-1094	Study population not of interest for review [potentially relevant studies from this review were assessed for eligibility]
Carr, R. (1974) Radiological aspects of recurrent meningitis. Proceedings of the Royal Society of Medicine 67(11): 1147-50	Study design not of interest for review [case series]
Cho, T. A and Venna, N. (2010) Management of acute, recurrent, and chronic meningitides in adults. Neurologic Clinics 28(4): 1061-1088	Study design not of interest for review [narrative review]
Coccia, M. R, Facklam, R. R, Saravolatz, L. D et al. (1998) Recurrent pneumococcal bacteremia:	Study population not of interest for review [less than 50% of the population with meningitis]

Study	Reason for exclusion
34 episodes in 15 patients. Clinical infectious diseases 26(4): 982-5	
Conger, J. D, Edwards, E. A, Jacoby, W. J et al. (1971) Recurrent bacterial meningitis: immunologic observations. Military Medicine 136(3): 248-51	Study design not of interest for review [case report]
Damodaran, A, Aneja, S, Malhotra, V. L et al. (1996) Sensorineural hearing loss following acute bacterial meningitis - A prospective evaluation. Indian Pediatrics 33(9): 763-766	Country not of interest [not an OECD high income country]
Deveci, O, Uysal, C, Varol, S et al. (2015) Evaluation of posttraumatic recurrent bacterial meningitis in adults. Ulusal Travma ve Acil Cerrahi Dergisi = Turkish Journal of Trauma & Emergency Surgery: TJTESUlus Travma Acil Cerrahi Derg 21(4): 261-5	Country not of interest [not an OECD high income country]
Dorand, R.D and Adams, G. (1976) Relapse during penicillin treatment of group B streptococcal meningitis. Journal of Pediatrics 89(2): 188-190	Study design not of interest for review [case report]
Drummond, D. S, De Jong, A. L, Giannoni, C et al. (1999) Recurrent meningitis in the pediatric patient - The Otolaryngologist's role. International Journal of Pediatric Otorhinolaryngology 48(3): 199-208	Study design not of interest for review [case series]
Einarsdottir, H.M, Erlendsdottir, H, Kristinsson, K.G et al. (2005) Nationwide study of recurrent invasive pneumococcal infections in a population with a low prevalence of human immunodeficiency virus infection. Clinical Microbiology and Infection 11(9): 744-749	Study population not of interest for review [less than 50% of the population with meningitis]
Eljamel, M. S and Foy, P. M. (1990) Acute traumatic CSF fistulae: the risk of intracranial infection. British journal of neurosurgery 4(5): 381-5	Comparison not of interest for review [Data for risk factors not presented for those with and without recurrence]
Etuwewe, O. M, Swann, N, Hollingshead, S et al. (2009) Effect of recurrent invasive pneumococcal disease on serum anti-pneumolysin IgG titres in HIV infected adults. Vaccine 27(29): 3881-4	Country not of interest [not an OECD high income country]
Federico, G, Tumbarello, M, Spanu, T et al. (2001) Risk factors and prognostic indicators of bacterial meningitis in a cohort of 3580 postneurosurgical patients. Scandinavian Journal of Infectious Diseases 33(7): 533-7	Comparison not of interest for review [compares risk factors for nosocomial bacterial meningitis infection between those with meningitis/central nervous system infections and those without an infection]
Font, B, Lliminana, C, Fontanals, D et al. (2001) Eleven-year study of recurrent pneumococcal bacteremia. European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis 20(9): 636-8	Study population not of interest for review [participants with pneumonia/empyema]
Franco, S. M; Cornelius, V. E; Andrews, B. F. (1992) Long-term outcome of neonatal meningitis. American Journal of Diseases of Children 146(5): 567-71	Comparison not of interest for review [compares participants with meningitis with those without meningitis]
Freudenhammer, M, Karampatsas, K, Le Doare, K et al. (2021) Invasive Group B Streptococcus	Study population not of interest for review [less than 50% of the population with meningitis]

Study	Reason for exclusion
Disease With Recurrence and in Multiples: Towards a Better Understanding of GBS Late-Onset Sepsis. Frontiers in Immunology 12: 617925	
Friedland, I. R and Klugman, K. P. (1991) Recurrent penicillin-resistant pneumococcal meningitis after chloramphenicol therapy. Pediatric infectious disease journal 10(9): 705-707	Study design not of interest for review [case report]
Friedman, J. A; Ebersold, M. J; Quast, L. M. (2001) Post-traumatic cerebrospinal fluid leakage. World Journal of Surgery 25(8): 1062-6	Duplicate [reports the same data as in the original study Friedman 2000]
Friedman, J. A; Ebersold, M. J; Quast, L. M. (2000) Persistent posttraumatic cerebrospinal fluid leakage. Neurosurgical focus 9(1): e1	No outcomes of interest for review [Not possible to calculate risk of recurrence]
Gibson, R. M and Kurukchy, T. (1974) Neurosurgical aspects of recurrent meningitis. Proceedings of the Royal Society of Medicine 67(11): 1150-4	Study design not of interest for review [narrative review]
Ginsberg, L. (2004) Difficult and recurrent meningitis. Journal of Neurology, Neurosurgery and Psychiatry 75(suppl1)	Study design not of interest for review [narrative review and case series]
Ginsberg, L and Kidd, D. (2008) Chronic and recurrent meningitis. Practical Neurology 8(6): 348-361	Study design not of interest for review [narrative review]
Gold, A. J; Lieberman, E; Wright Jr, H. T. (1969) Bacteriologie relapse during ampicillin treatment of hemophilias influenzae meningitis. Journal of pediatrics 74(5): 135-141	Unavailable
Gold, A. J, Lieberman, E, Wright, H. T et al. (1969) Bacteriologic relapse during ampicillin treatment of Hemophilus influenzae meningitis. Journal of pediatrics 74(5): 779-81	Study design not of interest for review [case report]
Green, P.A, Singh, K.V, Murray, B.E et al. (1994) Recurrent group B streptococcal infections in infants: Clinical and microbiologic aspects. Journal of Pediatrics 125(6i): 931-938	Study design not of interest for review [case series (also <50% had meningitis)]
Grimwood, K and Dawson, K. P. (1982) Management of acute bacterial meningitis in childhood. New Zealand Medical Journal 95(713): 545-548	Study design not of interest for review [narrative review]
Haeney, M. R; Ball, A. P; Thompson, R. A. (1981) Recurrent bacterial meningitis due to genetic deficiencies of terminal complement components (C5 and C6). Immunobiology 158(01feb): 101-106	Study design not of interest for review [case report]
Hand, W. L and Sanford, J. P. (1970) Posttraumatic bacterial meningitis. Annals of internal medicine 72(6): 869-874	Study design not of interest for review [case series]
Hermans, P. E; Goldstein, N. P; Wellman, W. E. (1972) Mollaret's meningitis and differential diagnosis of recurrent meningitis. Report of case, with review of the literature. The American journal of medicine 52(1): 128-140	Study population not of interest for review [population with Mollaret's meningitis]
Hetem, D. J, Woerdeman, P. A, Bonten, M. J et al. (2010) Relationship between bacterial	Study population not of interest for review [secondary meningitis refers to meningitis

Study	Reason for exclusion
colonization of external cerebrospinal fluid drains and secondary meningitis: a retrospective analysis of an 8-year period. Journal of NeurosurgeryJ Neurosurg 113(6): 1309-13	following another illness/event (in this case, meningitis following having a CSF drain), rather than a second/recurrent episode of meningitis following a first episode]
Hirtz, D. G. (1997) Febrile seizures. Pediatrics in Review 18(1): 5-8; quiz 9	Study design not of interest for review [narrative review]
Hosoglu, S, Ayaz, C, Ceviz, A et al. (1997) Recurrent bacterial meningitis: a 6-year experience in adult patients. Journal of Infection 35(1): 55-62	Study design not of interest for review [case series]
Janocha-Litwin, J and Simon, K. (2013) Recurrent meningitis--a review of current literature. Przeglad EpidemiologicznyPrzegl Epidemiol 67(1): 41-5, 125	Study design not of interest for review [narrative review]
Jones, H. M. (1974) The problem of recurrent meningitis. Proceedings of the Royal Society of Medicine 67(11): 1141-7	Study design not of interest for review [case series]
Khan, I. A. (1972) Recurrent meningitis. Proceedings of the Royal Society of Medicine 65(4): 370-2	Study design not of interest for review [case report]
Khuri-Bulos, N. (1973) Meningococcal meningitis following rifampin prophylaxis. American Journal of Diseases of Children 126(5): 689-91	Study design not of interest for review [case report]
Kirkpatrick, B; Reeves, D.S; Macgowan, A.P. (1994) A review of the clinical presentation, laboratory features, antimicrobial therapy and outcome of 77 episodes of pneumococcal meningitis occurring in children and adults. Journal of Infection 29(2): 171-182	Comparison not of interest for review [no comparative data on risk factors between those with and without recurrence]
Klemola, E. (1970) Recurrent virus meningitis. British Medical Journal 1(5695): 564	Study design not of interest for review [letter to the editor]
Kline, M. W. (1989) Review of recurrent bacterial meningitis. Pediatric infectious disease journal 8(9): 630-4	Study design not of interest for review [narrative review]
Kline, M. W. (1992) Recurrent bacterial meningitis. Antibiotics & ChemotherapyAntibiot Chemother 45: 254-61	Study design not of interest for review [narrative review]
Korinek, A. M, Baugnon, T, Golmard, J. L et al. (2006) Risk factors for adult nosocomial meningitis after craniotomy: role of antibiotic prophylaxis. Neurosurgery 59(1): 126-33; discussion 126	No outcomes of interest for review
Kushnick, T. (1972) Recurrent meningitis. Clinical Pediatrics 11(5): 308-9	Study design not of interest for review [case report]
Lai, L. T, Trooboff, S, Morgan, M. K et al. (2014) The risk of meningitis following expanded endoscopic endonasal skull base surgery: a systematic review. Journal of Neurological Surgery Part B Skull BaseJ 75(1): 18-26	No outcomes of interest for review
Lee, S. J, Cohen, J, Chan, J et al. (2020) Infectious Complications of Expanded Endoscopic Transsphenoidal Surgery: A Retrospective Cohort Analysis of 100 Cases. Journal of Neurological Surgery Part B Skull	No outcomes of interest for review [Risk of developing first episode of meningitis, not recurrent meningitis]

Study	Reason for exclusion
BaseJ 81(5): 497-504	
Lieb, G. (1997) Recurrent bacterial meningitis. Alpe Adria Microbiology Journal 6(4): 243-252	Study design not of interest for review [narrative review]
Lieb, G, Krauss, J, Collmann, H et al. (1996) Recurrent bacterial meningitis. European Journal of Pediatrics 155(1): 26-30	No outcomes of interest for review
Lund, E. (1964) Recurrent cases of pneumococcal meningitis. Acta Path microbiolscand61(3): 491-492	Study design not of interest for review [case series]
MacGee, E. E; Cauthen, J. C; Brackett, C. E. (1970) Meningitis following acute traumatic cerebrospinal fluid fistula. Journal of Neurosurgery 33(3): 312-6	Study population not of interest for review [less than 50% of the population with meningitis]
Maitra, S and Ghosh, S. K. (1989) Recurrent pyogenic meningitis. A retrospective study. Quarterly Journal of Medicine 73(270): 919-929	No outcomes of interest for review [All had recurrent meningitis, so cannot calculate risk of recurrence]
Merino, J, Rodriguez-Valverde, V, Lamelas, J. A et al. (1983) Prevalence of deficits of complement components in patients with recurrent meningococcal infections. Journal of infectious diseases 148(2): 331	Study design not of interest for review [abstract]
Mollaret, P. (1968) Acute recurrent bacterial meningitis, mostly from pneumococci and sometimes from nteningococci franchi. Expansion Sci fkanc: 217-224	Unavailable
Morel, J, Casoetto, J, Jospe, R et al. (2010) De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. Critical Care 14 (6)	Study population not of interest for review [less than 50% of the population had meningitis]
Moroti, R, Olaru, I. D, Niculae, C. M et al. (2018) Predisposing conditions and outcome in adult patients with recurrent pneumococcal meningitis. Neurology Asia 23(4): 313-317	Country not of interest [not an OECD high income country]
Mufson, M.A, Hao, J.B, Stanek, R.J et al. (2012) Clinical features of patients with recurrent invasive Streptococcus pneumoniae disease. American Journal of the Medical Sciences 343(4): 303-309	Study population not of interest for review [less than 50% of the population with meningitis]
Nottidge, V. A. (1981) Pneumococcal meningitis in childhood. Nigerian Journal of Paediatrics 8(3): 65-69	Country not of interest [not an OECD high income country]
Ozdirim, E. (1981) Recurrent meningitis in childhood. (Hacettepe series of 53 cases). Turkish Journal of Pediatrics 23(1): 29-36	Unavailable
Petersen, B. H, Lee, T. J, Snyderman, R et al. (1979) Neisseria meningitidis and Neisseria gonorrhoeae bacteremia associated with C6, C7, or C8 deficiency. Annals of internal medicine 90(6): 917-20	Study design not of interest for review [a mix of narrative review and case reports]
Pikis, A, Kavaliotis, J, Tsikoulas, J et al. (1996) Long-term sequelae of pneumococcal meningitis in children. Clinical Pediatrics 35(2): 72-8	No outcomes of interest for review
Platonov, A. E, Beloborodov, V. B, Gabrilovitch, D. I et al. (1992) Immunological evaluation of	Country not of interest [not an OECD high income country]

Study	Reason for exclusion
late complement component-deficient individuals. Clinical Immunology and Immunopathology 64(2): 98-105	
Potter, P. C, Frasch, C. E, van der Sande, W. J et al. (1990) Prophylaxis against Neisseria meningitidis infections and antibody responses in patients with deficiency of the sixth component of complement. Journal of infectious diseases 161(5): 932-7	Country not of interest [not an OECD high income country]
Rajeshwari, K and Sharma, A. (1995) Remediable recurrent meningitis. Indian Pediatrics 32(4): 491-6	Country not of interest [not an OECD high income country]
Rosenberg, J and Galen, B. T. (2017) Recurrent Meningitis. Current Pain & Headache ReportsCurr Pain Headache Rep 21(7): 33	Study design not of interest for review [narrative review]
Ruas, R and Ribeiro, N. (2018) Meningoencephalocele causing recurrent meningitis. Clinical Case ReportsClin Case Rep 6(5): 944-945	Study design not of interest for review [case report]
Scherzer, E and Deisenhammer, E. (1968) Accidental convulsions in recurrent post-traumatic meningitis. Electroencephalography & Clinical NeurophysiologyElectroencephalogr Clin Neurophysiol 24(1): 92-3	Conference abstract
Shalita, A. R. (1964) Cerebrospinal Fluid Rhinorrhea in the Etiology of Recurrent Pneumococcal Meningitis. North Carolina Medical JournalN C Med J 25: 426-8	Study design not of interest for review [case report]
Siegler, J. (1964) Recurrent Pyogenic Meningitis Due to an Osteoma of the Frontal Sinus. Journal of Laryngology & OtologyJ Laryngol Otol 78: 226-8	Study design not of interest for review [case report]
Simon, F, Luscan, R, Khonsari, R. H et al. (2019) Management of Gorham Stout disease with skull-base defects: Case series of six children and literature review. International Journal of Pediatric Otorhinolaryngologyint J Pediatr Otorhinolaryngol 124: 152-156	Study design not of interest for review [case series]
Spader, H. S, Hertzler, D. A, Kestle, J. R et al. (2015) Risk factors for infection and the effect of an institutional shunt protocol on the incidence of ventricular access device infections in preterm infants. Journal of Neurosurgery. Pediatrics. 15(2): 156-60	No outcomes of interest for review
Spink, W. W and Su, C. K. (1960) Persistent menace of pneumococcal meningitis. JAMA (Chicago, Ill.) 173(14): 1545-1548	Study design not of interest for review [case series]
Tang, L. M and Chen, S. T. (1994) Relapsing bacterial meningitis in adults. Quarterly Journal of Medicine 87(8): 511-518	Country not of interest [not an OECD high income country]
Tebruegge, M and Curtis, N. (2008) Epidemiology, etiology, pathogenesis, and diagnosis of recurrent bacterial meningitis. Clinical Microbiology Reviews 21(3): 519-37	Systematic review; potentially relevant references for the review were checked
Tedder, D. G, Ashley, R, Tyler, K. L et al. (1994) Herpes simplex virus infection as a cause of	Study population not of interest for review [participants with recurrent lymphotic meningitis]

Study	Reason for exclusion
benign recurrent lymphocytic meningitis. Annals of Internal Medicine 121(5): 334-338	
Ter Horst, L, Brouwer, M. C, van der Ende, A et al. (2020) Community-acquired Bacterial Meningitis in Adults With Cerebrospinal Fluid Leakage. Clinical Infectious Diseases 70(11): 2256-2261	No outcomes of interest for review
Ter Horst, L, Brouwer, M. C, van der Ende, A et al. (2020) Recurrent Community-Acquired Bacterial Meningitis in Adults. Clinical infectious diseases 9: 9	No outcomes of interest for review [insufficient presentation of the results]
Tuygun, N; Tanir, G; Aytekin, C. (2010) Recurrent bacterial meningitis in children: our experience with 14 cases. Turkish Journal of Pediatrics 52(4): 348-53	Country not of interest [not an OECD high income country]
van Driel, J. J, Bekker, V, Spanjaard, L et al. (2008) Epidemiologic and microbiologic characteristics of recurrent bacterial and fungal meningitis in the Netherlands, 1988-2005. Clinical infectious diseases 47(5): e42-51	No outcomes of interest for review [reports are age, sex and causative organisms/serotypes, which is more of a description of the groups than risk factors]
Vanopdenbosch, L. J, Dedeken, P, Casselman, J. W et al. (2011) MRI with intrathecal gadolinium to detect a CSF leak: a prospective open-label cohort study. Journal of Neurology, Neurosurgery & PsychiatryJ Neurol Neurosurg Psychiatry 82(4): 456-8	Study population not of interest for review [less than 50% of the population with meningitis]
Vaswani, N. D, Gupta, N, Yadav, R et al. (2021) Seven versus Ten Days Antibiotics Course for Acute Pyogenic Meningitis in Children: A Randomized Controlled Trial. Indian Journal of Pediatrics 88(3): 246-251	Country not of interest [not an OECD high income country]
Vermeersch, H; Kluyskens, P; Vanderstock, L. (1980) The temporal bone as route of infection in recurrent meningitis. Journal of Otolaryngology 9(3): 199-201	Study design not of interest for review [case report]
Wang, J, Li, Y, Chen, S et al. (2016) Long-term outcomes of a transmastoid lateral semicircular canal approach to congenital CSF otorrhea in children associated with recurrent meningitis and severe inner ear malformation. International Journal of Pediatric Otorhinolaryngology 87: 185-189	Country not of interest [not an OECD high income country]
Yadav, J.S; Mohindra, S; Francis, A.A. (2011) CSF rhinorrhea-feasibility of conservative management in children. International Journal of Pediatric Otorhinolaryngology 75(2): 186-189	Country not of interest [not an OECD high income country]
Yaldiz, C, Ozdemir, N, Yaman, O et al. (2015) Intracranial repair of posttraumatic cerebrospinal fluid rhinorrhea associated with recurrent meningitis. Journal of Craniofacial Surgery 26(1): 170-3	Country not of interest [not an OECD high income country]
Young, L. M; Haddow, J. E; Klein, J. O. (1968) Relapse following ampicillin treatment of acute Hemophilus influenzae meningitis. Pediatrics 41(2): 516-8	Study design not of interest for review [case report]
Zimmermann, P; Gwee, A; Curtis, N. (2017) The	Study design not of interest for review [narrative

Study	Reason for exclusion
controversial role of breast milk in GBS late-onset disease. Journal of infection 74suppl1: S34-S40	review]

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What factors (individually or in combination) are associated with an increased risk of recurrent bacterial meningitis?

No research recommendation was made for this review.