National Institute for Health and Care Excellence

Draft for consultation

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

[I2] Evidence review for long-term complications and follow-up for meningococcal disease

NICE guideline number tbc

Evidence review underpinning recommendations 1.12.1 to 1.12.10, and 1.13.1 to 1.13.10 in the NICE guideline

September 2023

Draft for consultation

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

Contents

Long-term complications and follow-up for meningococcal disease

Review question

What is the risk of long-term complications in 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. Despite effective therapy, a range of long-term complications can occur in children of all ages and in adults.

The aim of this review is to evaluate the risk of long-term complications following meningococcal disease to inform patients, parents, carers and health care practitioners.

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) with confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis).
Prognostic factors	Meningococcal disease
Comparison	No meningococcal disease (healthy cohort)
Outcome	**Critical** Population: adults, infants and children Proportion of those with the following complications (measured after resolution of the acute phase of illness*) • All-cause mortality • Disorders of consciousness (for example, minimally conscious state, persistent vegetative state) • Long-term motor deficits • Long-term cognitive deficits • Long-term behavioural deficits • Long-term psychological impairment • Any hearing impairment • Any visual impairment • Diagnosis of epilepsy • Skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention • Speech and language disorder Population: adults • Headache Population: infants and children • Moderate developmental delay • Severe developmental delay • Growth plate abnormality

- Hydrocephalus with a shunt

Important
None

*For infants and children below school-age, cognitive deficits, behavioural deficits, and speech and language disorder will be assessed at school-age or later.

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

Six studies were included for this review, 4 prospective cohort studies (Borg 2009, Fellick 2001, Vermunt 2011, Viner 2012), and 2 retrospective cohort studies (Sander 1984, Shen 2021).

Studies with univariate analyses were included in this review because only 2 studies (Borg 2009, Viner 2012) reported multivariate analyses and did not cover all relevant age groups or report all outcomes of interest.

The included studies are summarised in Table 2.

One study reported all-cause mortality (Shen 2021); 1 study reported long-term motor deficits (Fellick 2001), 2 studies reported long-term cognitive deficits (Sander 1984, Viner 2012), 3 studies reported long-term behavioural deficits (Fellick 2001, Vermunt 2011, Viner 2012), and 3 studies reported long-term psychological impairment (Borg 2009, Sander 1984, Viner 2012). Three studies reported any hearing impairment (Fellick 2001, Sander 1984, Viner 2012), and 2 studies reported any visual impairment (Sander 1984, Viner 2012). Two studies reported diagnosis of epilepsy (Fellick 2001, Viner 2012), 1 study reported skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention (Viner 2012), 1 study reported speech and language disorder (Viner 2012), and 1 study reported headache (Sander 1984).

All studies reported meningococcal disease as potential risk factor.

Three studies were conducted in children (Fellick 2001, Vermunt 2011, Viner 2012), and 1 study included participants aged 15 to 19 years who were classified as children (Borg 2009). Two studies were conducted in adults (Sander 1984, Shen 2021).

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.

1 Summary of included studies

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

3 **Table 2: Summary of included studies**

Study	Population	Risk factor	Outcomes	Comments
Borg 2009 Prospective cohort study UK	N=202 Participants aged 15 to 19 years who had invasive meningococcal disease, compared against age- and sex-matched controls Age in years at follow-up (mean; SD): 19 (2)	• Meningococcal disease (both meningitis and septicaemia; meningitis alone; septicaemia alone)	• Long-term psychological impairment	Follow-up: 18-36 months 33% of participants with meningococcal disease had meningitis alone, and data on disease type was missing for 1% of participants Age- and sex-matched controls were used, and the analysis was adjusted for life stress, but unclear if there was residual confounding
Fellick 2001 Prospective cohort study UK	N=230 Children who had meningococcal disease, compared against age- and sex-matched controls Age in months at follow-up (median; IQR): 133 (121-161)	• Meningococcal disease (meningococcal meningitis; meningococcal septicaemia; mixed disease)	• Long-term motor deficits • Long term behavioural deficits • Any hearing impairment • Diagnosis of epilepsy	Follow-up: Not reported (Participants had meningococcal disease between 1988 and 1990, and assessments took place between 1998 and 2000. Therefore, follow-up could be up to 12 years) 16 participants (14% of meningococcal disease group) had meningitis alone Age- and sex-matched controls were used, and no significant

Study	Population	Risk factor	Outcomes	Comments
				differences in baseline characteristics between groups
Sander 1984 Retrospective cohort study Norway	N=135 Male survivors of systemic meningococcal disease during military service, compared against soldiers who were about the same age as the patients Age in years at time of military service (mean; SEM): Meningococcal disease: 21 (0.14) No meningococcal disease: 20 (0.13)	• Meningococcal disease (meningococcal meningitis with or without septicaemia; septicaemia only)	• Long-term cognitive deficits • Long-term psychological impairment • Any hearing impairment • Any visual impairment • Headache	Follow-up: 3-15 years No attempts were made to control for confounders identified (age)
Shen 2021 Retrospective cohort study France	N=14128 Patients hospitalised with invasive meningococcal disease, compared against age- and sex-matched controls Age in years at diagnosis (median; IQR): Meningococcal disease: 21 (4-52)	• Meningococcal disease	• All-cause mortality	Follow-up in years (mean; SD): 3 (2) Age- and sex-matched controls were used, but unclear if there was residual confounding and limited information regarding baseline characteristics provided
Vermunt 2011 Prospective cohort study	N=2089 Survivors of meningococcal septic shock,	• Meningococcal disease	• Long-term behavioural deficits	Follow-up (mean): 13 years Patients and

Study	Population	Risk factor	Outcomes	Comments
Netherlands	compared against normative Dutch sample Age in years at diagnosis (median; range): 9 (0-17)			reference group have comparable age ranges, but limited information regarding baseline characteristics provided, and unclear if there was any residual confounding
Viner 2012 Prospective cohort study UK	N=573 Children who had serogroup B meningococcal disease, compared against age- and sex-matched controls Age in years at follow-up (mean; SD): 7 (3)	• Meningococcal disease (septicaemia alone; meningitis alone; both meningitis and septicaemia; other)	• Long-term cognitive deficits • Long-term behavioural deficits • Long-term psychological impairment • Any hearing impairment • Any visual impairment • Diagnosis of epilepsy • Skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention • Speech and language disorder	Follow-up (median): 4 years Age- and sex-matched controls were used, and matched analysis was conducted for cognitive deficits, behavioural deficits, psychological impairment (when assessed with strengths and difficulties questionnaire or DAWBA and anxiety disorders, specific phobias, and autistic spectrum disorder), sensorineural hearing loss, epilepsy, and communication disability. However, no matched analysis was conducted for the remaining psychological impairment outcomes, visual impairment, skin, soft tissue or orthopaedic

Study	Population	Risk factor	Outcomes	Comments
				complications, or absent or minimum communication.

ADHD: attention deficit hyperactivity disorder; DAWBA: The Development and Wellbeing Assessment; IQ: intelligence quotient; IQR: interquartile range; SD: standard deviation; SEM: standard error of the mean

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 very low quality due to high or moderate risk of bias in some of the domains of the QUIPs checklist, and imprecision due to small number of events. The evidence was stratified by age; however, there was insufficient evidence to stratify according to receipt of critical care or type of meningococcal disease. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

Overall, the evidence was seriously or very seriously imprecise, so cannot be taken as definitive evidence of presence or absence of association.

All-cause mortality

In adults, evidence showed a strong association between meningococcal disease and all-cause mortality.

Motor deficits

In children, evidence showed a strong association between meningococcal disease and motor problems (assessed with the Movement ABC scale).

Cognitive and developmental complications

In children, there was a strong association between meningococcal disease and long-term cognitive deficits when measured as an intelligence quotient (IQ) less than 85. There was no evidence of an increased risk of cognitive deficit when measured as an IQ less than 70.

In children, there was a strong association between meningococcal disease and memory problems.

In children, there was some evidence for a possible association between meningococcal disease and substantial communication disability (90% CI 1.21 to 25.97), however, this was not statistically significant (when using standard 95% CI) and there was no evidence for an increased risk of absent/minimum communication.

In adults, there was a strong association between meningococcal disease and concentration problems, impaired memory, and headache.

Behavioural and psychological complications

In children, evidence showed a strong association between meningococcal disease and a possible attention deficit hyperactivity disorder (ADHD) diagnosis assessed using parent and

teacher DSM-IV questionnaire scores (Connor's Rating Scales). There was also a strong association between meningococcal disease and ADHD when assessed using parent, self-report, and teacher-rated DSM-IV questionnaire scores (Development and Well-being Assessment [DAWBA]). However, there was no evidence of an increased risk of a formal ADHD diagnosis associated with meningococcal disease.

In children, there was a strong association between meningococcal disease and conduct disorder. There was no evidence of an increased risk associated with meningococcal disease for problem behaviour (assessed with the Adult Self Report scale), or oppositional defiant disorder.

In children, there was a strong association between meningococcal disease and long-term mental health problems (assessed using the Strengths and Difficulties Questionnaire), and an increased risk of having any mental disorder (at ≥50% or ≥70% probabilities using DSM-IV criteria assessed with the DAWBA). The evidence showed a strong association between meningococcal disease and depressive symptoms when measured with Beck Depression Inventory-II scale. However, there was no evidence for an increased risk of depression associated with meningococcal disease when assessed using parent, self-report, and teacher-rated DSM-IV questionnaire scores (DAWBA). There was possibly an association between meningococcal disease and social phobia (90% CI 1.17 to 137.95), separation anxiety disorder (90% CI 1.03 to 14.74) and autism spectrum disorder (90% CI 1.17 to 18.09), however, these associations were not statistically significant (using the standard 95% CI). There was no evidence of an increased risk associated with meningococcal disease for agoraphobia, specific phobias, panic disorder, generalised anxiety disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), or eating disorder.

In adults, there was a strong association between meningococcal disease and irritability.

Hearing impairment

In children, evidence showed a strong association between meningococcal disease and profound, or moderately severe, bilateral sensorineural hearing loss, and any sensorineural hearing loss. There was possibly an association between meningococcal disease and any hearing impairment (90% CI 1.19 to 8.56), however, this was not statistically significant (using standard 95% CI).

In adults, there was some evidence of a possible association between meningococcal disease and hearing impairment when reported as noise in the ear or tinnitus (90% CI 1.42 to 165.33), however, this was not statistically significant (using standard 95% CI), and there was no evidence of an increased risk of reduced hearing.

Visual impairment

In children, there was no evidence of an increased risk associated with meningococcal disease of being registered blind.

In adults, there was no evidence of an association between meningococcal disease and visual disturbance.

Epilepsy

In children, there was possibly an association between meningococcal disease and epilepsy when reported as seizures of any type (90% CI 1.13 to 42.08), however, this was not statistically significant (using the standard 95% CI). There was no evidence of an increased risk of a diagnosis of epilepsy associated with meningococcal disease.

Skin, soft tissue or orthopaedic complications

In children, there was a strong association between meningococcal disease and amputation with substantial disability.

There were a number of outcomes in the protocol that were not reported by any studies, including disorders of consciousness, growth plate abnormality, and hydrocephalus with a shunt. No evidence was available for babies.

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because this topic was an epidemiological review which does not involve a comparison of competing courses of action. Although the review could lead to recommendations for follow-up with opportunity costs it was not thought that the recommendations would substantially alter current practice and it was not anticipated that there would be the comparative effectiveness data to formulate a meaningful economic analysis.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Meningococcal disease is associated with high rates of mortality and morbidity. All-cause mortality and disorders of consciousness were prioritised as critical outcomes for all age groups because of the severity of these outcomes. Similarly, long-term motor deficits; long-term cognitive deficits; long-term behavioural deficits; long-term psychological impairment; any hearing impairment; any visual impairment; diagnosis of epilepsy; skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention; and speech and language disorder were prioritised as critical outcomes in all age groups because of the potential long-term impact of these outcomes in terms of functional impairment and quality of life.

As above, moderate developmental delay, severe developmental delay and growth plate abnormality were prioritised as critical outcomes because of the potential impact of these on daily functioning and quality of life; however, they were only included for babies and children because they are not relevant to people who contracted meningococcal disease in adulthood. Headache and hydrocephalus with a shunt were also selected as critical outcomes for adults, and babies and children, respectively, because these outcomes could impact on quality of life and were expected to be commonly reported in studies.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence for all outcomes identified in this review was assessed as being very low quality, and the main reasons for downgrading the evidence were risk of bias (for example, arising from issues

with study participation due to limited information about baseline characteristics, participants lost to follow-up, subjective measurement of outcome, failure to adjust for confounding factors, and insufficient presentation of analytical strategy) and imprecision due to small numbers of events.

No evidence was found that reported disorders of consciousness, growth plate abnormality, or hydrocephalus with a shunt. No evidence was available for babies.

Benefits and harms

The committee considered the evidence for long-term complications associated with meningococcal disease and noted that the quality of the evidence was very low for all outcomes and findings were mostly seriously or very seriously imprecise and should not be taken as definitive evidence of associations (or lack thereof). The committee made recommendations based on the best available evidence and their knowledge and experience. The committee noted that no eligible evidence was identified for babies; however, in the absence of evidence the committee agreed, based on their knowledge and experience, that it was reasonable to extrapolate from the evidence on children and adults as meningococcal disease could have similar impacts for other ages. Because meningococcal disease is very rare in neonates the protocol for this evidence review did not include neonates. However, based on their clinical knowledge and experience, the committee agreed that the recommendations about long-term complications that applied to babies (aged 28 days to 1 year) would also apply to neonates.

The committee agreed, based on the evidence of long-term complications identified in this review, that it is important that people with meningococcal disease should not be discharged from hospital until relevant assessments have taken place and follow up with appropriate services has been arranged so that they receive appropriate care and are not lost to follow-up. The committee were aware that assessment of some complications (for example, hearing loss) can be done in hospital whereas some complications should be assessed in the community (for example, developmental problems). The committee also acknowledged that some people would have profound complications that are apparent at discharge, but some people may not, so appropriate follow-up arrangements will depend on individual circumstances. Therefore, the committee agreed that requirements for follow-up should be identified before discharging people with meningococcal disease from hospital, taking account of the potential for the complications identified in the evidence (which were also in line with clinical knowledge and experience). Although evidence on the association between meningococcal disease and renal morbidities was not considered as part of this review, the committee were aware, based on their knowledge and experience, that some people that are treated in intensive care for sepsis, including meningococcal disease, will have ongoing renal morbidities. The committee felt that not mentioning the risk of renal morbidities in the recommendations would be considered a gap in the guidance and could cause confusion.

The committee discussed that information (including any plans for follow-up) needs to be shared with community teams (the GP, and if appropriate health visitor and school nurse) to best enable professionals to identify and/or manage any complications of meningococcal disease. The committee emphasised that this information should be communicated at or before discharge to avoid any gaps in the provision of care. The committee acknowledged that in their experience people may have queries or concerns and may need support after discharge and recommended that the patient and their family members and carers are informed about their main point of contact.

Evidence showed that meningococcal disease was strongly associated with borderline IQ (although not intellectual disability), memory problems, and may be associated with communication disability in children. Based on this evidence, and their clinical knowledge and experience the committee recommended that preparation for hospital discharge should

include referral to community neurodevelopmental follow-up for neonates, babies, children, and young people.

The committee noted that the evidence showed several behavioural and psychological sequalae following meningococcal disease in children, including increased risk of any mental disorder, symptoms of ADHD, conduct disorder, depressive symptoms, and possible associations with social phobia, separation anxiety disorder and autism spectrum disorder. The committee acknowledged that the evidence for long-term psychological impairments following meningococcal disease in adults was limited, although there was an increased risk of irritability and some evidence in 15–19-year-olds. Based on the evidence and their clinical knowledge and experience, the committee agreed that cognitive and psychological support needs should be considered as part of planning for discharge for people with meningococcal disease and a referral to psychological services should be made where needs are identified.

The evidence for epilepsy as a long-term complication of meningococcal disease was mixed. There was some evidence for an association between meningococcal disease in children and seizures of any type. However, there was no evidence of an increased risk associated with meningococcal disease for a diagnosis of epilepsy. In the committee's experience, although some people may need long-term anti-epileptic drugs following meningococcal disease, about 60 to 70% of people may not, as seizures may be a transient effect of the acute phase of illness, rather than an ongoing issue related to, for example, a diagnosis of epilepsy. Therefore, the committee were concerned about unnecessary long-term use of anti-epileptic drugs and agreed that people who are on anti-epileptic drugs during acute illness and at hospital discharge should have the requirement for such medication reviewed 3 months after hospital discharge by appropriate specialists. The committee recommended a 3-month follow-up period based on consensus opinion that this would give sufficient time to see if seizures were a transient effect of the illness.

The evidence showed a strong association between diagnosis of meningococcal disease in children and amputation with substantial disability. This also corresponded with the clinical knowledge and experience of the committee and with their awareness of evidence from non-comparative cohort studies (for example, Bache 2006), that orthopaedic complications such as amputation, bone growth arrests and growth plate damage are well-established consequences of meningococcal disease. The committee agreed that where acute orthopaedic complications (such as amputation) have been identified, the preparation for discharge should include arranging post-discharge follow-up with an orthopaedic surgeon. The committee discussed that people with orthopaedic complications may be particularly susceptible to psychological issues due to the impact on daily functioning, quality of life, and potentially on appearance. Therefore, the committee agreed that referral to psychological services should be considered for people with orthopaedic complications.

Based on their clinical knowledge and experience, the committee were aware that orthopaedic and skin complications would require ongoing management. For example, people with such complications will need dressing changes and wound care after discharge, that could be a burden for them and their family. Therefore, the committee agreed that ongoing management of orthopaedic and skin complications should be addressed in liaison with tissue viability and community nursing services, and people should be referred to rehabilitation services for assessment as needed.

Whilst there was no evidence of association between meningococcal disease and some of the ways hearing impairment were reported, the weight of the evidence supported an association. As hearing loss can have a serious impact on quality of life, the committee felt that hearing assessment should be done as soon as possible and recommended a formal audiological assessment within 4 weeks of being fit to test, ideally before discharge. The committee noted that for neonates this should be a detailed hearing test using auditory evoked brain responses rather than the newborn rapid otoacoustic emission screen. Based on their clinical knowledge and experience, the committee were aware that if cochlear

implants are needed, they should be inserted within 6 months to reduce the likelihood of cochlear ossification (which would impact feasibility of cochlear implants), and this highlighted the importance of prompt hearing assessment. As the presence and degree of hearing loss needs to be established before referral for cochlear implants can be considered, any delays associated with hearing assessment would also cause delays to assessment for cochlear implants. For the same reasons, the committee agreed that once severe or profound deafness has been identified, it is important that assessment for cochlear implants happens urgently.

In addition to the actions discussed above that should occur before people are discharged from hospital, the committee agreed that people should be followed up 4 to 6 weeks after discharge to discuss any complications associated with meningococcal disease and to ensure appropriate referrals are made and potential complications are not missed. For neonates, babies, children and young people, this review should be undertaken by a paediatrician, whereas for adults the committee did not specify who should undertake it as there could be variation in practice. The committee agreed this review should cover all possible associated morbidities, specifically the results of hearing test and hearing loss, damage to bones and joints, skin complications (including scarring from necrosis), psychosocial problems, and neurological and developmental problems as meningococcal disease had associations with these complications. However, the committee acknowledged that for adults the results of hearing tests may not be available at 4 to 6 weeks after discharge as, having a cold, for example, could make someone not fit to test and then the results of their hearing test could be delayed. The committee agreed that the overall review should not be delayed if the results of hearing tests are unavailable, due to the importance of identifying and addressing any other complications early, but that the results of hearing tests should be reviewed as soon as they are available. The committee agreed that neurological and developmental problems in neonates, babies, children, and young people should be reviewed in liaison with community child development services which is in line with routine practice, and neurological problems and care needs should be reviewed in adults.

For neonates, babies, children and young people, the committee agreed that long-term monitoring is required to identify latent or evolving sequelae (for example, neurodevelopmental, orthopaedic, psychosocial, behavioural, and educational issues). The committee agreed that babies should be reviewed 1 year after discharge to assess for the complications identified in the evidence (neurodevelopmental, orthopaedic, sensory, and psychosocial); and community child development services should follow-up and assess babies, children, and young people for neurodevelopmental complications for at least 2 years after discharge, and refer to relevant services (for example, neurodisability services may be needed based on severity of complications) and agree follow-up as appropriate. The committee recommended that healthcare professionals (including school nurses, health visitors, and GPs) should be alert for late-onset complications of meningococcal disease and be aware that complications may not appear until key transition points (for example, starting nursery, primary school, or secondary school). The committee agreed that this recommendation would provide an important safety net to minimise the risk of long-term complications being missed if they occur after the recommended period for formal follow-up. The committee discussed that remaining vigilant to the possibility of late-onset orthopaedic effects of meningococcal disease was particularly important because, in their experience, these complications can often present several years after acute illness. They were also aware of studies reporting presentation of such complications up to 9 or 10 years after the initial illness (Bache 2006, Belthur 2003).

Although the protocol for this review did not specifically include educational outcomes in those with meningococcal disease, associated complications were included (cognitive and developmental complications) and the committee discussed that the impact on education may not always be apparent, as it may not necessarily be that children and younger people are underachieving, rather that they could be achieving more if they had specific support. Therefore, the committee made a consensus recommendation that professionals in

education and early years settings should be aware of the potential impact of meningococcal disease on educational outcomes, and that records of past episodes of meningococcal disease should be kept and the need for educational support should be reviewed regularly in those who have had meningococcal disease (even when there have been no known complications). Similarly, the committee agreed that people in work or education may require a phased return and/or referral for assessments for special needs (including driving) by appropriate services if complications are present.

The committee acknowledged the strong association between meningococcal disease and all-cause mortality in adults but agreed that this was not something that could be addressed directly by a recommendation. However, in their experience, it is likely that higher rates of all-cause mortality would be secondary to some of the other complications identified in this review; therefore, the recommendations made will help to address the increased risk observed.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee made a cross reference to the NICE guideline on rehabilitation after critical illness in adults (2009) to address the relief of symptoms and to restore normal functions in people who develop long-term complications of meningococcal disease.

Given the evidence on the long-term complications resulting from meningococcal disease, the committee made recommendations to ensure that the relevant assessments were undertaken in order to deliver appropriate care and avoid people being lost to follow-up. The committee reasoned that this could avert downstream costs and adverse impacts on health-related quality of life and educational attainment.

The committee considered that it was cost-effective to follow-up and assess babies, children, and young people for neurological complications for at least 2 years after discharge as such complications may not be apparent before then. The committee reasoned that early recognition and management was important to mitigate health and educational harms and that follow-up to achieve this would represent a good use of NHS resources.

Some of the recommendations made by the committee relate to vigilance and awareness about the possibility of late-onset complications which may impact on health-related quality of life or education. Whilst these recommendations have a negligible resource impact the committee believed they help to promote better recognition and management of people with meningococcal disease who do develop such late-onset complications.

No significant resource impact is anticipated from these recommendations which the committee felt are in line with current NHS practice.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.12.1 to 1.12.10, and 1.13.1 to 1.13.10. Other evidence supporting these recommendations can be found in evidence reviews on long-term complications and follow-up for bacterial meningitis (see evidence review I1) and support for confirmed meningitis or meningococcal disease (see evidence review K4).

References – included studies

Prognostic

Borg 2009

Borg, J., Christie, D., Coen, P. G. et al. (2009). Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study, Pediatrics 123(3), e502-e509

Fellick 2001

Fellick, J. M., Sills, J. A., Marzouk, O. et al. (2001). Neurodevelopmental outcome in meningococcal disease: a case-control study, Archives of Disease in Childhood 85(1), 6-11

Sander 1984

Sander, J., Bay, D., Gedde-Dahl, T. W. et al. (1984). Late sequelae after meningococcal disease. a controlled study in young men, NIPH Annals 7(1), 3-11

Shen 2021

Shen, J., Bouee, S., Aris, E. et al. (2021). Long-term mortality and state financial support in invasive meningococcal disease-real-world data analysis using the French National Claims Database (SNIIRAM), Infectious Diseases & Therapy 17, 17

Vermunt 2011

Vermunt, L. C., Buysse, C. M., Joosten, K. F. et al. (2011). Survivors of septic shock caused by Neisseria meningitidis in childhood: psychosocial outcomes in young adulthood, Pediatric Critical Care Medicine 12(6), e302-e309

Viner 2012

Viner, R. M., Booy, R., Johnson, H. et al. (2012). Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study, Lancet Neurology 11(9), 774-783

Economic

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

Other

Bache 2006

Bache, C. E. and Torode, I. P. (2006). Orthopaedic sequelae of meningococcal septicemia, Journal of Pediatric Orthopedics 26(1), 135-139

Belthur 2003

Belthur, M. V., Bradish, C. F., Gibbons, P. J. (2003). Late orthopaedic sequelae following meningococcal septicaemia, The Journal of Bone and Joint Surgery, 87, B:236-240

NICE 2018

National Institute for Health and Care Excellence (2018). Post-traumatic stress disorder. Available at: https://www.nice.org.uk/guidance/ng116 [Accessed 03/02/2023]

Appendices

Appendix A Review protocols

Review protocol for review question: What is the risk of long-term complications in meningococcal disease?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021281472
Review title	Long-term complications and follow-up for meningococcal disease
Review question	What is the risk of long-term complications in meningococcal disease?
Objective	To determine the risk of long-term complications in meningococcal disease
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • MEDLINE & MEDLINE In-Process • Web of Science (WoS) Searches will be restricted by: • OECD geographic study filter • Prognostic study filter • English language studies • Human studies • Date: 1980 onwards as currently used antibiotics were not in common usage prior to this date Other searches:

Field	Content
	• Inclusion lists of systematic reviews • Reference lists of included studies • Forward and backward citation searches of key studies The full search strategies will be published in the final review.
Condition or domain being studied	Long-term complications of meningococcal disease
Population	Inclusion: All adults, young people, children and babies (excluding neonates) with 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.
Intervention/Exposure/Test	Meningococcal disease
Comparator/Reference standard/Confounding factors	No meningococcal disease (healthy cohort)
Types of study to be included	Include published full text papers: • Systematic reviews of cohort studies or case-control studies • Cohort studies (prospective or retrospective) • Case-control studies Studies with univariate analyses will only be included if there are insufficient studies with multivariate analyses for a given long-term complication. 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)
Other exclusion criteria	Country limitations: limit studies to OECD high-income countries

Field	Content
	Date limitations: 1980 (1980 as currently used antibiotics were not in common usage prior to this date). Language limitations: studies published not in English-language Conference abstracts will not be considered.
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)	Population: adults Proportion of those with the following complications (measured after resolution of the acute phase of illness): • All-cause mortality • Disorders of consciousness (e.g., minimally conscious state, persistent vegetative state) • Long-term motor deficits • Long-term cognitive deficits • Long-term behavioural deficits • Long-term psychological impairment • Any hearing impairment • Any visual impairment • Diagnosis of epilepsy • Skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention • Speech and language disorder • Headache Population: infants and children Proportion of those with the following complications (measured after resolution of the acute phase of illness*): • All-cause mortality • Disorders of consciousness (e.g., minimally conscious state, persistent vegetative state) • Long-term motor deficits

Field	Content
	• Long-term cognitive deficits • Long-term behavioural deficits • Long-term psychological impairment • Any hearing impairment • Any visual impairment • Moderate developmental delay • Severe developmental delay • Diagnosis of epilepsy • Skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention • Growth plate abnormality • Speech and language disorder • Hydrocephalus with a shunt *For infants and children below school-age, cognitive, behavioural deficits, and speech and language disorder will be assessed at school-age or later.
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. 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 complications, 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

Field	Content
	• Quality in Prognostic Studies (QUIPS) tool for prognostic studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same factors 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:** Decision making thresholds • Strong association: <0.5 and >2.00 • Moderate association: <0.80 and >1.25 • Small association: any statistically significant association • No association: no statistically significant association
Analysis of sub-groups	Evidence will be stratified by: **Age:** • Younger and older Infants: >28 days to ≤1 year of age • Children: >1 year to <18* years of age • Adults: ≥18* years of age

<table>
<tr><th>Field</th><th>Content</th></tr>
<tr><td></td><td>Meningococcal disease:
• Meningococcal septicaemia alone
• Meningococcal septicaemia and meningitis
• Non-specific meningococcal disease
Receipt of critical care:
• Received critical care (defined as level 2 (high dependency) or level 3 (ICU))
• Did not receive critical care (defined as level 2 (high dependency) or level 3 (ICU))

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</td></tr>
<tr><td>Type and method of review</td><td><table>
<tr><td>☐</td><td>Intervention</td></tr>
<tr><td>☐</td><td>Diagnostic</td></tr>
<tr><td>☒</td><td>Prognostic</td></tr>
<tr><td>☐</td><td>Qualitative</td></tr>
<tr><td>☐</td><td>Epidemiologic</td></tr>
<tr><td>☐</td><td>Service Delivery</td></tr>
<tr><td>☐</td><td>Other (please specify)</td></tr>
</table></td></tr>
<tr><td>Language</td><td>English</td></tr>
<tr><td>Country</td><td>England</td></tr>
<tr><td>Anticipated or actual start date</td><td>20/09/2021</td></tr>
<tr><td>Anticipated completion date</td><td>07/12/2023</td></tr>
<tr><td>Stage of review at time of this submission</td><td><table>
<tr><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
</table></td></tr>
</table>

Field	Content		
	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 (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		

Field	Content	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021281472	
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, meningococcal disease, long-term complications, systematic review	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ICU: intensive care unit; MEDLINE: Medical Literature Analysis and Retrieval System Online; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; QUIPS: Quality in Prognosis Studies; ROBIS: risk of bias in systematic reviews; WoS: Web of Science

Appendix B Literature search strategies

Literature search strategies for review question: What is the risk of long-term complications in meningococcal disease?

Clinical Search

This was a combined search to cover both this review (I2) and evidence review I1 on long-term complications and follow-up for bacterial meningitis.

Database (s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to December 17, 2021
Date of last search: 20 December 21

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/ or exp Neisseria Meningitidis/
2	((bacter* or infect*) adj3 (mening* or leptomening* or subarachnoid space?)).ti,ab.
3	((e coli or escherichia coli or h?emophilus or hib or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or streptococc* or GBS or s pneumon*) adj3 (septic* or sepsis* or bacter?emi? or infect*)).ti,ab.
4	(meningit* or mening?encephalitis* or mening* encephalitis*).ti,ab.
5	(Neisseria* mening* or n mening*).ti,ab.
6	or/1-5
7	Meningococcal Infections/
8	meningococc*.ti,ab.
9	or/7-8
10	exp Hearing Loss/ or exp Epilepsy/ or Adolescent Behavior/ or Mobility Limitation/ or exp Hydrocephalus/ or exp Neurologic Manifestations/ or Purpura/ or Consciousness/ or exp Educational Status/ or Academic Success/ or Headache/ or exp Mental Disorders/
11	(((vision* or visual or eyesight* or sight* or hear*) adj3 (disabilit* or disorder* or dysfunction* or impair* or loss*)) or deaf* or blind*).ti,ab.
12	(headache* or migraine* or cephalgi* or cephalalgi*).ti,ab.
13	(speech* adj2 language* adj2 (abnormal* or deficit* or difficult* or disorder* or delay* or dysfunction* or impair* or problem* or development* or outcome*)).ti,ab.
14	(epileps* or seizure*).ti,ab.
15	(development* adj3 delay*).ti,ab.
16	((academic* or education* or school*) adj2 (achieve* or attain* or success* or performance*)).ti,ab.
17	(((post traumatic or posttraumatic) adj2 (stress* or neuros*)) or PTSD).ti,ab.
18	((hydrocephalus or cerebrospinal fluid) adj3 shunt*).ti,ab.
19	((psycholog* or psychiat* or neuro psycholog* or neuropsycholog*) adj2 (outcome* or function* or morbidit* or distress or adjustment*)).ti,ab.
20	((cogniti* or neuro cogniti* or neurocogniti* or learning or behavio?r* or intellec* or functional* or motor* or psychomotor* or communicat*) adj2 (abnormal* or deficit* or difficult* or disabilit* or disorder* or dysfunction* or impair* or problem*)).ti,ab.
21	(purpur* or scar? or scarring).ti,ab.
22	sequela*.ti,ab.
23	consciousness.ti,ab.
24	((minimal* or impair* or deteriorat*) adj conscious* state*).ti,ab.
25	vegetativ* state*.ti,ab.
26	(mortalit* adj (rate? or score?)).ti,ab.
27	all cause mortalit*.ti,ab.
28	df.fs.
29	or/10-28
30	Growth Plate/ or Bone Diseases, Developmental/ or Soft Tissue Infections/ or exp Skin Diseases/ or exp Skin/pa or exp Tissues/pa
31	(growth plate* or phys#s or physeal or epiphys*).ti,ab.
32	((musculoskeletal or skelet* or orthop?ed* or bone* or osseous or limb*) adj4 (lesion* or complicat* or damag* or impair* or abnormal* or morbid* or problem* or necros#s or amputat* or change* or infect* or disease* or length* or gangrene* or deficien* or defect* or salvage or disabilit*)).ti,ab.
33	((skin or tissue* or epithelium or membrane* or muscle* or derma* or dermis or cutaneous or cutis) adj4 (lesion* or complicat* or damag* or impair* or abnormal* or morbid* or problem* or necros#s or eruption* or vasculitis or bleed* or mottl* or blotch* or change* or infect* or disease*)).ti,ab.
34	(rash* or petechia*).ti,ab.
35	or/30-34
36	29 or 35
37	Follow-Up Studies/ or Population Surveillance/ or Risk Factors/ or Risk Assessment/ or Incidence/ or Prevalence/ or Prognosis/ or Survivors/ or Sickness Impact Profile/ or "Quality of Life"/
38	(follow up* or followup* or risk* or incidence or prevalence or prognos?s or survivor*).ti,ab.
39	screening.ti.

#	Searches
40	or/37-39
41	6 and 29 and 40
42	9 and 36 and 40
43	41 or 42
44	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or (animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
45	43 not 44
46	limit 45 to English language
47	limit 46 to yr="1980 -Current"
48	afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/
49	"Organisation for Economic Co-Operation and Development"/
50	australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/
51	European Union/
52	Developed Countries/
53	or/49-52
54	48 not 53
55	47 not 54

1 **Database (s): Wiley Cochrane** Issue 12 of 12, December 2021
2 Date of last search: 20 December 2021

#	Search
#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: [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 h?emophilus or hib or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or streptococc* or GBS or s pneumon*) NEAR/3 (septic* or sepsis* or bacter?emi? or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or mening* encephalitis*):ti,ab,kw
#13	(Neisseria* mening* or n mening*):ti,ab,kw
#14	{or #1-#13}
#15	MeSH descriptor: [Meningococcal Infections] this term only
#16	meningococc*:ti,ab,kw
#17	#15 OR #16
#18	MeSH descriptor: [Hearing Loss] explode all trees
#19	MeSH descriptor: [Epilepsy] explode all trees
#20	MeSH descriptor: [Adolescent Behavior] this term only
#21	MeSH descriptor: [Mobility Limitation] this term only
#22	MeSH descriptor: [Hydrocephalus] explode all trees
#23	MeSH descriptor: [Neurologic Manifestations] explode all trees
#24	MeSH descriptor: [Purpura] this term only
#25	MeSH descriptor: [Consciousness] this term only

#	Search
#26	MeSH descriptor: [Consciousness Disorders] this term only
#27	MeSH descriptor: [Educational Status] explode all trees
#28	MeSH descriptor: [Academic Success] this term only
#29	MeSH descriptor: [Headache] this term only
#30	MeSH descriptor: [Mental Disorders] explode all trees
#31	(((vision* or visual or eyesight* or sight* or hear*) NEAR/3 (disabilit* or disorder* or dysfunction* or impair* or loss*)) or deaf* or blind*):ti,ab,kw
#32	(headache* or migraine* or cephalgi* or cephalalgi*):ti,ab,kw
#33	(speech* NEAR/2 language* NEAR/2 (abnormal* or deficit* or difficult* or disorder* or delay* or dysfunction* or impair* or problem* or development* or outcome*)):ti,ab,kw
#34	(epileps* or seizure*):ti,ab,kw
#35	(development* NEAR/3 delay*):ti,ab,kw
#36	((academic* or education* or school*) NEAR/2 (achieve* or attain* or success* or performance*)):ti,ab,kw
#37	(((post traumatic or posttraumatic) NEAR/2 (stress* or neuros*)) or PTSD):ti,ab,kw
#38	((hydrocephalus or cerebrospinal fluid) near/3 shunt*):ti,ab,kw
#39	((psycholog* or psychiat* or neuro psycholog* or neuropsycholog*) NEAR/2 (outcome* or function* or morbidit* or distress or adjustment*)):ti,ab,kw
#40	((cogniti* or neuro cogniti* or neurocogniti* or learning or behavio?r* or intellec* or functional* or motor* or psychomotor* or communicat*) NEAR/2 (abnormal* or deficit* or difficult* or disabilit* or disorder* or dysfunction* or impair* or problem*)):ti,ab,kw
#41	(purpur* or scar? or scarring):ti,ab,kw
#42	sequela*:ti,ab,kw
#43	consciousness:ti,ab,kw
#44	((minimal* or impair* or deteriorat*) NEAR conscious* state*):ti,ab,kw
#45	vegetativ* state*:ti,ab,kw
#46	(mortalit* NEAR (rate? or score?)):ti,ab,kw
#47	all cause mortalit*:ti,ab,kw
#48	{or #18-#47}
#49	MeSH descriptor: [Growth Plate] this term only
#50	MeSH descriptor: [Bone Diseases, Developmental] this term only
#51	MeSH descriptor: [Soft Tissue Infections] this term only
#52	MeSH descriptor: [Skin Diseases] explode all trees
#53	MeSH descriptor: [Skin] explode all trees and with qualifier(s): [pathology - PA]
#54	MeSH descriptor: [Tissues] explode all trees and with qualifier(s): [pathology - PA]
#55	(growth plate* or phys#s or physeal or epiphys*):ti,ab,kw
#56	((musculoskeletal or skelet* or orthop?ed* or bone* or osseous or limb*) NEAR/4 (lesion* or complicat* or damag* or impair* or abnormal* or morbid* or problem* or necros#s or amputat* or change* or infect* or disease* or length* or gangrene* or deficien* or defect* or salvage or disabilit*)):ti,ab,kw
#57	((skin or tissue* or epithelium or membrane* or muscle* or derma* or dermis or cutaneous or cutis) NEAR/4 (lesion* or complicat* or damag* or impair* or abnormal* or morbid* or problem* or necros#s or eruption* or vasculitis or bleed* or mottl* or blotch* or change* or infect* or disease*)):ti,ab,kw
#58	(rash* or petechia*):ti,ab,kw
#59	{or #49-#58}
#60	#48 or #59
#61	MeSH descriptor: [Follow-Up Studies] this term only
#62	MeSH descriptor: [Population Surveillance] this term only
#63	MeSH descriptor: [Risk Factors] this term only
#64	MeSH descriptor: [Risk Assessment] this term only
#65	MeSH descriptor: [Incidence] this term only
#66	MeSH descriptor: [Prevalence] this term only
#67	MeSH descriptor: [Prognosis] this term only
#68	MeSH descriptor: [Survivors] this term only
#69	MeSH descriptor: [Sickness Impact Profile] this term only
#70	MeSH descriptor: [Quality of Life] this term only
#71	(follow-up* or followup* or risk* or incidence or prevalence or prognos?s or survivor*):ti,ab,kw
#72	screening:ti
#73	{or #61-#72}
#74	#14 and #48 and #73
#75	#17 and #60 and #73
#76	#74 or #75
#77	conference:pt or (clinicaltrials or trialsearch):so
#78	#76 NOT #77 with Cochrane Library publication date Between Jan 1980 and Dec 2021

1 **Database (s): Ovid Embase** 1974 to 2021 December 17
2 Date of last search: 20 December 21

#	Searches
1	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/ or neisseria meningitidis/
2	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
3	((e coli or escherichia coli or h?emophilus or hib or h influenz* or listeria* or meningococc* or pneumococc* or gram-

#	Searches
	negativ* bacill* or streptococc* or GBS or s pneumon*) adj3 (septic* or sepsis* or bacter?emi? or infect*)).ti,ab.
4	(meningit* or mening?encephalitis* or mening* encephalitis*).ti,ab.
5	(Neisseria* mening* or n mening*).ti,ab.
6	or/1-5
7	Meningococcosis/ or Meningococcemia/
8	meningococc*.ti,ab.
9	or/7-8
10	exp *sensory dysfunction/ or exp *"seizure, epilepsy and convulsion"/ or exp *mental disease/ or exp *"disorders of higher cerebral function"/ or *walking difficulty/ or exp *speech disorder/ or exp *hydrocephalus/ or exp *neurologic disease/ or *purpura/ or *consciousness/ or *consciousness disorder/ or *"speech and language"/ or *educational status/ or *academic achievement/ or *headache/
11	(((vision* or visual or eyesight* or sight* or hear*) adj3 (disabilit* or disorder* or dysfunction* or impair* or loss*)) or deaf* or blind*).ti,ab.
12	(headache* or migraine* or cephalgi* or cephalalgi*).ti,ab.
13	(speech* adj2 language* adj2 (abnormal* or deficit* or difficult* or disorder* or delay* or dysfunction* or impair* or problem* or development* or outcome*)).ti,ab.
14	(epileps* or seizure*).ti,ab.
15	(development* adj3 delay*).ti,ab.
16	((academic* or education* or school*) adj2 (achieve* or attain* or success* or performance*)).ti,ab.
17	(((post traumatic or posttraumatic) adj2 (stress* or neuros*)) or PTSD).ti,ab.
18	((hydrocephalus or cerebrospinal fluid) adj3 shunt*).ti,ab.
19	((psycholog* or psychiat* or neuro psycholog* or neuropsycholog*) adj2 (outcome* or function* or morbidit* or distress or adjustment*)).ti,ab.
20	((cogniti* or neuro cogniti* or neurocogniti* or learning or behavio?r* or intellec* or functional* or motor* or psychomotor* or communicat*) adj2 (abnormal* or deficit* or difficult* or disabilit* or disorder* or dysfunction* or impair* or problem*)).ti,ab.
21	(purpur* or scar? or scarring).ti,ab.
22	sequela*.ti,ab.
23	consciousness.ti,ab.
24	((minimal* or impair* or deteriorat*) adj conscious* state*).ti,ab.
25	vegetativ* state*.ti,ab.
26	(mortalit* adj (rate? or score?)).ti,ab.
27	all cause mortalit*.ti,ab.
28	df.fs.
29	or/10-28
30	*epiphysis plate/ or *bone dysplasia/ or *skin/ or *tissues/ or *soft tissue infection/ or *skin disease/
31	(growth plate* or phys#s or physeal or epiphys*).ti,ab.
32	((musculoskeletal or skelet* or orthop?ed* or bone* or osseous or limb*) adj4 (lesion* or complicat* or damag* or impair* or abnormal* or morbid* or problem* or necros#s or amputat* or change* or infect* or disease* or length* or gangrene* or deficien* or defect* or salvage or disabilit*)).ti,ab.
33	((skin or tissue* or epithelium or membrane* or muscle* or derma* or dermis or cutaneous or cutis) adj4 (lesion* or complicat* or damag* or impair* or abnormal* or morbid* or problem* or necros#s or eruption* or vasculitis or bleed* or mottl* or blotch* or change* or infect* or disease*)).ti,ab.
34	(rash* or petechia*).ti,ab.
35	or/30-34
36	29 or 35
37	*follow up/ or *health survey/ or *risk factor/ or *risk assessment/ or *incidence/ or *prevalence/ or *prognosis/ or *survivor/ or *Sickness Impact Profile/ or *"quality of life"/
38	(follow up* or followup* or risk* or incidence or prevalence or prognos?s or survivor*).ti,ab.
39	screening.ti.
40	or/37-39
41	6 and 29 and 40
42	9 and 36 and 40
43	41 or 42
44	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
45	43 not 44
46	limit 45 to English language
47	limit 46 to yr="1980 -Current"
48	limit 47 to (conference abstract or conference paper or conference review or conference proceeding)
49	47 not 48
50	afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or

#	Searches
	maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/
51	"organisation for economic co-operation and development"/
52	exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or exp united kingdom/ or "turkey (republic)"/ or exp united states/ or western europe/
53	european union/
54	developed country/
55	or/51-54
56	50 not 55
57	49 not 56

1 **Database (s): Epistemonikos**

2 Date of last search: 20 December 2021

#	Search
	(advanced_title_en:((advanced_title_en:((meningitis OR meningococc* OR meningoencephalitis OR neisseria)) OR advanced_abstract_en:((meningitis OR meningococc* OR meningoencephalitis OR neisseria)))) OR advanced_abstract_en:((advanced_title_en:((meningitis OR meningococc* OR meningoencephalitis OR neisseria)) OR advanced_abstract_en:((meningitis OR meningococc* OR meningoencephalitis OR neisseria))))) AND (advanced_title_en:((advanced_title_en:((complication* OR long-term OR long term OR morbidity OR mortality OR consciousness OR outcome* OR cognit* OR hear* OR visual OR vision OR epileps* OR speech OR headache* OR disabilit* OR motor defici* OR skin OR scar* OR growth OR purpura* OR sequlae* OR petechia*)) OR advanced_abstract_en:((complication* OR long-term OR long term OR morbidity OR mortality OR consciousness OR outcome* OR cognit* OR hear* OR visual OR vision OR epileps* OR speech OR headache* OR disabilit* OR motor defici* OR skin OR scar* OR growth OR purpura* OR sequlae* OR petechia*)))) OR advanced_abstract_en:((advanced_title_en:((complication* OR long-term OR long term OR morbidity OR mortality OR consciousness OR outcome* OR cognit* OR hear* OR visual OR vision OR epileps* OR speech OR headache* OR disabilit* OR motor defici* OR skin OR scar* OR growth OR purpura* OR sequlae* OR petechia*)) OR advanced_abstract_en:((complication* OR long-term OR long term OR morbidity OR mortality OR consciousness OR outcome* OR cognit* OR hear* OR visual OR vision OR epileps* OR speech OR headache* OR disabilit* OR motor defici* OR skin OR scar* OR growth OR purpura* OR sequlae* OR petechia*))))) [Filters: protocol=no, classification=systematic-review, cochrane=missing, min_year=1980, max_year=2021]

3 **Economic Search**

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

5

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

8 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

#	Searches
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2021 March 10, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to March 09, 2021
Date of last search: 11 March 2021
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
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.

#	Searches
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
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

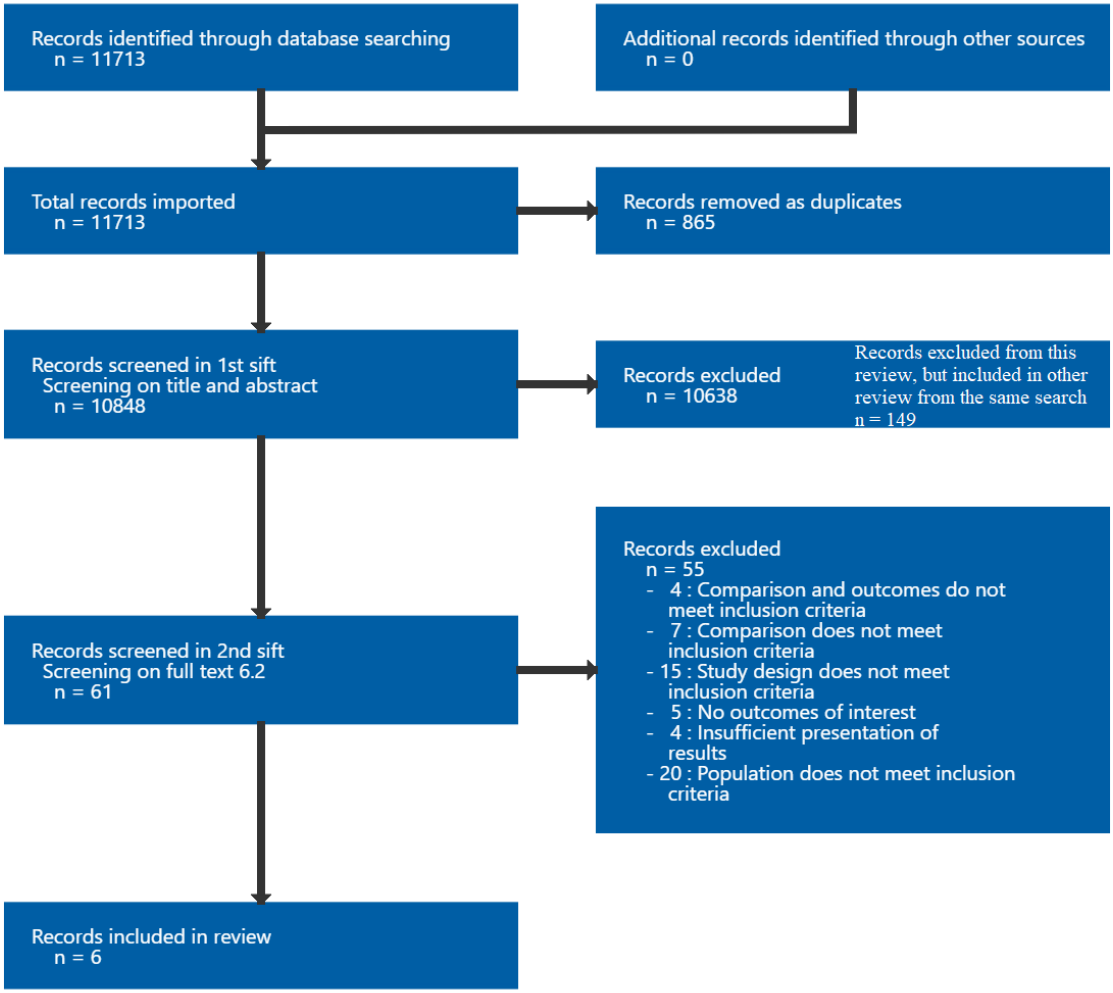
#	Searches
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

1
2

Appendix C Prognostic evidence study selection

Study selection for: What is the risk of long-term complications in meningococcal disease?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the risk of long-term complications in meningococcal disease?

Table 4: Evidence tables – prognostic evidence

Borg, 2009

Bibliographic Reference	Borg, J.; Christie, D.; Coen, P. G.; Booy, R.; Viner, R. M.; Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study; Pediatrics; 2009; vol. 123 (no. 3); e502-9

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	January 1999 - June 2000
Inclusion criteria	Meningococcal disease: Children and adults aged 15-19 years with invasive meningococcal disease. Meningococcal disease was confirmed by primary clinical diagnosis, positive culture, polymerase chain reaction (PCR), or serodiagnosis. No meningococcal disease: Age-matched and sex-matched control participants.
Exclusion criteria	Not reported
Patient characteristics	Characteristics of all participants: Age in years at follow-up (mean; SD in parentheses): 19 (2) Sex: male: 94 (47%); female: 108 (53%) Characteristics of participants with meningococcal disease: Disease type: Both meningitis and septicaemia: 40/101 (40%); Meningitis alone: 33/101 (33%); Septicaemia alone: 27/101

	(27%); Missing data on disease type: 1/101 (1%) Participants admitted to the ICU: 52/97[1] (54%) [1]Data on ICU admission were available for 97 participants
Population of interest/comparison	Meningococcal disease: Children and adults who had meningococcal disease No meningococcal disease: Age-matched and sex-matched controls without meningococcal disease
Duration of follow-up	18-36 months after invasive meningococcal disease
Sources of funding	Not industry funded
Sample size	N=202 Meningococcal disease group: n=101 No meningococcal disease group: n=101
Other information	33% of participants with meningococcal disease had meningitis alone, and data not presented separately for this group

ICU: intensive care unit; PCR: polymerase chain reaction; SD: standard deviation

Outcomes

Meningococcal disease versus no meningococcal disease: Long-term psychological impairment

Outcome	**Meningococcal disease vs No meningococcal disease, N2 = 101, N1 = 101**
Long-term psychological impairment (depressive symptoms on the BDI-II) adjusted Odds ratio/95% CI	2.7 (1.2 to 6.5)

BDI-II: the Beck Depression Inventory II; CI: confidence interval

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited baseline characteristics and no exclusion criteria reported)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of meningococcal disease provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of the outcome (that is, the Beck Depression Inventory II (BDI-II) reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, and the analysis was adjusted for life stress, but limited baseline characteristics reported and unclear if there was residual confounding)*
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 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

BDI-II: the Beck Depression Inventory II; QUIPS: Quality in Prognosis Studies

Fellick, 2001

Bibliographic Reference	Fellick, J. M.; Sills, J. A.; Marzouk, O.; Hart, C. A.; Cooke, R. W.; Thomson, A. P.; Neurodevelopmental outcome in meningococcal disease: a case-control study; Archives of Disease in Childhood; 2001; vol. 85 (no. 1); 6-11

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	November 1988 - August 1990
Inclusion criteria	Meningococcal disease: Children with meningococcal disease. The diagnosis was confirmed by positive blood and/or CSF cultures or antigen test No meningococcal disease: Age- and sex-matched controls without meningococcal disease
Exclusion criteria	Meningococcal disease: Major neurodevelopmental disability by parental and GP questionnaires No meningococcal disease: Previous meningococcal disease
Patient characteristics	Characteristics of all participants: Age at follow up in months (median; IQR in parenthesis): 133 (121-161) Sex: male: 124/230 (64%); female: 106/230 (46%) Characteristics of participants with meningococcal disease: Age at time of diagnosis in months (median; IQR in parenthesis): 16 (7-50) Disease classification: Meningococcal meningitis: 16 (11%); Meningococcal septicaemia: 44 (29%); Mixed disease: 92 (60.5%)
Population of	Survivors of meningococcal disease compared to age and sex matched controls where possible.

interest/comparison	
Duration of follow-up	Not reported[1] [1]Participants had meningococcal disease between 1988 and 1990, and assessments took place between 1998 and 2000. Therefore, follow-up could be up to 12 years.
Sources of funding	Not industry funded
Sample size	N=230 Meningococcal disease: n=115 No meningococcal disease: n=115
Other information	16 participants had meningitis alone and data not presented separately for this group. 29 participants with meningococcal disease received PICU care.

CSF: cerebrospinal fluid; GP: general practitioner; IQR: interquartile range; PICU: paediatric intensive care unit

Outcomes

Meningococcal disease versus no meningococcal disease: Long-term motor deficits, long-term behavioural deficits, any hearing impairment, and diagnosis of epilepsy

Outcome	Meningococcal disease, N = 115	No Meningococcal disease, N = 115
Diagnosis of epilepsy Combined the following reported outcomes: “poorly controlled epilepsy with mixed seizure type” and "microcephaly and spastic quadriplegia with epilepsy and cortical blindness” Custom value	2/115	0/115
Long-term motor deficit	19/115	5/115

Outcome	Meningococcal disease, N = 115	No Meningococcal disease, N = 115
Reported as ' The Movement ABC scores above the 95th percentile'. Lower values are better Custom value		
Long-term behavioural deficits Reported as 'Formal ADHD diagnosis'. Lower values are better Custom value	3/115	1/115
Long-term behavioural deficits Reported as 'Possible ADHD diagnosis via parent and teacher DSM-IV questionnaire scores'. Lower values are better Custom value	8/84	0/115
Any hearing impairment Combined the following reported outcomes: “bilateral severe to profound sensorineural loss; unilateral loss; unilateral high frequency loss; mild high frequency loss; and mild unilateral or bilateral conductive losses”. Custom value	19/109	3/55

ADHD: attention deficit hyperactivity disorder; DSM-IV: the Diagnostic and Statistical Manual of Mental Disorders fourth edition; The Movement ABC: The Movement Assessment Battery for Children

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Low risk of bias *(Method used to identify study population, inclusion criteria, exclusion criteria, and baseline characteristics of the study population were appropriate and adequately provided)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Baseline characteristics of participants lost to follow up is described, and they had higher age at*

Section	Question	Answer
		diagnosis (16 months vs. 82 months) and lower cases of meningitis alone (16 vs. 0) and fulminant cases (29 vs. 2). Data is available for all participants for diagnosis of epilepsy and long-term motor deficits, about 74% to 86% for behavioural deficits, and about 71% for hearing impairment.)
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of prognostic factor reported)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Moderate risk for behavioural deficits: The measurement of outcome is somewhat subjective (reported by parents and teachers). Low risk for diagnosis of epilepsy, motor deficit, hearing impairment, and skin, soft tissue or orthopaedic complications: Description of valid and reliable measurement of outcomes reported.)*
Study Confounding	Study Confounding Summary	Low risk of bias *(Matched on age, sex and GP practice, and no significant differences in baseline characteristics/potential confounders between groups.)*
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 *(Moderate risk for behavioural deficit. Low risk for diagnosis of epilepsy, motor deficits, and hearing impairment.)*
Overall risk of bias and directness	Directness	Directly applicable *(11% of participants had meningococcal meningitis alone, but this is below threshold for being considered indirect.)*

GP: general practitioner; QUIPS: Quality in Prognosis Studies

Sander, 1984

Bibliographic Reference	Sander, J.; Bay, D.; Gedde-Dahl, T. W.; Borchgrevink, H. M.; Froholm, L. O.; Oftedal, S. I.; Vandvik, B.; Late sequelae after meningococcal disease. A controlled study in young men; NIPH Annals; 1984; vol. 7 (no. 1); 3-11

Study details

Country/ies where study was carried out	Norway
Study type	Retrospective cohort study
Study dates	1982
Inclusion criteria	Meningococcal disease: Male survivors of systemic meningococcal disease during military service between 1967-1979. Meningococcal disease was confirmed by CSF leukocytes >100x109/L and blood samples for antibody and antigen. No meningococcal disease: Soldiers who were about the same age as the patients
Exclusion criteria	Not reported
Patient characteristics	Characteristics of all participants: Age in years at time of military service - mean (SEM) Meningococcal disease: 21 (0.14) No Meningococcal disease: 20 (0.13) Sex: male 135 (100%) Characteristics of participants with meningococcal disease: Disease classification: Meningococcal meningitis with or without septicaemia: 57 (80.3%); Septicaemia only: 14 (19.7%)

Population of interest/comparison	Male survivors of meningococcal disease compared to males without meningococcal disease during military service
Duration of follow-up	3-15 years
Sources of funding	Not reported
Sample size	N=135 Meningococcal disease: n=71 No Meningococcal disease: n=64 Excluded: n=35 (did not return questionnaire)
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not

CSF: cerebrospinal fluid; ICU: intensive care unit; SEM: standard error of the mean

Outcomes

Meningococcal disease versus no meningococcal disease: Long-term cognitive deficits, long-term psychological impairment, any hearing impairment, any visual impairment, and headache

Outcome	Meningococcal disease, N = 71	No Meningococcal disease, N = 64
Any hearing impairment Reported as 'Reduced hearing'. Lower values are better. No of events	n = 5	n = 3
Any hearing impairment Reported as 'Noise in the ear (tinnitus)'. Lower values are better No of events	n = 8	n = 0

Outcome	Meningococcal disease, N = 71	No Meningococcal disease, N = 64
Any visual impairment Reported as 'Visual disturbance'. Lower values are better. No of events	n = 5	n = 3
Headache Lower values are better No of events	n = 22	n = 6
Long-term cognitive deficits Reported as 'concentration problems'. Lower values are better. No of events	n = 12	n = 0
Long-term cognitive deficits Reported as 'impaired memory'. Lower values are better. No of events	n = 11	n = 0
Long-term psychological impairment Reported as 'irritability'. Lower values are better. No of events	n = 19	n = 5

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding recruitment period; inclusion and exclusion criteria and baseline characteristics)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	High risk of bias *(Data available for 79.4% of participants initially contacted. Data is available for all participants who returned the questionnaire. No attempt to collect data from participants who dropped out and no suggestion of the impact on the data.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable measurement of the prognostic factor.)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Definitions of all outcomes (Long-term cognitive deficits; Any hearing impairment; Any visual impairment; Headache; Long-term psychological impairment) not reported. Measurement, method and setting of outcome measurement were adequately reported.)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounder/baseline difference identified such as age.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Very limited information on analysis but no evidence of selective reporting of results.)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

1

2 **Shen, 2021**

Bibliographic Reference	Shen, J.; Bouee, S.; Aris, E.; Emery, C.; Beck, E. C.; Long-Term Mortality and State Financial Support in Invasive Meningococcal Disease-Real-World Data Analysis Using the French National Claims Database (SNIIRAM); Infectious Diseases & Therapy; 2021; vol. 17; 17

3 **Study details**

Country/ies where study was carried out	France
Study type	Retrospective cohort study
Study dates	1 January 2012 - 31 December 2017
Inclusion criteria	Meningococcal disease: All patients who were hospitalised with invasive meningococcal disease (ICD-10 diagnosis codes A39.0 to A39.9) between 1st January 2012 and 31st December 2017. No meningococcal disease: Age- and sex-matched controls who were living in the same area as the corresponding meningococcal disease patients and were not hospitalised.
Exclusion criteria	Not reported
Patient characteristics	Characteristic of participants with meningococcal disease: Age in years at diagnosis - median - IQR in parenthesis: 21 (4-52) ≤1 year of age: n=470 >1 year to ≤19 years of age: n=1197 ≥20 years of age: n=1865
Population of	Survivors of invasive meningococcal disease compared to age, sex and area of residence matched controls

interest/comparison	
Duration of follow-up	Invasive meningococcal disease: Mean ± SD: 3 ± 2 years Median (range): 3 (0-6) years No invasive meningococcal disease: Mean ± SD: 3 ± 2 years Median (range): 3 (0-6) years
Sources of funding	Industry funded
Sample size	N=14128 Invasive meningococcal disease: 3532 No invasive meningococcal disease: 10596
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

ICD: international classification of diseases; ICU: intensive care unit; IQR: interquartile range; SD: standard deviation

Outcomes

Meningococcal disease versus no meningococcal disease: All-cause mortality

Outcome	**Invasive meningococcal disease, N = 3532**	**No invasive meningococcal disease, N = 10596**
All-cause mortality Lower values are better No of events	n = 456	n = 344

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited reporting of participant characteristics and inclusion and exclusion criteria)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Retrospective data from national insurance database (SNIIRAM) was used, and data is available for all participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of prognostic factor provided. Valid and reliable assessment of prognostic factor)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Description and measurement of the outcome not provided. The outcome is objective (all-cause mortality))*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Participants were matched for age, sex and area of residence, but limited information regarding baseline characteristics reported and unclear if there is residual confounding.)*
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

QUIP: Quality in Prognosis Studies; SSNIIRAM: The French national insurance claims database

1

2 **Vermunt, 2011**

Bibliographic Reference Vermunt, L. C.; Buysse, C. M.; Joosten, K. F.; Duivenvoorden, H. J.; Hazelzet, J. A.; Verhulst, F. C.; Utens, E. M.; Survivors of septic shock caused by Neisseria meningitidis in childhood: psychosocial outcomes in young adulthood; Pediatric Critical Care Medicine; 2011; vol. 12 (no. 6); e302-9

3 **Study details**

Country/ies where study was carried out	Netherlands
Study type	Prospective cohort study
Study dates	2005 - 2006
Inclusion criteria	Meningococcal disease: Survivors of meningococcal septic shock caused by Neisseria meningitidis that required intensive care at the PICU of Erasmus MC-Sophia Children's Hospital between August 1, 1988 and June 1, 2001, and were aged between 16-31 years at follow-up. No meningococcal disease: Normative Dutch sample
Exclusion criteria	Insufficient knowledge of the Dutch language
Patient characteristics	Characteristics of participants with meningococcal disease: Age in years at the time of illness - median (range): 9 (0-17) Mean age in years at time of follow-up: 22 Sex: male: 28 (48%), female 30 (52%) Diagnosis was confirmed by the presence of clinical features (for example, septic shock with petechiae or purpura), positive blood culture in 83% of participants and positive CSF culture or pleocytosis in 47% of participants.

Population of interest/comparison	Survivors of septic shock caused by Neisseria meningitidis in childhood compared to reference groups from the Netherlands Central Bureau of Statistics.
Duration of follow-up	Mean duration of follow up 13 years
Sources of funding	Not industry funded
Sample size	N=2089 Meningococcal disease: n=58 No meningococcal disease: n=2031 Excluded from meningococcal disease group: n=25 (refused to participate on practical grounds (7), emotional grounds (6), or unknown reasons (12))

CSF: cerebrospinal fluid; PICU: paediatric intensive care unit

Outcomes

Meningococcal disease versus no meningococcal disease: Long-term behavioural deficits

Outcome	Meningococcal disease, N = 58	No meningococcal disease, N = 2031
Long-term behavioural deficits (problem behaviour; assessed with the Adult Self Report) Custom value	6/37	205/2031

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Method used to identify study population, inclusion criteria, and exclusion criteria provided. However, limited information regarding baseline characteristics provided, and 30% (25/83) of potential participants contacted refused to participate.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data available for all participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of prognostic factor provided.)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Definition of problem behaviour not provided, and the measurement of outcome was somewhat subjective (Dutch version of Adult Self-Report).)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Patients and reference group have comparable age ranges, but limited information about baseline characteristics provided and unclear if there is any residual confounding.)*
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

QUIPS: Quality in Prognosis Studies

1 **Viner, 2012**

Bibliographic Reference	Viner, R. M.; Booy, R.; Johnson, H.; Edmunds, W. J.; Hudson, L.; Bedford, H.; Kaczmarski, E.; Rajput, K.; Ramsay, M.; Christie, D.; Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study; Lancet Neurology; 2012; vol. 11 (no. 9); 774-83

2

3 **Study details**

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	May 2008 - September 2010
Inclusion criteria	Meningococcal disease: Children who had serogroup B meningococcal disease and were aged 1 month to 13 years at disease. Meningococcal disease was confirmed by positive culture or polymerase chain reaction (PCR). No meningococcal disease: Age-matched and sex-matched control participants.
Exclusion criteria	Not reported
Patient characteristics	Characteristics of all participants: Age in years at follow-up (mean; SD in parentheses): 7 (3) Sex: male: 328 (57%); female: 245 (43%) Characteristics of participants with meningococcal disease: Age in years at meningococcal disease (median): 1.64 years Disease classification: Septicaemia alone: 155/245 (63%); Meningitis alone: 35/245 (14%); Both meningitis and septicaemia: 44/245 (18%); Other: 1/245 (<1%); Insufficient information: 10/245 (4%)

	Participants with meningococcal disease admitted to intensive care unit (ICU): 72/245 (29%)
Population of interest/comparison	Meningococcal disease: Children who had serogroup B meningococcal disease No meningococcal disease: Age-matched and sex-matched controls without meningococcal disease
Duration of follow-up	Median 4 years (range 3-6 years)
Sources of funding	Not industry funded
Sample size	N=573 Full sample: Meningococcal disease: n=245 No meningococcal disease: n=328 Matched sample: Meningococcal disease: n=221 No meningococcal disease: n=221
Other information	14% of children with meningococcal disease had meningitis alone, and data not presented separately for this group.

ICU: intensive care unit; PCR: polymerase chain reaction; SD: standard deviation

Outcomes

Meningococcal disease versus no meningococcal disease: Long-term psychological impairment; any visual impairment; skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention; and speech and language disorder

Outcome	Meningococcal disease, N = 245	No meningococcal disease, N = 328
Long-term psychological impairment (social phobia) Custom value	2/149	0/229
Long-term psychological impairment (panic disorder) Custom value	0/150	0/229
Long-term psychological impairment (agoraphobia) Custom value	0/149	0/229
Long-term psychological impairment (post-traumatic stress disorder) Custom value	0/150	0/229
Long-term psychological impairment (obsessive compulsive disorder) Custom value	0/150	0/229
Long-term psychological impairment (depression) Custom value	0/150	1/229
Long-term psychological impairment (eating disorder) Custom value	1/149	0/228
Any visual impairment (registered blind)	1/239	0/322

Outcome	Meningococcal disease, N = 245	No meningococcal disease, N = 328
Custom value		
Skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention (amputation with substantial disability) Custom value	3/239	0/322
Speech and language disorder (absent or minimum communication) Custom value	1/239	1/322

Meningococcal disease versus no meningococcal disease: Long-term cognitive deficits, long-term behavioural deficits, long-term psychological impairment, any hearing impairment, diagnosis of epilepsy, and speech and language disorder

Outcome	Meningococcal disease vs No meningococcal disease, N2 = 245, N1 = 328
Long-term cognitive deficits (borderline IQ<85) matched analysis Odds ratio/95% CI	2.4 (1.1 to 5)
Long-term cognitive deficits (intellectual disability or IQ<70) matched analysis Odds ratio/95% CI	2.1 (0.2 to 24.9)
Long-term cognitive deficits (participants with low scores (>1 SD below the control mean) in ≥2 aspects of memory) matched analysis Odds ratio/95% CI	2.3 (1.2 to 4.3)

Outcome	Meningococcal disease vs No meningococcal disease, N2 = 245, N1 = 328
Long-term behavioural deficits (oppositional defiant disorder) matched analysis Odds ratio/95% CI	1.6 (0.7 to 4)
Long-term behavioural deficits (conduct disorder) matched analysis Odds ratio/95% CI	7.9 (1 to 66)
Long-term psychological impairment (participants with abnormal difficulties scores; assessed with strengths and difficulties questionnaire) matched analysis Odds ratio/95% CI	3.4 (1.8 to 6.4)
Long-term psychological impairment (any mental health disorder ≥50% probability, assessed with the development and wellbeing assessment) matched analysis Odds ratio/95% CI	2.1 (1.1 to 4.3)
Long-term psychological impairment (any mental health disorder ≥70% probability, assessed with the development and wellbeing assessment) matched analysis Odds ratio/95% CI	2.7 (1.1 to 6.8)
Long-term psychological impairment (generalised anxiety disorder) matched analysis Odds ratio/95% CI	3.2 (0.3 to 31)

Outcome	Meningococcal disease vs No meningococcal disease, N2 = 245, N1 = 328
Long-term psychological impairment (separation anxiety disorder) matched analysis Odds ratio/95% CI	3.9 (0.8 to 19.1)
Long-term psychological impairment (specific phobias) matched analysis Odds ratio/95% CI	3.3 (0.7 to 16.9)
Long-term behavioural deficit (attention deficit hyperactivity disorder; ADHD) matched analysis Odds ratio/95% CI	4.9 (1.3 to 18.4)
Long-term psychological impairment (autistic spectrum disorder) matched analysis Odds ratio/95% CI	4.6 (0.9 to 158)
Any hearing impairment (profound bilateral sensorineural hearing loss; wears a cochlear implant or hearing loss ≥90 dB) matched analysis Odds ratio/95% CI	8.2 (1.2 to 100)
Any hearing impairment (moderately severe bilateral sensorineural hearing loss; hearing loss ≥40 dB) matched analysis Odds ratio/95% CI	11 (1.4 to 86)
Any hearing impairment (any sensorineural hearing loss; unilateral or bilateral; hearing	13.2 (1.7 to 102)

Outcome	Meningococcal disease vs No meningococcal disease, N2 = 245, N1 = 328
loss ≥20 dB) matched analysis Odds ratio/95% CI	
Diagnosis of epilepsy (epilepsy; seizures of any type) matched analysis Odds ratio/95% CI	6.9 (0.8 to 60)
Speech and language disorder (substantial communication disability) matched analysis Odds ratio/95% CI	5.6 (0.9 to 100)

ADHD: attention deficit hyperactivity disorder; CI: confidence interval; dB: decibels; IQ: intelligence quotient; SD: standard deviation

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information about baseline characteristics of the study participants and exclusion criteria reported)*
Study Attrition	Study Attrition Summary	High risk of bias *(High risk for other psychological impairment, cognitive deficits (low scores in ≥2 aspects of memory), and behavioural deficits: The data was available for about 65% of participants. Low risk for hearing impairment, visual impairment, skin and soft tissue complication, diagnosis of epilepsy, psychological impairment assessed with strengths and difficulties questionnaire, cognitive deficits (IQ<85 and IQ<70), and speech and language disorder: The data was available for 96%-100% of participants.)*
Prognostic factor measurement	Prognostic factor Measurement	Low risk of bias *(Description of valid and reliable measurement of prognostic factor reported)*

Section	Question	Answer
	Summary	
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of valid and reliable measurement of outcomes (that is, the Wechsler Pre-school and Primary Scale of Intelligence, the Wechsler Abbreviated Scale of Intelligence, the Strengths and Difficulties Questionnaire, the Behaviour Rating Inventory of Executive Function, and pure tone audiometry) reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Some attempts were made to control for potential confounders (for example, using age- and sex-matched controls, and for conduct disorder, ADHD, and psychological impairment assessed with strengths and difficulties questionnaire and DAWBA, the analysis was adjusted for sex), but limited baseline characteristics reported and unclear if there was residual confounding)*
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

ADHD: attention deficit hyperactivity disorder; DAWBA: The Development and Wellbeing Assessment; IQ: intelligence quotient; QUIPS: Quality in Prognosis Studies

Appendix E Forest plots

Forest plots for review question: What is the risk of long-term complications in 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 is the risk of long-term complications in meningococcal disease?

Table 5: Evidence profile for the risk of long-term motor deficits, cognitive deficits, and behavioural deficits in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meningococcal disease	Control	Relative (95% CI)	Absolute		
Long-term motor deficits (The Movement ABC scores above the 95th percentile) (follow-up up to 12 years)												
1 (Fellick 2001)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19/115 (16.5%)	5/115 (4.3%)	RR 3.8 (1.47 to 9.83)	122 more per 1000 (from 20 more to 384 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (borderline IQ <85; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 2.4 (1.10 to 5.24)	NC	VERY LOW	CRITICAL
Long-term cognitive deficits (intellectual disability or IQ <70; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 2.1 (0.20 to 22.05)	NC	VERY LOW	CRITICAL
Long-term cognitive deficits (participants with low scores (>1 SD below the control mean) in ≥2 aspects of memory; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 2.3 (1.20 to 4.41)	NC	VERY LOW	CRITICAL
Long-term behavioural deficits (formal ADHD diagnosis) (follow-up up to 12 years)												
1 (Fellick 2001)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/115 (2.6%)	1/115 (0.87%)	RR 3 (0.32 to 28.42)	17 more per 1000 (from 6 fewer to 238 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (possible ADHD diagnosis via parent and teacher DSM-IV questionnaire scores) (follow-up up to 12 years)												

1 (Fellick 2001)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	8/84 (9.5%)	0/115 (0%)	RR 23.2 (1.36 to 396.45)	100 more per 1000 (from 30 more to 160 more)[3]	VERY LOW	CRITICAL
Long-term behavioural deficits (problem behaviour; assessed with the Adult Self Report) (follow-up mean 13 years)												
1 (Vermunt 2011)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	6/37 (16.2%)	205/2031 (10.1%)	RR 1.61 (0.76 to 3.38)	62 more per 1000 (from 24 fewer to 240 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (oppositional defiant disorder; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 1.6 (0.70 to 3.66)	NC	VERY LOW	CRITICAL
Long-term behavioural deficits (conduct disorder; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 7.9 (1.00 to 62.41)	NC	VERY LOW	CRITICAL
Long-term behavioural deficits (ADHD; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 4.9 (1.30 to 18.47)	NC	VERY LOW	CRITICAL

ADHD: attention deficit hyperactivity disorder; CI: confidence interval; DSM-IV: the Diagnostic and Statistical Manual of Mental Disorders fourth edition; IQ: intelligence quotient; NC: not calculable; NR: not reported; OR: odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio, SD: standard deviation; The Movement ABC: The Movement Assessment Battery for Children

**The total number of events is less than 150 in the whole sample, but it is not reported for matched sample*

[1] <150 events

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

[3] Absolute effect calculated based on risk difference

[4] <300-≥150 events

1

2 **Table 6: Evidence profile for the risk of long-term psychological impairment in children**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meningococcal disease	Control	Relative (95% CI)	Absolute		
Long-term psychological impairment (depressive symptoms on the BDI-II; adjusted) (follow-up 18-36 months)												
1 (Borg 2009)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	NR	NR	OR 2.7 (1.20 to 6.07)	NC	VERY LOW	CRITICAL
Long-term psychological impairment (social phobia) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/149 (1.3%)	0/229 (0%)	POR 12.7 (0.74 to 217.78)	13 more per 1000 (from 8 fewer to 35 more)[4]	VERY LOW	CRITICAL
Long-term psychological impairment (panic disorder) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	0/150 (0%)	0/229 (0%)	RD 0.0 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL
Long-term psychological impairment (agoraphobia) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	0/149 (0%)	0/229 (0%)	RD 0.0 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL
Long-term psychological impairment (post-traumatic stress disorder) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	0/150 (0%)	0/229 (0%)	RD 0.0 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL
Long-term psychological impairment (obsessive compulsive disorder) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	0/150 (0%)	0/229 (0%)	RD 0.0 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	VERY LOW	CRITICAL

Long-term psychological impairment (depression) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/150 (0%)	1/229 (0.44%)	POR 0.19 (0 to 10.52)	4 fewer per 1000 (from 4 fewer to 40 more)	VERY LOW	CRITICAL
Long-term psychological impairment (eating disorder) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/149 (0.67%)	0/228 (0%)	POR 12.56 (0.23 to 691.69)	10 more per 1000 (from 10 fewer to 20 more)[4]	VERY LOW	CRITICAL
Long-term psychological impairment (participants with abnormal difficulties scores; assessed with strengths and difficulties questionnaire) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 3.40 (1.80 to 6.42)	NC	VERY LOW	CRITICAL
Long-term psychological impairment (any mental health disorder ≥50% probability, assessed with the development and wellbeing assessment) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 2.10 (1.10 to 4.01)	NC	VERY LOW	CRITICAL
Long-term psychological impairment (any mental health disorder ≥70% probability, assessed with the development and wellbeing assessment) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 2.70 (1.10 to 6.63)	NC	VERY LOW	CRITICAL
Long-term psychological impairment (generalised anxiety disorder; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 3.20 (0.30 to 34.13)	NC	VERY LOW	CRITICAL
Long-term psychological impairment (separation anxiety disorder; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 3.90 (0.80 to 19.01)	NC	VERY LOW	CRITICAL
Long-term psychological impairment (specific phobias; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 3.30 (0.70 to 15.56)	NC	VERY LOW	CRITICAL

Long-term psychological impairment (autistic spectrum disorder; matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	NR*	NR*	OR 4.60 (0.90 to 23.51)	NC	VERY LOW	CRITICAL

BDI-II: the Beck Depression Inventory II; CI: confidence interval; NC: not calculable; NR: not reported; OIS: optimal information size; OR: odds ratio; POR: Peto odds ratio; QUIPS: Quality in Prognosis Studies; RD: risk difference; RR: risk ratio
**The total number of events is less than 150 in the whole sample, but it is not reported for matched sample*
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Estimate may be imprecise as cannot determine if OIS criteria have been met because data on the number of events is not reported
[3] <150 events
[4] Absolute effect calculated based on risk difference
[5] Sample size ≥200-<400

Table 3: Evidence profile for the risk of any hearing impairment; any visual impairment; diagnosis of epilepsy; skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention; and speech and language disorder in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Meningococcal disease**	**Control**	**Relative (95% CI)**	**Absolute**		
Any hearing impairment (bilateral severe to profound sensorineural loss, unilateral loss, unilateral high frequency loss, mild high frequency loss, and mild unilateral or bilateral conductive losses) (follow-up up to 12 years)												
1 (Fellick 2001)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19/109 (17.4%)	3/55 (5.5%)	RR 3.2 (0.99 to 10.33)	120 more per 1000 (from 1 fewer to 509 more)	VERY LOW	CRITICAL
Any hearing impairment (profound bilateral sensorineural hearing loss; wears a cochlear implant or hearing loss ≥90 dB) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 8.20 (1.20 to 56.03)	NC	VERY LOW	CRITICAL
Any hearing impairment (moderately severe bilateral sensorineural hearing loss; hearing loss ≥40 dB) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 11.00 (1.40 to 86.43)	NC	VERY LOW	CRITICAL
Any hearing impairment (any sensorineural hearing loss; unilateral or bilateral hearing loss ≥20 dB) (matched analysis) (follow-up median 4 years)												
1 (Viner	observational	serious[2]	no serious	no serious	very serious[1]	none	NR*	NR*	OR 13.20 (1.70	NC	VERY LOW	CRITICAL

2012)	studies		inconsistency	indirectness					to 102.49)			
Any visual impairment (registered blind) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/239 (0.42%)	0/322 (0%)	POR 10.46 (0.2 to 550.5)	0 more per 1000 (from 10 fewer to 20 more)[3]	VERY LOW	CRITICAL
Diagnosis of epilepsy ("poorly controlled epilepsy with mixed seizure type" or "microcephaly and spastic quadriplegia with epilepsy and cortical blindness") (follow-up up to 12 years)												
1 (Fellick 2001)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/115 (1.7%)	0/115 (0%)	POR 7.45 (0.46 to 119.90)	20 more per 1000 (from 10 fewer to 50 more)[3]	VERY LOW	CRITICAL
Diagnosis of epilepsy (epilepsy; seizures of any type) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 6.90 (0.80 to 59.51)	NC	VERY LOW	CRITICAL
Skin, soft tissue or orthopaedic complications causing scarring and/or requiring surgical intervention (amputation with substantial disability) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/239 (1.3%)	0/322 (0%)	POR 10.55 (1.07 to 104.39)	10 more per 1000 (from 3 fewer to 28 more)[3]	VERY LOW	CRITICAL
Speech and language disorder (absent or minimum communication) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/239 (0.42%)	1/322 (0.31%)	POR 1.35 (0.08 to 22.38)	1 more per 1000 (from 3 fewer to 62 more)	VERY LOW	CRITICAL
Speech and language disorder (substantial communication disability) (matched analysis) (follow-up median 4 years)												
1 (Viner 2012)	observational studies	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	NR*	NR*	OR 5.60 (0.90 to 34.84)	NC	VERY LOW	CRITICAL

CI: confidence interval; db: decibels; NC: not calculable; NR: not reported; OR: odds ratio; POR: Peto odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**The total number of events is less than 150 in the whole sample, but it is not reported for matched sample*
[1] <150 events
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[3] Absolute effect calculated based on risk difference

Table 8: Evidence profile for the risk of long-term complications in adults

Quality assessment							No of patients	Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Meningococcal disease**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 3 years)												
1 (Shen 2021)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	456/3532 (12.9%)	344/10596 (3.2%)	RR 3.98 (3.48 to 4.55)	97 more per 1000 (from 81 more to 115 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (concentration problems) (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/71 (16.9%)	0/64 (0%)	RR 22.57 (1.36 to 373.66)	170 more per 1000 (from 80 more to 260 more)[4]	VERY LOW	CRITICAL
Long-term cognitive deficits (impaired memory) (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/71 (15.5%)	0/64 (0%)	RR 20.76 (1.25 to 345.4)	150 more per 1000 (from 70 more to 240 more)[4]	VERY LOW	CRITICAL
Long-term psychological impairment (irritability) (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/71 (26.8%)	5/64 (7.8%)	RR 3.43 (1.36 to 8.64)	190 more per 1000 (from 28 more to 597 more)	VERY LOW	CRITICAL
Any hearing impairment (reduced hearing) (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/71 (7%)	3/64 (4.7%)	RR 1.5 (0.37 to 6.04)	23 more per 1000 (from 30 fewer to 236 more)	VERY LOW	CRITICAL
Any hearing impairment (noise in the ear or tinnitus) (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/71 (11.3%)	0/64 (0%)	RR 15.35 (0.9 to 260.69)	110 more per 1000 (from 40 more to 190 more)[4]	VERY LOW	CRITICAL
Any visual impairment (visual disturbance) (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/71 (7%)	3/64 (4.7%)	RR 1.5 (0.37 to 6.04)	23 more per 1000 (from 30 fewer to 236 more)	VERY LOW	CRITICAL

Headache (follow-up 3-15 years)												
1 (Sander 1984)	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	22/71 (31%)	6/64 (9.4%)	RR 3.31 (1.43 to 7.63)	217 more per 1000 (from 40 more to 622 more)	VERY LOW	CRITICAL

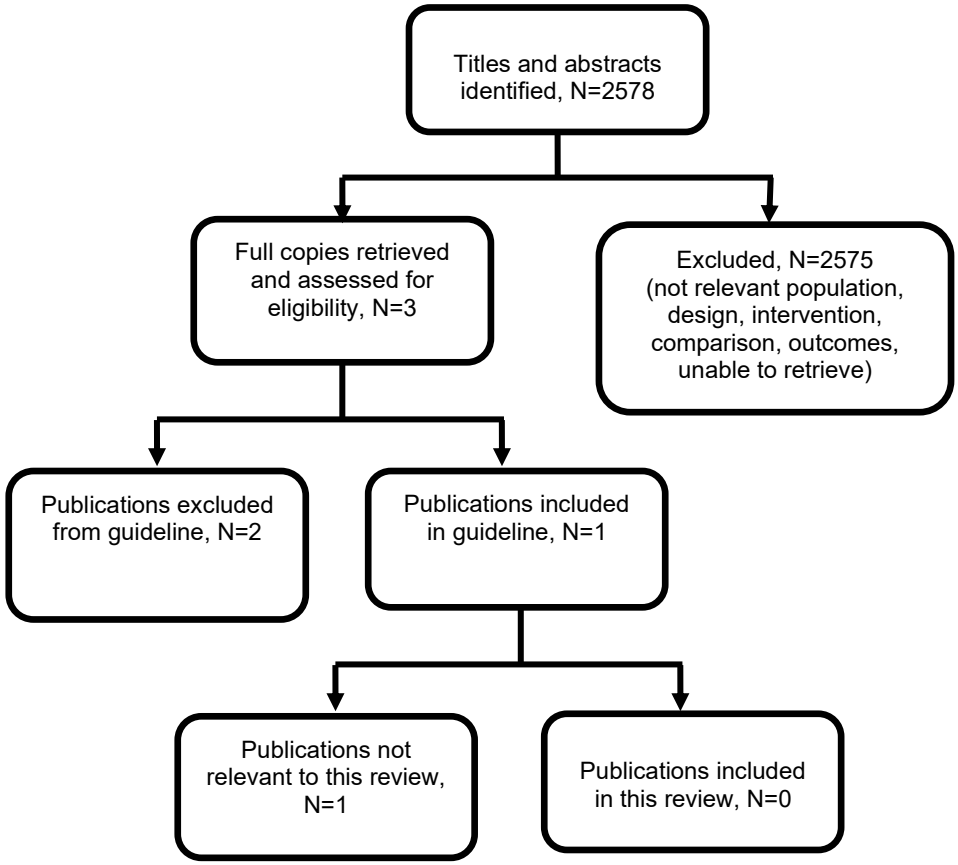
CI: confidence interval; QUIPS: Quality in Prognosis Studies; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[3] <150 events
[4] Absolute effect calculated based on risk difference

Appendix G Economic evidence study selection

Study selection for: What is the risk of long-term complications in 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 2).

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the risk of long-term complications in meningococcal disease?

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

Appendix I Economic model

Economic model for review question: What is the risk of long-term complications in meningococcal disease?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the risk of long-term complications in meningococcal disease?

Excluded diagnostic studies

The excluded studies table only lists the studies that were considered and then excluded at the full-text stage for this review (N=55) and not studies (N=149) that were considered and then excluded from the search at the full-text stage as per the PRISMA diagram in Appendix C for the other review question in the same search.

Table 4: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Adams-Chapman, I., Bann, C. M., Das, A. et al. (2013) Neurodevelopmental outcome of extremely low birth weight infants with Candida infection. Journal of Pediatrics 163(4): 961-7.e3	- Population does not meet inclusion criteria
Al-Hasan, M. N., Huskins, W. C., Lahr, B. D. et al. (2011) Epidemiology and outcome of Gram-negative bloodstream infection in children: a population-based study. Epidemiology & Infection 139(5): 791-6	- Population does not meet inclusion criteria
Als, L. C., Nadel, S., Cooper, M. et al. (2013) Neuropsychologic function three to six months following admission to the PICU with meningoencephalitis, sepsis, and other disorders: a prospective study of school-aged children. Critical Care Medicine 41(4): 1094-103	- Population does not meet inclusion criteria
Als, L. C., Picouto, M. D., Hau, S. M. et al. (2015) Mental and physical well-being following admission to pediatric intensive care. Pediatric Critical Care Medicine 16(5): e141-9	- Population does not meet inclusion criteria
Als, L. C., Tennant, A., Nadel, S. et al. (2015) Persistence of Neuropsychological Deficits Following Pediatric Critical Illness. Critical Care Medicine 43(8): e312-5	- Population does not meet inclusion criteria
Appel, M.; Pauleto, A. C.; Cunha, L. A. (2002) Osteochondral sequelae of meningococcemia: radiographic aspects. Journal of Pediatric Orthopedics 22(4): 511-6	- Study design does not meet inclusion criteria
Bache, C. E. and Torode, I. P. (2006) Orthopaedic sequelae of meningococcal septicemia. Journal of Pediatric Orthopedics	- Study design does not meet inclusion criteria

Study	Code [Reason]
26(1): 135-9	
Bedford, H., de Louvois, J., Halket, S. et al. (2001) Meningitis in infancy in England and Wales: follow up at age 5 years. BMJ 323(7312): 533-6	- Population does not meet inclusion criteria
Belthur, M. V.; Bradish, C. E.; Gibbons, P. J. (2005) Late orthopaedic sequelae following meningococcal septicaemia. JOURNAL OF BONE AND JOINT SURGERY-BRITISH VOLUME 87b(2): 236-240	- Study design does not meet inclusion criteria
Berg, S., Trollfors, B., Hugosson, S. et al. (2002) Long-term follow-up of children with bacterial meningitis with emphasis on behavioural characteristics. European Journal of Pediatrics 161(6): 330-6	- Population does not meet inclusion criteria
Bunker-Wiersma, H. E., Koopmans, R. P., Kuipers, T. W. et al. (2008) Single nucleotide polymorphisms in genes of circulatory homeostasis in surviving pediatric intensive care patients with meningococcal infection. Pediatric Critical Care Medicine 9(5): 517-23	- No outcomes of interest
Buysse, C. M. P., Vermunt, L. C. A. C., Raat, H. et al. (2009) Surviving meningococcal septic shock in childhood: Long-term physical and psychological outcomes. Netherlands Journal of Critical Care 13(5): 237-246	- Insufficient presentation of results *Continuous data reported, and insufficient information about the number of people and events in the reference group*
Buysse, C. M., Raat, H., Hazelzet, J. A. et al. (2008) Surviving meningococcal septic shock: health consequences and quality of life in children and their parents up to 2 years after pediatric intensive care unit discharge. Critical Care Medicine 36(2): 596-602	- Comparison and outcomes do not meet inclusion criteria *Comparison between those with meningococcal disease and healthy controls does not include any outcomes of interest*
Buysse, C. M., Raat, H., Hazelzet, J. A. et al. (2008) Long-term health status in childhood survivors of meningococcal septic shock. Archives of Pediatrics & Adolescent Medicine 162(11): 1036-41	- Comparison and outcomes do not meet inclusion criteria *Comparison between those with meningococcal disease and healthy controls does not include any outcomes of interest*
Buysse, C. M., Vermunt, L. C., Raat, H. et al. (2010) Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Critical Care (London, England) 14(3): r124	- Comparison does not meet inclusion criteria
Buysse, Corinne M. P., Raat, Hein, Hazelzet, Jan A. et al. (2007) Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents.	- Comparison and outcomes do not meet inclusion criteria *Comparison between those with meningococcal disease and healthy controls*

Study	Code [Reason]
QUALITY OF LIFE RESEARCH 16(10): 1567-1576	*does not include any outcomes of interest*
Dastouri, F., Hosseini, A. M., Haworth, E. et al. (2014) Complications of serogroup B meningococcal disease in survivors: a review. Infectious Disorders - Drug Targets 14(3): 205-12	- Study design does not meet inclusion criteria *No comparison with healthy controls*
Douglas, S. A.; Sanli, H.; Gibson, W. P. (2008) Meningitis resulting in hearing loss and labyrinthitis ossificans - does the causative organism matter?. Cochlear Implants International 9(2): 90-6	- Population does not meet inclusion criteria
Drake, R.; Dravitski, J.; Voss, L. (2000) Hearing in children after meningococcal meningitis. Journal of Paediatrics & Child Health 36(3): 240-3	- Study design does not meet inclusion criteria
Ehrlich, T. R., Von Rosenstiel, I. A., Grootenhuis, M. A. et al. (2005) Long-term psychological distress in parents of child survivors of severe meningococcal disease. Pediatric Rehabilitation 8(3): 220-4	- Population does not meet inclusion criteria
Elrod, J., Mannhard, D., Mohr, C. et al. (2019) Plastic and Orthopaedic Interventions and Long-Term Sequelae in Children with Meningococcal Septicemia-40 Years of Experience at the University Children's Hospital Zurich. European Journal of Pediatric Surgery 29(5): 462-469	- Study design does not meet inclusion criteria
Gangoiti, I., Valle, J. R., Sota, M. et al. (2018) Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. European Journal of Emergency Medicine 25(4): 274-280	- Comparison does not meet inclusion criteria
Gedde-Dahl, T. W., Hoiby, E. A., Schillinger, A. et al. (1983) An epidemiological, clinical and microbiological follow-up study of incident meningococcal disease cases in Norway, winter 1981-1982. Material and epidemiology in the MenOPP project. NIPH Annals 6(2): 155-68	- No outcomes of interest
Haralambous, E., Hibberd, M. L., Hermans, P. W. et al. (2003) Role of functional plasminogen-activator-inhibitor-1 4G/5G promoter polymorphism in susceptibility, severity, and outcome of meningococcal	- Comparison does not meet inclusion criteria

Study	Code [Reason]
disease in Caucasian children. Critical Care Medicine 31(12): 2788-93	
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): 193-9	- No outcomes of interest
Howitz, M., Lambertsen, L., Simonsen, J. B. et al. (2009) Morbidity, mortality and spatial distribution of meningococcal disease, 1974-2007. Epidemiology & Infection 137(11): 1631-40	- Comparison does not meet inclusion criteria
Howitz, Michael F., Simonsen, Jacob, Krause, Tyra Grove et al. (2009) Risk of Adverse Birth Outcome After Group B Meningococcal Disease Results From A Danish National Cohort. PEDIATRIC INFECTIOUS DISEASE JOURNAL 28(3): 199-203	- No outcomes of interest
Huang, L., Heuer, O. D., Jansen, S. et al. (2020) Clinical and economic burden of invasive meningococcal disease: Evidence from a large German claims database. PLoS ONE [Electronic Resource] 15(1): e0228020	- Comparison and outcomes do not meet inclusion criteria *Comparison between those with meningococcal disease and healthy controls dose not include any outcomes of interest*
Jonsdottir, K. E. (1986) Meningococcal disease in Iceland, 1975-1984. Antonie van Leeuwenhoek, International Journal of General and Molecular Microbiology 52(3): 258	- Study design does not meet inclusion criteria
Kaplan, S. L., Schutze, G. E., Leake, J. A. et al. (2006) Multicenter surveillance of invasive meningococcal infections in children. Pediatrics 118(4): e979-84	- Study design does not meet inclusion criteria
Kennedy, I. T. R., van Hoek, A. J., Ribeiro, S. et al. (2017) Short-term changes in the health state of children with group B meningococcal disease: A prospective, national cohort study. PLoS ONE [Electronic Resource] 12(5): e0177082	- Comparison does not meet inclusion criteria
Lundbo, L. F., Harboe, Z. B., Clausen, L. N. et al. (2016) Genetic Variation in NFKBIE Is Associated With Increased Risk of Pneumococcal Meningitis in Children. EBioMedicine 3: 93-99	- No outcomes of interest
Meert, Kathleen L., Reeder, Ron, Maddux, Aline B. et al. (2020) Trajectories and Risk Factors for Altered Physical and	- Population does not meet inclusion criteria

Study	Code [Reason]
Psychosocial Health-Related Quality of Life After Pediatric Community-Acquired Septic Shock*. PEDIATRIC CRITICAL CARE MEDICINE 21(10): 869-878	
Moss, P. D. (1982) Outcome of meningococcal group B meningitis. Archives of Disease in Childhood 57(8): 616-21	- Population does not meet inclusion criteria *Participants had meningococcal meningitis, so this study is included in bacterial meningitis review (6.1)*
Olbrich, K. J., Muller, D., Schumacher, S. et al. (2018) Systematic Review of Invasive Meningococcal Disease: Sequelae and Quality of Life Impact on Patients and Their Caregivers. Infectious Diseases & Therapy 7(4): 421-438	- Population does not meet inclusion criteria *Systematic review includes studies of meningitis alone*
Oostenbrink, R., Maas, M., Moons, K. G. et al. (2002) Sequelae after bacterial meningitis in childhood. Scandinavian Journal of Infectious Diseases 34(5): 379-82	- Population does not meet inclusion criteria *Participants with bacterial meningitis*
Pickering, L., Jennum, P., Ibsen, R. et al. (2018) Long-term health and socioeconomic consequences of childhood and adolescent onset of meningococcal meningitis. European Journal of Pediatrics 177(9): 1309-1315	- Population does not meet inclusion criteria *Participants with bacterial meningitis*
Ploetz, Frans B. (2008) Importance of follow-up research in children surviving meningococcal septic shock. CRITICAL CARE MEDICINE 36(7): 2217-2217	- Study design does not meet inclusion criteria
Roed, C., Omland, L. H., Engsig, F. N. et al. (2010) Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study. PLoS ONE [Electronic Resource] 5(3): e9662	- Population does not meet inclusion criteria *67.2% of participants had meningococcal meningitis alone, so this study is included in bacterial meningitis review (6.1)*
Sadarangani, M., Scheifele, D. W., Halperin, S. A. et al. (2015) Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clinical Infectious Diseases 60(8): e27-35	- Comparison does not meet inclusion criteria
Schmand, B., de Bruin, E., de Gans, J. et al. (2010) Cognitive functioning and quality of life nine years after bacterial meningitis. Journal of Infection 61(4): 330-4	- Population does not meet inclusion criteria *Participants with meningitis*
Shears, D., Nadel, S., Gledhill, J. et al. (2005) Short-term psychiatric adjustment of children and their parents following	- Study design does not meet inclusion criteria

Study	Code [Reason]
meningococcal disease. Pediatric Critical Care Medicine 6(1): 39-43	
Shears, D., Nadel, S., Gledhill, J. et al. (2007) Psychiatric adjustment in the year after meningococcal disease in childhood. Journal of the American Academy of Child & Adolescent Psychiatry 46(1): 76-82	- Study design does not meet inclusion criteria
Smith, I., Bjornevik, A. T., Augland, I. M. et al. (2006) Variations in case fatality and fatality risk factors of meningococcal disease in Western Norway, 1985-2002. Epidemiology & Infection 134(1): 103-10	- Study design does not meet inclusion criteria
Stovall, S. H. and Schutze, G. E. (2002) Meningococcal infections in children from Arkansas. Pediatric Infectious Disease Journal 21(5): 366-70	- Study design does not meet inclusion criteria
Strifler, L., Morris, S. K., Dang, V. et al. (2016) The Health Burden of Invasive Meningococcal Disease: A Systematic Review. Journal of the Pediatric Infectious Diseases Societ 5(4): 417-430	- Population does not meet inclusion criteria *Systematic review includes studies with bacterial meningitis*
Tonjum, T., Nilsson, F., Bruun, J. N. et al. (1983) The early phase of meningococcal disease. NIPH Annals 6(2): 175-81	- Comparison does not meet inclusion criteria *Comparison is not healthy cohort*
Tucci, M., Lebel, M. H., Gauthier, M. et al. (1995) Admission to a pediatric intensive care unit for bacterial meningitis: Review of 168 cases. Journal of Intensive Care Medicine 10(5): 253-260	- Population does not meet inclusion criteria
van de Beek, D., Schmand, B., de Gans, J. et al. (2002) Cognitive impairment in adults with good recovery after bacterial meningitis. Journal of Infectious Diseases 186(7): 1047-52	- Population does not meet inclusion criteria *Participants with meningitis*
van Zellem, L., Utens, E. M., de Wildt, S. N. et al. (2014) Analgesia-sedation in PICU and neurological outcome: a secondary analysis of long-term neuropsychological follow-up in meningococcal septic shock survivors. Pediatric Critical Care Medicine 15(3): 189-96	- Study design does not meet inclusion criteria
Vermunt, L. C., Buysse, C. M., Aarsen, F. K. et al. (2009) Long-term cognitive functioning in children and adolescents who survived septic shock caused by Neisseria meningitidis. British Journal of Clinical	- Insufficient presentation of results *Compared with normative reference group (from previously published data), and insufficient information was reported about the number of people and events in the*

Study	Code [Reason]
Psychology 48(pt2): 195-208	*reference group*
Vermunt, L. C., Buysse, C. M., Joosten, K. F. et al. (2010) Recovery in parents of children and adolescents who survived septic shock caused by Neisseria meningitidis: a cross-sectional study. Intensive & Critical Care Nursing 26(3): 128-37	- Population does not meet inclusion criteria
Vermunt, L. C., Buysse, C. M., Joosten, K. F. et al. (2008) Behavioural, emotional, and post-traumatic stress problems in children and adolescents, long term after septic shock caused by Neisseria meningitidis. British Journal of Clinical Psychology 47(pt3): 251-63	- Insufficient presentation of results *Insufficient information about the number of people and events in the reference group*
Vermunt, L. C., Buysse, C. M., Joosten, K. F. et al. (2008) Self-esteem in children and adolescents after septic shock caused by Neisseria meningitidis: scars do matter. Journal of Adolescent Health 42(4): 386-93	- Insufficient presentation of results *Continuous data reported, and insufficient information about the number of people and events in the reference group*
Wang, B., Clarke, M., Thomas, N. et al. (2014) The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children. Pediatric Infectious Disease Journal 33(3): 316-8	- Study design does not meet inclusion criteria

1

2 **Excluded economic studies**

3 No economic evidence was identified for this review.

4

Appendix K Research recommendations – full details

Research recommendations for review question: What is the risk of long-term complications in meningococcal disease?

No research recommendation was made for this review.