National Institute for Health and Care Excellence

Final

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

[A4] Evidence review for risk factors associated with meningococcal disease

NICE guideline NG240

Evidence review underpinning recommendation 1.1.14 and 1.1.15 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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What factors are associated with an increased risk of meningococcal disease?

Introduction

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

The diagnosis of meningococcal disease is frequently hindered by the non-specific nature of the early symptoms and signs, which may mimic those found in other serious conditions or milder viral illnesses.

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

Summary of the protocol

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

Table 1: Summary of the protocol

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected or confirmed 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)
Outcome	**Critical** • Risk ratios for diagnosis of meningococcal disease* • Odds ratios for diagnosis of meningococcal disease* **Important** None * Diagnosis of meningococcal disease must be made based on any diagnostic laboratory test for N. meningitidis.

N. meningitidis: Neisseria meningitidis.

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are

described in the review protocol in appendix A and the methods document (supplementary document 1).

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

Prognostic evidence

Included studies

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

Four studies were included for this review, 1 prospective cross-sectional study (Waterfield 2021), 1 prospective matched cohort study (Tully 2006), and 2 retrospective cohort studies (Mandal 2017, Yusuf 1999). Limited prospective studies and multivariate analyses were identified, so retrospective studies and univariate analyses were included.

The included studies for the prognostic evidence review are summarised in Table 2.

Two studies included babies and children (Yusuf 1999, Waterfield 2021), 1 study included adolescents aged between 15 and 19 years (Tully 2006), 1 study included adults aged 18 to 19 years (Mandal 2017).

Risk factors for meningococcal disease reported by the papers could be categorised as: demographic (Mandal 2017, Tully 2006), biological/clinical (Tully 2006, Waterfield 2021, Yusuf 1999), maternal and perinatal (Tully 2006, Yusuf 1999), and health behaviour and social (Tully 2006). All studies compared these risk factors for meningococcal disease relative to a no meningococcal disease control group (without further specification).

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	Risk factor	Outcomes	Comments
Mandal 2017 Retrospective cohort study UK	N=1,315,630 Cases of meningococcal disease in university students were identified from HPZone (a national, web-based case management tool capturing all meningococcal	• Demographic factor: ○ University student	Diagnosis of meningococcal disease	2014/2015 epidemiological year was selected as it was prior to the emergency introduction of the MenACWY immunisation programme in August 2015. Meningococcal disease diagnosed based on positive

Study	Population	Risk factor	Outcomes	Comments
	cases reported to Public Health England) and matched with laboratory-confirmed cases in the national surveillance dataset for 2014/15. Student MD cases compared against non-students with denominators calculated based on English population estimates. Characteristics not reported for the included sample			PCR test. Only unadjusted data available. Some control for age as restricted inclusion to 2013 and 2014 school leavers
Tully 2006 Prospective matched cohort study UK	N=288 Adolescents aged 15-19 who were admitted to the hospital with primary clinical diagnosis of meningococcal disease (including meningococcal meningitis alone) and their matched controls (recruited from GP and matched by sex and closest date of birth). Meningococcal disease (n=144): Age in years (median): 17.6 Sex: male: 74 (51%); female 70 (49%) Serogroup: n=66 (58%) serogroup B, n=43 (38%) serogroup C, n=1 (0.9%) serogroup W135, n=1 (0.9%) serogroup Y, n=3 ungroupable	• Demographic factors: ○ University student • Biological/clinical factors: ○ Preceding/prodromal illness in 2 weeks before diagnosis/interview (unadjusted and adjusted to control for high season of MD) ○ Recent infection with Epstein-Barr virus (defined as positive for viral capsid antibody IgG) ○ Deficiency in mannose-binding lectin (low producers) ○ Infection with Influenza A H3N2 subtype during past year (titre >320) ○ Infection with Influenza A H1N1 subtype during past year (titre >320) ○ Infection with Influenza B during	Diagnosis of meningococcal disease	Diagnosis of meningococcal disease based on culture, or detection by PCR of N. meningitidis from a normally sterile site or serodiagnosis. n=114 (79%) confirmed microbiologically by culture, PCR or serology test. No significant differences in symptoms or intensive case admission between microbiologically proved and unproved cases. Adjusted data available for factors where the difference between MD and no MD groups had a significance level of $p < 0.2$ in univariate analyses (having received a vaccine against serogroup C meningococci, preceding illness, intimate kissing,

Study	Population	Risk factor	Outcomes	Comments
	No meningococcal disease (n=144): Age in years (median): 17.7 Sex: male: 74 (51%); female 70 (49%)	the past year (titre >80) ○ Did not receive meningococcal vaccination (adjusted estimate available for receipt of vaccine) • Maternal and perinatal factors: ○ Preterm birth (gestational age <37 weeks) • Health behaviour and social factors: ○ Regular smoker (≥ 1 cigarettes/day) ○ Passive smoke exposure (multiple close contacts who smoke in 2 weeks before diagnosis/interview) ○ Regular consumption of illegal drugs (once a week or more) ○ Any alcohol consumed in 2 weeks before diagnosis/interview ○ Multiple intimate kissing contacts in 2 weeks before diagnosis/interview ○ Shared bedroom in 2 weeks before diagnosis/interview ○ Living in dormitory accommodation ○ Attended bar or party in 2 weeks before diagnosis/interview		being a student and preterm birth). Factors adjusted for in multivariate model included socioeconomic status (defined as household ownership of car and home and based on occupation) and seasonality of MD (high season defined as ≥70 MD cases/week). Data not extracted for population-level risk factors.
Waterfield 2021 Prospective cross-sectional study UK	N=1329 Children (aged under 18 years) presenting to a participating paediatric emergency department; fever (≥38°C); new-onset non-blanching rash or	• Biological/clinical factors: ○ Vaccines not up to date for age ○ Did not receive the meningococcal B vaccine ○ Did not receive the meningococcal C vaccine	Diagnosis of meningococcal disease	Diagnosis based on a positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF). No consideration of confounding factors

Study	Population	Risk factor	Outcomes	Comments
	features suggestive of meningococcal infection Meningococcal disease (n=19): Age in months (median; interquartile range (IQR) in parentheses): 37 (9-58) Sex: male: 16 (84%); female: 3 (16%) Serogroup of N. meningitidis: B N=17 (89%); C N=1 (5%); W N=1 (5%) No meningococcal disease (n=1310): Age in months (median; interquartile range (IQR) in parentheses): 24 (12-48) Sex: male: 765 (58%); female: 545 (42%) No further details provided for those negative for meningococcal disease			reported. Data not extracted for population-level risk factors.
Yusuf 1999 Retrospective cohort study USA	N=283291 Children 3 years or younger who were born in the Atlanta metropolitan area and identified in Georgia's birth certificate database. Meningococcal disease (n=47): Age in years: median/mean not reported (0-3 years)	• Biological/clinical factors: ○ Any abnormal condition in newborn • Maternal and perinatal factors: ○ Low birth weight (<2.5 kg) ○ Pre-term birth (gestational age <37 weeks) ○ Maternal smoking during pregnancy	Diagnosis of meningococcal disease	Diagnosis was confirmed by the isolation of N. meningitidis in blood or CSF. Of the risk factors of interest, adjusted data only available for maternal smoking during pregnancy (estimate adjusted for mother's age, ethnicity, receipt of medicaid, marital status, and education). No adjustment for

Study	Population	Risk factor	Outcomes	Comments
	Sex: male: 28 (60%); female 19 (40%) Serogroup B n=17 (36%); serogroup C n=10 (21%), serogroup Y n=5 (11%); serogroup W135 n=1 (2%); serogroup information not available for n=14 No meningococcal disease (n=283244): Age in years: median/mean not reported (0-3 years) Sex: male: 144896 (51%); female 138348 (49%)			potential confounding factors for other risk factors. Data not extracted for population-level risk factors.

CSF: cerebrospinal fluid; GP: general practitioner; IQR: interquartile range; MD: meningococcal disease; N. meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction

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 across several domains (for example, bias arising from the reliance on self-report and recall for some risk factors, a lack of clear specification of methods of measurement for the risk factors, and no or limited control for confounding factors), and imprecision due to a very low number of events. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

No meta-analyses were conducted for any of the risk factors due to insufficient evidence after stratifying for age. It was not possible to stratify by the population that did not receive a diagnosis of meningococcal disease (the control group), as all studies compared risk factors for meningococcal disease relative to a no meningococcal disease control group (without further specification).

Risk factors for meningococcal disease in babies and children

There was no evidence of an increased risk of meningococcal disease in babies and children in the evidence reviewed, due to missing vaccines (vaccines not up to date for age, did not receive the meningococcal B vaccine, or did not receive the meningococcal C vaccine), any

abnormal condition as a newborn, low birth weight, or pre-term birth. However, as the findings were seriously or very seriously imprecise for all these risk factors, they should not be taken as definitive evidence of a lack of association.

There was some evidence showing a strong association between maternal smoking during pregnancy and a diagnosis of meningococcal disease in babies and children (estimate adjusted for mother's age, ethnicity, receipt of medicaid, marital status, and education).

Risk factors for meningococcal disease in adolescents (15-19 years)

There was no evidence of an increased risk of meningococcal disease in adolescents in the evidence reviewed, due to being a university student, recent infection with Epstein-Barr virus, deficiency in mannose-binding lectin, infection with influenza A H3N2 or H1N1 subtype or influenza B during the past year, being a regular smoker, passive smoke exposure, the consumption of any alcohol in the 2 weeks prior to diagnosis or interview, or living in dormitory accommodation. However, as the findings were seriously or very seriously imprecise for all these risk factors, they should not be taken as definitive evidence of a lack of association.

There was some evidence showing a strong association between preceding/prodromal illness in the 2 weeks before diagnosis or interview and a diagnosis of meningococcal disease in adolescents (estimate adjusted for socioeconomic status and seasonality of meningococcal disease).

There was some evidence that receiving the meningococcal serogroup C vaccine reduced the risk of a diagnosis of meningococcal disease in adolescents (estimate adjusted for socioeconomic status and seasonality of meningococcal disease).

Pre-term birth showed a strong association with a diagnosis of meningococcal disease in adolescents (estimate adjusted for socioeconomic status and seasonality of meningococcal disease).

There was some evidence showing a moderate association between regular consumption of illegal drugs and a diagnosis of meningococcal disease in adolescents. The association between attending a bar or party (in the 2 weeks prior to diagnosis or interview) and a diagnosis of meningococcal disease was not statistically significant but only just crossed the line of no effect.

There was some evidence showing a strong association between multiple intimate kissing contacts and a diagnosis of meningococcal disease in adolescents (estimate adjusted for socioeconomic status and seasonality of meningococcal disease), and a moderate association for sharing a bedroom.

Risk factors for meningococcal disease in adults (18-19 years)

There was some evidence showing a strong association between being a university student and a diagnosis of meningococcal disease in adults (aged 18 to 19 years).

See appendix F for full GRADE tables.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline, but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because this review does not involve a comparison of competing courses of action.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

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

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence was very low quality and the reasons for downgrading were risk of bias (arising from issues with measurement of the prognostic factor and failure to adjust for confounding factors) and imprecision due to a very low number of events.

Evidence was found for demographic, biological/clinical, maternal and perinatal, and health behaviour and social risk factors.

Benefits and harms

The committee acknowledged that the evidence was limited and very low quality. The committee discussed the evidence identified for this review and made recommendations based on this evidence and on their clinical knowledge and experience.

There was evidence showing that receiving the meningococcal serogroup C vaccine reduced the risk of a diagnosis of meningococcal disease in adolescents. The committee noted that in the evidence reviewed, missing vaccines was not significantly associated with an increased risk of meningococcal disease for babies and children. However, the findings were seriously imprecise with very low numbers of babies and children who had not received relevant vaccinations (around 1% event rates), and this should not be taken as definitive evidence of absence of association. The committee agreed that although the evidence reviewed for vaccinations was limited, drawing on their clinical knowledge and experience, it was important to consider receipt of meningococcal vaccinations as part of assessing the risk of meningococcal disease and included this in the recommendation.

There was evidence showing a strong association between being a university student and a diagnosis of meningococcal disease in adults (aged 18 to 19 years). Increased risk of meningococcal disease was also associated with multiple kissing contacts, sharing a bedroom, and regular consumption of illegal drugs. The committee agreed that it was important that healthcare professionals be on heightened alert to the possibility of meningococcal disease in people who are students in further or higher education particularly those in halls of residence or other large shared accommodations. The committee noted that risk would also increase for those in close contact with people with meningococcal disease outside of the educational setting, and included in the recommendation that healthcare professionals should ascertain whether close contact with an infected person or presence in an area with an outbreak of meningococcal disease had occurred and factor this into the assessment.

Based on their clinical knowledge and experience, the committee agreed that there are certain groups of people, particularly those that have complement deficiency or inhibition, or splenectomy or splenic dysfunction, who might be more at risk of developing meningococcal disease. The committee discussed family history of meningococcal disease as a potential indicator of immune deficiency given that most deficiency syndromes (including complement deficiency) are inherited. The committee also highlighted that a previous episode of meningococcal disease may suggest potential immunodeficiency and make people more susceptible to another episode. Based on clinical consensus, the committee recommended that healthcare professionals should be on heightened alert to the possibility of meningococcal disease in people with these risk factors. The recommendations also direct people who have had a previous episode of meningococcal disease to consider risk factors for recurrent meningococcal disease (based on Evidence review J2).

Evidence showed an association between preceding/prodromal illness in the 2 weeks before diagnosis or interview and a diagnosis of meningococcal disease in adolescents. The committee noted that this risk factor was not clearly specified and could include heterogeneous conditions and symptoms. The committee agreed not to include this in the recommendations about risk factors for meningococcal disease but noted that early signs or symptoms should be captured by Evidence review A3 (signs and symptoms of meningococcal disease).

The committee discussed evidence showing an increased risk of meningococcal disease associated with pre-term birth and maternal smoking during pregnancy, but agreed not to include these risk factors as they are not specific to meningococcal disease, and they did not want to detract attention from risk factors that may be more useful in terms of aiding recognition.

Cost effectiveness and resource use

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

Recommendations supported by this evidence review

This evidence review supports recommendation 1.1.14 and 1.1.15.

References – included studies

Prognostic

Mandal 2017

Mandal, S., Campbell, H., Ribeiro, S., Gray, S., Carr, T., White, J., Ladhani, S. N., Ramsay, M. E., Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine, Vaccine, 35, 5814-5818, 2017

Tully 2006

Tully, J., Viner, R. M., Coen, P.G., Stuart, J. M., Zambon, M., Peckham, C., Booth, C., Klein, N., Kaczmarski, E., Booy, R., Risk and protective factors for meningococcal disease in adolescents: matched cohort study, BMJ, 332, 445-450, 2006

Waterfield 2021

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

Yusuf 1999

Yusuf, H. R., Rochat, R. W., Baughman, W. S., Gargiullo, P. M., Perkins, B. A., Brantley, M. D., Stephens, D. S., Maternal cigarette smoking and invasive meningococcal disease: a cohort study among young children in Metropolitan Atlanta, 1989-1996, American Journal of Public Health, 89, 712-717, 1999

Economic

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

Appendices

Appendix A Review protocols

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

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021245990
Review title	Risk factors associated with meningococcal disease
Review question	What factors are associated with an increased risk of meningococcal disease?
Objective	This review aims to determine the risk factors (alone or in combination) that are associated meningococcal disease
Searches	The following databases will be searched: Embase MEDLINE Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Searches will be restricted by: Date limitations: No date limit English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Meningococcal disease

Field	Content
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected or confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis). Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis.
Prognostic factors	Any risk factors, alone or in combination
Comparator/Reference standard/Confounding factors	Absence of risk factor(s)
Types of study to be included	• Systematic reviews • Prospective cohort studies with multivariate analyses • If insufficient prospective cohort studies: retrospective cohort studies with multivariate analyses Studies with univariate analyses will only be included if there are insufficient studies with multivariate analyses for a given risk factor or combination. Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: age (if not possible to stratify) Conference abstracts will not be considered.
Other exclusion criteria	Countries other than OECD high income countries

Field	Content
	Studies published not in English-language
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	• Risk ratios for diagnosis of meningococcal disease* • Odds ratios** for diagnosis of meningococcal disease* * Diagnosis of meningococcal disease must be made based on any diagnostic laboratory test for N. meningitidis. **adjusted odds ratios will be included where multivariate analyses are available
Secondary outcomes (important outcomes)	N/A
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. 5% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the risk factors, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklist: • ROBIS tool for systematic reviews • Quality in Prognostic Studies (QUIPS) tool for prognostic studies

Field	Content
	The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same factor and the definitions used and approach to analysis in the primary papers is sufficiently consistent, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies). Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/" **Minimally important differences** • Strong association: <0.5 and >2.00 • Moderate association: <0.80 and >1.25 • Small association: any statistically significant association • No association: no statistically significant association

Analysis of sub-groups	Evidence will be stratified by:
	• Population that do not receive a diagnosis of meningococcal disease:
	  ○ Non-meningococcal sepsis
	  ○ Non-meningococcal meningitis

Field	Content	
	○ Absence of sepsis and meningitis • Age: ○ Younger Infants: >28 days to ≤3 months of age ○ Older infants: >3 months to <1 year of age ○ Children: ≥1 year to <18* years of age ○ Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children. Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age: ○ Young and middle aged adults ○ Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☒	Prognostic

Field	Content			
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	18/03/2021			
Anticipated completion date	07/12/2023			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance			
Review team members	National Guideline Alliance			
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.			
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines			

Field	Content	
	(including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=245990	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Prognostic, diagnostic, meningococcal disease, signs and symptoms, risk factors, systematic review	
Details of existing review of same topic by same authors	None	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated

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

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; N. meningitidis: Neisseria meningitidis; N/A: not applicable; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; PRESS: Peer Review of Electronic Search Strategies; QUIPS: Quality in Prognostic Studies; ROBIS: Risk of Bias in Systematic Review.

Appendix B Literature search strategies

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

This was a combined search to cover both this review (evidence review 1.2b) and also evidence review 1.2a on signs and symptoms associated with meningococcal disease; evidence reviews 1.1a and 1.1b on signs, symptoms and risk factors associated with bacterial meningitis.

Clinical Search

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

Embase Classic+Embase 1947 to 2022 November 07, **Ovid MEDLINE(R) ALL** 1946 to November 07, 2022

Date of last search: 08 November 2022

Multifile database codes: emczd = Embase Classic+Embase; medall = Ovid MEDLINE(R) ALL

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use medall
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis* or mening* encephalitis*).ti,ab.
9	Meningococcal Infections/ or exp Neisseria meningitidis/
10	9 use medall
11	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
12	11 use emczd
13	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
14	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
15	(Neisseria* mening* or n mening*).ti,ab.
16	or/2,4-8,10,12-15
17	"Signs and Symptoms"/ or Fever/ or Vomiting/ or Nausea/ or Diarrhea/ or Chills/ or Shivering/ or Sleepiness/ or Headache/ or Photophobia/ or Intracranial Pressure/ or exp Consciousness Disorders/ or *Coma/ or Seizures/ or

#	Searches
	Seizures, Febrile/ or Irritable Mood/ or Crying/ or Decerebrate State/ or Lethargy/ or Fatigue/ or Confusion/ or Malnutrition/ or exp Purpura/ or Muscle Hypotonia/ or exp Tachycardia/
18	17 use medall
19	*physical disease by body function/ or *fever/ or *vomiting/ or *nausea/ or *diarrhea/ or *chill/ or *shivering/ or *somnolence/ or *headache/ or *photophobia/ or *intracranial pressure/ or exp *consciousness disorder/ or *coma/ or *seizure/ or *febrile convulsion/ or *irritability/ or *crying/ or *decerebration/ or *lethargy/ or *fatigue/ or *confusion/ or *malnutrition/ or exp *purpura/ or *muscle hypotonia/ or exp *tachycardia/
20	19 use emczd
21	((head or cranial or intracranial) adj3 pain*).ti,ab.
22	((stiff* or rigid*) adj3 (neck* or nuchal or cervical or spine or spinal)).ti,ab.
23	(light adj3 (intoleran* or sensitiv*)).ti,ab.
24	((tense or bulge or bulging or full*) adj3 fontanelle?).ti,ab.
25	((raise? or rise or high or elevat*) adj3 intracranial pressure?).ti,ab.
26	((level? or decreas*) adj3 consciousness).ti,ab.
27	(irritab* or petulan* or bad mood or moody).ti,ab.
28	((symphyseal or cheek) adj3 sign?).ti,ab.
29	(abnormal adj3 postur*).ti,ab.
30	(muscle? adj3 (atonic or flaccid*)).ti,ab.
31	((decreas* or alter* or chang*) adj3 (conscious* or mental state?)).ti,ab.
32	((hemorrhagic or haemorrhagic) adj3 rash).ti,ab.
33	(capillar* adj2 refill*).ti,ab.
34	((cold or clammy or temperature) adj3 (hand? or feet or extremities)).ti,ab.
35	((limb? or extremities or arms or legs) adj3 pain*).ti,ab.
36	((mottled or mottling) adj3 (skin or epidermal)).ti,ab.
37	((elevated or rapid* or fast*) adj3 (heart?beat or heart rate)).ti,ab.
38	(sign? or symptom* or complain*).ti,ab.
39	(clinical adj3 (manifestation* or feature* or finding* or aspect*)).ti,ab.
40	(present* adj3 (feature* or finding* or factor*)).ti,ab. or presentation*.ti.
41	(physical* adj3 (manifest* or characteristic* or featur* or finding*)).ti,ab.
42	or/18,20-41
43	exp "SENSITIVITY AND SPECIFICITY"/ or Likelihood Functions/ or Diagnostic Test Routine/ or Differential Diagnosis/
44	43 use medall
45	"sensitivity and specificity"/ or statistical model/ or differential diagnosis/ or *diagnostic accuracy/ or diagnostic test accuracy study/
46	45 use emczd
47	Prognosis/
48	(sensitivity or specificity).ti,ab.
49	((pre test or pretest or post test or posttest) adj probability).ti,ab.
50	((predict* adj3 (value* or factor*)) or (PPV or NPV)).ti,ab.

#	Searches
51	likelihood ratio*.ti,ab.
52	(ROC curve* or AUC).ti,ab.
53	diagnos*.ti.
54	((diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)) or (accurat* adj5 diagnos*)).ti,ab.
55	gold standard.ab.
56	di.fs.
57	or/44,46-56
58	Obstetric Labor, Premature/ or Premature Birth/ or Infant, Premature/ or Fetal Membranes, Premature Rupture/ or Ear, Inner/ or exp Smoking/ or Tobacco Smoke Pollution/ or Cochlear Implants/ or Spleen/ or Splenectomy/ or *Socioeconomic Factors/ or Environment/ or Crowding/ or exp Otitis Media/ or exp Sinusitis/ or exp Pneumonia/ or Mastoiditis/ or Cochlear Implantation/ or Streptococcal Infections/
59	58 use medall
60	*premature labor/ or *prematurity/ or *premature fetus membrane rupture/ or *inner ear/ or exp *smoking/ or *passive smoking/ or *cochlea prosthesis/ or *spleen/ or *splenectomy/ or *socioeconomics/ or *environment/ or "crowding (area)"/ or exp *otitis media/ or exp *sinusitis/ or exp *pneumonia/ or *mastoiditis/ or *cochlear implantation/ or *streptococcus infection/
61	60 use emczd
62	((preterm* or pre-term* or premature*) adj10 (birth* or born* or deliver* or labour* or labor* or infant* or newborn* or new-born* or neonate* or neo-nate* or baby or babies or child or children)).ti,ab.
63	((premature* or prolong*) adj2 rupture*).ti,ab.
64	(inner adj ear).ti,ab.
65	smok*.ti,ab.
66	(cochlea* adj2 implant*).ti,ab.
67	((spleen* or splen*) adj3 (impair* or dysfunc* or absen* or non-function* or nonfunction*)).ti,ab.
68	splenectom*.ti,ab.
69	asplenia.ti,ab.
70	((crowd* or over-crowd* or overcrowd*) adj3 (environment* or place* or premise* or house* or household* or venue* or condition* or living or setting* or transport* or sleep* or room*)).ti,ab.
71	((partial or incomplet*) adj2 immuni*).ti,ab.
72	((vaccin* or immuni*) adj coverage*).ti,ab.
73	(contiguous* adj (spread or foci)).ti,ab.
74	(contiguous adj3 infection*).ti,ab.
75	(otitis media* or sinusitis* or pneumonia* or mastoiditis*).ti,ab.
76	(streptococc* adj (infect* or diseas*)).ti,ab.
77	or/59,61-76
78	Risk/ or Risk Factors/
79	78 use medall
80	*risk/ or *risk factor/
81	80 use emczd
82	risk?.ti.

#	Searches
83	risk factor?.ab.
84	or/79,81-83
85	16 and 77 and 84
86	16 and 42 and 57
87	16 and 42 and 84
88	*"Signs and Symptoms"/ use medall
89	*physical disease by body function/ use emczd
90	(signs adj2 symptom*).ti,ab.
91	or/88-90
92	16 and 91
93	85 or 86 or 87 or 92
94	limit 93 to English language [General Exclusions filter applied]

Database(s): Cochrane Library – Wiley interface

Cochrane Database of Systematic Reviews, Issue 11 of 12, November 2022, **Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2022

Date of last search: 08 November 2022

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	MeSH descriptor: [Neisseria meningitidis] explode all trees
#10	((bacter* or infect*) near/3 (mening* or leptomening* or subarachnoid space*)):ti,ab,kw
#11	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or (h next influenz*) or listeria* or pneumococc* or (gram next negativ* next bacill*) or streptococc* or GBS or (s next pneumon*)) near/3 (septic* or sepsis* or bacteraemi* or bacteremi* or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or (mening* next encephalitis*)).:ti,ab,kw
#13	((neisseria* next mening*) or (n next mening*)):ti,ab,kw
#14	MeSH descriptor: [Meningococcal Infections] this term only
#15	meningococc*:ti,ab,kw
#16	{or #1-#15}
#17	MeSH descriptor: [Signs and Symptoms] this term only

#	Searches
#18	MeSH descriptor: [Fever] this term only
#19	MeSH descriptor: [Vomiting] this term only
#20	MeSH descriptor: [Nausea] this term only
#21	MeSH descriptor: [Diarrhea] this term only
#22	MeSH descriptor: [Chills] this term only
#23	MeSH descriptor: [Shivering] this term only
#24	MeSH descriptor: [Sleepiness] this term only
#25	MeSH descriptor: [Headache] this term only
#26	MeSH descriptor: [Photophobia] this term only
#27	MeSH descriptor: [Intracranial Pressure] this term only
#28	MeSH descriptor: [Consciousness Disorders] explode all trees
#29	MeSH descriptor: [Coma] this term only
#30	MeSH descriptor: [Seizures] this term only
#31	MeSH descriptor: [Seizures, Febrile] this term only
#32	MeSH descriptor: [Irritable Mood] this term only
#33	MeSH descriptor: [Crying] this term only
#34	MeSH descriptor: [Decerebrate State] this term only
#35	MeSH descriptor: [Lethargy] this term only
#36	MeSH descriptor: [Fatigue] this term only
#37	MeSH descriptor: [Confusion] this term only
#38	MeSH descriptor: [Malnutrition] this term only
#39	MeSH descriptor: [Purpura] explode all trees
#40	MeSH descriptor: [Muscle Hypotonia] this term only
#41	MeSH descriptor: [Tachycardia] explode all trees
#42	((head or cranial or intracranial) near/3 pain*):ti,ab,kw
#43	((stiff* or rigid*) near/3 (neck* or nuchal or cervical or spine or spinal)):ti,ab,kw
#44	(light near/3 (intoleran* or sensitiv*)):ti,ab,kw
#45	((tense or bulge or bulging or full*) near/3 fontanelle*):ti,ab,kw
#46	((raise* or rise or high or elevat*) near/3 intracranial pressure*):ti,ab,kw
#47	((level* or decreas*) near/3 consciousness):ti,ab,kw
#48	(irritab* or petulan* or "bad mood" or moody):ti,ab,kw
#49	((symphyseal or cheek) near/3 sign*):ti,ab,kw
#50	(abnormal near/3 postur*):ti,ab,kw
#51	(muscle* near/3 (atonic or flaccid*)):ti,ab,kw
#52	((decreas* or alter* or chang*) near/3 (conscious* or "mental state" or "mental states")):ti,ab,kw
#53	((hemorrhagic or haemorrhagic) near/3 rash):ti,ab,kw

#	Searches
#54	(capillar* near/2 refill*):ti,ab,kw
#55	((cold or clammy or temperature) near/3 (hand* or feet or extremities)):ti,ab,kw
#56	((limb* or extremities or arms or legs) near/3 pain*):ti,ab,kw
#57	((mottled or mottling) near/3 (skin or epidermal)):ti,ab,kw
#58	((elevated or rapid* or fast*) near/3 (heartbeat or "heart beat" or "heart rate")):ti,ab,kw
#59	(sign? or symptom* or complain*):ti,ab,kw
#60	(clinical near/3 (manifest* or featur* or finding* or aspect*)):ti,ab,kw
#61	(present* near/3 (feature* or finding* or factor*)):ti,ab,kw or presentation*:ti
#62	(physical* near/3 (manifest* or characteristic* or featur* or finding*)):ti,ab,kw
#63	{or #17-#62}
#64	MeSH descriptor: [Sensitivity and Specificity] explode all trees
#65	MeSH descriptor: [Likelihood Functions] this term only
#66	MeSH descriptor: [Diagnostic Tests, Routine] this term only
#67	MeSH descriptor: [Diagnosis, Differential] this term only
#68	MeSH descriptor: [Prognosis] this term only
#69	((sensitivity or specificity)):ti,ab,kw
#70	((("pre test" or pretest or "post test" or posttest) next probability)):ti,ab,kw
#71	(((predict* near/3 (value* or factor*)) or (PPV or NPV))):ti,ab,kw
#72	("likelihood ratio*"):ti,ab,kw
#73	(("ROC curve*" or AUC)):ti,ab,kw
#74	diagnos*:ti
#75	(((diagnos* near/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)) or (accurat* near/5 diagnos*))):ti,ab,kw
#76	"gold standard":ab
#77	MeSH descriptor: [] explode all trees and with qualifier(s): [diagnosis - DI]
#78	{or #64-#77}
#79	MeSH descriptor: [Obstetric Labor, Premature] this term only
#80	MeSH descriptor: [Premature Birth] this term only
#81	MeSH descriptor: [Infant, Premature] this term only
#82	MeSH descriptor: [Fetal Membranes, Premature Rupture] this term only
#83	MeSH descriptor: [Ear, Inner] this term only
#84	MeSH descriptor: [Smoking] explode all trees
#85	MeSH descriptor: [Tobacco Smoke Pollution] this term only
#86	MeSH descriptor: [Cochlear Implants] this term only
#87	MeSH descriptor: [Spleen] this term only
#88	MeSH descriptor: [Splenectomy] this term only
#89	MeSH descriptor: [Socioeconomic Factors] this term only

#	Searches
#90	MeSH descriptor: [Environment] this term only
#91	MeSH descriptor: [Crowding] this term only
#92	MeSH descriptor: [Otitis Media] this term only
#93	MeSH descriptor: [Sinusitis] this term only
#94	MeSH descriptor: [Pneumonia] explode all trees
#95	MeSH descriptor: [Mastoiditis] this term only
#96	MeSH descriptor: [Cochlear Implantation] this term only
#97	MeSH descriptor: [Cochlear Implantation] this term only
#98	(((preterm* or "pre term*" or prematur*) near/10 (birth* or born* or deliver* or labour* or labor* or infant* or newborn* or "new born*" or neonate* or "neo nate*" or baby or babies or child or children))):ti,ab,kw
#99	(((premature* or prolong*) near/2 rupture*)):ti,ab,kw
#100	((inner next ear)):ti,ab,kw
#101	smok*:ti,ab,kw
#102	((cochlea* near/2 implant*)):ti,ab,kw
#103	(((spleen* or splen*) near/3 (impair* or dysfunc* or absen* or "non function*" or nonfunction*))):ti,ab,kw
#104	(splenectom*):ti,ab,kw
#105	(asplenia):ti,ab,kw
#106	(((crowd* or "over crowd*" or overcrowd*) near/3 (environment* or place* or premise* or house* or household* or venue* or condition* or living or setting* or transport* or sleep* or room*))):ti,ab,kw
#107	(((partial or incomplet*) near/2 immuni*)):ti,ab,kw
#108	(((vaccin* or immuni*) next coverage*)):ti,ab,kw
#109	((contiguous* next (spread or foci))):ti,ab,kw
#110	((contiguous near/3 infection*)):ti,ab,kw
#111	(("otitis media*" or sinusitis* or pneumonia* or mastoiditis*)):ti,ab,kw
#112	((streptococc* next (infect* or diseas*))):ti,ab,kw
#113	{or #79-#112}
#114	MeSH descriptor: [Risk] this term only
#115	MeSH descriptor: [Risk Factors] this term only
#116	risk*:ti
#117	"risk factor*":ab
#118	{or #114-#117}
#119	#16 and #63
#120	#16 and #113
#121	MeSH descriptor: [Signs and Symptoms] this term only
#122	((signs near/2 symptom*)):ti,ab,kw
#123	#121 or #122
#124	#16 and #123

#	Searches
#125	#119 or #120 or #124
#126	"conference":pt or (clinicaltrials or trialsearch):so
#127	#125 not #126

Economic Search

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

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

Date of last search: 11 March 2021

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

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

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

Date of last search: 10 November 2022

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

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or

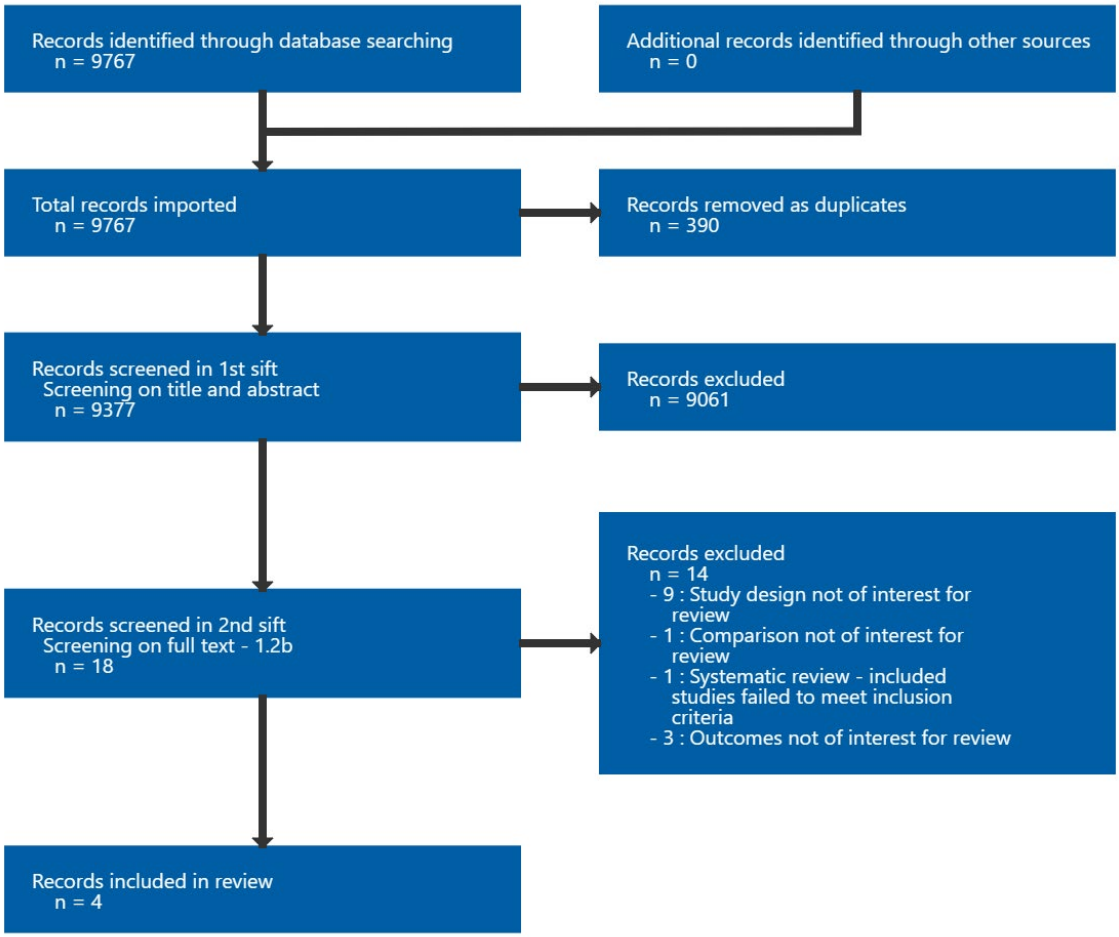
#	Searches
	meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* 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
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

#	Searches
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/
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 review question: What factors are associated with an increased risk of meningococcal disease?

Figure 1: Study selection flow chart



Appendix D Evidence tables

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

Table 5: Evidence tables

Mandal, 2017

Bibliographic Reference Mandal, S; Campbell, H; Ribeiro, S; Gray, S; Carr, T; White, J; Ladhani, S. N; Ramsay, M. E.; Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine; Vaccine; 2017; vol. 35 (no. 43); 5814-5818

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	July 2014 - June 2015
Inclusion criteria	Cases of meningococcal disease in university students were identified from HPZone (a national, web-based case management tool capturing all meningococcal cases reported to Public Health England) and matched with laboratory-confirmed cases in the national surveillance dataset for 2014/15. Student MD cases compared against non-students with denominators calculated based on English population estimates. 2014/2015 epidemiological year was selected as it was prior to the emergency introduction of the MenACWY immunisation programme in August 2015.

Exclusion criteria	Those recorded as probable or possible meningococcal disease (without laboratory confirmation) on HPZone were excluded from further analysis
Patient characteristics	N=1,315,630 Characteristics not reported for the included sample.
Risk factor(s) of interest	Demographic factor: • University student
Confounding factor(s) of interest	Only unadjusted data available. Some control for age as restricted inclusion to 2014 school leavers (1st year university students; born between 1 September 1995 and 31 August 1996 and diagnosed between September 2014 and June 2015) and 2013 school leavers (born between 1 September 1994 and 31 August 1995; 1st year university students after gap year or 2nd year university students).
Duration of follow-up	Not applicable
Setting	Not reported
Sources of funding	Not industry funded
Other information	Meningococcal disease diagnosed based on positive PCR test

PCR: positive polymerase chain reaction

Outcomes

Demographic risk factors for diagnosis of meningococcal disease
In those with a presence of a risk factor, the numbers refer to a total number with meningococcal disease and with factor / total number with factor; in those with an absence of a risk factor, the numbers refer to a total number with meningococcal disease and without factor / total number without factor.

Outcome	**N = 1315630**

Outcome	**N = 1315630**
University student Custom value	34/397620
Non-student Custom value	11/918010

Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Study appears to have included all relevant young adults recorded in HPZone (a national, web-based case management tool capturing all meningococcal cases reported to Public Health England) and matched with laboratory-confirmed cases in the national surveillance dataset. Baseline characteristics not reported for the cohort of interest (those with comparative data).)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all adults of interest.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Data available for all participants and risk factor extracted from database with objective and valid methods of measurement)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Diagnosis of meningococcal disease based on PCR)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Only unadjusted data available. Although age is not a confounding factor as the cohort were selected from very narrow age groups (18 – 19 years old))*
Statistical Analysis	Statistical Analysis	Moderate risk of bias *(Statistical analysis used for the study was not described. Comparative data reported for quite a*

Section	Question	Answer
and Reporting	and Presentation Summary	*narrow population so may not fully represent the population of interest.)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

Tully, 2006

Bibliographic Reference	Tully, J; Viner, R.M; Coen, P.G; Stuart, J.M; Zambon, M; Peckham, C; Booth, C; Klein, N; Kaczmarski, E; Booy, R.; Risk and protective factors for meningococcal disease in adolescents: matched cohort study; BMJ; 2006; vol. 332 (no. 7539); 445-450

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study Matched cohort study
Study dates	January 1999 - June 2000
Inclusion criteria	Adolescents aged 15-19 who were admitted to the hospital with primary clinical diagnosis of meningococcal disease (including meningococcal meningitis alone) and their matched controls (recruited from GP and matched by sex and closest date of birth)

Exclusion criteria	Cases identified after the fifth day of admission to hospital; death of patient; attending doctor declined to participate; patient did not speak English; approval from the local research ethics committee were not obtained.
Patient characteristics	N=288 Meningococcal disease (n=144): Age in years (median): 17.6 Sex: male: 74 (51%); female 70 (49%) Serogroup: n=66 (58%) serogroup B, n=43 (38%) serogroup C, n=1 (0.9%) serogroup W135, n=1 (0.9%) serogroup Y, n=3 ungroupable No meningococcal disease (n=144): Age in years (median): 17.7 Sex: male: 74 (51%); female 70 (49%)
Risk factor(s) of interest	Demographic factors: • University student Clinical/biological risk factors: • Preceding/prodromal illness in 2 weeks before diagnosis/interview (unadjusted and adjusted to control for high season of MD) • Recent infection with Epstein-Barr virus (defined as positive for viral capsid antibody IgG) • Deficiency in mannose-binding lectin (low producers) • Infection with Influenza A H3N2 subtype during past year (titre >320) • Infection with Influenza A H1N1 subtype during past year (titre >320) • Infection with Influenza B during the past year (titre >80)

	• Did not receive meningococcal vaccination (adjusted estimate available for receipt of vaccine) Maternal and perinatal risk factors: • Preterm birth (gestational age <37 weeks) Health behaviour and social risk factors: • Regular smoker (≥ 1 cigarettes/day) • Passive smoke exposure (multiple close contacts who smoke in 2 weeks before diagnosis/interview) • Regular consumption of illegal drugs (once a week or more) • Any alcohol consumed in 2 weeks before diagnosis/interview • Multiple intimate kissing contacts in 2 weeks before diagnosis/interview • Shared bedroom in 2 weeks before diagnosis/interview • Living in dormitory accommodation • Attended bar or party in 2 weeks before diagnosis/interview
Confounding factor(s) of interest	Adjusted data available for factors where the difference between MD and no MD groups had a significance level of $p < 0.2$ in univariate analyses (having received a vaccine against serogroup C meningococci, preceding illness, intimate kissing, being a student and preterm birth). Factors adjusted for in multivariate model included socioeconomic status (defined as household ownership of car and home and based on occupation) and seasonality of MD (high season defined as ≥70 MD cases/week).
Duration of follow-up	NA
Setting	Secondary care (hospital) for cases and primary care for controls
Sources of funding	Not industry funded
Other information	Diagnosis of meningococcal disease based on culture, or detection by PCR of N. meningitidis from a normally sterile site or serodiagnosis. n=114 (79%) confirmed microbiologically by culture, PCR or serology test. No significant differences in symptoms or intensive case admission between microbiologically proved and unproved cases. Data not extracted for population-level risk factors.

GP: general practitioner; MD: meningococcal disease; N. meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction

Outcomes

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

Demographic risk factors for a diagnosis of meningococcal disease

Outcome	**N = 288**
University student Custom value	50/96
Non-student Custom value	94/192

Clinical/biological risk factors for a diagnosis of meningococcal disease

Outcome	**N = 288**
Preceding/prodromal illness in 2 weeks before diagnosis/interview (adjusted estimate) Custom value	aOR 2.9 (95% CI: 1.4-5.9)
Preceding/prodromal illness in 2 weeks before diagnosis/interview Custom value	76/121
No preceding/prodromal illness in 2 weeks before diagnosis/interview Custom value	68/167
Recent infection with Epstein-Barr virus (positive for viral capsid antibody IgG)	105/194

Outcome	N = 288
Data available for 85% of sample across those with and without risk factor Custom value	
No recent infection with Epstein-Barr virus (negative for viral capsid antibody IgG) Data available for 85% of sample across those with and without risk factor Custom value	24/51
Deficiency in mannose-binding lectin (low producers) Data available for 77% of sample across those with and without risk factor Custom value	20/33
No deficiency in mannose-binding lectin (medium or high producers) Data available for 77% of sample across those with and without risk factor Custom value	92/190
Infection with Influenza A H3N2 subtype during past year (titre >320) Data available for 82% of sample across those with and without risk factor Custom value	48/93
No recent infection with Influenza A H3N2 subtype (titre ≤320) Data available for 82% of sample across those with and without risk factor Custom value	68/143
Infection with Influenza A H1N1 subtype during past year (titre >320) Data available for 82% of sample across those with and without risk factor Custom value	16/32
No recent infection with Influenza A H1N1 subtype (titre ≤320) Data available for 82% of sample across those with and without risk factor	100/204

Outcome	N = 288
Custom value	
Infection with Influenza B during the past year (titre >80) Data available for 82% of sample across those with and without risk factor Custom value	10/18
No recent infection with Influenza B (titre ≤80) Data available for 82% of sample across those with and without risk factor Custom value	106/218
Received meningococcal vaccination (meningococcal serogroup C vaccine; adjusted estimate) Custom value	aOR 0.12 (95% CI: 0.04-0.37)
Did not receive meningococcal vaccination (meningococcal serogroup C vaccine) Custom value	107/196
Did not receive meningococcal vaccination (meningococcal serogroup C vaccine) Custom value	37/91

Maternal and perinatal risk factors for a diagnosis of meningococcal disease

Outcome	N = 282
Pre-term birth (gestational age <37 weeks) Data available for 98% of whole sample across those with and without the risk factor) Custom value	14/21
Term birth (gestational age ≥38 weeks) Data available for 98% of whole sample across those with and without the risk factor)	128/261

Outcome	N = 282
Custom value	
Pre-term birth (adjusted estimate) Custom value	aOR 3.7 (95% CI: 1.0-13.5)

Health behaviour and social risk factors for a diagnosis of meningococcal disease

Outcome	N = 288
Regular smoker (≥ 1 cigarettes/day) Custom value	47/92
Smokes <1 cigarette/day Custom value	97/196
Passive smoke exposure (multiple close contacts who smoke in 2 weeks before diagnosis/interview) Custom value	104/196
Limited passive smoke exposure Custom value	40/92
Regular consumption of illegal drugs (once a week or more) Custom value	23/36
No or occasional consumption of illegal drugs (frequency of use less than once a week) Custom value	121/252
Any alcohol consumed in 2 weeks before diagnosis/interview Custom value	123/236

Outcome	N = 288
No alcohol consumed in 2 weeks before diagnosis/interview Custom value	21/52
Multiple intimate kissing contacts in 2 weeks before diagnosis/interview (adjusted estimate) Custom value	aOR 3.7 (95% CI: 1.7-8.1)
Multiple intimate kissing contacts in 2 weeks before diagnosis/interview Custom value	42/64
≤1 intimate kissing contacts in 2 weeks before diagnosis/interview Custom value	102/224
Shared bedroom in 2 weeks before diagnosis/interview Custom value	96/170
Did not share bedroom in the 2 weeks before diagnosis/interview Custom value	48/118
Living in dormitory accommodation Custom value	10/18
Not living in dormitory accommodation Custom value	134/270
Attended bar or party in 2 weeks before diagnosis/interview Custom value	128/243

Outcome	N = 288
Did not attend a bar or party in the 2 weeks before diagnosis/interview Custom value	16/45

Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Study excluded patients who died. This could introduce a possibility that factors associated with more severe forms of illness are not adequately captured. Baseline characteristics presented for all included patients for key characteristics.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all children of interest included in the study. 9 patients were recruited, but not included in the study as it was not possible to collect questionnaire data (2 died, 2 later refused to participate, 5 lost to follow-up). Reasons, key characteristics and attempts to collect information on participants who dropped out of the study were not described. However, it is unlikely that a small proportion of participants lost to follow up (6%) would impact the results.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Some risk factors are objective (shared bedroom; living in dormitory; preceding illness; recent infection with Epstein-Barr virus; Mannose-binding lectin deficiency; infection with Influenza A H3N2 subtype during past year; infection with Influenza A H1N1 subtype during past year; infection with Influenza B during the past year; received meningococcal vaccination; pre-term birth) but many of the risk factors based on self-report (regular smoker; passive smoke exposure; regular consumption of illegal drugs; any alcohol consumed; multiple intimate kissing contacts, attended bar or party). No clear specification of methods of measurement for many of the risk factors and unclear if definitions of thresholds pre-specified (any alcohol consumption in past 2 weeks does not appear consistent with definitions of regular smoking or regular illicit drug use). Missing data for some of the risk factors of interest (missing data for between 15% and 23% of sample) and reasons for missing data not provided. Also potential for recall bias is higher in MD group than in no MD group as although memory aides (timelines, calendars, and personal diaries) used for cases the time interval since exposure will*

Section	Question	Answer
		be longer than for controls who are recalling the immediate 2 weeks prior to interview.)
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Outcome of interest is adequately measured. 80% of cases were confirmed by laboratory tests.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Adjusted estimates available for factors where the difference between MD and no MD groups had a significance level of p < 0.2 in univariate analyses (having received a vaccine against serogroup C meningococci, preceding illness, intimate kissing, being a student and preterm birth), but for other risk factors only unadjusted data reported)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Statistical analysis used was adequate for the design of the study, however, multivariate analysis limited to factors with a univariate significance level of P < 0.2)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

Waterfield, 2021

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

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study Cross-sectional study
Study dates	November 2017 to June 2019
Inclusion criteria	Children (aged under 18 years) presenting to a participating paediatric emergency department; fever (≥38°C); new-onset non-blanching rash or features suggestive of meningococcal infection
Exclusion criteria	Pre-existing haematological condition (such as, haematological malignancy, idiopathic thrombocytopenic purpura, or coagulopathy); existing diagnosis of Henoch-Schönlein purpura
Patient characteristics	N=1329 Meningococcal disease (N=19): Age in months (median; interquartile range (IQR) in parentheses): 37 (9-58) Sex: male: 16 (84%); female: 3 (16%) Serogroup of N. meningitidis: B N=17 (89%); C N=1 (5%); W N=1 (5%) No meningococcal disease (N=1310): Age in months (median; interquartile range (IQR) in parentheses): 24 (12-48) Sex: male: 765 (58%); female: 545 (42%) No further details provided for those negative for meningococcal disease

Risk factor(s) of interest	Clinical/biological risk factors: • Vaccines not up-to-date for age • Did not receive the meningococcal B vaccine • Did not receive the meningococcal C vaccine
Confounding factor(s) of interest	No consideration of confounding factors reported
Duration of follow-up	NA
Setting	Secondary care (hospital)
Sources of funding	Not industry funded
Other information	Diagnosis based on a positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF). Data not extracted for population-level risk factors

CSF: cerebrospinal fluid; IQR: interquartile range; N. meningitidis: Neisseria Meningitidis; PCR: positive polymerase chain reaction

Outcomes

Clinical/biological risk factors for diagnosis of meningococcal disease

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

Outcome	**N = 1329**
Vaccines not up to date for age	0/51

Outcome	N = 1329
Data available for 97% of sample across those with and without the risk factor Custom value	
Vaccines up to date for age Data available for 97% of sample across those with and without the risk factor Custom value	19/1239
Did not receive the meningococcal B vaccine Data available for 97% of sample across those with and without the risk factor Custom value	7/349
Received the meningococcal B vaccine Data available for 97% of sample across those with and without the risk factor Custom value	12/938
Did not receive the meningococcal C vaccine Data available for 97% of sample across those with and without the risk factor Custom value	5/300
Received the meningococcal C vaccine Data available for 97% of sample across those with and without the risk factor Custom value	14/987

Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias *(The sampling frame, period and place of recruitment, and inclusion and exclusion*

Section	Question	Answer
		criteria are adequately described)
Study Attrition	Study Attrition Summary	Low risk of bias *(No loss to follow-up)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Limited detail on how vaccine status measured and may rely on self-report and recall)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Diagnosis based on a positive culture or PCR test for N. meningitidis or other bacterial pathogen from a sterile body site (for example, blood or CSF))*
Study Confounding	Study Confounding Summary	High risk of bias *(No consideration of confounding factors reported)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and there was no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable

Yusuf, 1999

Bibliographic Reference Yusuf, H. R; Rochat, R. W; Baughman, W. S; Gargiullo, P. M; Perkins, B. A; Brantley, M. D; Stephens, D. S.; Maternal cigarette smoking and invasive meningococcal disease: A cohort study among young children in Metropolitan Atlanta, 1989-1996; American Journal of Public Health; 1999; vol. 89 (no. 5); 712-717

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	January 1989 - December 1995
Inclusion criteria	All children 3 years or younger who were born in the Atlanta metropolitan area and identified in Georgia's birth certificate database.
Exclusion criteria	Children for whom information was missing.
Patient characteristics	N=283291 Meningococcal disease (n=47): Age in years: median/mean not reported (0-3 years) Sex: male: 28 (60%); female 19 (40%) Serogroup B n=17 (36%); serogroup C n=10 (21%), serogroup Y n=5 (11%); serogroup W135 n=1 (2%); serogroup information not available for n=14 No meningococcal disease (n=283244): Age in years: median/mean not reported (0-3 years) Sex: male: 144896 (51%); female 138348 (49%)
Risk factor(s) of interest	Maternal and perinatal risk factors: • Low birth weight (<2.5 kg)

	• Pre-term birth (gestational age <37 weeks) • Maternal smoking during pregnancy Biological/clinical risk factors: • Any abnormal condition in newborn (defined as anaemia, injury during birth, fetal alcohol syndrome, respiratory distress syndrome, meconium aspiration syndrome, seizures, and other or unclassified conditions)
Confounding factor(s) of interest	Of the risk factors of interest, adjusted data only available for maternal smoking during pregnancy (estimate adjusted for mother's age, ethnicity, receipt of medicaid, marital status, and education). No adjustment for potential confounding factors for other risk factors.
Duration of follow-up	NA
Setting	Secondary care (hospital)
Sources of funding	No sources of funding reported.
Other information	Diagnosis was confirmed by the isolation of N. meningitidis in blood or CSF. Data not extracted for population-level risk factors

CSF: cerebrospinal fluid; N. meningitidis: Neisseria Meningitidis

Outcomes

Risk factors for diagnosis of meningococcal disease

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

Outcome	**N = 283291**

Outcome	N = 283291
Low birth weight (<2.5 kg) Custom value	6/23397
Birth weight ≥2.5 kg Custom value	41/259894
Pre-term birth (gestational age <37 weeks) Custom value	7/29517
Term birth (gestational age ≥37 weeks) Custom value	40/253774
Maternal smoking during pregnancy (adjusted estimate) Custom value	aRR 2.93 (95% CI: 1.52-5.66)
Maternal smoking during pregnancy Custom value	16/29267
No maternal smoking during pregnancy Custom value	31/254024
Any abnormal condition in newborn Custom value	3/10460
No abnormal condition in newborn Custom value	44/272831

Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias *(Study appears to have included all relevant children identified from Georgia's birth certificate database. Baseline characteristics presented for all patients for key characteristics.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all children.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Birth weight and gestational age objective but maternal smoking during pregnancy based on self-report, and no clear specification of methods of measurement for any of the risk factors.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Meningococcal disease diagnosis confirmed by the isolation of N. meningitidis in blood or CSF.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Of the risk factors of interest, adjusted data only available for maternal smoking during pregnancy (estimate adjusted for mother's age, ethnicity, receipt of medicaid, marital status, and education). No adjustment for potential confounding factors for other risk factors.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Statistical analysis used was adequate for the design of the study and there was no evidence of selective reporting of the results.)*
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Directly applicable *(Not clear how many of included patients were neonates, <25% is assumed (and therefore evidence is directly applicable) due to use of population level data.)*

Appendix E Forest plots

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

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

Appendix F **GRADE tables**

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

Table 6: Evidence profile for risk factors associated with diagnosis of meningococcal disease in babies and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of factor	Absence of factor	Relative (95% CI)	Absolute		
Vaccines not up to date for age												
1 (Waterfield 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/51 (0%)	19/1239 (1.5%)	RR 0.61 (0.04 to 9.99)	6 fewer per 1000 (from 15 fewer to 138 more)	VERY LOW	CRITICAL
Did not receive the meningococcal B vaccine												
1 (Waterfield 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/349 (2%)	12/938 (1.3%)	RR 1.57 (0.62 to 3.95)	7 more per 1000 (from 5 fewer to 38 more)	VERY LOW	CRITICAL
Did not receive the meningococcal C vaccine												
1 (Waterfield 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/300 (1.7%)	14/987 (1.4%)	RR 1.17 (0.43 to 3.24)	2 more per 1000 (from 8 fewer to 32 more)	VERY LOW	CRITICAL
Any abnormal condition in newborn												
1 (Yusuf 1999)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/10460 (0.03%)	44/272831 (0.02%)	RR 1.78 (0.55 to 5.73)	0 more per 1000 (from 0 fewer to 1 more)	VERY LOW	CRITICAL
Low birth weight (<2.5 kg)												
1 (Yusuf	observational	serious[1]	no serious	no serious	very	none	6/23397	41/259894	RR 1.63 (0.69	0 more per 1000 (from	VERY	CRITICAL

1999)	studies		inconsistency	indirectness	serious[2]		(0.03%)	(0.02%)	to 3.83)	0 fewer to 0 more)	LOW	
Pre-term birth (gestational age <37 weeks)												
1 (Yusuf 1999)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/29517 (0.02%)	40/253774 (0.02%)	RR 1.5 (0.67 to 3.36)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Maternal smoking during pregnancy (adjusted estimate)												
1 (Yusuf 1999)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/29267 (0.05%)	31/254024 (0.01%)	aRR 2.93 (1.52 to 5.65)	0 more per 1000 (from 0 more to 1 more)	VERY LOW	CRITICAL

aRR: adjusted relative risk; CI: confidence interval; QUIPS: Quality in Prognosis Studies; RR: relative risk
[1]Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2]<150 events

Table 7: Evidence profile for risk factors associated with diagnosis of meningococcal disease in adolescents (15-19 years)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Presence of factor**	**Absence of factor**	**Relative (95% CI)**	**Absolute**		
University student												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	50/96 (52.1%)	94/192 (49%)	RR 1.06 (0.84 to 1.35)	29 more per 1000 (from 78 fewer to 171 more)	VERY LOW	CRITICAL
Preceding/prodromal illness in 2 weeks before diagnosis/interview (adjusted estimate)												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	76/121 (62.8%)	68/167 (40.7%)	aOR 2.9 (1.41 to 5.95)	259 more per 1000 (from 85 more to 396 more)	VERY LOW	CRITICAL
Recent infection with Epstein-Barr virus												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	105/194 (54.1%)	24/51 (47.1%)	RR 1.15 (0.84 to 1.58)	71 more per 1000 (from 75 fewer to 273 more)	VERY LOW	CRITICAL
Deficiency in mannose-binding lectin												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/33 (60.6%)	92/190 (48.4%)	RR 1.25 (0.92 to 1.71)	121 more per 1000 (from 39 fewer to 344 more)	VERY LOW	CRITICAL

Infection with Influenza A H3N2 subtype during past year												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	48/93 (51.6%)	68/143 (47.6%)	RR 1.09 (0.84 to 1.41)	43 more per 1000 (from 76 fewer to 195 more)	VERY LOW	CRITICAL
Infection with Influenza A H1N1 subtype during past year												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/32 (50%)	100/204 (49%)	RR 1.02 (0.7 to 1.48)	10 more per 1000 (from 147 fewer to 235 more)	VERY LOW	CRITICAL
Infection with Influenza B during the past year												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/18 (55.6%)	106/218 (48.6%)	RR 1.14 (0.74 to 1.77)	68 more per 1000 (from 126 fewer to 374 more)	VERY LOW	CRITICAL
Received meningococcal vaccination (meningococcal serogroup C vaccine; adjusted estimate)												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	37/91 (40.7%)	107/196 (54.6%)	aOR 0.12 (0.04 to 0.37)	420 fewer per 1000 (from 244 fewer to 500 fewer)	VERY LOW	CRITICAL
Did not receive meningococcal vaccination (meningococcal serogroup C vaccine)												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	107/196 (54.6%)	37/91 (40.7%)	RR 1.34 (1.02 to 1.77)	138 more per 1000 (from 8 more to 313 more)	VERY LOW	CRITICAL
Pre-term birth (gestational age <37 weeks; adjusted estimate)												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/21 (66.7%)	128/261 (49%)	OR 3.7 (1.01 to 13.59)	290 more per 1000 (from 2 more to 439 more)	VERY LOW	CRITICAL
Regular smoker (≥ 1 cigarettes/day)												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47/92 (51.1%)	97/196 (49.5%)	RR 1.03 (0.81 to 1.32)	15 more per 1000 (from 94 fewer to 158 more)	VERY LOW	CRITICAL
Passive smoke exposure												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	104/196 (53.1%)	40/92 (43.5%)	RR 1.22 (0.93 to 1.59)	96 more per 1000 (from 30 fewer to 257 more)	VERY LOW	CRITICAL
Regular consumption of illegal drugs (once a week or more)												
1 (Tully	observational	serious[1]	no serious	no serious	very	none	23/36	121/252	RR 1.33 (1.01	158 more per 1000 (from	VERY	CRITICAL

2006)	studies		inconsistency	indirectness	serious[2]		(63.9%)	(48%)	to 1.76)	5 more to 365 more)	LOW	
Any alcohol consumed in 2 weeks before diagnosis/interview												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	123/236 (52.1%)	21/52 (40.4%)	RR 1.29 (0.91 to 1.84)	117 more per 1000 (from 36 fewer to 339 more)	VERY LOW	CRITICAL
Multiple intimate kissing contacts in 2 weeks before diagnosis/interview (adjusted estimate)												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	42/64 (65.6%)	102/224 (45.5%)	aOR 3.7 (1.7 to 8.08)	300 more per 1000 (from 132 more to 416 more)	VERY LOW	CRITICAL
Shared bedroom in 2 weeks before diagnosis/interview												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	96/170 (56.5%)	48/118 (40.7%)	RR 1.39 (1.08 to 1.79)	159 more per 1000 (from 33 more to 321 more)	VERY LOW	CRITICAL
Living in dormitory accommodation												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/18 (55.6%)	134/270 (49.6%)	RR 1.12 (0.73 to 1.72)	60 more per 1000 (from 134 fewer to 357 more)	VERY LOW	CRITICAL
Attended bar or party in 2 weeks before diagnosis/interview												
1 (Tully 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	128/243 (52.7%)	16/45 (35.6%)	RR 1.48 (0.98 to 2.23)	171 more per 1000 (from 7 fewer to 437 more)	VERY LOW	CRITICAL

aOR: adjusted odds ratio; CI: confidence interval; QUIPS: Quality in Prognosis Studies; RR: relative risk
[1]Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2]<150 events

Table 8: Evidence profile for risk factors associated with diagnosis of meningococcal disease in adults (18-19 years)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of factor	Absence of factor	Relative (95% CI)	Absolute		
University student												
1 (Mandal 2017)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	34/397620 (0.009%)	11/918010 (0.001%)	RR 7.14 (3.62 to 14.08)	0 more per 1000 (from 0 more to 0 more)	VERY LOW	CRITICAL

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

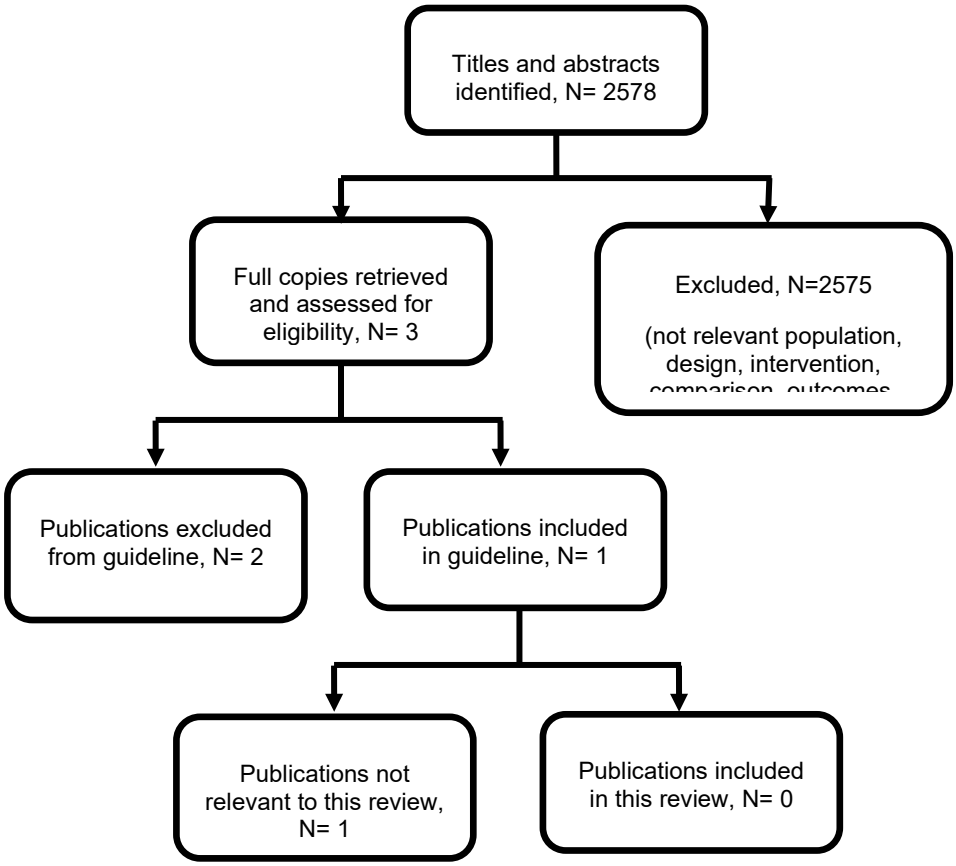
[1]*Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2]*<150 events*

Appendix G Economic evidence study selection

Study selection for: What factors are associated with an increased risk of 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 2: Study selection flow chart



Appendix H Economic evidence tables

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

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

Appendix I Economic model

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

No economic analysis was conducted for this review question.

Appendix J Excluded studies

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

Excluded prognostic studies

Table 4: Excluded studies and reasons for their exclusion

Study	Reason
Cao, S, Yang, C, Gan, Y et al. (2015) The Health Effects of Passive Smoking: An Overview of Systematic Reviews Based on Observational Epidemiological Evidence. PLoS ONE 10(10): e0139907	- Study design not of interest for review *An overview of systematic reviews*
Close, R.M, Ejidokun, O.O, Verlander, N.Q et al. (2011) Early diagnosis model for meningitis supports public health decision making. Journal of Infection 63(1): 32-38	- Outcomes not of interest for review *Data only available on age, sex, and winter season (population-level risk factors)*
Domingo, P, Muniz-Diaz, E, Baraldes, M. A et al. (2002) Associations between Fc gamma receptor IIA polymorphisms and the risk and prognosis of meningococcal disease. American journal of medicine 112(1): 19-25	- Study design not of interest for review *Case-control study*
Dubey, Himanshu, Oster, Philipp, Fazeli, Mir Sohail et al. (2022) Risk Factors for Contracting Invasive Meningococcal Disease and Related Mortality: A Systematic Literature Review and Meta-analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 119: 1-9	- Systematic review - included studies failed to meet inclusion criteria
Harrison, L. H, Kreiner, C. J, Shutt, K. A et al. (2008) Risk factors for meningococcal disease in students in grades 9-12. Pediatric Infectious Disease Journal 27(3): 193-199	- Study design not of interest for review *Case series*
Honish, L, Soskolne, C.L, Senthilselvan, A et al. (2008) Modifiable risk factors for invasive meningococcal disease during an Edmonton, Alberta outbreak, 1999-2002. Canadian Journal of Public Health 99(1): 46-51	- Study design not of interest for review *Case-control study*
Murray, R. L; Britton, J; Leonardi-Bee, J. (2012) Second hand smoke exposure and the risk of invasive meningococcal disease in children:	- Study design not of interest for review *Case-control and cohort studies included in the*

Study	Reason
systematic review and meta-analysis. BMC Public Health 12: 1062	*systematic review. Studies included in this review were assessed for potential inclusion*
Nelson, S. J, Charlett, A, Orr, H. J et al. (2001) Risk factors for meningococcal disease in university halls of residence. Epidemiology and Infection 126(2): 211-217	- Study design not of interest for review *Retrospective ecological study*
Nielsen, H.E, Andersen, E.A, Andersen, J et al. (2001) Diagnostic assessment of haemorrhagic rash and fever. Archives of Disease in Childhood 85(2): 160-165	- Outcomes not of interest for review *Signs and symptoms rather than risk factors for diagnosis*
Norheim, G, Sadarangani, M, Omar, O et al. (2014) Association between population prevalence of smoking and incidence of meningococcal disease in Norway, Sweden, Denmark and the Netherlands between 1975 and 2009: a population-based time series analysis. BMJ Open 4(2): e003312	- Study design not of interest for review *Population based time series*
Olcen, P, Kjellander, J, Danielsson, D et al. (1981) Epidemiology of Neisseria meningitidis: Prevalence and symptoms from the upper respiratory tract in family members to patients with meningococcal disease. Scandinavian Journal of Infectious Diseases 13(2): 105-109	- Study design not of interest for review *Neisseria meningitidis carrier rate*
Smith, I, Bjoornevik, A.T, Augland, I.M.B et al. (2006) Variations in case fatality and fatality risk factors of meningococcal disease in Western Norway, 1985-2002. Epidemiology and Infection 134(1): 103-110	- Outcomes not of interest for review *Risk factors for death or sequelae with meningococcal disease*
Spyromitrou-Xioufi, P; Tsirigotaki, M; Ladomenou, F. (2020) Risk factors for meningococcal disease in children and adolescents: a systematic review and META-analysis. European Journal of Pediatrics 179(7): 1017-1027	- Study design not of interest for review *Majority of studies case-control . Studies included in this review were assessed for potential inclusion*
Stephens, D. S, Hajjeh, R. A, Baughman, W. S et al. (1995) Sporadic meningococcal disease in adults: Results of a 5-year population- based study. Annals of Internal Medicine 123(12): 937-940	- Comparison not of interest for review *Comparison signs and symptoms of different serogroups*

Excluded economic studies

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

Appendix K Research recommendations – full details

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

No research recommendations were made for this review question.