National Institute for Health and Care Excellence

Final

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

[J2] Evidence review for factors associated with recurrent meningococcal disease

NICE guideline NG240

Evidence review underpinning recommendations 1.10.1 to 1.10.2, 1.10.5, 1.14.2 to 1.14.4 and 1.14.7 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Review question

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

Introduction

Meningococcal disease (meningococcal sepsis with or without an associated meningitis) is a rare but serious infection, which can occur in any age group. Recurrent meningococcal disease is exceptionally rare but may indicate an underlying disorder predisposing to the infection.

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

Summary of the protocol

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

Table 1: Summary of the protocol

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with recurrent meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis)
Prognostic factors	Any risk factors, alone or in combination
Comparison	Absence of risk factor(s)
Outcome	**Critical** • Risk ratios for recurrence of meningococcal disease • Odds ratios* for recurrence of meningococcal disease *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 (supplementary document 1).

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

Prognostic evidence

Included studies

Two studies were included for this review (D'Amelio 1992, Zimran 1987); both retrospective cohort studies reporting on complement deficiency as a prognostic factor for recurrent meningococcal disease in babies, children and adults combined.

The included studies are summarised in Table 2.

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

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
D'Amelio 1992 Retrospective cohort study Italy	N=59, n=6 with recurrent meningococcal disease Individuals with =>1 episode of meningococcal infection(s) Those with normal complement activity (n=49): • age at 1st episode [n (%)]: <14 years = 31 (63) , >14 years = 18 (37) Those with complement deficiency (n=10): • age at 1st episode [n (/%)]: <14 years = 3 (30), >14 years = 7 (70)	• complement deficiency	• recurrence of meningococcal disease	No multivariate analysis
Zimran 1987 Retrospective	N=110, n=8 with recurrent meningococcal disease	• complement deficiency	• recurrence of meningococcal disease	No multivariate analysis

Study	Population	Prognostic factor	Outcomes	Comments
cohort study Israel	Patients with meningococcal meningitis or bacteraemia Those with complement deficiency (n=10): • age [years; n (%)]: 0-4=0, 5-9=3 (30), 10-19=4 (40), 20-29=3 (30), 30-39=0, 40-69=0 Those without complement deficiency (n=100): • age [years; n (%)]: 0-4=49 (49), 5-9=25 (25), 10-19=18 (18), 20-29=3 (3), 30-39=3 (3), 40-69=2 (2)			

See the full evidence tables in appendix D and the forest plot 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 and imprecision due to a very low number of events.

It was not possible to stratify the evidence by the groups outlined in the protocol.

The evidence showed that the presence of complement deficiency was strongly associated with an increased risk of recurrent meningococcal disease in babies, children and adults combined.

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 meningococcal disease; therefore, risk ratios and odds ratios for recurrence of meningococcal disease 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 outcome identified in this review was rated as very low quality and the reasons for downgrading the evidence were risk of bias (arising from study participation, 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 1 prognostic factor only, complement deficiency.

Benefits and harms

The committee considered the evidence for factors associated with an increased risk of recurrent meningococcal disease and noted that evidence was only identified for a single prognostic factor and the quality of the evidence was very low. The committee made recommendations based on the best available evidence and their clinical knowledge and experience. Because meningococcal disease is very rare in neonates the protocol for this evidence review did not include neonates. However, based on their clinical knowledge and experience, the committee agreed that the recommendations about recurrent meningococcal disease that applied to babies (aged 28 days to 1 year) would also apply to neonates.

The evidence reviewed showed a strong association between presence of complement deficiency and an increased risk of recurrent meningococcal disease in babies, children and adults combined. Based on this evidence, and their clinical knowledge and experience, the committee recommended that congenital complement deficiency or acquired inhibition should be considered as a risk factor for recurrent meningococcal disease. Based on their experience, the committee also agreed that other reasons for primary or secondary immunodeficiency, such as HIV and splenectomy or splenic dysfunction, would increase susceptibility to infection more broadly and would therefore also be associated with an increased risk of recurrent meningococcal disease.

Based on the evidence reviewed that showed that an increased risk of recurrent meningococcal disease was associated with complement deficiency, and the consensus clinical opinion of the committee, it was recommended that a detailed drug history should be taken, because immunomodulatory drugs such as eculizumab may suppress the immune system and increase susceptibility to infections caused by Neisseria meningitidis (Joint Formulary Committee 2022).

The committee acknowledged the limited evidence base identified for this review and made recommendations based on their clinical knowledge and experience. The committee discussed including a recommendation for further research given that evidence was only identified for 1 prognostic factor. However, they agreed that this was not appropriate because

the prognostic factors of interest and recurrent meningococcal disease are both sufficiently rare that very large sample sizes would be required to give reliable results, and it would be difficult to recruit large numbers as people with known immunodeficiency would receive interventions to prevent recurrent infections such that future episodes rarely occur.

The committee agreed it was important to make recommendations about the actions that should be taken following both a first episode and a recurrent episode of meningococcal disease. 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 meningococcal disease

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 invasive meningococcal disease (Simmons 2015) 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, so recommended this should be done following a first episode of meningococcal disease. However, the committee agreed they would be less likely to suspect HIV in babies and children 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 meningococcal disease 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 meningococcal disease.

The committee recommended that in addition to a drug history (discussed above), an immunisation history should be taken. They agreed taking an immunisation history was important to identify both people who have not had routine vaccinations for 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.

People with a recurrent episode of meningococcal disease

The committee agreed that people with recurrent meningococcal disease should be reviewed by appropriate immunology and infection specialists (paediatric immunology and infectious disease specialist for 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 meningococcal disease were the same as or similar to those made following a single episode. The committee agreed that a detailed immunisation and drug history should be taken, and adults should be offered a HIV test, as per the recommendations above. However, they agreed that a HIV test should also be offered to babies and children with recurrent meningococcal disease, in the absence of additional risk factors for HIV due to the increased likelihood of there being an underlying immunodeficiency in people with recurrent meningococcal disease discussed above.

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 recurrent meningococcal disease was rare. 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 meningococcal disease would promote awareness which in turn would facilitate more timely, appropriate, and cost-effective management. The committee considered that their management recommendations for recurrent meningococcal disease 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 1.10.1 to 1.10.2, 1.10.5, 1.14.2 to 1.14.4 and 1.14.7. Other evidence supporting these recommendations can be found in the evidence review on factors associated with recurrent bacterial meningitis (see evidence review J1).

References – included studies

Prognostic

D'Amelio 1992

D'Amelio, R, Agostoni, A, Biselli, R, Brai, M, Caruso, G, Cicardi, M, et al. Complement deficiency and antibody profile in survivors of meningococcal meningitis due to common serogroups in Italy. Scandinavian Journal of Immunology 35(5):589-95 1992

Zimran 1987

Zimran, A, Rudensky, B, Kramer, M. R, Tedesco, F, Ehrenfeld, M, Raz, et al. Hereditary complement deficiency in survivors of meningococcal disease: high prevalence of C7/C8 deficiency in Sephardic (Moroccan) Jews. Quarterly Journal of Medicine 63(240):349-58, 1987

Economic

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

Other

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]

Simmons 2015

Simmons RD, Kirwan P, Beebeejaun K, Riordan A, Borrow R, Ramsay ME, Delpech V, Lattimore S, Ladhani S. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Medicine 13:1-9, 2015

Appendices

Appendix A Review protocol

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

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021279523
Review title	Risk factors associated with recurrent meningococcal disease
Review question	What factors (individually or in combination) are associated with an increased risk of recurrent meningococcal disease?
Objective	To determine the risk factors (individually or in combination) that are associated with recurrent meningococcal disease
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 meningococcal disease

Field	Content
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with recurrent meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial 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 meningococcal disease • Odds ratios* for recurrence of bacterial meningitis *adjusted odds ratios will be included where multivariate analyses are available
Secondary outcomes (important outcomes)	N/A
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-

Field	Content
	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/

Field	Content
	Minimally important differences: • Strong association: <0.5 and >2.00 • Moderate association: <0.80 and >1.25 • Small association: any statistically significant association • No association: no statistically significant association

Analysis of sub-groups	Evidence will be stratified by:
	• Age:
	  ○ Younger Infants: >28 days to ≤3 months of age
	  ○ Older infants: >3 months to <1 year of age
	  ○ Children: ≥1 year to <18* years of age
	  ○ Adults: ≥18* years of age
	• Meningococcal disease:
	  ○ Meningococcal septicaemia alone
	  ○ Meningococcal septicaemia and meningitis
	  ○ Non-specific meningococcal disease
	
	*There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children.
	
	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
	• Age:
	  ○ Young and middle aged adults
	  ○ Older adults*
	*There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold.
	
	Where evidence is stratified or subgrouped the committee will consider on a case by case basis if

Field	Content			
	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		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	Named contact: National Guideline Alliance			

Field	Content
	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=279523
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Prognostic, diagnostic, meningococcal disease, recurrent, signs and symptoms, risk factors, systematic

Field	Content	
	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 meningococcal disease?

Clinical Search

This was a combined search to cover both this review evidence review J1 on risk factors for recurrent bacterial meningitis.

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
40	risk?.ti.
41	risk factor?.ab.

#	Searches
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}
#30	#18 AND #29
#31	MeSH descriptor: [Ventriculoperitoneal Shunt] this term only
#32	(shunt*):ti,ab,kw

#	Searches
#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

#	Searches
	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.
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

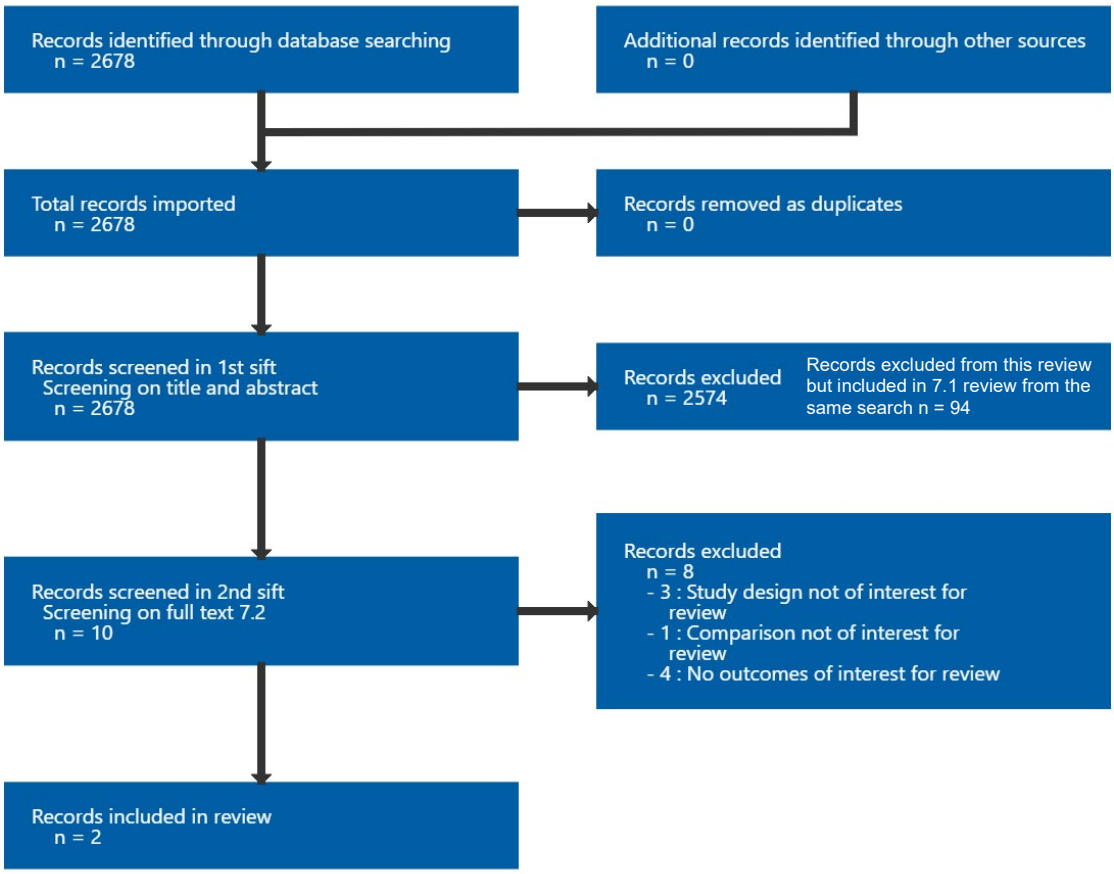
#	Searches
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or 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
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/

#	Searches
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

Appendix C Prognostic evidence study selection

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

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 meningococcal disease?

Table 4: Evidence tables

Study details	Results and risk of bias assessment using the QUIPs checklist
Full citation D'Amelio, R; Agostoni, A; Biselli, R; Brai, M; Caruso, G; Cicardi, M; Corvetta, A; Fontana, L; Misiano, G; Perricone, R; al, et; Complement deficiency and antibody profile in survivors of meningococcal meningitis due to common serogroups in Italy; Scandinavian Journal of Immunology; 1992; vol. 35 (no. 5); 589-95 **Ref Id** 8558004 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Study dates** 1985 to 1989 **Inclusion criteria** Individuals with =>1 episode of meningococcal infection(s) identified in the national surveillance system. **Exclusion criteria** Those in whom meningococcal serogroup was not identified	**Results** **Prognostic factor: complement deficiency; outcome: recurrent meningococcal disease in babies, children and adults combined** | | recurrent meningococcal disease | no recurrent meningococcal disease | total | | --- | --- | --- | --- | | complement deficiency | 5 | 5 | 10 | | no complement deficiency | 5 | 44 | 49 | | total | 10 | 49 | 59 | **1. Risk of bias: Study participation (High/Moderate/Low)** Low: individuals who had meningococcal disease identified via a national surveillance system **2. Risk of bias: Study attrition (High/Moderate/Low)** Low: retrospective data from a national surveillance system **3. Risk of bias: Prognostic factor measurement (High/Moderate/Low)** Low: Description of the complement analysis provided **4. Risk of bias: Outcome measurement (High/Moderate/Low)** Moderate: no definition of recurrent meningococcal disease provided; also in 39 out of 59 the diagnosis was bacteriologically confirmed but in 20 the diagnosis was based on clinical data only

Study details	Results and risk of bias assessment using the QUIPs checklist
Patient characteristics N=59, n=6 had recurrent meningococcal disease Meningococcal serogroup: A=10%, B=22%, C=68% In n=39 out of N=59 the diagnosis was bacteriologically confirmed, in n=20 the diagnosis was based on clinical data only. n=7 received a single meningococcal capsular polysaccharides vaccine Complement system n=49 had haemolytic activity within the normal range n=10 had undetectable haemolytic activity (selective deficiencies: n=1 of C6, n=3 of C7 and n=6 of C8β) Those with normal complement activity (n=49): Meningococcal serogroup (n/%): A=6/12, B=13/27, C=30/61 Male sex (n/%): 25/51 Age at 1st episode (n/%): <14 years = 31/63 , >14 years = 18/37 Presentation (n/%): sporadic episodes = 44/90, recurrences = 5/10, high severity* = 4/8. Those with complement deficiency (n=10): Meningococcal serogroup (n/%): A=0, B=0, C=10/100 Male sex (n/%): 5/50 Age at 1st episode (n/%): <14 years = 3/30, >14 years = 7/70 Presentation (n/%): sporadic episodes = 5/50, recurrences = 5/50, high severity* = 3/30 *high severity defined as the disease characterised by the presence of meningococcemia, sometimes accompanied by disseminated intravascular coagulation, arthritis or encephalitis **Risk factor(s) of interest** • complement deficiency **Confounding factor(s)**	**5. Risk of bias: Study confounding (High/Moderate/Low)** High: No attempts were made to control for age as a potential confounder (the groups differed substantially, in those with complement deficiency 70% were older than 14 years whereas in those without complement deficiency, there were 37% in the same age group). No attempts were made to control for other potential confounders either (for example, disease presentation and meningococcal serogroups) that differed between the groups **6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)** High: The observed baseline differences between the groups were not addressed in the analysis. 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
No confounding factors were explicitly identified and controlled for by the authors, but the groups differed in age, disease presentation and meningococcal serogroups **Setting** A national surveillance system	
Full citation Zimran, A; Rudensky, B; Kramer, M. R; Tedesco, F; Ehrenfeld, M; Raz, R; Greif, Z; Gelber, M; Lishner, M; Golan, E; al, et; Hereditary complement deficiency in survivors of meningococcal disease: high prevalence of C7/C8 deficiency in Sephardic (Moroccan) Jews; Quarterly Journal of Medicine; 1987; vol. 63 (no. 240); 349-58 **Ref Id** 8558150 **Country/ies where the study was carried out** Israel **Study type** Retrospective cohort study **Study dates** 1971 to 1985 **Inclusion criteria** Patients with meningococcal meningitis or bacteraemia located trough the medical records of 10 major Israeli hospitals and then invited for examination by mail/telephone call. Meningococcal infection was identified by positive cultures of either CSF or blood or both. **Exclusion criteria**	**Results** **Prognostic factor: complement deficiency; outcome: recurrent meningococcal disease in babies, children and adults combined** | | recurrent meningococcal disease | no recurrent meningococcal disease | total | | --- | --- | --- | --- | | complement deficiency | 4 | 6 | 10 | | no complement deficiency | 4 | 96 | 100 | | total | 8 | 102 | 110 | **1. Risk of bias: Study participation (High/Moderate/Low)** Moderate: no exclusion criteria reported **2. Risk of bias: Study attrition (High/Moderate/Low)** Low: participants with meningococcal meningitis / bacteraemia were identified through the medical records of 10 major hospitals in Israel **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 meningococcal disease meningitis provided; also in 20 out of 59 the diagnosis was based on clinical data only (in others it was confirmed bacteriologically)

Study details	Results and risk of bias assessment using the QUIPs checklist
None reported **Patient characteristics** N=110, n=8 with recurrent meningococcal disease n=10 with severe complement deficiency (CH50=0) of which n=4 had C7 and n=6 C8 deficiency. n=100 had mean CH50 49.8 ±13.5 (SD) units, range 20-79 units. Other characteristics Those with complement deficiency: Age (n/%): 0-4=0, 5-9=3/30, 10-19=4/40, 20-29=3/30, 30-39=0, 40-69=0; Ethnicity (n): Ashkenazi=0, Sephardi=7, Yemenite=1, Arab=2, Ethiopian=0, Gentile=0, undefined=0; Clinical features (n/%): meningitis=3/30, meningitis & bacteraemia=6/60, bacteraemia=1/10, recurrent meningitis=4/40, meningitis in siblings: simultaneous=0, remote=4/40 Those without complement deficiency: Age (n/%): 0-4=49/49, 5-9=25/25, 10-19=18/18, 20-29=3/3, 30-39=3/3, 40-69=2/2; Ethnicity (n): Ashkenazi=39, Sephardi=31, Yemenite=9, Arab=9, Ethiopian=2, Gentile=1, undefined=9; Clinical features (n/%): meningitis=62/62, meningitis & bacteraemia=26/26, bacteraemia=12/12, recurrent meningitis=4/4, meningitis in siblings: simultaneous=2/2, remote=0/0 **Risk factor(s) of interest** • complement deficiency **Confounding factor(s)** No confounding factors were explicitly identified and controlled for by the authors, but the groups differed in age and some of the clinical features of meningococcal infection. The authors only reported a very limited	**5. Risk of bias: Study confounding (High/Moderate/Low)** High: No attempts were made to control for age as a potential confounder (the groups differed substantially in some age categories, in those with complement deficiency there were no new-borns (0-4 months), 40% were aged 10-19 years, and 30% were aged 20-29 years whereas in those without complement deficiency, there were 49%, 18% and 3% in these age groups, respectively). No attempts were made to control for other potential confounders either (for example, clinical features), and only a very limited number of baseline characteristics were presented. **6. Risk of bias: Statistical analysis and reporting (High/Moderate/Low)** High: The observed baseline differences between the groups were not addressed in the analysis. There was no evidence of selective reporting of the results **Source of funding** Supported in part by a Junior Scientist's Grant from the Hebgrew University-Hadassah Joint Research Fund awarded to Dr A. Zimran and the Progetto Finalizzato Ingegneria GEnetica e Basi Molecolari of the CNR, Italy, awarded to F. Tedesco **Other information**

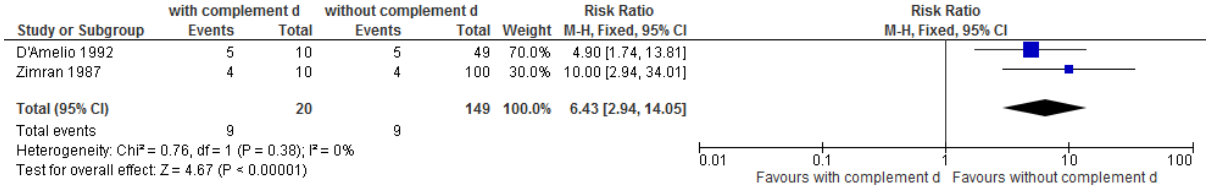
Study details	Results and risk of bias assessment using the QUIPs checklist
number of baseline characteristics. **Setting** Hospital	

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 meningococcal disease?

Figure 2: Complement deficiency as a prognostic factor for recurrent meningococcal disease in babies, children and adults combined



Appendix F GRADE tables

GRADE tables for review question: What factors (individually or in combination) are associated with an increased risk of recurrent meningococcal disease?

Table 5: Evidence profile for complement deficiency as a prognostic factor for recurrent meningococcal disease in babies, children and adults combined

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of complement deficiency	Absence of complement deficiency	Relative (95% CI)	Absolute		
Recurrent meningococcal disease												
2 (D'Amelio 1992; Zimran 1987)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	9/20 (45%)	9/149 (6%)	RR 6.43 (2.94 to 14.05)	328 more per 1000 (from 117 more to 788 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: relative risk; QUIPS: Quality in Prognosis Studies

[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS

[2] Evidence downgraded by 2 levels due to risk of very serious imprecision. Number of events <150

Appendix G Economic evidence study selection

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

A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 3).

Figure 3: 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 meningococcal disease?

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 meningococcal disease?

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 meningococcal disease?

Excluded prognostic studies

The excluded studies table only lists the studies that were considered and then excluded at the full-text stage for this review (N=8) and not studies (N=94) that were considered and then excluded from the search at the full-text stage as per the PRISMA diagram in Appendix C for the other review question in the same search.

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Cabellos, C, Pelegrin, I, Benavent, E et al. (2019) Impact of pre-hospital antibiotic therapy on mortality in invasive meningococcal disease: a propensity score study. European Journal of Clinical Microbiology and Infectious Diseases 38(9): 1671-1676	No outcomes of interest for review
Cooke, R. P. D; Zafar, M; Haeney, M. R. (1987) Recurrent meningococcal meningitis associated with deficiencies of C8 and anti-meningococcal antibody. Journal of Clinical and Laboratory Immunology 23(1): 53-56	Study design not of interest for review [case report]
Hongeng, S, Wilimas, J. A, Harris, S et al. (1997) Recurrent Streptococcus pneumoniae sepsis in children with sickle cell disease. Journal of Pediatrics 130(5): 814-6	No outcomes of interest for review
Krone, M, Lam, T. T, Claus, H et al. (2020) Recurrent invasive meningococcal infections - quantifying the risk, Germany, 2002 to 2018. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease BulletinEuro Surveill 25(25): 6	No outcomes of interest for review
Kuijpers, T. W, Nguyen, M, Hopman, C. T et al. (2010) Complement factor 7 gene mutations in relation to meningococcal infection and clinical recurrence of meningococcal disease. Molecular Immunology 47(4): 671-7	No outcomes of interest for review
Platonov, A. E, Kuijper, E. J, Vershinina, I. V et al. (1998) Meningococcal disease and polymorphism of FcgammaRIIa (CD32) in late complement component-deficient individuals. Clinical & Experimental ImmunologyClin Exp Immunol 111(1): 97-101	Comparison not of interest for review [compares the distributions of IIa-R131 and IIa-H131 allotypes in participants with late complement component-deficiency and meningococcal disease]
Retchless, A. C, Kretz, C. B, Rodriguez-Rivera, L. D et al. (2020) Oropharyngeal microbiome of a college population following a meningococcal disease outbreak. Scientific ReportsSci 10(1): 632	Study design not of interest for review [cross-sectional]
Ronne, T., Lind, I., Buhl, L.H (1986) Recurrent	Study design not of interest for review [a short

Study	Reason for exclusion
localized outbreaks of group C meningococcal disease and selective vaccination programmes. International Journal of General and Molecular Microbiology; vol. 52 (no. 3); 221-222	description of 3 group C meningococcal disease outbreaks in the Randers area, The Netherlands]

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 meningococcal disease?

No research recommendation was made for this review.