National Institute for Health and Care Excellence

Final

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

[I1] Evidence review for long-term complications and follow-up for bacterial meningitis

NICE guideline NG240

Evidence review underpinning recommendations 1.12.1 to 1.12.4, 1.12.7 to 1.12.10, and 1.13.1 to 1.13.11 and the recommendation for research on long-term outcomes of bacterial meningitis in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Review question

What is the risk of long-term complications in bacterial meningitis?

Introduction

Bacterial 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 bacterial meningitis 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 (including neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis.
Prognostic factors	Bacterial meningitis
Comparison	No bacterial meningitis (healthy cohort)
Outcome	**Critical** Population: adults, neonates, 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 • Speech and language disorder Population: adults • Headache Population: neonates, infants and children • Moderate developmental delay • Severe developmental delay • Educational achievement

	• Hydrocephalus with a shunt **Important** None *For infants and children below school-age, educational, cognitive, 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

Twenty-five studies were included for this review, 16 prospective cohort studies (Anderson 2004, Bedford 2001, Berg 2002, Christie 2011, de Louvois 2007, Feldman 1988, Grimwood 1995, Hoogman 2007, Hugosson 1997, Kloek 2020, Pickering 2018, Schmidt 2006, Stevens 2003, Taylor 1990, Tejani 1982, Vartzelis 2011), and 9 retrospective cohort studies (D'Angio 1995, Koomen 2003, Moss 1982, Roed 2010a, Roed 2010b, Roed 2011, Roed 2012, Roed 2013, Zelano 2020).

Studies with univariate analyses were included in this review because only 3 studies (Anderson 2004, Grimwood 1995, Koomen 2003) 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.

Four studies reported all-cause mortality (Roed 2010a, Roed 2010b, Roed 2011, Roed 2012), and 8 studies reported long-term motor deficits (Bedford 2001, Berg 2002, D'Angio 1995, Grimwood 1995, Hugosson 1997, Moss 1982, Pickering 2018, Roed 2011). Eleven studies reported long-term cognitive deficits (Bedford 2001, Christie 2011, D'Angio 1995, Grimwood 1995, Hoogman 2007, Kloek 2020, Koomen 2003, Schmidt 2006, Stevens 2003, Taylor 1990, Tejani 1982), 6 studies reported long-term behavioural deficits (Bedford 2001, Berg 2002, Grimwood 1995, Koomen 2003, Taylor 1990, Vartzelis 2011), and 2 studies reported long-term psychological impairment (Christie 2011, Koomen 2003). Ten studies reported any hearing impairment (Bedford 2001, Berg 2002, Christie 2011, D'Angio 1995, Grimwood 1995, Hugosson 1997, Koomen 2003, Moss 1982, Roed 2011, Stevens 2003), 7 studies reported any visual impairment (Bedford 2001, Berg 2002, Grimwood 1995, Moss 1982, Pickering 2018, Roed 2011, Stevens 2003), 10 studies reported educational achievement (Anderson 2004, Christie 2011, D'Angio 1995, de Louvois 2007, Feldman 1988, Grimwood 1995, Koomen 2003, Roed 2013, Taylor 1990, Tejani 1982), 6 studies reported diagnosis of epilepsy (Bedford 2001, D'Angio 1995, Grimwood 1995, Roed 2011, Stevens 2003, Zelano 2020), 2 studies reported speech and language disorder (Bedford 2001, Berg 2002), and 2 studies reported hydrocephalus with a shunt (Grimwood 1995, Stevens 2003).

All studies reported bacterial meningitis as potential risk factor.

One study was conducted in neonates (Stevens 2003), 4 studies included babies (Bedford 2001, D'Angio 1995, de Louvois 2007, Vartzelis 2011), 14 studies reported on children (Anderson 2004, Berg 2002, Christie 2011, Feldman 1988, Grimwood 1995, Hugosson 1997, Koomen 2003, Moss 1982, Pickering 2018, Roed 2010b, Roed 2011, Roed 2013, Taylor 1990, Tejani 1982), and 6 studies were conducted in adults (Hoogman 2007, Kloek 2020, Roed 2010a, Roed 2012, Schmidt 2006, Zelano 2020).

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

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

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

Table 2: Summary of included studies

Study	Population	Risk factor	Outcomes	Comments
Anderson 2004 Prospective cohort study Australia	N=203 Children aged 3 months to 14 years who had bacterial meningitis, compared against grade- and sex-matched controls. Bacterial meningitis group: Age in months at admission (median; range): 17 (3-79)	• Bacterial meningitis	• Educational achievement	Follow-up: 12 years Socioeconomic status, sex and age were treated as covariates suggesting baseline differences and residual confounding. No adjusted data reported.
Bedford 2001 Prospective cohort study England and Wales	N=2975 Children who survived an episode of acute bacterial meningitis, compared against age- and sex-matched controls Age: Not reported	• Bacterial meningitis	• Long-term motor deficits • Long-term cognitive deficits • Long term behavioural deficits • Any hearing impairment • Any visual impairment • Diagnosis of epilepsy • Speech and language disorder	Follow-up: 5 years Age- and sex-matched controls were used but unclear if there was any residual confounding as limited information about baseline characteristics reported
Berg 2002	N=608	• Bacterial	• Long-term motor	Follow-up: 2-13

Study	Population	Risk factor	Outcomes	Comments
Prospective cohort study Sweden	Children aged 0-4 years who had bacterial meningitis, compared against sibling controls Age in years at diagnosis (median; range): Bacterial meningitis group: 9.6 (6.5-14.3) Control group: 11 (6.1-15.3)	meningitis (H. influenzae; S. pneumoniae; and N. meningitidis)	deficits • Long-term behavioural deficits • Any hearing impairment • Any visual impairment • Speech and language disorder	years (calculated based on age at diagnosis and follow-up) Controls were siblings of the closet age rather than age matched and unclear if there was any residual confounding
Christie 2011 Prospective cohort study UK	N=168 Children who survived bacterial meningitis, compared against sibling controls, or similarly aged young person Age in years at follow-up (median; range): Bacterial meningitis group: 7.7 (3-20) Control group: 7.6 (3-20)	• Bacterial meningitis (S. pneumoniae)	• Long-term cognitive deficits • Long-term psychological impairment • Any hearing impairment • Educational achievement	Follow-up (median; range): 6 (1-17.55) years Matched analysis for hearing impairment and cognitive deficits; and unmatched analysis for psychological impairment and educational achievement were conducted
D'Angio 1995 Retrospective cohort study USA	N=120 Navajo children who had bacterial meningitis, compared against sibling and age-matched controls Age in years at follow-up (mean): 9.3	• Bacterial meningitis (H. influenzae)	• Long-term motor deficits • Long-term cognitive deficits • Any hearing impairment • Educational achievement • Diagnosis of epilepsy	Follow-up: 3.6-15 years Sibling or age-matched controls were used, but statistical analyses were not adjusted for confounders identified, such as per capita incomes and Hollingshead socioeconomic status scores
de Louvois 2007 Prospective cohort study	N=1219 Children aged 16 years who had bacterial	• Bacterial meningitis	• Educational achievement	Follow-up: 16 years Age- and sex-matched

Study	Population	Risk factor	Outcomes	Comments
England and Wales	meningitis in infancy, compared against age- and sex-matched controls Age: Not reported			controls used, but unclear if there was difference in baseline characteristics as such data not reported
Feldman 1988 Prospective cohort study USA	N=35 Children who had H. influenzae meningitis, compared against age-matched siblings Age in years at follow-up (mean; SD): 13.3 (1.2)	• Bacterial meningitis (H. influenzae)	• Educational achievement	Follow-up: 10-12 years Age-matched controls were used, but unclear if there was residual confounding as limited baseline characteristics reported
Grimwood 1995 Prospective cohort study Australia	N=260 Children who had bacterial meningitis, compared against grade- and sex-matched children without history of meningitis Age in years at follow-up (mean; SD): 9 (2)	• Bacterial meningitis (H. influenzae; S. pneumoniae; N. meningitidis; and other or unknown)	• Long-term motor deficits • Long-term cognitive deficits • Long-term behavioural deficits • Any hearing impairment • Any visual impairment • Educational achievement • Diagnosis of epilepsy • Hydrocephalus with a shunt	Follow-up (mean): 6.7 years Statistical analyses for IQ <80, behavioural deficits, educational achievement, balance, dysdiadochokinesis, fine motor function, coordination, and visual impairment were adjusted for age, sex, mother's educational level, paternal occupation, and ethnicity. No adjusted data reported for IQ 70-80, IQ <70, cerebral palsy, spasticity, hearing impairment, and epilepsy.
Hoogman 2007 Prospective cohort study	N=227 Adults who survived bacterial meningitis,	• Bacterial meningitis (Pneumococcal or meningococcal	• Long-term cognitive deficits	Follow-up: up to 5.7 years Test battery T scores were

Study	Population	Risk factor	Outcomes	Comments
Netherlands	compared against healthy cohort Age in years at follow-up (mean; SD): 46 (15.4)	meningitis)		corrected for age and education, but no definition or measurement of cofounders reported
Hugosson 1997 Prospective cohort study Sweden	N=42 Children who had bacterial meningitis before the age of seven, compared against age-matched students or healthy volunteer blood donors Age in months at diagnosis (range): Bacterial meningitis group: 2-83	• Bacterial meningitis (H. influenzae; and N. meningitidis)	• Long-term motor deficits • Any hearing impairment	Follow-up: 17-27 years Age-matched controls were used, but unclear if there was any residual cofounding
Kloek 2020 Prospective cohort study Netherlands	N=149 Participants aged >16 years who had bacterial meningitis, compared against their partners or proxies Age in years at follow-up (median; IQR): Bacterial meningitis group: 63 (56-69) Control group: 65 (54-68)	• Bacterial meningitis	• Long-term cognitive deficits	Follow-up: 1-5 years No attempt to control or match for confounders
Koomen 2003 Retrospective cohort study Netherlands	N=984 Children who had bacterial meningitis, compared against school-age siblings and close friends Age in years at follow-up (median; range): Bacterial	• Bacterial meningitis (N. meningitidis; S. pneumoniae; S. agalactiae; E. coli; and L. monocytogenes)	• Long-term cognitive deficits • Long-term behavioural deficits • Long-term psychological impairment • Any hearing impairment • Educational achievement	Follow-up: Median 6.2 years (range 3.2-10 years) The analysis was adjusted for age and sex

Study	Population	Risk factor	Outcomes	Comments
	meningitis group: 8.5 (4.3-14.9) Control group: 9.1 (3.2-14.9)			
Moss 1982 Retrospective cohort study UK	N=120 Children who had bacterial meningitis, compared against age- and sex-matched controls Age in years and months at diagnosis (range): Bacterial meningitis group: 1 month - 7 years 10 months	• Bacterial meningitis (N. meningitidis)	• Long-term motor deficits • Any hearing impairment • Any visual impairment	Follow-up: 5-9 years Age- and sex-matched controls were used, but unclear if there was residual confounding
Pickering 2018 Prospective cohort study Denmark	N=5480 Children who had meningococcal meningitis before the age of 18 years, compared against age- and sex-matched controls Age in years at diagnosis: Bacterial meningitis group (mean; SD): 8 (6) Control group (median): 6	• Bacterial meningitis (Meningococcal meningitis)	• Long-term motor deficits • Any visual impairment	Follow-up: Not reported (The study stated that participants had meningitis at age 8 years, and assessments took place at age 30 years. Therefore, follow-up could be about 22 years) Age- and sex-matched controls were used, but unclear if there was residual confounding Long-term motor deficit is an indirect outcome as disorders of nervous system, that could include different types of neurological disorders, were reported
Roed 2010a Retrospective	N=10655 Children who had	• Bacterial meningitis (Pneumococcal	• All-cause mortality	Follow-up: up to 30 years Age- and sex-

Study	Population	Risk factor	Outcomes	Comments
cohort study Denmark	pneumococcal meningitis, compared against age- and sex-matched controls Age in years at diagnosis (median; IQR): Bacterial meningitis group: 44 (3-63) Control group: 44 (3-63)	meningitis)		matched controls were used, but no attempts were made to control for confounders (infectious disease and neoplasm) identified
Roed 2010b Retrospective cohort study Denmark	N=24545 Patients who had meningococcal meningitis or meningococcal disease, compared against age- and sex-matched controls Age in years at diagnosis (median; IQR): Bacterial meningitis group: 9 (2-18) Control group: 9 (2-18)	• Bacterial meningitis (meningococcal meningitis)	• All-cause mortality	Follow-up: up to 30 years Meningococcal meningitis: 3297/4909 (67%) Age- and sex-matched controls were used, but unclear if there was any residual confounding
Roed 2011 Retrospective cohort study Denmark	N=8694 Children who had H. influenzae meningitis, compared against age- and sex-matched controls Age in years at diagnosis (median; IQR): Bacterial meningitis group: 1.1 (1-2) Control group: 1.1 (1-2)	• Bacterial meningitis (H. influenzae)	• All-cause mortality • Long-term motor deficits • Any hearing impairment • Any visual impairment • Diagnosis of epilepsy	Follow-up: Median 21.3 years (IQR: 17-26 years) Age- and sex-matched controls were used, but no attempts to control for potential confounders (infectious disease and ear diseases) identified
Roed 2012 Retrospective cohort study Denmark	N=1140 Patients who had Listeria meningitis, compared against	• Bacterial meningitis (Listeria meningitis)	• All-cause mortality	Follow-up: up to 30 years Age- and sex-matched controls were

Study	Population	Risk factor	Outcomes	Comments
	age- and sex-matched controls Age in years at diagnosis (median; IQR): Bacterial meningitis group: 62 (50-73) Control group: 62 (50-73)			used, but no attempts to control for confounders (infectious disease and cancer) identified
Roed 2013 Retrospective cohort study Denmark	N=16802 Patients who had bacterial meningitis, compared against full siblings Age in years at diagnosis (mean; SD): Bacterial meningitis group: 2 (1)	• Bacterial meningitis (meningococcal, pneumococcal, and H. influenzae meningitis)	• Educational achievement	Follow-up: Not reported (Participants had meningitis at age 2 years and were followed up until age 35. Therefore, follow-up could be about 33 years) Age- and sex-matched controls were used, but unclear if there was residual confounding
Schmidt 2006 Prospective cohort study Germany	N=89 (whole study N=148) Patients with confirmed bacteriological or ≥2 laboratory signs of bacterial CNS infection plus signs of bacterial meningitis, compared against age- and sex-matched controls Age in years at follow-up (mean; SD): 45 (14)	• Bacterial meningitis (S. pneumoniae; N. meningitidis; S. aureus; Streptococci; L. monocytogenes)	• Long-term cognitive deficits	Follow-up: 6 years Study also included 59 participants with viral meningitis, but this group was not of interest for current review so was not extracted Age- and sex-matched controls were used, but no attempts to control for potential confounders (socioeconomic status) identified
Stevens 2003	N=273	• Bacterial meningitis (L.	• Long-term cognitive deficits	Follow-up: Not reported

Study	Population	Risk factor	Outcomes	Comments
Prospective cohort study England and Wales	Children who had neonatal bacterial meningitis, compared against age- and sex-matched controls Age in years at follow-up (mean; SD): 9 (0.3)	monocytogenes ; Gram negative bacteria; E. coli; Group B streptococci)	• Any hearing impairment • Any visual impairment • Diagnosis of epilepsy • Hydrocephalus with a shunt	(Participants had neonatal meningitis and were assessed at age 9-10 years, so follow-up could be 9-10 years) Age- and sex-matched controls were used, but unclear if there was residual confounding Unclear whether participants were preterm or term neonates as no such data reported
Taylor 1990 Prospective cohort study Canada	N=194 Children who had H. influenzae meningitis, compared against school-age siblings Age in years at follow-up (mean; SD): 11 (3)	• Bacterial meningitis (H. influenzae type b)	• Long-term cognitive deficits • Long-term behavioural deficits • Educational achievement	Follow-up: Not reported (Participants had meningitis at age 17.3 months and were assessed at age 9.6 years, so follow-up could be about 8 years) No attempts were made to control potential confounders
Tejani 1982 Prospective cohort study USA	N=37 Children who had H. influenzae meningitis, compared against sibling controls Age in months/years at diagnosis (range): Bacterial meningitis group: 2 months to 6 years	• Bacterial meningitis (H. influenzae type b)	• Long-term cognitive deficits • Educational achievement	Follow-up: up to 4 years All children in the bacterial meningitis group were admitted to ICU No attempts were made to identify or control for confounders
Vartzelis 2011	N=60 Children who had	• Bacterial meningitis (N. meningitidis; S.	• Long-term behavioural deficits	Follow-up: Not reported (The study stated that

Study	Population	Risk factor	Outcomes	Comments
Prospective cohort study Greece	bacterial meningitis when they were aged >6 months, compared against healthy children or teenagers from the extended families of the patients Age in years at follow-up (mean; SD): 13 (3)	pneumoniae; H. influenzae; and Group B streptococcus)		participants were assessed when they were aged between 7 and 17 years) No attempts were made to identify or control for confounders
Zelano 2020 Retrospective cohort study Sweden	N=39040 (whole study N=48329) Patients aged >18 years who had bacterial meningitis, compared against age- and sex-matched controls Age in years at diagnosis: >18 years	• Bacterial meningitis	• Diagnosis of epilepsy	Follow-up: up to 17 years Study also included participants with other brain infections, such as herpes simplex virus encephalitis (N=443), tick-borne encephalitis (N=886), abscess (N=938), other meningitis (N=5778), and other encephalitis (N=1244), but these groups were not of interest for current review so was not extracted Age- and sex-matched controls were used, but unclear if there was residual confounding

CNS: central nervous system; E. coli: Escherichia coli; H. influenzae: Haemophilus influenzae; ICU: intensive care unit; IQ: intelligence quotient; IQR: interquartile range; L. monocytogenes: Listeria monocytogenes; N. meningitidis: Neisseria meningitidis; SD: standard deviation; S. aureus: Staphylococcus aureus; S. agalactiae: Streptococcus agalactiae; S. pneumoniae: Streptococcus pneumoniae

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

This section is a narrative summary of the findings of the review, as presented in the GRADE tables in appendix F. For details of the committee's confidence in the evidence and how this affected recommendations, see The committee's discussion and interpretation of the evidence.

The evidence was assessed as being very low quality due to high or moderate risk of bias in some of the domains of the QUIPs checklist, serious heterogeneity, the inclusion of indirect outcomes, 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.

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 children and adults, evidence showed a moderate association between bacterial meningitis and all-cause mortality.

Motor deficits

In babies, bacterial meningitis was strongly associated with neuromotor disabilities or cerebral palsy.

In children, bacterial meningitis was also strongly associated with long-term motor deficits, when measured as impairments in gross motor function, fine motor function (in adjusted and unadjusted analyses), abnormal coordination, abnormal balance, dysdiadochokinesis, and inpatient admission for cerebral palsy or another paralytic syndrome. There was a moderate association between bacterial meningitis and disorders of the nervous system. There was no evidence for an association between bacterial meningitis and spasticity, or abnormal oculomotor test, or nystagmus or tremor of the hands and exaggerated knee jerks, or cerebral palsy, or use of outpatient services for cerebral palsy or another paralytic syndrome.

Cognitive and developmental complications

In neonates, bacterial meningitis was strongly associated with an increased risk of long-term cognitive deficits when measured as an intelligence quotient (IQ) less than 70. There was no evidence of an increased risk of cognitive deficit when measured as an IQ between 70 and 80.

In babies, bacterial meningitis was also strongly associated with long-term cognitive deficits when defined as learning difficulties and an IQ less than 70.

In babies, bacterial meningitis was strongly associated with poor educational achievement when measured as the number who achieved less than 4 General Certificate of Secondary Education (GCSE) exam passes, or number who repeated a grade, or number in receipt of special educational assistance.

In babies, bacterial meningitis was strongly associated with speech and/or language problems.

In children, bacterial meningitis was strongly associated with long-term cognitive deficits when measured as a full-scale IQ of less than 80 (adjusted and unadjusted analyses), a verbal IQ of less than 85, and functional limitation in terms of cognition rated by parents on the Health Utilities Index (HUI-2). There was no evidence of an increased risk of cognitive deficit when measured as full-scale IQ of less than 85 or less than 90.

In children, bacterial meningitis was strongly associated with having serious educational problems (based on parental report) in terms of speed, and concentration problems.

In children, bacterial meningitis was strongly associated with receipt of special educational assistance, being unable to read, deficient school achievement (based on parental report), and referral to a special needs school. There was a small but statistically significant association between bacterial meningitis and a lower rate of completion of high school education or obtaining a degree from college or university. There was no evidence that receiving more family help with homework, requiring remedial help such as tutoring, poor academic achievement (assessed with the Wide Range Achievement Test and Gilmore Oral Reading Test), reading or arithmetic ability below appropriate grade level, repeating a grade, vocational education, or speech difficulties, were associated with bacterial meningitis.

In adults, there was a strong association between bacterial meningitis and cognitive impairment, impaired executive function, and impaired non-verbal learning/memory. There was no evidence for an increased risk of impaired attention, impaired short-term/working memory, impaired verbal learning/memory, or impaired visuo-constructive functions associated with bacterial meningitis.

Behavioural and psychological complications

In babies, bacterial meningitis was strongly associated with long-term behavioural problems (based on parent/GP report or on the number scoring above cut-off based on the total score of the Child Behaviour Checklist [CBCL]). There was no evidence of an increased risk associated with bacterial meningitis for internalising or externalising problems (based on number scoring above cut-off on subscales of the CBCL).

In children, there was a strong association between bacterial meningitis and problems with adjustment at school (assessed using CBCL subscale). There were moderate associations between bacterial meningitis and long-term behavioural deficits when measured as the number scoring above cut-off based on total CBCL score or having serious educational problems (based on parental report) in terms of hyperactivity. There was no evidence of an increased risk associated with bacterial meningitis for the teacher-report version of the CBCL based on total behaviour score or adjustment at school (adaptive function in clinical range), or internalising or externalising problems (assessed using subscales of the CBCL).

In children, bacterial meningitis was strongly associated with psychological distress as reported by parents (scoring above cut-off on the Strengths and Difficulties Questionnaire), serious educational problems (based on parental report) in terms of depressed mood, and functional impairment in terms of emotion (assessed with HUI-2). There was no evidence of an increased risk associated with bacterial meningitis for depressive symptoms (assessed with self-report or parent-report versions of the Moods and Feelings Questionnaire), or psychological distress based on self-report. There was no evidence of an increased risk of DSM-IV ADHD symptoms (in terms of inattention, or hyperactivity-impulsiveness), or of functional impairment (scoring below cut-off for adaptive functioning on the Vineland Adaptive Behaviour Scale) associated with bacterial meningitis.

Hearing impairment

In neonates, there was a possible association between bacterial meningitis and sensorineural hearing loss (90% CI 1.14 to 150.83), however this was not statistically significant (using standard 95% CI).

In babies, there was a moderate association between bacterial meningitis and any hearing impairment.

In children, there was a strong association between bacterial meningitis and any hearing impairment. There was no evidence for an increased risk associated with bacterial meningitis of attending outpatient services for hearing problems.

Visual impairment

In neonates, there was no evidence of an increased risk of bilateral impairment of visual acuity associated with bacterial meningitis.

In babies, bacterial meningitis was strongly associated with ocular or visual disorders.

In children, there was a strong association between bacterial meningitis and sensitivity to light. There was a moderate association between bacterial meningitis and having diseases of the eye or adnexa. There was no evidence of an increased risk associated with bacterial meningitis for impaired vision (based on parental report), abnormalities of vision (based on medical examination), having vision worse than 6/9 or N5, squints, inpatient admission rates for eye diseases, or use of outpatient services for eye diseases.

Epilepsy

In neonates, there was no evidence of an increased risk of seizure disorder or absence seizures associated with bacterial meningitis.

In babies, bacterial meningitis was strongly associated with seizure disorders.

In children, there was a strong association between inpatient admission rates for epilepsy/seizure disorders and bacterial meningitis. There was no evidence of increased risks associated with bacterial meningitis for a diagnosis of epilepsy, or use of outpatient services for epilepsy/seizure disorders.

In adults, there was a strong association between bacterial meningitis and a diagnosis of epilepsy.

Hydrocephalus with a shunt

In neonates, there was no evidence of an increased risk associated with bacterial meningitis for persistent hydrocephalus requiring a shunt.

In children, there was no evidence of an increased risk of ventriculoperitoneal shunt associated with bacterial meningitis.

There were a number of outcomes in the protocol that were not reported by any studies, including disorders of consciousness and headache.

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 will 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

Bacterial meningitis 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 and speech and language disorder were prioritised as critical outcomes in all age groups because of the potential long-term impact of these outcomes on the ability to carry out certain activities of daily life and on quality of life.

As above, moderate developmental delay, severe developmental delay and educational achievement 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 neonates, babies, and children because they will not be relevant to people who contracted bacterial meningitis in adulthood. Headache and hydrocephalus with a shunt were also selected as critical outcomes for adults, and neonates, 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 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, lack of information about prognostic factor measurement, subjective measurement of outcome, failure to adjust for confounding factors, and insufficient presentation of analytical strategy) and imprecision due to small number of events. There was also some heterogeneity that could not be explained by subgroup analysis and one instance of inclusion of an indirect outcome.

No evidence was found that reported disorders of consciousness or headache.

Benefits and harms

The committee considered the evidence for long-term complications associated with bacterial meningitis 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). Despite this, the committee made recommendations based on the best available evidence and their knowledge and experience. The committee were aware that in neonates and adults there was an absence of evidence for some outcomes (for example, long-term motor deficits in neonates and adults; and hearing impairment in adults); however, in the absence of evidence the committee felt, based on their knowledge and experience, that it was reasonable to extrapolate from the

evidence on babies and children as bacterial meningitis could have similar impacts for other ages.

The committee agreed, based on the evidence of long-term complications identified in this review, that it is important that people with bacterial meningitis 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 bacterial meningitis from hospital, taking account of the potential for the complications identified in the evidence.

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 bacterial meningitis. 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 bacterial meningitis was strongly associated with intellectual disability in neonates, babies, and children; with poor educational attainment and/or the need for special educational assistance in babies and children; and with speech and/or language problems in babies. 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, and children.

The committee noted that there was some evidence for an association between long-term behavioural problems, including problems with adjustment at school, following bacterial meningitis in babies and children. The evidence also showed that bacterial meningitis may increase the risk of psychological distress in children. No evidence was identified for long-term psychological impairments associated with bacterial meningitis in adults. However, based on their clinical knowledge and experience, the committee agreed that bacterial meningitis can increase the risk of post-traumatic stress disorder (PTSD) and other psychological sequelae, and recommended that cognitive and psychological support needs should be considered as part of planning for discharge for people with bacterial meningitis and a referral to psychological services should be made where needs are identified.

The evidence for epilepsy as a long-term complication of bacterial meningitis was mixed. There was some evidence for an association between a diagnosis of bacterial meningitis and seizure disorders (in babies) and inpatient admission rates for epilepsy/seizure disorders (in children). However, there was no evidence of an increased risk associated with bacterial meningitis for seizures in neonates, a diagnosis of epilepsy, or use of outpatient services for epilepsy in children. In the committee's experience, although some people may need long-term anti-epileptic drugs following meningitis, 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 an appropriate specialist. 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 that bacterial meningitis increased the risk of long-term hearing impairments for babies and children, and a possible association was identified for neonates. As hearing loss can have a serious impact on quality of life, the committee 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 their bacterial meningitis 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 this review should be undertaken by a hospital doctor. The committee agreed this review should cover all possible associated morbidities, specifically the results of hearing test and whether cochlear implants are needed, psychosocial problems, and neurological and developmental problems as bacterial meningitis had moderate to strong association 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, sensory, psychosocial, behavioural, and educational complications). The committee agreed that babies under 12 months should be reviewed 1 year after discharge by a paediatrician to assess for the complications identified in the evidence (neurodevelopmental, 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 also discussed that if a child or young person develops possible neurodevelopmental complications more than 2 years after discharge, their family members or carers should get advice from their GP. Therefore, the committee included a recommendation to raise awareness of this. The committee recommended that healthcare professionals (including school nurses, health visitors, and GPs) should be alert for late-onset complications of bacterial meningitis 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 evidence showed that bacterial meningitis can increase the risk of poor educational outcomes. The committee agreed 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, they recommended that family members or carers should inform their child or young person's school about past episode of meningitis, that this may affect their learning and that they may need additional reviews of their educational outcomes and learning needs (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 any additional needs or adaptations (including driving) by appropriate services if complications are present.

The committee acknowledged the moderate association between bacterial meningitis and all-cause mortality in children and 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.

The committee noted that the evidence was very limited for long-term complications following bacterial meningitis in neonates, with only 1 eligible study identified and this study is not recent (published in 2003). The committee discussed that quantifying the long-term complications of bacterial meningitis is important to allow appropriate counselling and follow-up of those at risk and to prioritise treatment and prevention strategies. The committee agreed to include a research recommendation to investigate the long-term outcomes after bacterial meningitis in infancy (see Appendix K).

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 bacterial meningitis.

Given the evidence on the health and educational harms resulting from bacterial meningitis, the committee made recommendations to ensure that the relevant assessments were undertaken to ensure that appropriate care is provided to people with bacterial meningitis and that they are not 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 neonates, 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 bacterial meningitis 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 1.12.4, 1.12.7 to 1.12.10, and 1.13.1 to 1.13.11, and the recommendation for research on long-term outcomes of bacterial meningitis. Other evidence supporting these recommendations can be found in evidence reviews on long-term complications and follow-up for meningococcal disease (see evidence review I2) and support for confirmed meningitis or meningococcal disease (see evidence review K4).

References – included studies

Prognostic

Anderson 2004

Anderson, V., Anderson, P., Grimwood, K. et al. (2004). Cognitive and executive function 12 years after childhood bacterial meningitis: effect of acute neurologic complications and age of onset, Journal of Pediatric Psychology 29(2), 67-81

Bedford 2001

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), 533-536

Berg 2002

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), 330-336

Christie 2011

Christie, D., Viner, R. M., Knox, K. et al. (2011). Long-term outcomes of pneumococcal meningitis in childhood and adolescence, European Journal of Pediatrics 170(8), 997-1006

D'Angio 1995

D'Angio, C. T., Froehlke, R. G., Plank, G. A. et al. (1995). Long-term outcome of Haemophilus influenzae meningitis in Navajo Indian children, Archives of Pediatrics & Adolescent Medicine 149(9), 1001-1008

de Louvois 2007

de Louvois, J., Halket, S., Harvey, D. (2007). Effect of meningitis in infancy on school-leaving examination results, Archives of Disease in Childhood 92(11), 959-962

Feldman 1988

Feldman, H. M. and Michaels, R. H. (1988). Academic achievement in children ten to 12 years after Haemophilus influenzae meningitis, Pediatrics 81(3), 339-344

Grimwood 1995

Grimwood, K., Anderson, V. A., Bond, L. et al. (1995). Adverse outcomes of bacterial meningitis in school-age survivors, Pediatrics 95(5), 646-656

Hoogman 2007

Hoogman, M., van de Beek, D., Weisfelt, M. et al. (2007). Cognitive outcome in adults after bacterial meningitis, Journal of Neurology, Neurosurgery & Psychiatry 78(10), 1092-1096

Hugosson 1997

Hugosson, S., Carlsson, E., Borg, E. et al. (1997). Audiovestibular and neuropsychological outcome of adults who had recovered from childhood bacterial meningitis, International Journal of Pediatric Otorhinolaryngology 42(2), 149-167

Kloek 2020

Kloek, A. T., Brouwer, M. C., Schmand, B. et al. (2020). Long-term neurologic and cognitive outcome and quality of life in adults after pneumococcal meningitis, Clinical Microbiology & Infection 26(10), 1361-1367

Koomen 2003

Koomen, I., Grobbee, D. E., Jennekens-Schinkel, A. et al. (2003). Parental perception of educational, behavioural and general health problems in school-age survivors of bacterial meningitis, Acta Paediatrica 92(2), 177-185

Moss 1982

Moss, P. D. (1982). Outcome of meningococcal group B meningitis, Archives of Disease in Childhood 57(8), 616-621

Pickering 2018

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

Roed 2010a

Roed, C., Engsig, F. N., Omland, L. H. et al. (2010). Long-term mortality in patients diagnosed with pneumococcal meningitis: a Danish nationwide cohort study, American Journal of Epidemiology 172(3), 309-317

Roed 2010b

Roed, C., Omland, L. H., Engsig, F. N. et al. (2010). Long-term mortality in patients diagnosed with meningococcal

Roed 2011

Roed, C., Engsig, F. N., Omland, L. H. et al. (2011). Long-term mortality in children diagnosed with Haemophilus influenzae meningitis: a Danish nationwide cohort study, Pediatric Infectious Disease Journal 30(8), e147-e154

Roed 2012

Roed, C., Engsig, F. N., Omland, L. H. et al. (2012). Long-term mortality in patients diagnosed with Listeria monocytogenes meningitis: a Danish nationwide cohort study, Journal of Infection 64(1), 34-40

disease: a Danish nationwide cohort study, PLoS ONE 5(3), e9662

Roed 2013

Roed, C., Omland, L. H., Skinhoj, P. et al. (2013). Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis, JAMA 309(16), 1714-1721

Schmidt 2006

Schmidt, H., Heimann, B., Djukic, M. et al. (2006). Neuropsychological sequelae of bacterial and viral meningitis, Brain 129(pt2), 333-345

Stevens 2003

Stevens, J. P., Eames, M., Kent, A. et al. (2003). Long term outcome of neonatal meningitis, Archives of Disease in Childhood Fetal & Neonatal Edition 88(3), F179-F184

Taylor 1990

Taylor, H. G., Mills, E. L., Ciampi, A. et al. (1990). The sequelae of Haemophilus influenzae meningitis in school-age children, New England Journal of Medicine 323(24), 1657-1663

Tejani 1982

Tejani, A., Dobias, B., Sambursky, J. (1982). Long-term prognosis after H. influenzae meningitis: prospective evaluation, Developmental Medicine & Child Neurology 24(3), 338-343

Vartzelis 2011

Vartzelis, G., Vasilopoulou, V., Katsioulis, A. et al. (2011). Functional and behavioral outcome of bacterial meningitis in school-aged survivors, Pediatrics International 53(3), 300-302

Zelano 2020

Zelano, J. and Westman, G. (2020). Epilepsy after brain infection in adults: a register-based population-wide study, Neurology 95(24), e3213-e3220

Economic

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

Other

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 bacterial meningitis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021281468
Review title	Long-term complications and follow-up for bacterial meningitis
Review question	What is the risk of long-term complications in bacterial meningitis?
Objective	To determine the risk of long-term complications in bacterial meningitis
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 bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (including neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Intervention/Exposure/Test	Bacterial meningitis
Comparator/Reference standard/Confounding factors	No bacterial meningitis (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

Field	Content
	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 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 (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 • Speech and language disorder • Headache Population: neonates, 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

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 • Educational achievement • Diagnosis of epilepsy • Speech and language disorder • Hydrocephalus with a shunt *For infants and children below school-age, educational, 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 • Quality in Prognostic Studies (QUIPS) tool for prognostic studies

Field	Content
	The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same 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:
	• Neonates: Birth to ≤28 days for term babies; birth to ≤28 days after due date for preterm babies
	  ○ Extremely and very preterm: <32 weeks
	  ○ Preterm: ≥32 weeks to <37 weeks
	  ○ Term: ≥37 weeks
	• Younger and older Infants: >28 days to ≤1 year of age

Field	Content	
	• Children: >1 year to <18* years of age • Adults: ≥18* years of age **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 **Infective organism:** • Neisseria meningitides • Streptococcus pneumonia • Haemophilus influenzae • group B streptococcus • Gram-negative bacilli • Listeria monocytogenes	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☒	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	

Field	Content
Country	England
Anticipated or actual start date	20/09/2021
Anticipated completion date	07/12/2023
Stage of review at time of this submission	Review stage / Started / Completed Preliminary searches ☑ ☑ Piloting of the study selection process ☑ ☑ Formal screening of search results against eligibility criteria ☑ ☑ Data extraction ☑ ☑ Risk of bias (quality) assessment ☑ ☑ Data analysis ☑ ☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (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

Field	Content	
	with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021281468	
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, bacterial meningitis, 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 bacterial meningitis?

Clinical Search

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

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

Database (s): Wiley Cochrane Issue 12 of 12, December 2021
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

Database (s): Ovid Embase 1974 to 2021 December 17
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

Database (s): Epistemonikos

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]

Economic Search

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

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

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA

#	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.

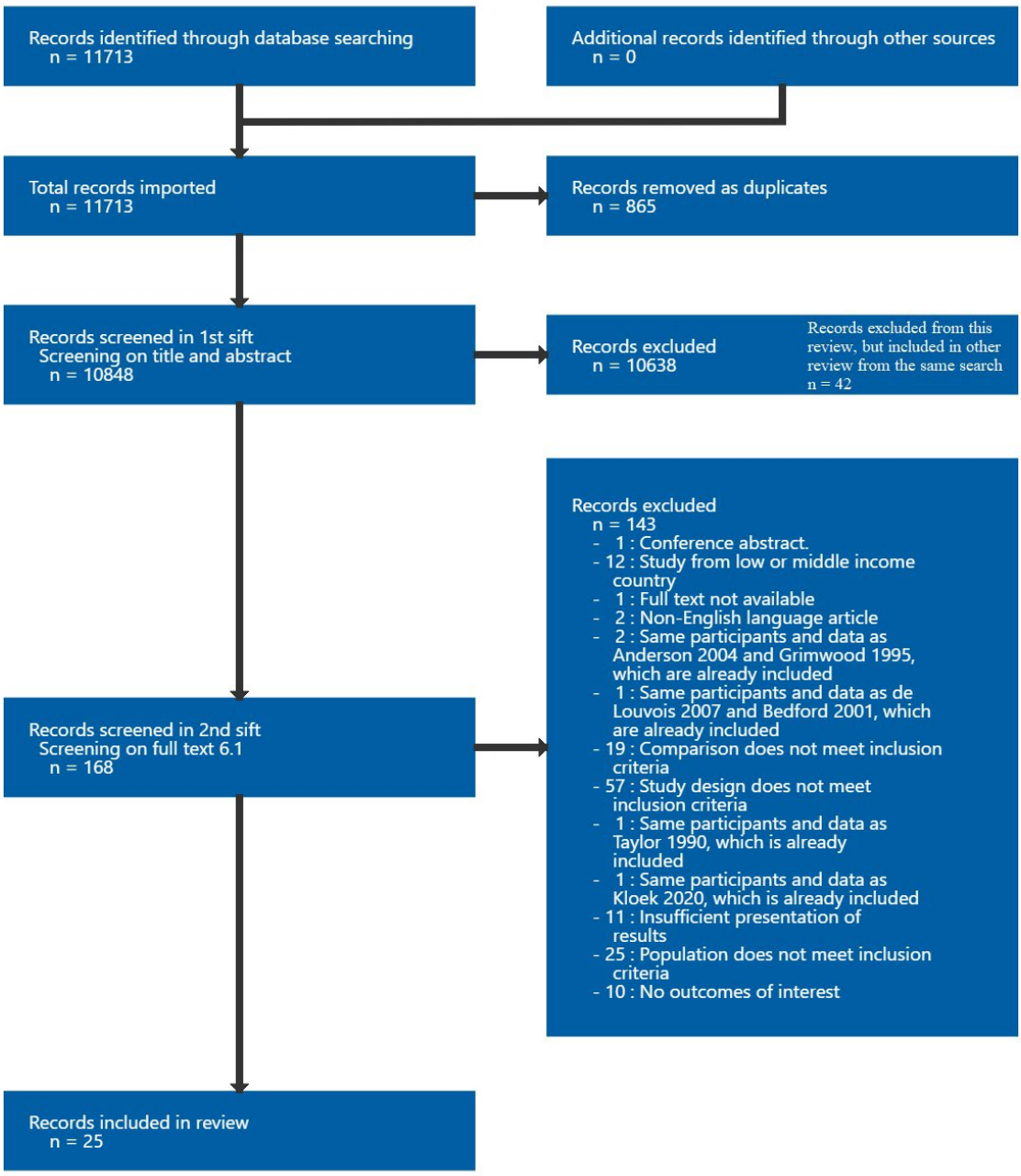
#	Searches
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* 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

Appendix C Prognostic evidence study selection

Study selection for: What is the risk of long-term complications in bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

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

Table 4: Evidence tables – prognostic evidence

Anderson, 2004

Bibliographic Reference	Anderson, V.; Anderson, P.; Grimwood, K.; Nolan, T.; Cognitive and executive function 12 years after childhood bacterial meningitis: effect of acute neurologic complications and age of onset; Journal of Pediatric Psychology; 2004; vol. 29 (no. 2); 67-81

Study details

Country/ies where study was carried out	Australia
Study type	Prospective cohort study
Study dates	1983 - 1986
Inclusion criteria	Bacterial meningitis group: Children 3 months - 14 years diagnosed with bacterial meningitis between 1983-1986. Bacterial meningitis was diagnosed via lumbar puncture and identification of bacteria from cerebrospinal fluid. Control group: Grade- and sex-matched controls with no previous history of meningitis
Exclusion criteria	Exclusion criteria from the original 1983 - 1986 cohort • Pre-existing neurologic and developmental deficits • Immunodeficiency states • Previous CNS surgery • Meningitis secondary to cranial trauma • Shunt infections

Patient characteristics	12-year follow-up sample (bacterial meningitis group and controls): Age at follow-up (years in mean; SD in parentheses): 12.8 (1.6) Sex: male: 111 (54.1%); female: 94 (48.9%) Clinical characteristics (bacterial meningitis group only): Years post illness (years in mean; SD in parentheses): 11.5 (0.9) Age at admission (months in median; range in parentheses): 17.0 (3-79) Age ≤12 months at admission (n; % in parentheses): 40 (37)
Population of interest/comparison	Bacterial meningitis group: Survivors of childhood bacterial meningitis compared to grade- and sex-matched controls. Control group: The controls were recruited from the classroom of each child by selecting the next same-sex student on the class register. If the parents of the control refused to approach the school a control was selected in a similar way from a neighbouring school
Duration of follow-up	12 years
Sources of funding	Not industry funded
Sample size	N=203[1] Bacterial meningitis group: n=107 Control group: n=96 [1]People were excluded for the following reasons: Excluded from original 1983-1996 cohort: n=15 due to exclusion criteria reported above (pre-existing neurologic and developmental deficits, immunodeficiency states, previous CNS surgery, or meningitis secondary to cranial trauma or shunt infections); n=8 mortality Excluded from follow-up (loss to follow-up at 7 years and 12 years combined): n=2 unable to complete tests; n=61 unable to be contacted; n=7 declined to participate; n=14 moved out of state; n=1 died from unrelated causes

Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

CNS: central nervous system; ICU: intensive care unit; SD: standard deviation

Outcomes

Bacterial meningitis group versus control group: Educational achievement

Outcome	**Bacterial meningitis group, N = 107**	**Control group, N = 96**
Educational achievement (requirement of special educational assistance) No of events	n = 29	n = 12

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data is available for nearly all participants (99%))*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of bacterial meningitis provided.)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description and measurement of outcome not reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Grade- and sex-matched controls were used. However, SES, sex and age were treated as covariates suggesting baseline differences between groups in SES and that there may be some residual confounding in terms of sex and age. Outcome data for educational achievement was not*

Section	Question	Answer
		adjusted)
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; SES: socioeconomic status

Bedford, 2001

Bibliographic Reference	Bedford, H.; de Louvois, J.; Halket, S.; Peckham, C.; Hurley, R.; Harvey, D.; Meningitis in infancy in England and Wales: follow up at age 5 years; BMJ; 2001; vol. 323 (no. 7312); 533-6

Study details

Country/ies where study was carried out	England and Wales
Study type	Prospective cohort study
Study dates	1985-1987
Inclusion criteria	Bacterial meningitis group: Children who survived an episode of acute bacterial meningitis between 1985 and 1987 Control group: Age- and sex-matched controls
Exclusion criteria	Not reported

Patient characteristics	Baseline characteristics not reported
Population of interest/comparison	Survivors of an acute bacterial meningitis attack between 1985 and 1987 compared to age- and sex- matched controls. The controls were from the same general practitioner's list.
Duration of follow-up	5 years
Sources of funding	Not industry funded
Sample size	N=2975 Bacterial meningitis group: n=1584 Control group: n=1391
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

ICU: intensive care unit

Outcomes

Bacterial meningitis group versus control group: Long-term motor deficits, long-term cognitive deficits, long-term behavioural deficits, any hearing impairment, any visual impairment, diagnosis of epilepsy, and speech and language disorder

Outcome	Bacterial meningitis group, N = 1584	Control group, N = 1391
Long-term motor deficits (neuromotor disabilities) No of events	n = 128	n = 13
Long-term cognitive deficits (learning difficulties) No of events	n = 118	n = 15

Outcome	Bacterial meningitis group, N = 1584	Control group, N = 1391
Long-term behavioural deficits (behavioural problems) No of events	n = 188	n = 46
Any hearing impairment (hearing problems) No of events	n = 408	n = 190
Any visual impairment (ocular or visual disorders) No of events	n = 217	n = 55
Diagnosis of epilepsy (seizure disorders) No of events	n = 116	n = 37
Speech and language disorder (speech and/or language problems) No of events	n = 247	n = 64

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Baseline characteristics for the sample were not reported. Method used to identify population, recruitment period and place of recruitment were not detailed enough.)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of the prognostic factor (that is, bacterial meningitis) not reported)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(The measurement of outcomes is somewhat subjective (measured by questionnaires from parents and general practitioners))*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Controls matched on age and sex but unclear if any residual confounding.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Statistical model not specified but no evidence of selective reporting.)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Berg, 2002

Bibliographic Reference	Berg, S.; Trollfors, B.; Hugosson, S.; Fernell, E.; Svensson, E.; Long-term follow-up of children with bacterial meningitis with emphasis on behavioural characteristics; European Journal of Pediatrics; 2002; vol. 161 (no. 6); 330-6

Study details

Country/ies where study was carried out	Sweden
Study type	Prospective cohort study
Study dates	1987-1989
Inclusion criteria	Bacterial meningitis group: Children aged 0-4 years at diagnosis with bacterial meningitis caused by H. influenzae, S.

	pneumoniae and N. meningitidis Control group: Sibling controls without neurological impairment and were aged 0-4 years in 1987-1989
Exclusion criteria	• People with severe neurological sequelae after meningitis • Serious concomitant condition prior to meningitis
Patient characteristics	Characteristics of all participants: Age at diagnosis (years in median; range in parentheses): Bacterial meningitis group: 9.6 (6.5-14.3) Sibling controls: 11 (6.1-15.3) Characteristics of bacterial meningitis group: Bacterial meningitis group: male: 311 (51%); female: 297 (49%) Etiology of bacterial meningitis: H. influenzae: 258/304 (84.9%); S. pneumoniae: 28/304 (9.2%); N. meningitidis: 18/304 (5.9%)
Population of interest/comparison	Survivors of childhood bacterial meningitis compared with siblings without major neurological impairment, aged 0–4 years in 1987–1989
Duration of follow-up	Not reported[1] [1]Children were 6-14 years when they filled out the questionnaire therefore follow up could be between 2 and 13 years
Sources of funding	Not reported
Sample size	N=608[2] Bacterial meningitis group: n=304 Sibling controls: n=304 [2]154 children with bacterial meningitis without sibling controls were excluded from this review due to lack of comparable control data. 14 children died as a result of their infection and 2 died from unrelated causes. 10 children with meningitis were excluded due to severe neurological sequalae and 12 were excluded due to pre-existing conditions. 39 children were lost to follow-up

	(34 could not be located and parents of 5 children declined).
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

H. influenzae: Haemophilus influenzae; ICU: intensive care unit; N. meningitidis: Neisseria meningitidis; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Bacterial meningitis group versus control group: Long-term motor deficits, long-term behavioural deficits, any hearing impairment, any visual impairment, and speech and language disorder

Outcome	Bacterial meningitis group, N = 304	Sibling controls, N = 304
Long-term behavioural deficits (Inattention according to DSM-IV) No of events	n = 11	n = 5
Long-term behavioural deficits (Hyperactivity-impulsiveness according to DSM-IV) No of events	n = 11	n = 4
Speech and language disorder (speech difficulties, reported by parents) No of events	n = 20	n = 16
Any hearing impairment (reported by parents) No of events	n = 60	n = 5
Any visual impairment (impaired vision, reported by parents) No of events	n = 47	n = 49
Any visual impairment (sensitivity to light, reported by parents) No of events	n = 33	n = 8

Outcome	Bacterial meningitis group, N = 304	Sibling controls, N = 304
Long-term motor deficits (individuals with worse gross motor function, such as ability to run, jump and ride a bicycle, than their peers; reported by parents) No of events	n = 27	n = 13
Long-term motor deficits (individuals with worse fine motor function, such as ability to cut with scissor, button and handle small objects; reported by parents) No of events	n = 22	n = 8

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

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	Low risk of bias *(Data available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of the prognostic factor (that is, bacterial meningitis) not reported.)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Moderate for the speech difficulties, vision, hearing, motor function, and sensitivity to light outcomes as these are reported by the parents and are therefore somewhat subjective. Low risk for the behavioural deficits outcome as DSM-IV diagnostic criteria for inattention, hyperactivity and impulsiveness was used.)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	High risk of bias *(Minimal attempt to control for confounders. Controls were siblings of the closest age, rather than age matched, and unclear if there was any residual confounding.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Statistical analysis used was adequate for the aims of the study but not for considering the risk of developing long term complications from bacterial meningitis due to exclusion of those with severe neurological sequalae. No evidence of selective reporting of the results.)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition.; QUIPS: Quality in Prognosis Studies

Christie, 2011

Bibliographic Reference	Christie, D.; Viner, R. M.; Knox, K.; Coen, P. G.; Wang, H.; El Bashir, H.; Legood, R.; Patel, B. C.; Booy, R.; Long-term outcomes of pneumococcal meningitis in childhood and adolescence; European Journal of Pediatrics; 2011; vol. 170 (no. 8); 997-1006

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	For bacterial meningitis group:

	• Bacterial meningitis diagnosed by either (1) the isolation of S. pneumoniae from the cerebrospinal fluid (CSF) or (2) Gram-positive diplococci seen on Gram stain of a CSF sample • Up to 14 years of age at onset of bacterial meningitis • No prior documented major neurological condition For the controls: • Sibling controls or similarly aged young individuals in the neighbourhood without a known episode of meningitis
Exclusion criteria	• Non-eligible for age (age at assessment <3 or >20) • No eligible age-matched controls
Patient characteristics	Characteristics of all participants: Age at follow-up (years in median; range in parentheses): Bacterial meningitis group: 7.7 (3 - 20) Control group: 7.6 (3 - 20) Sex: male: 116 (63.1%); female: 74 (36.9%)
Population of interest/comparison	Survivors of childhood bacterial meningitis compared to sibling matched or aged matched controls. The controls were either siblings (closest in age) or a similarly aged young person that had not had a known episode of meningitis in the local area who had agreed to be approached.
Duration of follow-up	Median duration of follow-up 6 years (range: 1 to 17.55 years)
Sources of funding	Not industry funded
Sample size	N=168 Matched bacterial meningitis cases: n=84 Matched controls: n=84 Eligible bacterial meningitis cases: n=97 Eligible controls: n=93

	13 children from bacterial meningitis group and 8 children from control groups, who were aged <3 years, were not included in final analysis as intelligence quotient assessment was not possible.
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; *S. pneumoniae: Streptococcus pneumoniae*

Outcomes

Bacterial meningitis group versus control group: Long-term cognitive deficits, long-term psychological impairment, any hearing impairment, and educational achievement

Outcome	Bacterial meningitis group, N = 97	Control group, N = 93
Any hearing impairment (partial or profound hearing impairment) Custom value	14/84	1/84
Educational achievement (special educational needs) Custom value	41/97	8/93
Long-term cognitive deficit (full-scale IQ <85) Custom value	10/84	3/84
Long-term cognitive deficit (Verbal IQ <85) Custom value	15/84	3/84
Long-term psychological impairment (participants with high depressive symptom scores assessed with the Moods and Feelings Questionnaire, reported by parents) Custom value	9/66	3/57

Outcome	Bacterial meningitis group, N = 97	Control group, N = 93
Long-term psychological impairment (participants with psychological distress scores above cut-off level assessed with the Strengths and Difficulties Questionnaire; reported by parents) Custom value	23/92	4/87
Long-term psychological impairment (participants with high depressive symptom scores assessed with the Moods and Feelings Questionnaire, reported by children) Custom value	7/36	6/37
Long-term psychological impairment (participants with psychological distress scores above cut-off level assessed with the Strengths and Difficulties Questionnaire; reported by children) Custom value	1/21	3/19

IQ: intelligence quotient

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, baseline characteristics, inclusion criteria, and exclusion criteria were appropriate and adequately provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data is available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of bacterial meningitis provided.)*
Outcome Measurement	Outcome Measurement	High risk of bias *(Description and reliable measurement of outcomes not reported.)*

Section	Question	Answer
	Summary	
Study Confounding	Study Confounding Summary	High risk of bias *(High risk for psychological impairment and educational achievement: Unmatched analysis was performed, and no attempts were made to control for potential important confounders. Moderate risk for any hearing impairment and cognitive deficits: Some attempt to control for confounder as controls were aged matched.)*
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	High High risk for psychological impairment and educational achievement. Moderate risk for hearing impairment and cognitive deficits.
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

D'Angio, 1995

Bibliographic Reference D'Angio, C. T.; Froehlke, R. G.; Plank, G. A.; Meehan, D. J.; Aguilar, C. M.; Lande, M. B.; Hugar, L.; Long-term outcome of Haemophilus influenzae meningitis in Navajo Indian children; Archives of Pediatrics & Adolescent Medicine; 1995; vol. 149 (no. 9); 1001-8

Study details

Country/ies where study was carried out	USA

Study type	Retrospective cohort study
Study dates	1990
Inclusion criteria	For bacterial meningitis group: • 100% Indian ancestry with at least 50% Navajo blood • <5 years old at the time of diagnosis • Clinical course consistent with meningitis • Abnormal cerebrospinal fluid white blood cell count for the patient's age • Growth of Hib in the blood and/or spinal fluid For sibling controls • 100% Indian ancestry with at least 50% Navajo blood For aged-matched controls • 100% Indian ancestry with at least 50% Navajo blood • Same sex • Same catchment area as hospital A • Birth date closest to the child in the bacterial meningitis group
Exclusion criteria	For bacterial meningitis: • Mixed organisms in the cerebrospinal fluid • Posttraumatic meningitis
Patient characteristics	Characteristics of all participants: Age at follow-up (years in mean; range in parentheses): 9.3 (1.2-18.5) Sex: male: 69 (57.5%); female: 51 (42.5%)[1] Bacterial meningitis group only: Age at time of diagnosis (months in mean; range in parentheses): 9.3 (2.3-23.4) [1]One age-matched control's sex was incorrectly assigned at enrolment, leading to the discrepancy between cases and age-matched controls.

Population of interest/comparison	Navajo children with Haemophilus meningitis at less than 5 years of age between January 1st 1975 and December 31st 1986 Compared to: • The nearest aged sibling living in the same home at the time of recruitment. If no full sibling was available a half sibling was chosen and if no siblings were present in the home no sibling control was chosen, and • One unrelated aged-matched control: children of the same sex from the catchment area of hospital A whose birth date were closest to those of the cases.
Duration of follow-up	3.6-15.0 years
Sources of funding	Not reported
Sample size	N=120 Bacterial meningitis group: n=41 Sibling controls n=38 Aged-matched controls n=41
Other information	The study stated that controls with any non-Hib infection, including meningitis, were not excluded; however, clear information on the number of controls with non-Hib infection not provided. The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

Outcomes

Bacterial meningitis group versus control group: Long-term motor deficits, Long-term cognitive deficits, any hearing impairment, educational achievement, and diagnosis of epilepsy

Outcome	Bacterial meningitis group, N = 41	Sibling controls, N = 38	Aged-matched controls, N = 41
Long-term cognitive deficit (IQ <70) Custom value	10/41	3/38	1/41
Educational achievement (requirement of special education) Custom value	11/41	7/38	0/41
Any hearing impairment (severe hearing loss) Custom value	2/41	0/38	0/41
Long-term motor deficits (cerebral palsy) Custom value	3/41	0/38	0/41
Educational achievement (retained in grade) Custom value	15/36	7/31	4/38
Diagnosis of epilepsy (seizures) Custom value	5/41	0/38	0/41

IQ: intelligence quotient

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)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data was available for 90-100% of participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of the prognostic factor (that is, bacterial meningitis) reported.)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Low risk for IQ <70 as it uses standardised tests: The Wechsler Preschool Scale of Intelligence, Wechsler Intelligence Scale for Children— Revised, Wechsler Adult Intelligence Scale, the Stanford Binet test, or the Bayley Scales of Infant Development (version 1). Low risk for motor deficits, hearing impairment, and diagnosis of epilepsy: Outcomes are objective, and description of outcomes reported. Moderate risk for special education as it is not defined and school records were used.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Controls were either nearest aged sibling or half sibling living in the same home at time of recruitment or age and sex matched controls from the same hospital catchment area. Cases and age-matched controls were stratified on the basis of socioeconomic status to control for differences; however, the analyses for outcomes of interest were not adjusted for potential confounders identified, such as per capita incomes and Hollingshead socioeconomic status scores)*
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

de Louvois, 2007

Bibliographic Reference	de Louvois, J.; Halket, S.; Harvey, D.; Effect of meningitis in infancy on school-leaving examination results; Archives of Disease in Childhood; 2007; vol. 92 (no. 11); 959-62

Study details

Country/ies where study was carried out	England and Wales
Study type	Prospective cohort study
Study dates	Participants were from a national incidence study of meningitis in infancy conducted in 1985–1987, but dates of the present study were not reported.
Inclusion criteria	Bacterial meningitis group: Children aged 16 years old who had confirmed bacterial meningitis in infancy and participated in follow-up studies when they were 5 and 13 years old Control group: Age- and sex-matched controls who participated in the five-year follow up study and the behavioural study whey they were aged 13
Exclusion criteria	Not reported
Patient characteristics	Sex: male: 348/750 (46%); female: 402/750 (54%)
Population of interest/comparison	Bacterial meningitis group: Children aged 16 years old who survived bacterial meningitis in infancy Control group: Age- and sex-matched controls who did not have bacterial meningitis
Duration of follow-up	16 years
Sources of funding	Not industry funded
Sample size	N=1219

	Bacterial meningitis group: n=739 Control group: n=480
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

ICU: intensive care unit

Outcomes

Bacterial meningitis group versus control group: Educational achievement

Outcome	Bacterial meningitis group, N = 461	Control group, N = 289
Educational achievement (children with special educational needs) No of events	n = 56	n = 10
Educational achievement (children achieved no passes at GCSE) No of events	n = 117	n = 19
Educational achievement (children achieved 1-4 passes at GCSE) No of events	n = 105	n = 41
Educational achievement (children achieved 5-10 passes at GCSE) No of events	n = 198	n = 189
Educational achievement (children achieved >10 passes at GCSE) No of events	n = 40	n = 39

GCSE: General Certificate of Secondary Education

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	High risk of bias *(62% (750/1219) of participants completed questionnaires. n=110 had moved house or could not be traced. No explanation given for remaining participants (n=359) lost to follow-up)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of the prognostic factor (that is, bacterial meningitis) not reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of outcome reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but no information regarding the measurement of potential confounders and limited number of baseline characteristics were presented)*
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	High
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Feldman, 1988

Bibliographic Reference	Feldman, H. M.; Michaels, R. H.; Academic achievement in children ten to 12 years after Haemophilus influenzae meningitis; Pediatrics; 1988; vol. 81 (no. 3); 339-44

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	1981-1982
Inclusion criteria	H. influenzae meningitis group: Children who had culture-proven H. influenzae meningitis Control group: Age-matched siblings
Exclusion criteria	Not reported
Patient characteristics	Characteristics of all participants: Age at follow-up (years in mean; SD in parentheses): 13.3 (1.2) Characteristics of bacterial meningitis group: Sex: 12/23 (52%); female: 11/23 (48%) Etiology of bacterial meningitis: H. influenzae: 23/23 (100%)
Population of interest/comparison	H. influenzae meningitis group: Children who had culture-proven H. influenzae meningitis when they were aged 12.4 months Control group: Age-matched siblings
Duration of follow-up	10-12 years
Sources of funding	Not industry funded

Sample size	N=35 H. influenzae meningitis group: n=24 Control group: n=11
Other information	One patient was admitted to hospital in coma, and seven patients had seizures during the illness. However, the study did not specify how many participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

H. influenzae: Haemophilus influenzae; ICU: intensive care unit; SD: standard deviation

Outcomes

H. influenzae meningitis group versus control group: Educational achievement

Outcome	**H. influenzae meningitis group, N = 24**	**Control group, N = 11**
Educational achievement (grade retentions in kindergarten, first, or second grade) Custom value	4/23	3/11
Educational achievement (requirement of remedial help such as private tutoring, school tutoring, resource room help, and special class placements) Custom value	9/23	5/11
Educational achievement (receiving more family help with homework) Custom value	13/23	1/11

H. influenzae: Haemophilus influenzae

Critical appraisal – NGA Critical appraisal – QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for 97% of children)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of bacterial meningitis provided)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Description of outcomes reported, but the measurement of outcomes is somewhat subjective (measured by school and parental reports, and a semi-structured open-ended interview))*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age-matched controls were used, 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

QUIPS: Quality in Prognosis Studies

Grimwood, 1995

Bibliographic Reference Grimwood, K.; Anderson, V. A.; Bond, L.; Catroppa, C.; Hore, R. L.; Keir, E. H.; Nolan, T.; Roberton, D. M.; Adverse outcomes of bacterial meningitis in school-age survivors; Pediatrics; 1995; vol. 95 (no. 5); 646-56

Study details

Country/ies where study was carried out	Australia
Study type	Prospective cohort study
Study dates	1983 - 1986
Inclusion criteria	Bacterial meningitis group: Children who had bacterial meningitis when they were aged 3 months to 14 years. Bacterial meningitis defined as the presence of clinical presentation and either of the following: (1) positive CSF culture; (2) CSF leukocytosis (≥100 x 106/L) and abnormal CSF biochemistry (glucose <45 mg/dL and protein >50 mg/dL) with positive blood culture or CSF antigen, or (3) abnormal CSF biochemistry and CSF leukocytosis (≥1500 x 106/L with ≥75% neutrophils) Control group: Grade- and sex-matched children with no history of meningitis
Exclusion criteria	Known pre-existing immunodeficiency conditions and neurologic or developmental anomalies, history of CNS surgery, and meningitis associated with cranial trauma or CSF shunt infections
Patient characteristics	Characteristics of all participants: Age at follow-up (years in mean; SD in parentheses): 9 (2) Sex: male: 141/260 (54%); female: 119/260 (46%) Characteristics of bacterial meningitis group: Age at admission (months in median): 18 Etiology of bacterial meningitis: H. influenzae type b: 100/131[1] (76%); S. pneumoniae: 18/131[1] (14%); N. meningitidis: 7/131[1] (5%); other or unknown: 6/131[1] (5%) [1]One child had two episodes of bacterial meningitis
Population of interest/comparison	Bacterial meningitis group: Children who had bacterial meningitis when they were aged 3 months to 14 years Control group: Grade- and sex-matched children who did not have meningitis
Duration of follow-up	Mean duration of follow-up 6.7 years

Sources of funding	Not industry funded
Sample size	N=260 Bacterial meningitis group: 130 Control group: 130 Excluded from follow-up (loss to follow-up from bacterial meningitis original cohort): n=26 unable to be contacted; n=1 declined to participate; n=1 died from unrelated causes
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

CNS: central nervous system; CSF: cerebrospinal fluid; H. influenzae: Haemophilus influenzae; ICU: intensive care unit; N. meningitidis: Neisseria meningitidis; SD: standard deviation; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Bacterial meningitis group versus control group: Long-term motor deficits, long-term cognitive deficits, any hearing impairment, diagnosis of epilepsy, and hydrocephalus with a shunt

Outcome	Bacterial meningitis group, N = 130	Control group, N = 130
Long-term cognitive deficit (Full-scale IQ 70-80) Custom value	7/130	1/130
Long-term cognitive deficit (Full-scale IQ <70) Custom value	7/130	0/130
Long-term motor deficit (cerebral palsy) Custom value	2/127	0/129
Long-term motor deficit (spasticity)	3/130	0/130

Outcome	Bacterial meningitis group, N = 130	Control group, N = 130
Custom value		
Any hearing impairment (mild to moderate and severe to profound) Custom value	8/130	0/130
Diagnosis of epilepsy Custom value	5/127	0/129
Hydrocephalus with a shunt (ventriculoperitoneal shunt) Custom value	2/127	0/129

IQ: intelligence quotient

Bacterial meningitis group versus control group: Long-term motor deficits, long-term cognitive deficits, long-term behavioural deficits, any visual impairment, and educational achievement

Outcome	Bacterial meningitis group vs Control group, N2 = 130, N1 = 130
Long-term cognitive deficit (borderline IQ <80) Bacterial meningitis group=12/130 vs. Control group=1/130; adjusted Odds ratio/95% CI	12 (1.6 to 91)
Long-term behavioural deficit (total behaviour score in clinical range assessed with the Child Behaviour Checklist; defined as a summary behaviour score >60) Bacterial meningitis group=36/119 vs. Control group=25/124; adjusted Odds ratio/95% CI	1.5 (1 to 2.3)
Long-term behavioural deficit (total behaviour score in clinical range assessed with the Teacher Report Form; defined as a summary behaviour score >60)	2.1 (0.8 to 5.6)

Outcome	Bacterial meningitis group vs Control group, N2 = 130, N1 = 130
Bacterial meningitis group=14/119 vs. Control group=7/124; adjusted Odds ratio/95% CI	
Long-term behavioural deficit (the school scale in clinical range assessed with the Child Behaviour Checklist) Bacterial meningitis group=14/119 vs. Control group=2/124; adjusted Odds ratio/95% CI	8.1 (1.7 to 53)
Long-term behavioural deficit (adaptive function in clinical range assessed with the Teacher Report Form) Bacterial meningitis group=17/119 vs. Control group=9/124; adjusted Odds ratio/95% CI	1.7 (0.7 to 4.2)
Educational achievement (unable to read) Bacterial meningitis group=16/130 vs. Control group=4/130; adjusted Odds ratio/95% CI	4 (1.4 to 11.6)
Long-term motor deficit (abnormal balance or standing on one leg test) Bacterial meningitis group=24/127 vs. Control group=10/129; adjusted Odds ratio/95% CI	2.4 (1.1 to 5.3)
Long-term motor deficit (dysdiadochokinesis) Bacterial meningitis group=81/127 vs. Control group=39/129; adjusted Odds ratio/95% CI	4.5 (2.5 to 8)
Long-term motor deficit (abnormal fine motor function or sequential finger-thumb opposition test) Bacterial meningitis group=25/127 vs. Control group=11/129; adjusted	2.6 (1.2 to 5.7)

Outcome	Bacterial meningitis group vs Control group, N2 = 130, N1 = 130
Odds ratio/95% CI	
Long-term motor deficit (abnormal coordination or finger-nose-finger test) Bacterial meningitis group=49/127 vs. Control group=11/129; adjusted Odds ratio/95% CI	7.1 (3.4 to 15.1)
Any visual impairment (abnormalities of vision) Bacterial meningitis group=12/127 vs. Control group=4/129; adjusted Odds ratio/95% CI	3.3 (0.9 to 14.2)

CI: confidence interval; IQ: intelligence quotient

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	Low risk of bias *(Data was available for 98%-100% (256/260 to 260/260) of participants for motor deficits, 100% (260/260) for cognitive deficits and educational achievement, 94% (243/260) for behavioural deficits, and 98% (256/260) for visual impairment, diagnosis of epilepsy and hydrocephalus with shunt)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of bacterial meningitis provided)*
Outcome Measurement	Outcome Measurement	Moderate risk of bias *(Low risk for cognitive deficits, behavioural deficits, and reading ability: Description of outcomes*

Section	Question	Answer
	Summary	*reported, and valid and reliable measurement of outcomes used (for example, the Teacher Report Form, the Child Behaviour Checklist and the Wechsler Intelligence Scale). Moderate risk for motor deficits, hearing impairment, visual impairment, epilepsy, and hydrocephalus with a shunt: Clear description of outcomes not provided, but the measurement of the outcomes is objective.)*
Study Confounding	Study Confounding Summary	High risk of bias *(High risk for full-scale IQ 70-80 and <70, cerebral palsy, spasticity, hearing impairment, epilepsy, and hydrocephalus with a shunt: No attempts were made to control for potential confounder specified in protocol (that is, age). Low risk for borderline IQ <80, behavioural deficits, educational achievement, balance, dysdiadochokinesis, fine motor function, coordination, and visual impairment: Potential confounders, such as age, sex, mother's education level, paternal occupation, and ethnicity, are accounted for in the analysis.)*
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 Moderate risk for IQ 70-80 and <70, cerebral palsy, spasticity, hearing impairment, epilepsy, and hydrocephalus with a shunt. Low risk for borderline IQ <80, behavioural deficits, educational achievement, balance, dysdiadochokinesis, fine motor function, coordination, and visual impairment.
Overall risk of bias and directness	Directness	Directly applicable

IQ: intelligence quotient; QUIPS: Quality in Prognosis Studies

Hoogman, 2007

Bibliographic Reference	Hoogman, M.; van de Beek, D.; Weisfelt, M.; de Gans, J.; Schmand, B.; Cognitive outcome in adults after bacterial meningitis; Journal of Neurology, Neurosurgery & Psychiatry; 2007; vol. 78 (no. 10); 1092-6

Study details

Country/ies where study was carried out	Netherlands
Study type	Prospective cohort study
Study dates	Not reported European Dexamethasone Study (EDS): Adults with bacterial meningitis - June 1993 and December 2001 Dutch Meningitis Cohort: Adults with community acquired bacterial meningitis October 1998 and April 2002
Inclusion criteria	Bacterial meningitis group: EDS • Survivors of pneumococcal or meningococcal meningitis, confirmed by CSF culture • >17 years Dutch Meningitis Cohort • Adults with community acquired bacterial meningitis, confirmed by CSF analysis (protein, glucose, and leucocyte count), and positive blood culture • 16-65 years Control group: Healthy cohort that includes partners, relatives or close friends of meningitis patients
Exclusion criteria	EDS and Dutch Meningitis Cohort: • Pre-existing serious illness (interfering with cognitive testing) • Pre-existing psychiatric disorders • Insufficient mastery of the Dutch language • Evidence of alcohol or other substance abuse
Patient characteristics	Characteristics of all participants: Age at follow-up (years in mean; SD in parentheses): 46.0 (15.4)

	Sex: male: 101 (44.5%); female: 126 (55.5%) Clinical characteristics of bacterial meningitis group during episode of meningitis: At presentation (at hospital admission with meningitis): Focal cerebral deficits: 29/155 (18.7%) Cranial nerve palsies: 21/155 (13.5%)
Population of interest/comparison	Adult survivors of bacterial meningitis compared to controls that consisted of partners, relatives or close friends. Three controls were included in both studies.
Duration of follow-up	Up to 5.7 years
Sources of funding	Not industry funded
Sample size	N=227 Bacterial meningitis group: n=155 Control group: n=72
Other information	Study pooled and reanalysed data from 3 prospective multicentre studies, from 2 research projects: the European Dexamethasone Study (EDS) and the Dutch Meningitis Cohort. Participants who could not be reliably assessed with the neuropsychological test battery (those with severe disability and low scores on the Glasgow Outcome Scale (GOS)) were excluded. 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; EDS: European Dexamethasone Study; GOS: Glasgow Outcome Scale; ICU: intensive care unit; SD: standard deviation

Outcomes

Bacterial meningitis group versus control group: Long-term cognitive deficit

Outcome	Bacterial meningitis group, N = 155	Control group, N = 72

Outcome	Bacterial meningitis group, N = 155	Control group, N = 72
Long-term cognitive deficit (cognitively impaired; defined as 3 or more impaired test results on neuropsychological test battery) No of events	n = 50	n = 5

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	Low risk of bias *(Data is available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Valid and reliable measurement and definition of prognostic factor provided.*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement of the outcome: use of standardised test battery.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No definition of confounders or how confounders were measured. However, test battery T scores were corrected for age and education with the control group as a reference.)*
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

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Hugosson, 1997

Bibliographic Reference	Hugosson, S.; Carlsson, E.; Borg, E.; Brorson, L. O.; Langeroth, G.; Olcen, P.; Audiovestibular and neuropsychological outcome of adults who had recovered from childhood bacterial meningitis; International Journal of Pediatric Otorhinolaryngology; 1997; vol. 42 (no. 2); 149-67

Study details

Country/ies where study was carried out	Sweden
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	Bacterial meningitis group: Patients who had bacterial meningitis before the age of seven Control group: Age-matched students or healthy volunteer blood donors
Exclusion criteria	Children with bilateral hearing loss or children who were handicapped with severe neurological sequelae, such as epilepsy, hemiplegia, tetraplegia, and hydrocephalus/mental retardation
Patient characteristics	Characteristics of bacterial meningitis group: Age at the time of diagnosis (range): 2-83 months Sex: male: 12/22 (55%); female: 10/22 (45%) Etiology of bacterial meningitis: H. influenzae: 16/22 (73%); N. meningitidis 6/22 (27%)

Population of interest/comparison	Bacterial meningitis group: Adults who had childhood bacterial meningitis Control group: Age-matched controls
Duration of follow-up	17-27 years
Sources of funding	Not industry funded
Sample size	N=42 Bacterial meningitis group: n=22 Control group: n=20
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

H. influenzae: Haemophilus influenzae; ICU: intensive care unit; N. meningitidis: Neisseria meningitidis

Outcomes

Bacterial meningitis group versus control group: Long-term motor deficits, and any hearing impairment

Outcome	Bacterial meningitis group, N = 22	Control group, N = 20
Long-term motor deficit (abnormal oculomotor test, such as slow pursuit test and voluntary saccade test) No of events	n = 5	n = 4
Any hearing impairment (sensorineural hearing loss or impairment) No of events	n = 9	n = 3

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided; no baseline characteristics present for control group)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of the prognostic factor (that is, bacterial meningitis) not reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of valid and reliable measurement of outcome reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age-matched controls were used, but limited number of baseline characteristics were presented and unclear if there was 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

Kloek, 2020

Bibliographic Kloek, A. T.; Brouwer, M. C.; Schmand, B.; Tanck, M. W. T.; van de Beek, D.; Long-term neurologic and cognitive outcome

Reference and quality of life in adults after pneumococcal meningitis; Clinical Microbiology & Infection; 2020; vol. 26 (no. 10); 1361-1367

Study details

Country/ies where study was carried out	Netherlands
Study type	Prospective cohort study
Study dates	October 2011 - March 2015
Inclusion criteria	Bacterial meningitis • >16 years • Community acquired acute bacterial meningitis confirmed by cerebrospinal fluid cultures or a positive PCR result • Typical CSF abnormalities Controls • Partners or proxies of the participants • Living in the same dwelling as the participants
Exclusion criteria	• Insufficient mastery of the Dutch language • Not living in the Netherlands • Mental impairment not attributed to meningitis
Patient characteristics	Characteristics of all participants: Age at follow-up (median years; IQR in parentheses): Bacterial meningitis group: 63 (56 - 69) Control group: 65 (54-68) Sex: male: 74 (49.7%); female: 75 (50.3%)
Population of interest/comparison	Adult survivors of community acquired bacterial meningitis compared to partners or proxies

Duration of follow-up	1 - 5 years
Sources of funding	Not industry funded
Sample size	N=149 Bacterial meningitis group: n=80 Controls: n=69 122 were excluded: 71 did not respond to letter or phone call and 51 declined to participate due to somatic illness, long distance travel, new episode of meningitis or migrated to another country.
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; GOS: Glasgow Outcome Scale; ICU: intensive care unit; IQR: interquartile range; PCR: polymerase chain reaction

Outcomes

Bacterial meningitis group versus control group: Long-term cognitive deficit

Outcome	**Bacterial Meningitis group, N = 80**	**Controls, N = 69**
Long-term cognitive deficit (cognitive impairment) Custom value	11/79	1/63

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.)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data is available for 95% of participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of valid and reliable measurement of prognostic factor provided.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of outcome provided. Standardised tests were used to assess the outcome (Cognitive Basic Assessment Test set (COGBAT) of the Vienna Test System (VTS), Schuhfried, Modling, Austria and The Cognitive and Emotional Consequences of Stroke (CLCE)-24 questionnaire))*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempt to control or match for confounders)*
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

CLCE: Cognitive and Emotional Consequences of Stroke; COGBAT: Cognitive Basic Assessment Test; QUIPS: Quality in Prognosis Studies; VTS: Vienna Test System

Koomen, 2003

Bibliographic Reference Koomen, I.; Grobbee, D. E.; Jennekens-Schinkel, A.; Roord, J. J.; van Furth, A. M.; Parental perception of educational, behavioural and general health problems in school-age survivors of bacterial meningitis; Acta Paediatrica; 2003; vol. 92 (no. 2); 177-85

Study details

Country/ies where study was carried out	Netherlands
Study type	Retrospective cohort study
Study dates	1999
Inclusion criteria	Bacterial meningitis group: Children who had bacterial meningitis caused by N. meningitidis, S. pneumoniae, S. agalactiae, E. coli or L. monocytogenes. Bacterial meningitis defined as detection of bacteria in the CSF Control group: School-age siblings and close friends
Exclusion criteria	Meningitis caused by H. influenzae type b or other less common pathogens, meningitis secondary to immunodeficiency or CNS surgery or CSF shunt infection or cranial trauma or relapsing meningitis, behavioural or cognitive deficits diagnosed before the bacterial meningitis, severe cognitive deficits diagnosed before or after the bacteria meningitis, and serious health conditions after meningitis (for example, cancer or cystic fibrosis)
Patient characteristics	Characteristics of all participants: Age at follow-up (years in median, range in parentheses): Bacterial meningitis group: 8.5 (4.3-13.6) Control group: 9.1 (3.2-14.9) Sex: male: 534 (54%); female: 450 (46%) Characteristics of bacterial meningitis group: Etiology of bacterial meningitis: N. meningitidis: 528 children (78%), S. pneumoniae: 113 (16%), S. agalactiae: 23 (3%), E. coli: 12 (2%), L. monocytogenes: 4 (1%)
Population of interest/comparison	Bacterial meningitis group: Children who had bacterial meningitis. The median age of children at infection was 1.8 years (range 0-9.5 years). Control group: School-age siblings and close friends
Duration of follow-up	Median 6.2 years (range 3.2-10 years)

Sources of funding	Not industry funded
Sample size	N=984 Bacterial meningitis group: n=680 Control group: n=304
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

CNS: central nervous system; CSF: cerebrospinal fluid; E. coli: Escherichia coli; H. influenzae: Haemophilus influenzae; ICU: intensive care unit; L. monocytogenes: Listeria monocytogenes; N. meningitidis: Neisseria meningitidis; S. agalactia: Streptococcus agalactiae; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Bacterial meningitis group versus control group: Long-term cognitive deficits, long-term behavioural deficits, long-term psychological impairment, and educational achievement

Outcome	**Bacterial meningitis group vs Control group, N2 = 680, N1 = 304**
Long-term cognitive deficit (cognition assessed with the HUI-2) Bacterial meningitis group=182/680 vs. Control group=18/304; adjusted Odds ratio/95% CI	5.9 (3.4 to 10.1)
Long-term behavioural deficit (hyperactive behaviour assessed with the School Achievement Rating Scale) Bacterial meningitis group=200/680 vs. Control group=53/304; adjusted Odds ratio/95% CI	1.8 (1.3 to 2.6)
Educational achievement (deficient school achievement assessed with the School Achievement Rating Scale) Bacterial meningitis group=136/680 vs. Control group=14/304; adjusted	5.6 (3 to 10.7)

Outcome	Bacterial meningitis group vs Control group, N2 = 680, N1 = 304
Odds ratio/95% CI	
Educational achievement (repeating a year) Bacterial meningitis group=111/680 vs. Control group=25/304; adjusted Odds ratio/95% CI	2.5 (1.5 to 4.2)
Educational achievement (referral to a special-needs school) Bacterial meningitis group=52/680 vs. Control group=5/304; adjusted Odds ratio/95% CI	5.5 (2 to 15.4)
Long-term cognitive deficit (slowness) Bacterial meningitis group=131/680 vs. Control group=19/304; adjusted Odds ratio/95% CI	3.7 (2.2 to 6.4)
Long-term cognitive deficit (concentration problems) Bacterial meningitis group=147/680 vs. Control group=16/304; adjusted Odds ratio/95% CI	5.7 (3.1 to 10.5)
Long-term psychological impairment (depressed mood) Bacterial meningitis group=49/680 vs. Control group=4/304; adjusted Odds ratio/95% CI	5 (1.8 to 14.3)
Long-term psychological impairment (emotion) Bacterial meningitis group=179/680 vs. Control group=20/304; adjusted Odds ratio/95% CI	4.9 (3 to 8.1)

CI: confidence interval; HUI-2: Health Utilities Index 2

Bacterial meningitis group versus control group: Any hearing impairment

Outcome	Bacterial meningitis group, N = 680	Control group, N = 304
Any hearing impairment (acquired hearing impairment) No of events	n = 48	n = 3

CI: confidence interval

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	Low risk of bias *(Data presented for 98% of children)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of bacterial meningitis provided)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Moderate risk for hearing impairment: No clear description of outcome, and it was reported by parents. Low risk for cognitive deficits, behavioural deficits, psychological impairment, and educational achievement: Description of outcomes reported, and valid and reliable measurements used (for example, the Health Utilities Index mark 2, the Functional Status II, and the School Achievement Rating Scale).)*
Study Confounding	Study Confounding Summary	Low risk of bias *(Age and sex are accounted for in the analysis)*
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)*

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Moss, 1982

Bibliographic Reference	Moss, P. D.; Outcome of meningococcal group B meningitis; Archives of Disease in Childhood; 1982; vol. 57 (no. 8); 616-21

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	1971-1974
Inclusion criteria	Bacterial meningitis group: 1 month - 7 years 10 months at time of meningococcal meningitis Control group: Age- and sex-matched controls
Exclusion criteria	Not reported
Patient characteristics	Bacterial meningitis group: Sex: male 34 (56.6%); female 26 (43.3%)

Population of interest/comparison	Survivors of bacterial meningitis compared to controls matched on sex and age.
Duration of follow-up	5-9 years
Sources of funding	Not reported
Sample size	N=120 Bacterial meningitis group: n=60 Control group: n=60
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

ICU: intensive care unit

Outcomes

Bacterial meningitis group versus control group: Long-term motor deficits, any hearing impairment, and any visual impairment

Outcome	Bacterial Meningitis, N = 60	Controls, N = 60
Any hearing impairment No of events	n = 6	n = 4
Any visual impairment (squints) No of events	n = 4	n = 4
Long-term motor deficits (nystagmus, or tremor of the hands and exaggerated knee jerks) No of events	n = 1	n = 1

Outcome	Bacterial Meningitis, N = 60	Controls, N = 60
Any visual impairment (vision worse than 6/9 or N5, assessed with Snellen types) No of events	n = 8	n = 10

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Minimal baseline characteristics for the sample were reported. Method used to identify population, recruitment period and place of recruitment were not detailed enough)*
Study Attrition	Study Attrition Summary	Low risk of bias *(The way the data is presented it is unclear if data is available for all participants, but there is no reason to suggested that it is not)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of the prognostic factor not reported.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of outcomes provided)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Some attempt made to identify and control for confounders. Reports that participants were matched by age and sex 'as far as possible' but does not report if there was residual confounding)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Statistical model unclear but no evidence of selective reporting)*
Overall risk of bias and directness	Risk of Bias	High

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Pickering, 2018

Bibliographic Reference	Pickering, L.; Jennum, P.; Ibsen, R.; Kjellberg, J.; Long-term health and socioeconomic consequences of childhood and adolescent onset of meningococcal meningitis; European Journal of Pediatrics; 2018; vol. 177 (no. 9); 1309-1315

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	1980 - 2012
Inclusion criteria	Meningococcal meningitis group: Patients who had meningococcal meningitis (ICD-8 codes: dia03609 or ICD-10 codes: diaDA390) before the age of 18 years. Patients were identified from the Danish National Patient Registry. Control group: Age- and sex-matched controls were born in the same year and living in the same municipality as the corresponding meningococcal meningitis patients.
Exclusion criteria	Not reported
Patient characteristics	Age at the meningitis diagnosis: Meningococcal meningitis group (years in mean; SD in parentheses): 8 (6) Control group (years in median): 6 Sex: Meningococcal meningitis group: male: 543/1028 (55%); female: 485/1028 (45%)

	Etiology of bacterial meningitis: N. meningitidis: 1028/1028 (100%)
Population of interest/comparison	Meningococcal meningitis group: Patients who had meningococcal meningitis before the age of 18 years. Control group: Age- and sex-matched controls
Duration of follow-up	Not reported[1] [1]Participants had meningococcal meningitis where they were aged 8 years, and assessments took place when they were aged 30 years. Therefore, follow-up could be about 22 years.
Sources of funding	Not industry funded
Sample size	N=5480 Bacterial meningitis group: 1028 Control group: 4452 Excluded from follow-up (loss to follow-up at 30 years of age): n=1049 (reason for exclusion/loss to follow up not stated clearly for each participant; however, the study stated that participants were followed until death, emigration or 31st December 2012, whichever event was the earliest)
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; N. meningitidis: Neisseria meningitidis; SD: standard deviation

Outcomes

Meningococcal meningitis group versus control group: Long-term motor deficits, and any visual impairment

Outcome[1]	**Meningococcal meningitis group vs Control group, N2 = 1028, N1 = 4452**
Long-term motor deficits[2] (disorders of the nervous system, at the age of 21-30 years)	1.78 (1.29 to 2.46)

Outcome[1]	**Meningococcal meningitis group vs Control group, N2 = 1028, N1 = 4452**
unadjusted Odds ratio/95% CI	
Any visual impairment (diseases of the eye and adnexa [tissues around the eye]; at the age of 21-30 years) unadjusted Odds ratio/95% CI	1.58 (1.1 to 2.26)

[1]*Unadjusted OR extracted as raw data not reported*
[2]indirect outcome as disorders of nervous system could include different types of neurological disorders
CI: confidence interval; OR: odds ratio

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(No clear information regarding method of prognostic factor measurement)*
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description and measurement of outcome not reported.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but unclear if there was residual confounding.)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Insufficient presentation of analytical strategy. There was no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable *(Visual impairment is directly applicable, but motor deficit is indirectly applicable as disorders of the nervous system are reported)*

QUIPS: Quality in Prognosis Studies

Roed, 2010a

Bibliographic Reference	Roed, C.; Engsig, F. N.; Omland, L. H.; Skinhoj, P.; Obel, N.; Long-term mortality in patients diagnosed with pneumococcal meningitis: a Danish nationwide cohort study; American Journal of Epidemiology; 2010; vol. 172 (no. 3); 309-17

Study details

Country/ies where study was carried out	Denmark
Study type	Retrospective cohort study
Study dates	1977 - 2006
Inclusion criteria	Pneumococcal meningitis group: Patients who had pneumococcal meningitis (ICD-8 code: 320.19 or ICD-10 code: G00.1) in the period of 1st January 1977 to 31st December 2006. Patients were identified from the Danish National Hospital Register. Control group: Age- and sex-matched controls who were born in Denmark, alive and living in Denmark at the index date* of the corresponding pneumococcal meningitis patients. Four controls for each meningitis patient were identified from the

	Danish Civil Registration System. *Index date defined as 1 year after the date of pneumococcal meningitis diagnosis
Exclusion criteria	Patients who died or emigrated or were lost to follow-up in the year after the diagnosis of meningitis, and patients who had other CNS infection before pneumococcal meningitis, did not live in Denmark at the date of pneumococcal meningitis diagnosis or were not born in Denmark
Patient characteristics	Age at the time of diagnosis (years in median; IQR in parentheses): Pneumococcal meningitis group: 44 (3-63) Control group: 44 (3-63) Sex: male: 5700 (53%); female: 4955 (47%) Etiology of bacterial meningitis: S. pneumoniae: 2131/2131 (100%)
Population of interest/comparison	Pneumococcal meningitis group: Patients who had pneumococcal meningitis Control group: Age- and sex-matched, population-based cohort
Duration of follow-up	Up to 30 years
Sources of funding	Not industry funded
Sample size	N=10655 Pneumococcal meningitis group: n=2131 Control group: 8524
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; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Pneumococcal meningitis group versus control group: All-cause mortality

Outcome	Pneumococcal meningitis group, N = 2131	Control group, N = 8524
All-cause mortality (up to 30 years) No of events	n = 584	n = 1739

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	Low risk of bias *(Data available for all participants, and Retrospective data from the Danish National Hospital Register, the Danish Civil Registration System and the Danish Register of Causes of Death was used)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Outcome (that is, all-cause mortality) is objective, and description of outcome reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but no attempts were made to control for other potential confounders identified (for example, infectious disease and neoplasm))*
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

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Roed, 2010b

Bibliographic Reference	Roed, C.; Omland, L. H.; Engsig, F. N.; Skinhoj, P.; Obel, N.; Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study; PloS ONE [Electronic Resource]; 2010; vol. 5 (no. 3); e9662

Study details

Country/ies where study was carried out	Denmark
Study type	Retrospective cohort study
Study dates	1977 – 2006
Inclusion criteria	Meningococcal meningitis group: Patients who had meningococcal meningitis or meningococcal disease (ICD-8 codes: 036.09-036.99 or ICD-10 codes: A39.0-A39.9) in the period of 1st January 1977 to 31st December 2006. Patients were identified from the Danish National Hospital Register. Control group: Age- and sex-matched controls who were born in Denmark, alive and living in Denmark at the index date[1] of the corresponding meningococcal meningitis or meningococcal disease patients. Four controls for each meningitis patient were identified from the Danish Civil Registration System. [1]Index date defined as 1 year after the date of meningococcal meningitis or meningococcal disease diagnosis
Exclusion criteria	Patients who died or emigrated or were lost to follow-up in one year after the diagnosis of meningococcal meningitis/disease, and patients who had other neuroinfections before meningococcal meningitis/disease, did not live in Denmark at the date of meningococcal meningitis/disease diagnosis or were not born in Denmark

Patient characteristics	Characteristics of all participants: Age at diagnosis (years in median; IQR in parentheses): Meningococcal meningitis group: 9 (2-18) Control group: 9 (2-18) Sex: male: 13305 (54%); female: 11240 (46%) Characteristics of meningococcal meningitis group: Etiology of bacterial meningitis: N. meningitidis: 4909/4909 (100%) Primary diagnosis: Meningococcal meningitis: 3297/4909 (67%); Acute meningococcaemia: 1211/4909 (25%); Chronic meningococcaemia: 23/4909 (0.5%); Waterhouse Friderichsen syndrome: 11/4909 (0.2%); Other specified conditions: 367/4909 (8%)
Population of interest/comparison	Meningococcal meningitis group: Patients who had meningococcal meningitis or meningococcal disease Control group: Age- and sex-matched, population-based cohort
Duration of follow-up	Up to 30 years
Sources of funding	Not industry funded
Sample size	N=24545 Meningococcal meningitis group: n=4909 Control group: n=985
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; N. meningitidis: Neisseria meningitidis

Outcomes

Meningococcal meningitis group versus control group: All-cause mortality

Outcome	Meningococcal meningitis group, N = 4909	Control group, N = 19636
All-cause mortality (up to 30 years) No of events	n = 312	n = 985

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	Low risk of bias *(Data was available for all participants,)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Outcome (that is, all-cause mortality) is objective, and description of outcome reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but no clear information regarding method of confounding factors measurement and unclear if 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

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Roed, 2011

Bibliographic Reference	Roed, C.; Engsig, F. N.; Omland, L. H.; Skinhoj, P.; Obel, N.; Long-term mortality in children diagnosed with Haemophilus influenzae meningitis: a Danish nationwide cohort study; Pediatric Infectious Disease Journal; 2011; vol. 30 (no. 8); e147-54

Study details

Country/ies where study was carried out	Denmark
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	H. influenzae meningitis group: Children who had H. influenzae meningitis (ICD-8 code: 320.09 or ICD-10 code: G00.0) at the age of 0-5 years in the period of 1977 to 1996. Patients were identified from the Danish National Hospital Register. Control group: Age- and sex-matched controls who are alive and living in Denmark at the index date[1] of the corresponding meningitis patients. Six controls for each meningitis patient were identified from the Danish Civil Registration System. [1]Index date defined as 1 year after the date of meningitis diagnosis
Exclusion criteria	Patients who died or emigrated or were lost to follow-up in one year after the diagnosis of meningitis, and patients who had other CNS infection before H. influenzae meningitis, did not live in Denmark at the index date or were not born in Denmark
Patient characteristics	Characteristics of all participants: Age at the time of diagnosis (years in median; IQR in parentheses): H. influenzae meningitis group: 1.1 (1-2)

	Control group: 1.1 (1-2) Sex: male: 4606 (53%); female: 4088 (47%) Characteristics of bacterial meningitis group: Etiology of bacterial meningitis: H. influenzae: 1242/1242 (100%)
Population of interest/comparison	H. influenzae meningitis group: Children who had H. influenzae meningitis Control group: Age- and sex-matched controls
Duration of follow-up	Median follow-up time of 21.3 years (IQR: 17-26 years)
Sources of funding	Part industry funded
Sample size	N=8694 H. influenzae meningitis group: n=1242 Control group: n=7452
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

CNS: central nervous system; H. influenzae: Haemophilus influenzae; ICU: intensive care unit; IQR: interquartile range

Outcomes

H. influenzae meningitis group versus control group: All-cause mortality

Outcome	H. influenzae meningitis group, N = 1242	Control group, N = 7452
All-cause mortality (up to 21.3 years) No of events	n = 11	n = 61

H. influenzae meningitis group versus control group: Long-term motor deficits, any hearing impairment, any visual impairment, and diagnosis of epilepsy

Outcome[1]	H. influenzae meningitis group vs Control group, N2 = 1242, N1 = 7452
Long-term motor deficits (inpatient admission rates for cerebral palsy and other paralytic syndrome; 15-<20 years from index date) unadjusted Relative risk/95% CI	3.67 (1.52 to 8.85)
Long-term motor deficits (hospital outpatient service rates for cerebral palsy and other paralytic syndrome; 15-<20 years from index date) unadjusted Relative risk/95% CI	1.49 (0.32 to 7.01)
Any hearing impairment (hospital outpatient service rates for hearing loss and acoustic neuritis in infectious diseases; 15-<20 years from index date) unadjusted Relative risk/95% CI	2.71 (0.94 to 7.79)
Any visual impairment (inpatient admission rates for eye diseases; 20-<25 years from index date) unadjusted Relative risk/95% CI	0.99 (0.22 to 4.42)
Any visual impairment (hospital outpatient service rates for eye diseases; 15-<20 years from index date) unadjusted Relative risk/95% CI	1.49 (0.74 to 2.98)
Diagnosis of epilepsy (inpatient admission rates for epilepsies/seizure disorders; 20-<25	2.61 (1.29 to 5.31)

Outcome[1]	H. influenzae meningitis group vs Control group, N2 = 1242, N1 = 7452
years from index date) unadjusted Relative risk/95% CI	
Diagnosis of epilepsy (hospital outpatient service rates for epilepsies/seizure disorders; 20-<25 years from index date) unadjusted Relative risk/95% CI	2.36 (0.46 to 12.17)

[1]Unadjusted RR extracted as raw data not reported
CI: confidence interval

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	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of prognostic not provided)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Moderate risk for motor deficits, hearing impairment, visual impairment, and epilepsy: Description of the valid and reliable measurement of outcomes not provided. Low risk for all-cause mortality: The Danish Register of Causes of death was used, and the outcome is objective.)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but not adjusted for confounders/baseline differences identified such as infectious diseases and ear diseases. No clear information regarding method of confounding factor measurement.)*
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

Roed, 2012

Bibliographic Reference	Roed, C.; Engsig, F. N.; Omland, L. H.; Skinhoj, P.; Obel, N.; Long-term mortality in patients diagnosed with Listeria monocytogenes meningitis: a Danish nationwide cohort study; Journal of Infection; 2012; vol. 64 (no. 1); 34-40

Study details

Country/ies where study was carried out	Denmark
Study type	Retrospective cohort study
Study dates	1977 – 2006
Inclusion criteria	Listeria monocytogenes meningitis group: Patients who had listeria meningitis (ICD-8 revision, code: 027.01) or listeria meningitis and meningoencephalitis (ICD-10 revision, code: A32.1) in the period of 1st January 1977 to 31st December 2006.

	Patients were identified from the Danish National Hospital Register. Control group: Age- and sex-matched controls who were born in Denmark, alive and living in Denmark at the index date[1] of the corresponding listeria meningitis patient. Nine controls for each meningitis patient were identified from the Danish Civil Registration System. [1]Index date defined as 1 year after the date of listeria meningitis diagnosis
Exclusion criteria	Patients who died or emigrated or were lost to follow-up in one year after the diagnosis of meningitis, and patients who were aged <16 years at listeria meningitis diagnosis or had other CNS infection before listeria meningitis, did not live in Denmark at the date of listeria meningitis diagnosis or were not born in Denmark
Patient characteristics	Characteristics of all participants: Age at the time of diagnosis (years in median; IQR in parentheses): Listeria meningitis group: 62 (50-73) Control group: 62 (50-73) Sex: male: 650 (57%); female: 490 (43%) Characteristics of bacterial meningitis group: Etiology of bacterial meningitis: Listeria monocytogenes: 114/114 (100%)
Population of interest/comparison	Listeria monocytogenes meningitis group: Patients who had listeria meningitis Control group: Age- and sex-matched, population-based cohort
Duration of follow-up	Up to 30 years
Sources of funding	Part industry funded
Sample size	N=1140 Listeria monocytogenes meningitis group: n=114 Control group: n=1026

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

Outcomes

Listeria meningitis group versus control group: All-cause mortality

Outcome	**Listeria meningitis group, N = 114**	**Control group, N = 1026**
All-cause mortality (up to 30 years) No of events	n = 57	n = 400

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	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement prognostic factor not reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Outcome (that is, all-cause mortality) is objective, and description of outcome reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but no attempts were made to control for other potential confounders identified (for example, infectious disease and cancer))*

Section	Question	Answer
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

Roed, 2013

Bibliographic Reference	Roed, C.; Omland, L. H.; Skinhoj, P.; Rothman, K. J.; Sorensen, H. T.; Obel, N.; Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis; JAMA; 2013; vol. 309 (no. 16); 1714-21

Study details

Country/ies where study was carried out	Denmark
Study type	Retrospective cohort study
Study dates	1977-2010
Inclusion criteria	Bacterial meningitis group: Patients who had meningococcal, pneumococcal, or H. influenzae meningitis (ICD-8 and ICD-10 codes) at the age of <12 years (<5 years for H. influenzae meningitis) in the period between 1st January 1977 and 1st January 2007, were born in Denmark in the period between 1st January 1975 and 1st January 1997 and did not have neuroinfections before bacterial meningitis. Patients were identified from the Danish National Registry of Patients (DNRP). Population-based cohort): Age- and sex-matched controls who were born on the same date as meningitis patients, were alive and were not diagnosed with meningitis before age 13 years. Four controls for each meningitis patient were identified

	from the Danish Civil Registration System. Sibling cohort: All full siblings of meningitis patients who were alive and living in Denmark at age 13 years.
Exclusion criteria	Patients who died or emigrated or were lost to follow-up before age 13 years.
Patient characteristics	Age at the time of diagnosis (years in mean; SD in parentheses): 2 (1) Sex: male: 9277/16802 (55%); female: 7525/16802 (45%) Etiology of bacterial meningitis: Meningococcal meningitis: 1338/2784 (48%); Pneumococcal meningitis: 455/2784 (16%); H. influenzae: 991/2784 (36%)
Population of interest/comparison	Bacterial meningitis group: Patients who had meningococcal, pneumococcal, or H. influenzae meningitis at the age of <12 years (<5 years for H. influenzae meningitis) Population-based cohort: Age- and sex-matched, population-based cohort Sibling cohort: All full siblings of the patients
Duration of follow-up	Not reported[1] [1]Participants were followed up until they were aged 35 years, and they had meningitis when they were aged about 2 years. Therefore, follow-up could be about 33 years.
Sources of funding	Not industry funded
Sample size	N=16802 Bacterial meningitis group: n=2784 Population-based cohort: n=11136 Sibling cohort: n=2882
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

H. influenzae: Haemophilus influenzae; ICD: international classification of diseases; ICU: intensive care unit; SD: standard deviation

Outcomes

Bacterial meningitis group versus population-based cohort versus sibling cohort: Educational achievement

Outcome	Bacterial meningitis group, N = 2784	Population-based cohort, N = 11136	Sibling cohort, N = 2882
Educational achievement (vocational education, such as carpenter, dental technician, or hairdresser) No of events	n = 748	n = 3032	n = 741
Educational achievement (high school education or completing the 12th school year) No of events	n = 960	n = 4614	n = 1029
Educational achievement (higher education, such as obtaining a degree from a college or university) No of events	n = 368	n = 1821	n = 431

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	Low risk of bias *(Data was available for 99.9% of participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of prognostic factor not provided)*
Outcome	Outcome Measurement	Low risk of bias

Section	Question	Answer
Measurement	Summary	*(Description of valid and reliable measurement of outcome reported)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Some attempts were made to control for potential confounders (using age- and sex-matched controls), 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

QUIPS: Quality in Prognosis Studies

Schmidt, 2006

Bibliographic Reference	Schmidt, H.; Heimann, B.; Djukic, M.; Mazurek, C.; Fels, C.; Wallesch, C. W.; Nau, R.; Neuropsychological sequelae of bacterial and viral meningitis; Brain; 2006; vol. 129 (no. pt2); 333-45

Study details

Country/ies where study was carried out	Germany
Study type	Prospective cohort study
Study dates	Not reported

Inclusion criteria	Bacterial meningitis group: Patients with confirmed bacteriological (positive culture or Gram stain) or ≥2 laboratory signs of bacterial CNS infection (CSF leucocytes ≥1000/µl, CSF lactate ≥3 mmol/l, CSF protein ≥1000 mg/l) plus clinical signs of bacterial meningitis Control group: Age- and sex-matched healthy controls with normal neurological examination.
Exclusion criteria	Age <15 years, age >70 years, poor skills in German, unclear clinical results to confirm diagnosis, alcoholic, other addictive disorders, sedatives or neuroleptic medication use, known affective or psychiatric disease, neurological conditions potentially affecting the CNS, systemic neoplasms, and serious recent life events that could interfere with neuropsychological testing
Patient characteristics	N=89 (whole study N=148; study also included 59 participants with viral meningitis, but this group was not of interest for the current review so was not extracted) Age at follow-up (years in mean; SD in parentheses): 45 (14) Sex: male: 51 (57%); female: 38 (43%) Etiology of bacterial meningitis: S. pneumoniae: 16/59 (27%); N. meningitidis: 16/59 (27%); S. aureus: 1/59 (2%); Streptococci: 5/59 (8%); L. monocytogenes: 3/59 (5%); Not identified: 18/59 (31%)
Population of interest/comparison	Bacterial meningitis group: Patients with confirmed bacterial meningitis Control group: Age- and sex-matched healthy controls
Duration of follow-up	6 years
Sources of funding	Not industry funded
Sample size	N=89 Bacterial meningitis group: n=59 Control group: n=30

Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

CNS: central nervous system; CSF: cerebrospinal fluid; ICU: intensive care unit; L. monocytogenes: Listeria monocytogenes; N. meningitidis: Neisseria meningitidis; SD: standard deviation; S. aureus: Staphylococcus aureus; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Bacterial meningitis group versus control group: Long-term cognitive deficits

Outcome	Bacterial meningitis group, N = 59	Control group, N = 30
Long-term cognitive deficit (impaired attention) No of events	n = 23	n = 6
Long-term cognitive deficit (impaired executive functions) No of events	n = 38	n = 8
Long-term cognitive deficit (impaired short-term/working memory) No of events	n = 35	n = 5
Long-term cognitive deficit (impaired verbal learning/memory) No of events	n = 18	n = 3
Long-term cognitive deficit (impaired non-verbal learning/memory) No of events	n = 12	n = 2
Long-term cognitive deficit (impaired visuo-constructive functions) No of events	n = 44	n = 8
Long-term cognitive deficit (pathological global cognitive sum score)	n = 22	n = 1

Outcome	Bacterial meningitis group, N = 59	Control group, N = 30
No of events		

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	Low risk of bias *(Data was available for all participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of bacterial meningitis provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of valid and reliable measurement of outcomes reported (for example, Wechsler Memory Scale-R))*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but no attempts were made to control for other potential confounders identified (for example, socioeconomic status))*
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	Directly applicable

Section	Question	Answer
directness		

QUIPS: Quality in Prognosis Studies

Stevens, 2003

Bibliographic Reference	Stevens, J. P.; Eames, M.; Kent, A.; Halket, S.; Holt, D.; Harvey, D.; Long term outcome of neonatal meningitis; Archives of Disease in Childhood Fetal & Neonatal Edition; 2003; vol. 88 (no. 3); F179-84

Study details

Country/ies where study was carried out	England and Wales
Study type	Prospective cohort study
Study dates	Participants were from a national incidence study of meningitis in infancy conducted in 1985–1987, but dates of the present study were not reported.
Inclusion criteria	Bacterial meningitis group: Children aged 9-10 years old who had confirmed neonatal bacterial meningitis (up to 28 days of life) caused by group B streptococci, Gram negative bacteria (for example, E. coli) or Listeria monocytogenes. Bacterial meningitis defined as positive CSF culture. Hospital control group: Controls matched for sex, birth date, birth weight (±500 g), and hospital of birth GP control group: Controls born at term and matched for sex and birth date
Exclusion criteria	Not reported
Patient characteristics	Characteristics of all participants: Age at follow-up (years in mean; SD in parentheses): 9 (0.3) Clinical characteristics of bacterial meningitis group:

	Etiology of bacterial meningitis: Listeria monocytogenes: 13/111 (12%); Gram negative bacteria: 7/111 (6%); E. coli: 42/111 (38%); Group B streptococci: 49/111 (44%)
Population of interest/comparison	Bacterial meningitis group: Children aged 9-10 years old who survived neonatal bacterial meningitis Hospital control group: Controls matched for sex, birth date, birth weight, and hospital of birth GP control group: Controls born at term and matched for sex and birth date
Duration of follow-up	Not reported* Patients had neonatal meningitis and were assessed at 9-10 years of age. Therefore, follow-up could be 9-10 years.
Sources of funding	Not industry funded
Sample size	N=273 Bacterial meningitis group: n=111 Hospital control group: n=113 GP control group: n=49
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not. Unclear whether participants were preterm or term neonates as no such data reported

CSF: cerebrospinal fluid; E. coli: Escherichia coli; GP: general practitioner; ICU: intensive care unit; SD: standard deviation

Outcomes

Bacterial meningitis group versus hospital control group versus GP control group: Long-term cognitive deficits, any hearing impairment, any visual impairment, diagnosis of epilepsy, and hydrocephalus with a shunt

Outcome	Bacterial meningitis group, N = 111	Hospital control group, N = 113	GP control group, N = 49
Long-term cognitive deficits (IQ 70-80)	n = 16	n = 12	n = 7

Outcome	Bacterial meningitis group, N = 111	Hospital control group, N = 113	GP control group, N = 49
No of events			
Long-term cognitive deficits (IQ <70) No of events	n = 15	n = 1	Not reported
Any hearing impairment (sensorineural hearing loss) No of events	n = 4	n = 0	n = 0
Any visual impairment (bilateral impairment of visual acuity) No of events	n = 19	n = 21	n = 4
Diagnosis of epilepsy (seizure disorder or absence seizures) No of events	n = 6	n = 2	Not reported
Hydrocephalus with a shunt (persistent hydrocephalus requiring a shunt) No of events	n = 3	n = 0	n = 0

GP: general practitioner; IQ: intelligence quotient

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Data was available for 96% of participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of the prognostic factor (that is, bacterial meningitis) reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of the outcomes reported. The measurement of outcomes, such as hearing impairment, visual impairment, diagnosis of epilepsy, and hydrocephalus with a shunt, is objective, and standardised test (Wechsler intelligence scale for children) is used for cognitive impairment.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Controls were matched for sex, birth date, and birth weight (±500 g), but limited number of baseline characteristics were presented 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

QUIPS: Quality in Prognosis Studies

Taylor, 1990

Bibliographic Reference	Taylor, H. G.; Mills, E. L.; Ciampi, A.; du Berger, R.; Watters, G. V.; Gold, R.; MacDonald, N.; Michaels, R. H.; The sequelae of Haemophilus influenzae meningitis in school-age children; New England Journal of Medicine; 1990; vol. 323 (no. 24); 1657-63

Study details

Country/ies where study was carried out	Canada
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	H. influenzae type b meningitis group: Children aged 6-14 years at the time of assessment who had one episode of meningitis, a sibling between 6 and 16 years old, and English as the primary language at School; lived in area that would make same-day transportation possible; and were willing to take part and had families willing for their children to participate. Control group: School-age siblings with normal neurologic histories, who had English as the primary language at School
Exclusion criteria	Not reported
Patient characteristics	Characteristics of all participants: Age at follow up (years in mean; SD in parentheses): 11 (3) Sex: male: 96 (49%); female: 98 (51%) Characteristics of participants with bacterial meningitis: Age at diagnosis (months in mean; SD in parentheses): 17 (15) Etiology of bacterial meningitis: H. influenzae type b: 97/97 (100%)
Population of interest/comparison	H. influenzae type b meningitis group: Children who had confirmed H. influenzae type b meningitis Control group: School-age siblings with normal neurologic histories
Duration of follow-up	Not reported[1] [1]Children were assessed when they were aged 9.6 years, and they had meningitis at the age of 17.3 months. Therefore, follow-up could be up to 8 years.

Sources of funding	Not industry funded
Sample size	N=194 H. influenzae type b meningitis group: n=97 Control group: n=97
Other information	The study did not specify whether participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)) or not.

H. influenzae: Haemophilus influenzae; ICU: intensive care unit; SD: standard deviation

Outcomes

H. influenzae type b meningitis group versus control group: Long-term cognitive deficits, long-term behavioural deficits, and educational achievement

Outcome	H. influenzae type b meningitis group, N = 97	Control group, N = 97
Long-term cognitive deficits (IQ <80) Custom value	4/97	0/97
Long-term behavioural deficits (Behavioural problems defined as T score in clinical range assessed with Child Behaviour Checklist or Teacher Report Form) Custom value	15/75	10/77
Long-term behavioural deficits (Poor adaptive functioning, defined as Vineland Adaptive Behavioural Scales composite score <80) Custom value	9/97	9/97
Educational achievement (limited academic skills assessed with Wide Range Achievement Test-Revised)	22/97	17/97

Outcome	H. influenzae type b meningitis group, N = 97	Control group, N = 97
Custom value		
Educational achievement (poor school achievement or grade repetition) Custom value	16/94	12/92
Educational achievement (need of special educational assistance) Custom value	24/92	12/92

H. influenzae: Haemophilus influenzae; IQ: intelligence quotient

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 baseline characteristics of the study population were appropriate and adequately provided, but exclusion criteria not provided.)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Moderate risk for long-term behavioural deficits: n=42 (22%) children are missing from analyses. No explanation given. Low risk for long-term cognitive deficits and educational achievement: Data was presented for ≥95% of participants.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Definition and clear specification of the method of measurement for prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement of outcomes was used (for example, Teacher Report Form, Child Behaviour Checklist and Wechsler Intelligence Scale).)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential important confounders (for example, age and sex))*
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	High
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: Quality in Prognosis Studies

Tejani, 1982

Bibliographic Reference	Tejani, A.; Dobias, B.; Sambursky, J.; Long-term prognosis after H. influenzae meningitis: prospective evaluation; Developmental Medicine & Child Neurology; 1982; vol. 24 (no. 3); 338-43

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	1974-1976
Inclusion criteria	H. influenzae type b meningitis group (age 2-24 months at the time of illness): Children who recovered from H. influenzae

	meningitis and were aged 2 months to 12 years at the time of illness. H. influenzae type b meningitis group (age >48 months at the time of illness): Children who recovered from H. influenzae meningitis and were aged >4 years at the time of illness. For both of the meningitis groups, H. influenzae meningitis was defined as detection of H. influenzae in cerebrospinal fluid. Control group: Sibling controls who did not have meningitis
Exclusion criteria	Patients who did not have a sibling control, and those with neurological or audio-visual abnormality
Patient characteristics	Age at the time of illness (range): H. influenzae type b meningitis group (age 2-24 months at the time of illness): 2-24 months H. influenzae type b meningitis group (age >48 months at the time of illness): 4 years 2 months to 6 years Control group: Not reported Etiology of bacterial meningitis: H. influenzae: 22/22 (100%)
Population of interest/comparison	H. influenzae type b meningitis group (age 2-24 months at the time of illness): Children aged 2 months to 12 years at the time of illness H. influenzae type b meningitis group (age >48 months at the time of illness): Children aged >4 years at the time of illness Control group: Sibling controls with no history of meningitis
Duration of follow-up	Up to 4 years
Sources of funding	Not reported
Sample size	N=37 H. influenzae type b meningitis group (age 2-24 months at the time of illness): n=13 H. influenzae type b meningitis group (age >48 months at the time of illness): n=9 Control group: n=15

	Excluded from follow-up psychometric assessment: n=2 neurological or audio-visual abnormality, and n=5 those without a sibling control
Other information	All patients were admitted to the ICU.

H. influenzae: Haemophilus influenzae; ICU: intensive care unit

Outcomes

H. influenzae type b meningitis group (age 2-24 months at the time of illness) versus control group: Long-term cognitive deficits

Outcome	H. influenzae type b meningitis group, N = 13	Control group, N = 8
Long-term cognitive deficits (Full-scale IQ <90) Custom value	3/8	2/8

H. influenzae type b meningitis group (age >48 months at the time of illness) versus control group: Long-term cognitive deficits; and educational achievement

Outcome	H. influenzae type b meningitis group, N = 9	Control group, N = 7
Long-term cognitive deficits (Full-scale IQ <90) Custom value	1/7	1/7
Educational achievement (reading ability below their appropriate grade level) Custom value	4/7	4/7
Educational achievement (arithmetic ability below their appropriate grade level) Custom value	5/7	5/7

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable measurement of the prognostic factor (that is, bacterial meningitis) reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Valid and reliable measurement of outcome was used (the Wechsler Preschool and Primary Scale of Intelligence Test, and the Wechsler Intelligence Scales for Children).)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to identify or control for potential important confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Analytical strategy and model development strategy not provided. There was no evidence of selective reporting of the 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

Vartzelis, 2011

Bibliographic Reference Vartzelis, G.; Vasilopoulou, V.; Katsioulis, A.; Hadjichristodoulou, C.; Theodoridou, M.; Functional and behavioral outcome of bacterial meningitis in school-aged survivors; Pediatrics International; 2011; vol. 53 (no. 3); 300-2

Study details

Country/ies where study was carried out	Greece
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	Bacterial meningitis group: Children with confirmed bacterial meningitis who were aged >6 months and between 7 and 17 years at the time of illness and assessment, respectively. Bacterial meningitis defined as positive CSF culture and >100 leukocytes/ml3 in CSF microscopy. Control group: Healthy children or teenagers from the extended families of the patients
Exclusion criteria	Children with systemic diseases and psychological conditions
Patient characteristics	Age at follow-up (years in mean; SD in parentheses): 13 (3) Sex: male: 42 (70%); female: 18 (30%) Etiology of bacterial meningitis: N. meningitidis: 16/30 (53%); S. pneumoniae: 7/30 (23%); H. influenzae: 6/30 (20%); Group B Streptococcus: 1/30 (3%)
Population of interest/comparison	Bacterial meningitis group: Children with confirmed bacterial meningitis Control group: Healthy children or teenagers from the extended families of the patients
Duration of follow-up	Not reported
Sources of funding	Not reported
Sample size	N=60 Bacterial meningitis group: n=30

	Control group: n=30
Other information	The study stated that data on admission to ICU was collected but did not specify/report how many participants received critical care (defined as level 2 (high dependency) or level 3 (ICU)).

CSF: cerebrospinal fluid; H. influenzae: Haemophilus influenzae; ICU: intensive care unit; N. meningitidis: Neisseria meningitidis; SD: standard deviation; S. pneumoniae: Streptococcus pneumoniae

Outcomes

Bacterial meningitis group versus control group: Long-term behavioural deficits

Outcome	Bacterial meningitis group, N = 30	Control group, N = 30
Long-term behavioural deficits (internalising problems, such as withdrawn, somatic complaints, anxious or depressed, assessed with the CBCL) Custom value	7/30	7/30
Long-term behavioural deficits (externalising problems, such as delinquent or aggressive behaviour, assessed with the CBCL) Custom value	6/30	4/30
Long-term behavioural deficits (total behavioural problems assessed with the CBCL) Custom value	8/30	5/30

CBCL: child behaviour checklist

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*

Section	Question	Answer
		characteristics of the study population were appropriate and adequately provided)
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 measurement of the prognostic factor (that is, bacterial meningitis) reported)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of outcome reported, and valid and reliable measurement of outcome (the Child Behaviour Checklist) used)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to identify or control for potential confounders)*
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

Zelano, 2020

Bibliographic Reference	Zelano, J.; Westman, G.; Epilepsy after brain infection in adults: A register-based population-wide study; Neurology; 2020; vol. 95 (no. 24); e3213-e3220

Study details

Country/ies where study was carried out	Sweden
Study type	Retrospective cohort study
Study dates	2000 - 2017
Inclusion criteria	Bacterial meningitis group: Patients aged >18 years who had inpatient hospital care for bacterial meningitis (ICD-10 code: A390, G00, G01, A17) and had survived 30 days after diagnosis/admission (index date). Participants were identified from the National Patient Register (NPR) Control group: Age- and sex-matched controls who did not have brain infection
Exclusion criteria	Bacterial meningitis group: Epilepsy-related diagnosis before the index date Control group: History of brain infection registered in the NPR
Patient characteristics	N=39040 (whole study N=48329; study also included participants with other brain infections, such as herpes simplex virus encephalitis (N=443), tick-borne encephalitis (N=886), abscess (N=938), other meningitis (N=5778), and other encephalitis (N=1244), but these groups were not of interest for the current review so were not extracted) Age at the time of diagnosis: >18 years Sex[1]: male: 23216 (48%); female: 25113 (52%) [1]Reported for whole study
Population of interest/comparison	Bacterial meningitis group: Patients aged >18 years who had inpatient hospital care for bacterial meningitis Control group: Age- and sex-matched controls
Duration of follow-up	Up to 17 years

Sources of funding	Not industry funded
Sample size	N=39040 Bacterial meningitis group: n=2812 Control group: n=36228
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

Outcomes

Bacterial meningitis group versus control group: Diagnosis of epilepsy

Outcome	**Bacterial meningitis group, N = 2812**	**Control group, N = 36228**
Diagnosis of epilepsy No of events	n = 118	n = 495

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	Low risk of bias *(Data was available for all participants)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Description and measurement of prognostic factor not provided)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Description and measurement of outcome not provided. No clear information regarding method of outcome measurement)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Age- and sex-matched controls were used, but unclear if there was residual confounding and no attempts were made to control for other potential confounders identified (for example, comorbidities))*
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	High
Overall risk of bias and directness	Directness	Directly applicable

NPR: National Patient Register; QUIPS: Quality in Prognosis Studies

Appendix E Forest plots

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

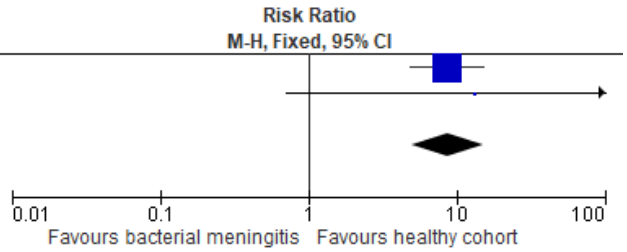
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Bacterial meningitis versus healthy cohort: The risk of long-term complications in younger and older babies

Figure 2: Long-term motor deficits (neuromotor disabilities or cerebral palsy; follow-up 3.6-15 years)

	Bacterial meningitis		No bacterial meningitis (healthy cohort)			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bedford 2001	128	1584	13	1391	97.6%	8.65 [4.91, 15.23]
D'Angio 1995	3	41	0	79	2.4%	13.33 [0.71, 252.10]
Total (95% CI)		**1625**		**1470**	**100.0%**	**8.76 [5.03, 15.27]**
Total events	131		13			

Heterogeneity: $Chi^2 = 0.08$, $df = 1$ ($P = 0.78$); $I^2 = 0\%$
Test for overall effect: $Z = 7.66$ ($P < 0.00001$)

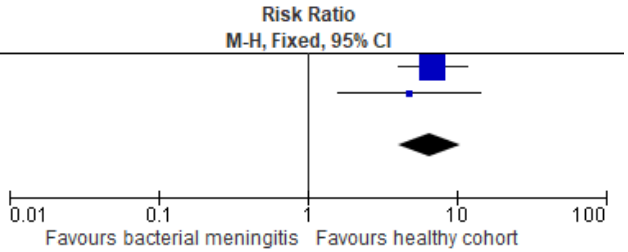


CI: confidence interval; M-H: Mantel-Haenszel

Figure 3: Long-term cognitive deficits (learning difficulties and IQ <70; follow-up 3.6-15 years)

	Bacterial meningitis		No bacterial meningitis (healthy cohort)			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bedford 2001	118	1584	15	1391	85.4%	6.91 [4.06, 11.76]
D'Angio 1995	10	41	4	79	14.6%	4.82 [1.61, 14.42]
Total (95% CI)		**1625**		**1470**	**100.0%**	**6.60 [4.07, 10.72]**
Total events	128		19			

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 7.63 (P < 0.00001)

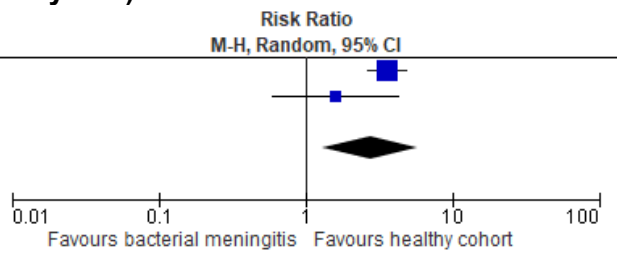


CI: confidence interval; IQ: intelligence quotient; M-H: Mantel-Haenszel

Figure 4: Long-term behavioural deficits (behavioural problems; follow-up up to 5 years)

	Bacterial meningitis		No bacterial meningitis (healthy cohort)			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Bedford 2001	188	1584	46	1391	67.7%	3.59 [2.62, 4.91]
Vartzelis 2011	8	30	5	30	32.3%	1.60 [0.59, 4.33]
Total (95% CI)		**1614**		**1421**	**100.0%**	**2.76 [1.31, 5.81]**
Total events	196		51			

Heterogeneity: Tau² = 0.19; Chi² = 2.32, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 2.68 (P = 0.007)

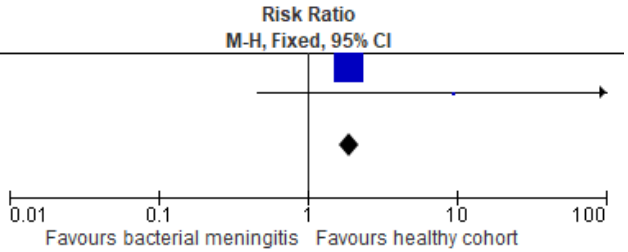


CI: confidence interval; M-H: Mantel-Haenszel

Figure 5: Any hearing impairment (follow-up 3.6-15 years)

Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bedford 2001	408	1584	190	1391	99.8%	1.89 [1.61, 2.20]
D'Angio 1995	2	41	0	79	0.2%	9.52 [0.47, 193.85]
Total (95% CI)		**1625**		**1470**	**100.0%**	**1.90 [1.62, 2.22]**
Total events	410		190			

Heterogeneity: Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 8.06 (P < 0.00001)

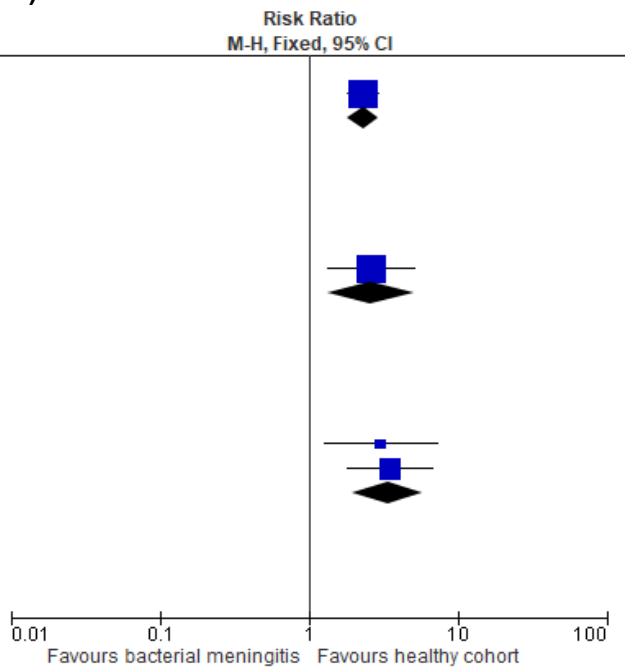


CI: confidence interval; M-H: Mantel-Haenszel

Figure 6: Educational achievement (lower rate is better; follow-up up to 16 years)

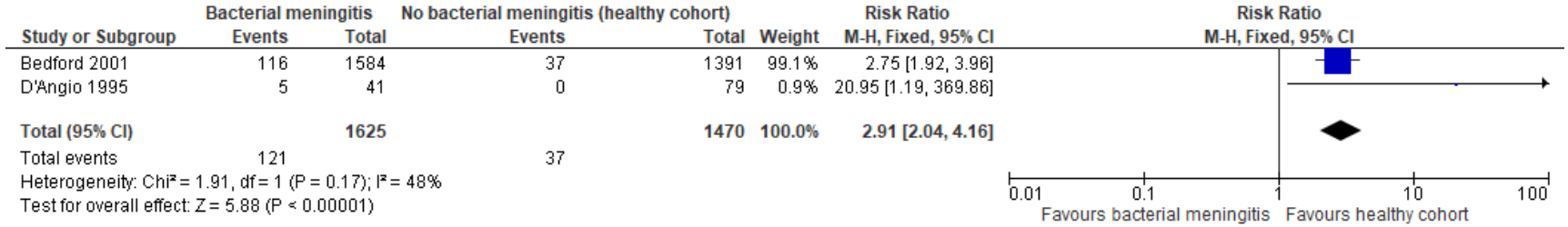
Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Children achieved 0-4 passes at GCSE						
de Louvois 2007	222	461	60	289	100.0%	2.32 [1.82, 2.96]
Subtotal (95% CI)		**461**		**289**	**100.0%**	**2.32 [1.82, 2.96]**
Total events	222		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.75 (P < 0.00001)						
2.7.2 Grade retention						
D'Angio 1995	15	36	11	69	100.0%	2.61 [1.34, 5.08]
Subtotal (95% CI)		**36**		**69**	**100.0%**	**2.61 [1.34, 5.08]**
Total events	15		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.83 (P = 0.005)						
2.7.3 Special educational assistance						
D'Angio 1995	11	41	7	79	28.0%	3.03 [1.27, 7.22]
de Louvois 2007	56	461	10	289	72.0%	3.51 [1.82, 6.77]
Subtotal (95% CI)		**502**		**368**	**100.0%**	**3.38 [1.98, 5.76]**
Total events	67		17			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 4.46 (P < 0.00001)						

Test for subgroup differences: Chi² = 1.59, df = 2 (P = 0.45), I² = 0%



CI: confidence interval; M-H: Mantel-Haenszel

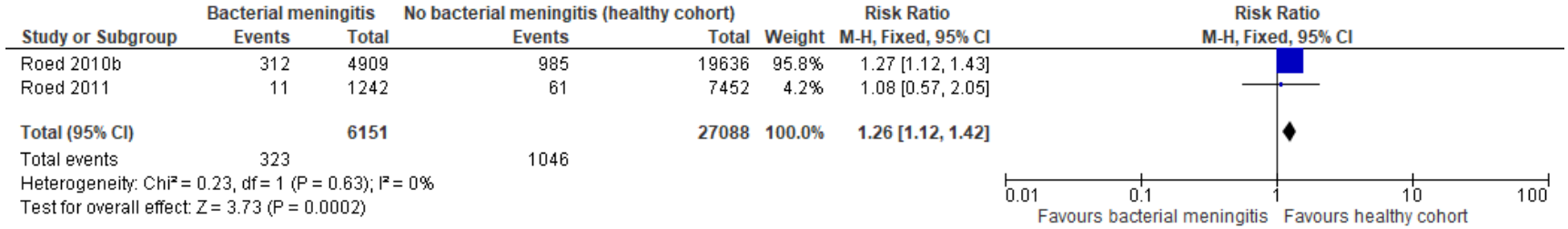
Figure 7: Diagnosis of epilepsy (follow-up 3.6-15 years)



CI: confidence interval; M-H: Mantel-Haenszel

Bacterial meningitis versus healthy cohort: The risk of long-term complications in children

Figure 8: All-cause mortality (follow-up 30 years)

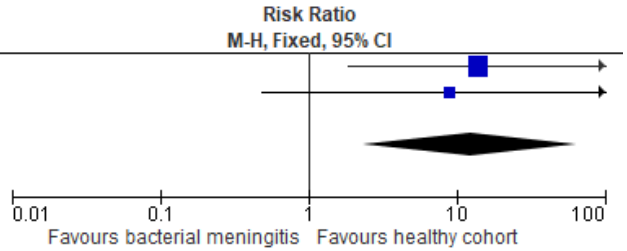


CI: confidence interval; M-H: Mantel-Haenszel

Figure 9: Long-term cognitive deficits (full scale IQ <80; follow-up up to 8 years)

Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grimwood 1995	14	130	1	130	66.7%	14.00 [1.87, 104.92]
Taylor 1990	4	97	0	97	33.3%	9.00 [0.49, 164.93]
Total (95% CI)		**227**		**227**	**100.0%**	**12.33 [2.36, 64.41]**
Total events	18		1			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.98 (P = 0.003)

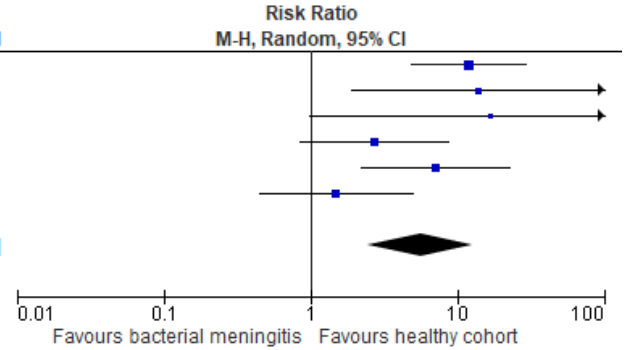


CI: confidence interval; IQ: intelligence quotient; M-H: Mantel-Haenszel

Figure 10: Any hearing impairment (follow-up up to 27 years)

Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Berg 2002	60	304	5	304	23.5%	12.00 [4.89, 29.47]
Christie 2011	14	84	1	84	11.1%	14.00 [1.88, 104.08]
Grimwood 1995	8	130	0	130	6.7%	17.00 [0.99, 291.51]
Hugosson 1997	9	22	3	20	19.8%	2.73 [0.86, 8.68]
Koomen 2003	48	680	3	304	19.8%	7.15 [2.25, 22.78]
Moss 1982	6	60	4	60	19.1%	1.50 [0.45, 5.05]
Total (95% CI)		**1280**		**902**	**100.0%**	**5.65 [2.49, 12.85]**
Total events	145		16			

Heterogeneity: Tau² = 0.54; Chi² = 11.06, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 4.13 (P < 0.0001)

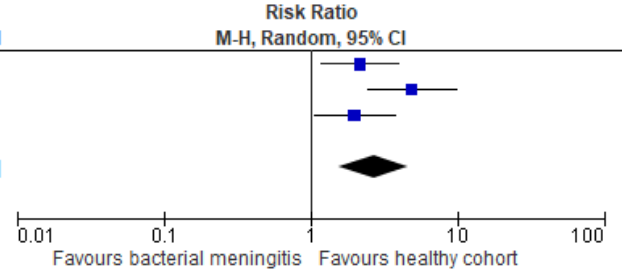


CI: confidence interval; M-H: Mantel-Haenszel

Figure 11: Educational achievement (special educational assistance; lower rate is better; follow-up up to 12 years)

Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anderson 2004	29	107	12	96	35.0%	2.17 [1.17, 4.01]
Christie 2011	41	97	8	93	30.8%	4.91 [2.43, 9.92]
Taylor 1990	24	92	12	92	34.2%	2.00 [1.07, 3.75]
Total (95% CI)		**296**		**281**	**100.0%**	**2.71 [1.58, 4.67]**
Total events	94		32			

Heterogeneity: Tau² = 0.12; Chi² = 4.22, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 3.60 (P = 0.0003)

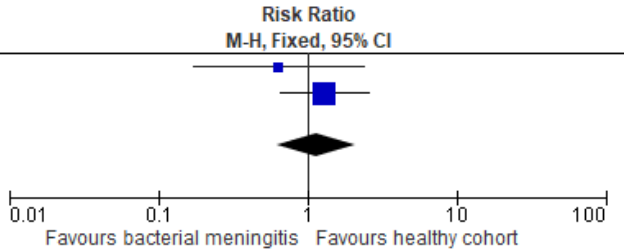


CI: confidence interval; M-H: Mantel-Haenszel

Figure 12: Educational achievement (grade retention; lower rate is better; follow-up up to 12 years)

Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feldman 1988	4	23	3	11	25.1%	0.64 [0.17, 2.37]
Taylor 1990	16	94	12	92	74.9%	1.30 [0.65, 2.60]
Total (95% CI)		**117**		**103**	**100.0%**	**1.14 [0.62, 2.09]**
Total events	20		15			

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.68)



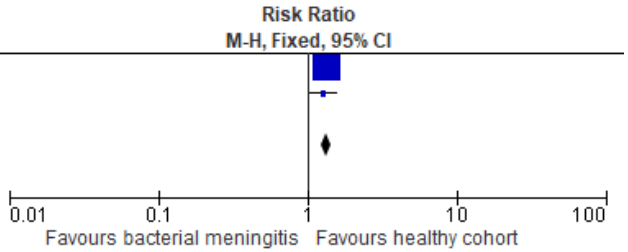
CI: confidence interval; M-H: Mantel-Haenszel

Bacterial meningitis versus healthy cohort: The risk of long-term complications in adults

Figure 13: All-cause mortality (follow-up up to 30 years)

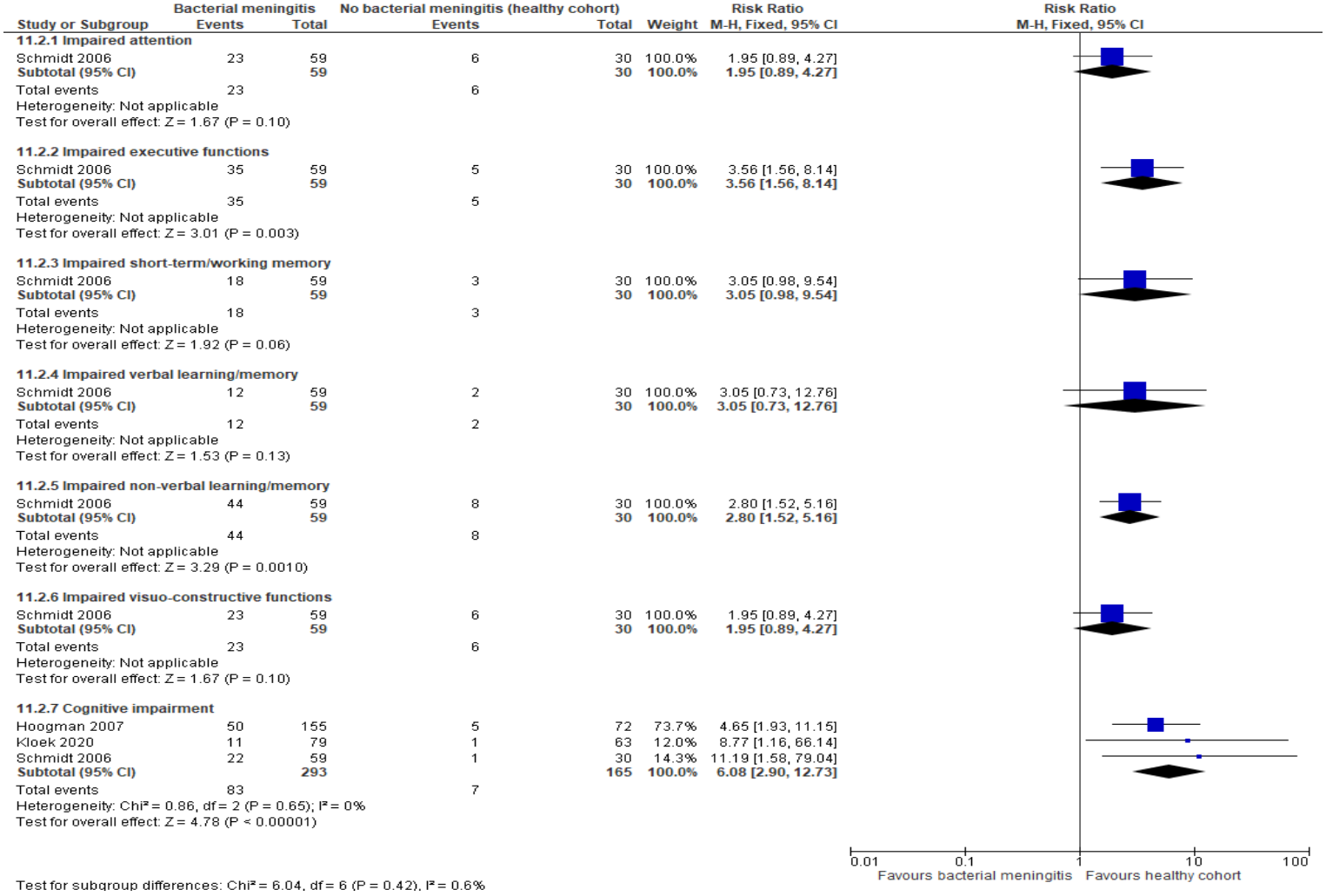
Study or Subgroup	Bacterial meningitis Events	Total	No bacterial meningitis (healthy cohort) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Roed 2010a	584	2131	1739	8524	89.7%	1.34 [1.24, 1.46]
Roed 2012	57	114	400	1026	10.3%	1.28 [1.05, 1.56]
Total (95% CI)		**2245**		**9550**	**100.0%**	**1.34 [1.24, 1.44]**
Total events	641		2139			

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 7.55 (P < 0.00001)



CI: confidence interval; M-H: Mantel-Haenszel

Figure 14: Long-term cognitive deficits (follow-up up to 6 years)



CI: confidence interval; M-H: Mantel-Haenszel

Appendix F GRADE tables

GRADE tables for review question: What is the risk of long-term complications in bacterial meningitis?

Table 5: Evidence profile for the risk of long-term complications in neonates

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bacterial meningitis	Control	Relative (95% CI)	Absolute		
Long-term cognitive deficits (IQ 70-80) (follow-up 9-10 years)												
1 (Stevens 2003)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/111 (14.4%)	19/162 (11.7%)	RR 1.23 (0.66 to 2.28)	27 more per 1000 (from 40 fewer to 150 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (IQ <70) (follow-up 9-10 years)												
1 (Stevens 2003)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/111 (13.5%)	1/113 (0.88%)	RR 15.27 (2.05 to 113.65)	126 more per 1000 (from 9 more to 997 more)	VERY LOW	CRITICAL
Any hearing impairment (sensorineural hearing loss) (follow-up 9-10 years)												
1 (Stevens 2003)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/111 (3.6%)	0/162 (0%)	RR 13.1 (0.71 to 240.88)	40 more per 1000 (from 1 fewer to 70 more)[3]	VERY LOW	CRITICAL
Any visual impairment (bilateral impairment of visual acuity) (follow-up 9-10 years)												
1 (Stevens 2003)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/111 (17.1%)	25/162 (15.4%)	RR 1.11 (0.64 to 1.91)	17 more per 1000 (from 56 fewer to 140 more)	VERY LOW	CRITICAL
Diagnosis of epilepsy (seizure disorder or absence seizures) (follow-up 9-10 years)												
1 (Stevens 2003)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/111 (5.4%)	2/113 (1.8%)	RR 3.05 (0.63 to 14.81)	36 more per 1000 (from 7 fewer to 244 more)	VERY LOW	CRITICAL

Hydrocephalus with a shunt (persistent hydrocephalus requiring a shunt) (follow-up 9-10 years)												
1 (Stevens 2003)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/111 (2.7%)	0/162 (0%)	RR 10.19 (0.53 to 195.31)	30 more per 1000 (from 10 fewer to 60 more)[3]	VERY LOW	CRITICAL

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

Table 6: Evidence profile for the risk of long-term complications in babies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
Long-term motor deficits (neuromotor disabilities or cerebral palsy) (follow-up 3.6-15 years)												
2*	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	131/1625 (8.1%)	13/1470 (0.88%)	RR 8.76 (5.03 to 15.27)	69 more per 1000 (from 36 more to 126 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (learning difficulties and IQ <70) (follow-up 3.6-15 years)												
2*	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	128/1625 (7.9%)	19/1470 (1.3%)	RR 6.6 (4.07 to 10.72)	72 more per 1000 (from 40 more to 126 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (behavioural problems) (follow-up up to 5 years)												
2*	observational studies	very serious[1]	serious[3]	no serious indirectness	serious[4]	none	196/1614 (12.1%)	51/1421 (3.6%)	RR 2.76 (1.31 to 5.81)	63 more per 1000 (from 11 more to 173 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (internalising problems, such as withdrawn, somatic complaints, anxious or depressed)												
1 (Vartzelis 2011)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/30 (23.3%)	7/30 (23.3%)	RR 1 (0.4 to 2.5)	0 fewer per 1000 (from 140 fewer to 350 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (externalising problems, such as delinquent or aggressive behaviour)												

1 (Vartzelis 2011)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/30 (20%)	4/30 (13.3%)	RR 1.5 (0.47 to 4.78)	67 more per 1000 (from 71 fewer to 504 more)	VERY LOW	CRITICAL
Any hearing impairment (follow-up 3.6-15 years)												
2*	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	410/1625 (25.2%)	190/1470 (12.9%)	RR 1.9 (1.62 to 2.22)	116 more per 1000 (from 80 more to 158 more)	VERY LOW	CRITICAL
Any visual impairment (ocular or visual disorders) (follow-up 5 years)												
1 (Bedford 2001)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	217/1584 (13.7%)	55/1391 (4%)	RR 3.46 (2.6 to 4.62)	97 more per 1000 (from 63 more to 143 more)	VERY LOW	CRITICAL
Educational achievement (children achieved 0-4 passes at GCSE; lower rate is better) (follow-up 16 years)												
1 (de Louvois 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	222/461 (48.2%)	60/289 (20.8%)	RR 2.32 (1.82 to 2.96)	274 more per 1000 (from 170 more to 407 more)	VERY LOW	CRITICAL
Educational achievement (repeating a grade; lower rate is better) (follow-up 3.6-15 years)												
1 (D'Angio 1995)	observational studies	serious[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/36 (41.7%)	11/69 (15.9%)	RR 2.61 (1.34 to 5.08)	257 more per 1000 (from 54 more to 650 more)	VERY LOW	CRITICAL
Educational achievement (special educational assistance; lower rate is better) (follow-up 16 years)												
2*	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	67/502 (13.3%)	17/368 (4.6%)	RR 3.38 (1.98 to 5.76)	110 more per 1000 (from 45 more to 220 more)	VERY LOW	CRITICAL
Educational achievement (children achieved ≥5 passes at GCSE; higher rate is better) (follow-up 16 years)												
1 (de Louvois 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	238/461 (51.6%)	228/289 (78.9%)	RR 0.65 (0.59 to 0.73)	276 fewer per 1000 (from 213 fewer to 323 fewer)	VERY LOW	CRITICAL
Diagnosis of epilepsy (follow-up 3.6-15 years)												
2*	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	121/1625 (7.4%)	37/1470 (2.5%)	RR 2.91 (2.04 to 4.16)	48 more per 1000 (from 26 more to 80 more)	VERY LOW	CRITICAL

Speech and language disorder (speech and/or language problems) (follow-up 5 years)												
1 (Bedford 2001)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	247/1584 (15.6%)	64/1391 (4.6%)	RR 3.39 (2.6 to 4.42)	110 more per 1000 (from 74 more to 157 more)	VERY LOW	CRITICAL

CI: confidence interval; GCSE: General Certificate of Secondary Education; IQ: intelligence quotient; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**See corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events
[3] Serious heterogeneity unexplained by subgroup analysis
[4] <300-≥150 events
[5] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 7: Evidence profile for the risk of all-cause mortality in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 30 years)												
2*	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	323/6151 (5.3%)	1046/27088 (3.9%)	RR 1.26 (1.12 to 1.42)	10 more per 1000 (from 5 more to 16 more)	VERY LOW	CRITICAL

CI: confidence interval; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**See corresponding forest plot*
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 8: Evidence profile for the risk of long-term motor deficits in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
Long-term motor deficits (gross motor function) (follow-up 2-13 years)												
1 (Berg	observational	very	no serious	no serious	very serious[2]	none	27/304	13/304	RR 2.08 (1.09 to	46 more per 1000	VERY LOW	CRITICAL

2002)	studies	serious[1]	inconsistency	indirectness			(8.9%)	(4.3%)	3.95)	(from 4 more to 126 more)		
Long-term motor deficits (fine motor function) (follow-up 2-13 years)												
1 (Berg 2002)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	22/304 (7.2%)	8/304 (2.6%)	RR 2.75 (1.24 to 6.08)	46 more per 1000 (from 6 more to 134 more)	VERY LOW	CRITICAL
Long-term motor deficits (spasticity) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/130 (2.3%)	0/130 (0%)	RR 7 (0.37 to 134.18)	20 more per 1000 (from 0 fewer to 50 more)[4]	VERY LOW	CRITICAL
Long-term motor deficits (abnormal oculomotor test) (follow-up 17-27 years)												
1 (Hugosson 1997)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/22 (22.7%)	4/20 (20%)	RR 1.14 (0.35 to 3.65)	28 more per 1000 (from 130 fewer to 530 more)	VERY LOW	CRITICAL
Long-term motor deficits (nystagmus, or tremor of the hands and exaggerated knee jerks) (follow-up 5-9 years)												
1 (Moss 1982)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/60 (1.7%)	1/60 (1.7%)	RR 1 (0.06 to 15.62)	0 fewer per 1000 (from 16 fewer to 244 more)	VERY LOW	CRITICAL
Long-term motor deficits (cerebral palsy) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/127 (1.6%)	0/129 (0%)	POR 7.57 (0.47 to 121.64)	20 more per 1000 (from 10 fewer to 40 more)[4]	VERY LOW	CRITICAL
Long-term motor deficits (abnormal balance or standing on one leg test; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	24/127 (18.9%)	10/129 (7.8%)	OR 2.4 (1.1 to 5.24)	90 more per 1000 (from 7 more to 228 more)	VERY LOW	CRITICAL
Long-term motor deficits (dysdiadochokinesis; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	81/127 (63.8%)	39/129 (30.2%)	OR 4.5 (2.5 to 8.1)	359 more per 1000 (from 218 more to 476 more)	VERY LOW	CRITICAL

Long-term motor deficits (abnormal fine motor function or sequential finger-thumb opposition test; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	25/127 (19.7%)	11/129 (8.5%)	OR 2.6 (1.2 to 5.63)	110 more per 1000 (from 15 more to 259 more)	VERY LOW	CRITICAL
Long-term motor deficits (abnormal coordination or finger-nose-finger test; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	49/127 (38.6%)	11/129 (8.5%)	OR 7.1 (3.4 to 14.83)	313 more per 1000 (from 155 more to 495 more)	VERY LOW	CRITICAL
Long-term motor deficits (disorders of the nervous system; unadjusted analysis) (follow-up 22 years)												
1 (Pickering 2018)	observational studies	very serious[1]	no serious inconsistency	serious[5]	serious[6]	none	NR	NR	OR 1.78 (1.29 to 2.46)	NC	VERY LOW	CRITICAL
Long-term motor deficits (inpatient admission rates for cerebral palsy and other paralytic syndrome; unadjusted analysis) (follow-up 15-<20 years)												
1 (Roed 2011)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	NR	NR	RR 3.67 (1.52 to 8.86)	NC	VERY LOW	CRITICAL
Long-term motor deficits (hospital outpatient service rates for cerebral palsy and other paralytic syndrome; unadjusted analysis) (follow-up 15-<20 years)												
1 (Roed 2011)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	NR	NR	RR 1.49 (0.32 to 6.94)	NC	VERY LOW	CRITICAL

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; RR: risk ratio

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

[2] <150 events

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

[4] Absolute effect calculated based on risk difference

[5] Outcome is indirect as it is reported as disorders of nervous system which may include different neurological deficits

[6] Estimate may be imprecise as cannot determine if OIS criteria have been met because data on the number of events is not reported

Table 9: Evidence profile for the risk of long-term cognitive deficits in children

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
Long-term cognitive deficits (full-scale IQ <90) (follow-up 4 years)												
1 (Tejani 1982)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/15 (26.7%)	3/15 (20%)	RR 1.33 (0.36 to 4.97)	66 more per 1000 (from 128 fewer to 794 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (full-scale IQ <85) (follow-up 6 years)												
1 (Christie 2011)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/84 (11.9%)	3/84 (3.6%)	RR 3.33 (0.95 to 11.68)	83 more per 1000 (from 2 fewer to 381 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (full-scale IQ <80) (follow-up up to 8 years)												
2*	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/227 (7.9%)	1/227 (0.4%)	RR 12.33 (2.36 to 64.41)	50 more per 1000 (from 6 more to 279 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (verbal IQ <85) (follow-up 6 years)												
1 (Christie 2011)	observational studies	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/84 (17.9%)	3/84 (3.6%)	RR 5 (1.5 to 16.64)	143 more per 1000 (from 18 more to 559 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (borderline IQ <80; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/130 (9.2%)	1/130 (0.77%)	OR 12 (1.6 to 89.99)	77 more per 1000 (from 5 more to 403 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (cognition assessed with the HUI-2; adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	182/680 (26.8%)	18/304 (5.9%)	OR 5.9 (3.4 to 10.24)	212 more per 1000 (from 117 more to 333 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (slowness; adjusted analysis) (follow-up 6.2 years)												
1 (Koomen	observational	no	no serious	no serious	serious[4]	none	131/680	19/304	OR 3.7 (2.2 to	135 more per 1000	VERY LOW	CRITICAL

2003)	studies	serious risk of bias	inconsistency	indirectness			(19.3%)	(6.3%)	6.22)	(from 65 more to 231 more)		
Long-term cognitive deficits (concentration problems; adjusted analysis)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	147/680 (21.6%)	16/304 (5.3%)	OR 5.7 (3.1 to 10.48)	188 more per 1000 (from 94 more to 315 more)	VERY LOW	CRITICAL

CI: confidence interval; HUI-2: Health Utilities Index 2; IQ: intelligence quotient; OR: odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**see corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events
[3] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[4] <300-≥150

Table 10: Evidence profile for the risk of long-term behavioural deficits in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
Long-term behavioural deficits (inattention) (follow-up 2-13 years)												
1 (Berg 2002)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/304 (3.6%)	5/304 (1.6%)	RR 2.2 (0.77 to 6.26)	20 more per 1000 (from 4 fewer to 87 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (hyperactivity-impulsiveness) (follow-up 2-13 years)												
1 (Berg 2002)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/304 (3.6%)	4/304 (1.3%)	RR 2.75 (0.89 to 8.54)	23 more per 1000 (from 1 fewer to 99 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (poor adaptive functioning) (follow-up 8 years)												
1 (Taylor 1990)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/97 (9.3%)	9/97 (9.3%)	RR 1 (0.41 to 2.41)	0 fewer per 1000 (from 55 fewer to 131 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (internalising or externalising problems)												

1 (Taylor 1990)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/75 (20%)	10/77 (13%)	RR 1.54 (0.74 to 3.21)	70 more per 1000 (from 34 fewer to 287 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (total behaviour score in clinical range assessed with the Child Behaviour Checklist, adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	36/119 (30.3%)	25/124 (20.2%)	OR 1.5 (1 to 2.25)	73 more per 1000 (from 0 more to 161 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (total behaviour score in clinical range assessed with the Teacher Report Form, adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/119 (11.8%)	7/124 (5.6%)	OR 2.1 (0.8 to 5.51)	55 more per 1000 (from 11 fewer to 191 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (the school scale in clinical range, adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/119 (11.8%)	2/124 (1.6%)	OR 8.1 (1.7 to 38.6)	101 more per 1000 (from 11 more to 371 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (adaptive function in clinical range; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	17/119 (14.3%)	9/124 (7.3%)	OR 1.7 (0.7 to 4.13)	45 more per 1000 (from 21 fewer to 172 more)	VERY LOW	CRITICAL
Long-term behavioural deficits (hyperactive behaviour; adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	200/680 (29.4%)	53/304 (17.4%)	OR 1.8 (1.3 to 2.49)	101 more per 1000 (from 41 more to 170 more)	VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events
[3] <300-≥150

Table 11: Evidence profile for the risk of long-term psychological impairment in children

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Bacterial	Control	Relative	Absolute		

studies		bias				considerations	meningitis		(95% CI)			
Long-term psychological impairment (participants with high depressive symptom scores assessed with the Moods and Feelings Questionnaire, reported by parents) (follow-up 6 years)												
1 (Christie 2011)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/66 (13.6%)	3/55 (5.5%)	RR 2.5 (0.71 to 8.78)	82 more per 1000 (from 16 fewer to 424 more)	VERY LOW	CRITICAL
Long-term psychological impairment (participants with high depressive symptom scores assessed with the Moods and Feelings Questionnaire, reported by children) (follow-up 6 years)												
1 (Christie 2011)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/36 (19.4%)	6/37 (16.2%)	RR 1.2 (0.45 to 3.22)	32 more per 1000 (from 89 fewer to 360 more)	VERY LOW	CRITICAL
Long-term psychological impairment (participants with psychological distress scores above cut-off level assessed with the Strengths and Difficulties Questionnaire; reported by parents) (follow-up 6 years)												
1 (Christie 2011)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/92 (25%)	4/87 (4.6%)	RR 5.44 (1.96 to 15.09)	204 more per 1000 (from 44 more to 648 more)	VERY LOW	CRITICAL
Long-term psychological impairment (participants with psychological distress scores above cut-off level assessed with the Strengths and Difficulties Questionnaire; reported by children) (follow-up 6 years)												
1 (Christie 2011)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/21 (4.8%)	3/19 (15.8%)	RR 0.3 (0.03 to 2.66)	111 fewer per 1000 (from 153 fewer to 262 more)	VERY LOW	CRITICAL
Long-term psychological impairment (depressed mood; adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	49/680 (7.2%)	4/304 (1.3%)	OR 5 (1.8 to 13.89)	49 more per 1000 (from 10 more to 143 more)	VERY LOW	CRITICAL
Long-term psychological impairment (emotion; lower rate is better; adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	179/680 (26.3%)	20/304 (6.6%)	OR 4.9 (3 to 8)	191 more per 1000 (from 109 more to 295 more)	VERY LOW	CRITICAL

CI: confidence interval; OR: odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *<150 events*
[3] *<300-≥150*

Table 12: Evidence profile for the risk of sensory impairments in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bacterial meningitis	Control	Relative (95% CI)	Absolute		
Any hearing impairment (follow-up up to 27 years)												
6*	observational studies	serious[1]	serious[2]	no serious indirectness	serious[3]	none	145/1280 (11.3%)	16/902 (1.8%)	RR 5.65 (2.49 to 12.85)	82 more per 1000 (from 26 more to 210 more)	VERY LOW	CRITICAL
Any hearing impairment (hospital outpatient service rates for hearing loss and acoustic neuritis in infectious diseases; unadjusted analysis) (follow-up 21.3 years)												
1 (Roed 2011)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	NR	NR	RR 2.71 (0.94 to 7.81)	NC	VERY LOW	CRITICAL
Any visual impairment (impaired vision reported by parents) (follow-up 2-13 years)												
1 (Berg 2002)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	47/304 (15.5%)	49/304 (16.1%)	RR 0.96 (0.66 to 1.38)	6 fewer per 1000 (from 55 fewer to 61 more)	VERY LOW	CRITICAL
Any visual impairment (sensitivity to light) (follow-up 2-13 years)												
1 (Berg 2002)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	33/304 (10.9%)	8/304 (2.6%)	RR 4.12 (1.94 to 8.78)	82 more per 1000 (from 25 more to 205 more)	VERY LOW	CRITICAL
Any visual impairment (abnormalities of vision; adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	12/127 (9.4%)	4/129 (3.1%)	OR 3.3 (0.9 to 12.1)	65 more per 1000 (from 3 fewer to 248 more)	VERY LOW	CRITICAL
Any visual impairment (vision worse than 6/9 or N5, assessed with Snellen types) (follow-up 5-9 years)												

1 (Moss 1982)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	8/60 (13.3%)	10/60 (16.7%)	RR 0.80 (0.34 to 1.89)	33 fewer per 1000 (from 160 fewer to 90 more)	VERY LOW	CRITICAL
Any visual impairment (squints) (follow-up 5-9 years)												
1 (Moss 1982)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	4/60 (6.7%)	4/60 (6.7%)	RR 1 (0.26 to 3.81)	0 fewer per 1000 (from 90 fewer to 90 more)	VERY LOW	CRITICAL
Any visual impairment (diseases of the eye and adnexa [tissues around the eye]; unadjusted analysis) (follow-up up to 22 years)												
1 (Pickering 2018)	observational studies	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	NR	NR	OR 1.58 (1.10 to 2.27)	NC	VERY LOW	CRITICAL
Any visual impairment (inpatient admission rates for eye diseases; unadjusted) (follow-up 20-<25 years)												
1 (Roed 2011)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	NR	NR	RR 0.99 (0.22 to 4.45)	NC	VERY LOW	CRITICAL
Any visual impairment (hospital outpatient service rates for eye diseases; 15-<20 years) (unadjusted) (follow-up 15-20 years)												
1 (Roed 2011)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	NR	NR	RR 1.49 (0.74 to 3.00)	NC	VERY LOW	CRITICAL

CI: confidence interval; NC: not calculable; NR: not reported; OIS: optimal information size; OR: odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**See corresponding forest plot*
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Serious heterogeneity unexplained by subgroup analysis
[3] <300-≥150
[4] Estimate may be imprecise as cannot determine if OIS criteria have been met because data on the number of events is not reported
[5] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[6] <150 events

Table 13: Evidence profile for the risk of poor educational achievement in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
Educational achievement (special educational assistance; lower rate is better) (follow-up up to 12 years)												

3*	observational studies	very serious[1]	serious[2]	no serious indirectness	very serious[3]	none	94/296 (31.8%)	32/281 (11.4%)	RR 2.71 (1.58 to 4.67)	195 more per 1000 (from 66 more to 418 more)	VERY LOW	CRITICAL
Educational achievement (receiving more family help with homework; lower rate is better) (follow-up 10-12 years)												
1 (Feldman 1988)	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/23 (56.5%)	1/11 (9.1%)	RR 6.22 (0.93 to 41.69)	475 more per 1000 (from 6 fewer to 1000 more)	VERY LOW	CRITICAL
Educational achievement (requirement of remedial help such as private tutoring, school tutoring, resource room help, and special class placements; lower rate is better) (follow-up 10-12 years)												
1 (Feldman 1988)	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/23 (39.1%)	5/11 (45.5%)	RR 0.86 (0.38 to 1.96)	64 fewer per 1000 (from 282 fewer to 436 more)	VERY LOW	CRITICAL
Educational achievement (limited academic skills; lower rate is better) (follow-up 8 years)												
1 (Taylor 1990)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	22/97 (22.7%)	17/97 (17.5%)	RR 1.29 (0.73 to 2.28)	51 more per 1000 (from 47 fewer to 224 more)	VERY LOW	CRITICAL
Educational achievement (reading ability below appropriate grade level; lower rate is better) (follow-up 4 years)												
1 (Tejani 1982)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/7 (57.1%)	4/7 (57.1%)	RR 1 (0.4 to 2.48)	0 fewer per 1000 (from 343 fewer to 846 more)	VERY LOW	CRITICAL
Educational achievement (arithmetic ability below appropriate grade level; lower rate is better) (follow-up 4 years)												
1 (Tejani 1982)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/7 (71.4%)	5/7 (71.4%)	RR 1 (0.52 to 1.94)	0 fewer per 1000 (from 343 fewer to 671 more)	VERY LOW	CRITICAL
Educational achievement (grade retention; lower rate is better) (follow-up up to 12 years)												
2*	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/117 (17.1%)	15/103 (14.6%)	RR 1.14 (0.62 to 2.09)	20 more per 1000 (from 55 fewer to 159 more)	VERY LOW	CRITICAL

Educational achievement (unable to read; lower rate is better) (adjusted analysis) (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/130 (12.3%)	4/130 (3.1%)	OR 4 (1.4 to 11.43)	82 more per 1000 (from 12 more to 235 more)	VERY LOW	CRITICAL
Educational achievement (deficient school achievement assessed with the School Achievement Rating Scale; lower rate is better) (adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	136/680 (20%)	14/304 (4.6%)	OR 5.6 (3 to 10.45)	167 more per 1000 (from 80 more to 289 more)	VERY LOW	CRITICAL
Educational achievement (repeating a year; lower rate is better) (adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	111/680 (16.3%)	25/304 (8.2%)	OR 2.5 (1.5 to 4.17)	139 more per 1000 (from 71 more to 185 more)	VERY LOW	CRITICAL
Educational achievement (referral to a special-needs school; lower rate is better) (adjusted analysis) (follow-up 6.2 years)												
1 (Koomen 2003)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	52/680 (7.6%)	5/304 (1.6%)	OR 5.5 (2 to 15.12)	68 more per 1000 (from 16 more to 185 more)	VERY LOW	CRITICAL
Educational achievement (vocational education; higher rate is better) (follow-up up to 35 years)												
1 (Roed 2013)	observational studies	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	748/2784 (26.9%)	3773/14018 (26.9%)	RR 1 (0.93 to 1.07)	0 fewer per 1000 (from 19 fewer to 19 more)	VERY LOW	CRITICAL
Educational achievement (high school education or completing the 12th school year; higher rate is better) (follow-up up to 35 years)												
1 (Roed 2013)	observational studies	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	960/2784 (34.5%)	5643/14018 (40.3%)	RR 0.86 (0.81 to 0.91)	56 fewer per 1000 (from 36 fewer to 76 fewer)	VERY LOW	CRITICAL
Educational achievement (higher education, such as obtaining a degree from a college or university; higher rate is better) (follow-up up to 35 years)												
1 (Roed 2013)	observational studies	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	368/2784 (13.2%)	2252/14018 (16.1%)	RR 0.82 (0.74 to 0.91)	29 fewer per 1000 (from 14 fewer to 42	VERY LOW	CRITICAL

										fewer)		

CI: confidence interval; OR: odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**See corresponding forest plot*
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Serious heterogeneity unexplained by subgroup analysis
[3] <150 events
[4] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[5] <300-≥150

Table 14: Evidence profile for the risk of diagnosis of epilepsy, speech and language disorder, and hydrocephalus with a shunt in a children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
Diagnosis of epilepsy (follow-up 6.7 years)												
1 (Grimwood 1995)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/127 (3.9%)	0/129 (0%)	RR 11.17 (0.62 to 199.97)	40 more per 1000 (from 0 more to 80 more)	VERY LOW	CRITICAL
Diagnosis of epilepsy (inpatient admission rates for epilepsies/seizure disorders; unadjusted analysis) (follow-up 20-<25 years)												
1 (Roed 2011)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	NR	NR	RR 2.61 (1.29 to 5.28)	NC	VERY LOW	CRITICAL
Diagnosis of epilepsy (hospital outpatient service rates for epilepsies/seizure disorders; unadjusted analysis) (follow-up 20-<25 years)												
1 (Roed 2011)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	NR	NR	RR 2.36 (0.46 to 12.11)	NC	VERY LOW	CRITICAL
Speech and language disorder (speech difficulties) (follow-up 2-13 years)												
1 (Berg 2002)	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/304 (6.6%)	16/304 (5.3%)	RR 1.25 (0.66 to 2.37)	13 more per 1000 (from 18 fewer to 72 more)	VERY LOW	CRITICAL
Hydrocephalus with a shunt (ventriculoperitoneal shunt) (follow-up 6.7 years)												
1 (Grimwood	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/127 (1.6%)	0/129 (0%)	POR 7.57 (0.47 to 121.64)	20 more per 1000 (from 10 fewer to	VERY LOW	CRITICAL

1995)										40 more)		

CI: confidence interval; NC: not calculable; NR: not reported; OIS: optimal information size; POR: Peto odds ratio; QUIPS: Quality in Prognosis Studies; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events
[3] Estimate may be imprecise as cannot determine if OIS criteria have been met because data on the number of events is not reported
[4] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 15: 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**	**Bacterial meningitis**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up up to 30 years)												
2*	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	641/2245 (28.6%)	2139/9550 (22.4%)	RR 1.34 (1.24 to 1.44)	76 more per 1000 (from 54 more to 99 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (impaired attention) (follow-up 6 years)												
1 (Schmidt 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/59 (39%)	6/30 (20%)	RR 1.95 (0.89 to 4.27)	190 more per 1000 (from 22 fewer to 654 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (impaired executive functions) (follow-up 6 years)												
1 (Schmidt 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35/59 (59.3%)	5/30 (16.7%)	RR 3.56 (1.56 to 8.14)	427 more per 1000 (from 93 more to 1000 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (impaired short-term/working memory) (follow-up 6 years)												
1 (Schmidt 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/59 (30.5%)	3/30 (10%)	RR 3.05 (0.98 to 9.54)	205 more per 1000 (from 2 fewer to 854 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (impaired verbal learning/memory) (follow-up 6 years)												
1 (Schmidt 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/59 (20.3%)	2/30 (6.7%)	RR 3.05 (0.73 to 12.76)	137 more per 1000 (from 18 fewer to 784 more)	VERY LOW	CRITICAL

Long-term cognitive deficits (impaired non-verbal learning/memory) (follow-up 6 years)												
1 (Schmidt 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	44/59 (74.6%)	8/30 (26.7%)	RR 2.8 (1.52 to 5.16)	480 more per 1000 (from 139 more to 1000 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (impaired visuo-constructive functions) (follow-up 6 years)												
1 (Schmidt 2006)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/59 (39%)	6/30 (20%)	RR 1.95 (0.89 to 4.27)	190 more per 1000 (from 22 fewer to 654 more)	VERY LOW	CRITICAL
Long-term cognitive deficits (cognitive impairment) (follow-up 6 years)												
3*	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	83/293 (28.3%)	7/165 (4.2%)	RR 6.08 (2.9 to 12.73)	216 more per 1000 (from 81 more to 498 more)	VERY LOW	CRITICAL
Diagnosis of epilepsy (follow-up 17 years)												
1 (Zelano 2020)	observational studies	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	118/2812 (4.2%)	495/36228 (1.4%)	RR 3.07 (2.52 to 3.74)	28 more per 1000 (from 21 more to 37 more)	VERY LOW	CRITICAL

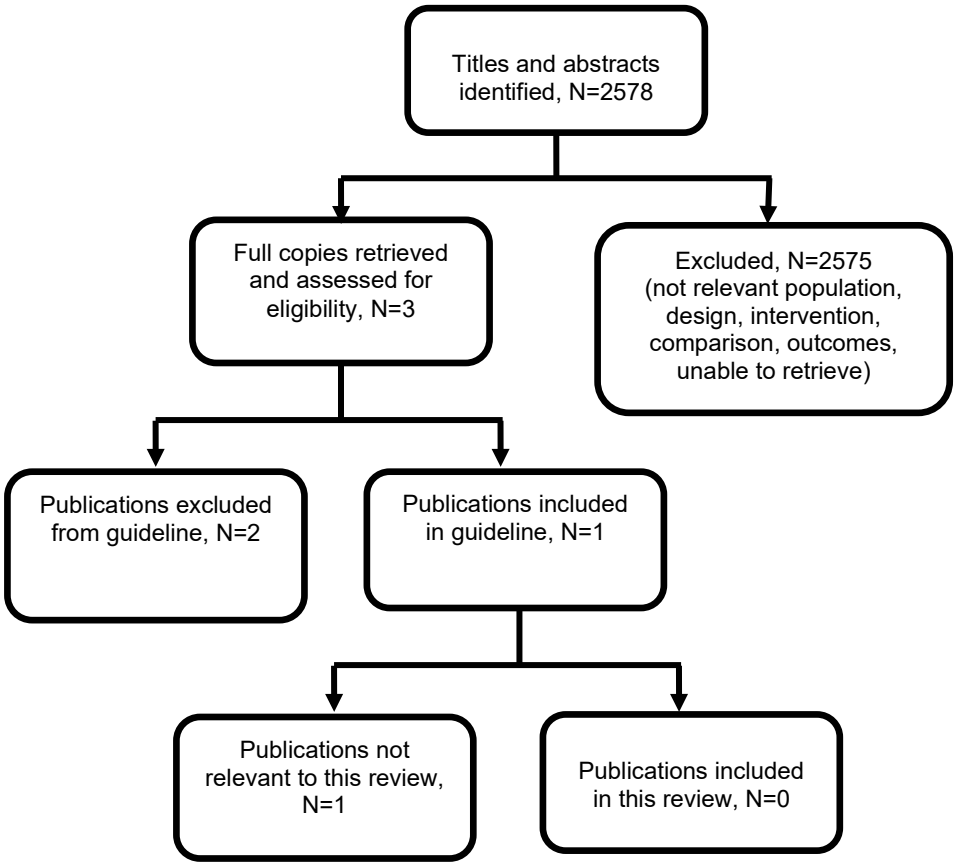
CI: confidence interval; QUIPS: Quality in Prognosis Studies; RR: risk ratio
**See corresponding forest plot*
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Appendix G Economic evidence study selection

Study selection for: What is the risk of long-term complications in bacterial meningitis?

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

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

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

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 bacterial meningitis?

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 bacterial meningitis?

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=143) and not studies (N=42) 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 16: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Adachi, N.; Ito, K.; Sakata, H. (2010) Risk factors for hearing loss after pediatric meningitis in Japan. Annals of Otology, Rhinology & Laryngology 119(5): 294-6	- Study design does not meet inclusion criteria
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
Ahmed, A. S. M. N. U., Khan, N. Z., Hussain, M. et al. (2013) Follow-up of cases of haemophilus influenzae type b meningitis to determine its long-term sequelae. Journal of Pediatrics 163(1 SUPPL): S44-S49	- Study from low or middle income country
Akpede, G. O., Abiodun, P. O., Ambe, J. P. et al. (1994) Presenting features of bacterial meningitis in young infants. Annals of Tropical Paediatrics 14(3): 245-252	- Study from low or middle income country
Akpede, G. O., Akuhwa, R. T., Ogiji, E. O. et al. (1999) Risk factors for an adverse outcome in bacterial meningitis in the tropics: A reappraisal with focus on the significance and risk of seizures. Annals of Tropical Paediatrics 19(2): 151-159	- Study from low or middle income country
Al-Asmary, S. M., Abdel-Fattah, M. M., Asal, A. A. et al. (2004) Emotional and behavioral problems among male Saudi schoolchildren and adolescents. Neurosciences 9(4): 299-306	- Population does not meet inclusion criteria
Al-Harbi, M.; Barakat, N.; Al-Khandary, M. (2008) Hearing screening in at risk newborn. Journal of Medical Sciences 8(7): 648-653	- Comparison does not meet inclusion criteria
Al-Harthi, A. A., Dagriri, K. A., Asindi, A. A. et al. (2000) Neonatal meningitis. Neurosciences 5(3): 162-5	- Study design does not meet inclusion criteria
Al-Husseinawi, A. K. (2021) A year of surveillance of acute flaccid paralysis in the children welfare	- Study from low or middle income country

Study	Code [Reason]
teaching hospital. Indian Journal of Forensic Medicine and Toxicology 15(3): 778-784	
Al-Mazrou, Y. Y., Musa, E. K., Abdalla, M. N. et al. (2003) Disease burden and case management of bacterial meningitis among children under 5 years of age in Saudi Arabia. SAUDI MEDICAL JOURNAL 24(12): 1300-1307	- Study design does not meet inclusion criteria
Ali, Z. (1995) Neonatal meningitis: A 3-year retrospective study at the Mount Hope Women's Hospital, Trinidad, West Indies. Journal of Tropical Pediatrics 41(2): 109-111	- Study design does not meet inclusion criteria
Alsubaie, S. and Alrabiaah, A. (2020) Clinical Characteristics, Acute Complications, and Neurologic Outcomes of Salmonella Meningitis in Saudi Infants and Children. Journal of Pediatric Infectious Diseases 15(1): 031-038	- Study design does not meet inclusion criteria
Anand, V. and Nair, P. M. (2014) Neonatal seizures: Predictors of adverse outcome. Journal of Pediatric Neurosciences 9(2): 97-9	- Study from low or middle income country
Anderson, V., Bond, L., Catroppa, C. et al. (1997) Childhood bacterial meningitis: impact of age at illness and acute medical complications on long term outcome. Journal of the International Neuropsychological Society 3(2): 147-58	- Same participants and data as Anderson 2004 and Grimwood 1995, which are already included
Andreu-Ballester, J. C., Gonzalez-Sanchez, A., Ballester, F. et al. (2010) Epidemiology of meningitis in the valencian community (Spain), 1995-2007: Hospital admissions incidence, causative agents, and mortality. Infectious Diseases in Clinical Practice 18(1): 29-36	- Study design does not meet inclusion criteria
Annegers, J. F., Hauser, W. A., Beghi, E. et al. (1988) The risk of unprovoked seizures after encephalitis and meningitis. Neurology 38(9): 1407-10	- Insufficient presentation of results *The incidence of unprovoked seizures in people with bacterial meningitis compared with expected incidence based on age-specific rates of unprovoked seizures in general population (from previously published data). Insufficient information about the number of people and events in the general population*
Antoniuk, S. A., Hamdar, F., Ducci, R. D. et al. (2011) Childhood acute bacterial meningitis: risk factors for acute neurological complications and neurological sequelae. Jornal de Pediatria 87(6): 535-40	- Study design does not meet inclusion criteria
Baldwin, R. L.; Sweitzer, R. S.; Freind, D. B. (1985) Meningitis and sensorineural hearing loss. Laryngoscope 95(7pt1): 802-5	- Study design does not meet inclusion criteria
Baraff, L. J.; Lee, S. I.; Schriger, D. L. (1993) Outcomes of bacterial meningitis in children: a meta-analysis. Pediatric Infectious Disease	- Comparison does not meet inclusion criteria

Study	Code [Reason]
Journal 12(5): 389-94	
Bellmunt, A. M., Roberts, R., Lee, W. T. et al. (2016) Does an Otolaryngology-Specific Database Have Added Value? A Comparative Feasibility Analysis. Otolaryngology - Head & Neck Surgery 155(1): 56-64	- Study design does not meet inclusion criteria
Beswick, R., Driscoll, C., Kei, J. et al. (2013) Which risk factors predict postnatal hearing loss in children?. Journal of the American Academy of Audiology 24(3): 205-13	- Study design does not meet inclusion criteria
Bohr, V.; Paulson, O. B.; Rasmussen, N. (1984) Pneumococcal meningitis. Late neurologic sequelae and features of prognostic impact. Archives of Neurology 41(10): 1045-9	- Study design does not meet inclusion criteria
Bozzola, M., Meazza, C., Bossi, G. et al. (2019) Growth Impairment in Acute Central Infectious Diseases. Journal of Pediatric Infectious Diseases 14(1): 11-12	- Study design 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
Carter, J. A.; Neville, B. G.; Newton, C. R. (2003) Neuro-cognitive impairment following acquired central nervous system infections in childhood: a systematic review. Brain Research - Brain Research Reviews 43(1): 57-69	- Comparison does not meet inclusion criteria
Chandran, A., Herbert, H., Misurski, D. et al. (2011) Long-term sequelae of childhood bacterial meningitis: an underappreciated problem. Pediatric Infectious Disease Journal 30(1): 3-6	- Study design does not meet inclusion criteria
Christiansen, M., Jensen, E. S., Brandt, C. T. et al. (2020) Otoacoustic emissions in patients with bacterial meningitis. International Journal of Audiology 59(9): 647-653	- Study design does not meet inclusion criteria *Included studies investigate the feasibility and diagnostic accuracy of hearing screening tools*
Christie, D., Rashid, H., El-Bashir, H. et al. (2017) Impact of meningitis on intelligence and development: A systematic review and meta-analysis. PLoS ONE [Electronic Resource] 12(8): e0175024	- Population does not meet inclusion criteria *Systematic review includes studies of viral meningitis*
Ciapponi, A., Elorriaga, N., Rojas, J. I. et al. (2014) Epidemiology of pediatric pneumococcal meningitis and bacteremia in Latin America and the caribbean: A systematic review and meta-analysis. Pediatric Infectious Disease Journal 33(9): 971-978	- No outcomes of interest

Study	Code [Reason]
Clark, L. J., Glennie, L., Audrey, S. et al. (2013) The health, social and educational needs of children who have survived meningitis and septicaemia: the parents' perspective. BMC Public Health 13: 954	- Study design does not meet inclusion criteria
Coenraad, S., Goedegebure, A., van Goudoever, J. B. et al. (2010) Risk factors for sensorineural hearing loss in NICU infants compared to normal hearing NICU controls. International Journal of Pediatric Otorhinolaryngology 74(9): 999-1002	- Comparison does not meet inclusion criteria
Coenraad, S., Goedegebure, A., van Goudoever, J. B. et al. (2011) Risk factors for auditory neuropathy spectrum disorder in NICU infants compared to normal-hearing NICU controls. Laryngoscope 121(4): 852-5	- Comparison does not meet inclusion criteria
Cushing, S. L., Papsin, B. C., Rutka, J. A. et al. (2009) Vestibular end-organ and balance deficits after meningitis and cochlear implantation in children correlate poorly with functional outcome. Otology & Neurotology 30(4): 488-95	- Insufficient presentation of results *Continuous outcomes (for example, scores) but not proportion of participants with outcome of interest reported*
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	- Population does not meet inclusion criteria
De Jonge, R. C. J., Swart, J. F., Koomen, I. et al. (2008) No structural cerebral differences between children with a history of bacterial meningitis and healthy siblings. Acta Paediatrica, International Journal of Paediatrics 97(10): 1390-1396	- No outcomes of interest
Doctor, B. A., Newman, N., Minich, N. M. et al. (2001) Clinical outcomes of neonatal meningitis in very-low birth-weight infants. Clinical Pediatrics 40(9): 473-80	- Comparison does not meet inclusion criteria *Comparison group is not healthy cohort*
Doder, Radoslava, Boskovic, Ksenija, Mikic, Sandra Stefan et al. (2011) Assessing the differences in quality of life in patients after acute neuroinfection. HEALTHMED 5(6): 2225-2232	- Full text not available
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	- Comparison 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
Drougia, A., Giapros, V., Krallis, N. et al. (2007) Incidence and risk factors for cerebral palsy in infants with perinatal problems: A 15-year review. Early Human Development 83(8): 541-547	- Population does not meet inclusion criteria

Study	Code [Reason]
Durand, M. L., Calderwood, S. B., Weber, D. J. et al. (1993) Acute bacterial meningitis in adults. A review of 493 episodes. New England Journal of Medicine 328(1): 21-8	- Study design does not meet inclusion criteria
Durisin, M., Arnoldner, C., Stover, T. et al. (2008) Audiological performance in cochlear implanted patients deafened by meningitis depending on duration of deafness. European Archives of Oto-Rhino-Laryngology 265(4): 381-8	- Comparison does not meet inclusion criteria
Dzupova, O., Rozsypal, H., Prochazka, B. et al. (2009) Acute bacterial meningitis in adults: predictors of outcome. Scandinavian Journal of Infectious Diseases 41(5): 348-54	- Study design does not meet inclusion criteria
Edmond, K., Clark, A., Korczak, V. S. et al. (2010) Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. The Lancet Infectious Diseases 10(5): 317-28	- Comparison does not meet inclusion criteria *Included studies compared the risk of sequelae between pneumococcal and Hib meningitis, but no comparison between bacterial meningitis and healthy cohort*
El-Naggar, W., Afifi, J., McMillan, D. et al. (2019) Epidemiology of Meningitis in Canadian Neonatal Intensive Care Units. Pediatric Infectious Disease Journal 38(5): 476-480	- No outcomes of interest *Short-term outcomes but not outcomes after resolution of acute phase of illness reported*
Erlangsen, A., Stenager, E., Conwell, Y. et al. (2020) Association Between Neurological Disorders and Death by Suicide in Denmark. JAMA 323(5): 444-454	- Study design does not meet inclusion criteria
Fellick, J. M. and Thomson, A. P. (2002) Long-term outcomes of childhood meningitis. Hospital Medicine (London) 63(5): 274-7	- Study design does not meet inclusion criteria
Fernandes, D., Goncalves-Pereira, J., Janeiro, S. et al. (2014) Acute bacterial meningitis in the intensive care unit and risk factors for adverse clinical outcomes: retrospective study. Journal of Critical Care 29(3): 347-50	- Comparison does not meet inclusion criteria
Ferwerda, B., Valls Seron, M., Jongejan, A. et al. (2016) Variation of 46 Innate Immune Genes Evaluated for their Contribution in Pneumococcal Meningitis Susceptibility and Outcome. EBioMedicine 10: 77-84	- No outcomes of interest
Flores-Cordero, J. M., Amaya-Villar, R., Rincon-Ferrari, M. D. et al. (2003) Acute community-acquired bacterial meningitis in adults admitted to the intensive care unit: clinical manifestations, management and prognostic factors. Intensive Care Medicine 29(11): 1967-73	- Study design does not meet inclusion criteria
Focke, N. K., Kallenberg, K., Mohr, A. et al. (2013) Distributed, limbic gray matter atrophy in patients after bacterial meningitis. Ajnr: American Journal of Neuroradiology 34(6): 1164-7	- No outcomes of interest

Study	Code [Reason]
Fuentes-Antras, J., Ramirez-Torres, M., Osorio-Martinez, E. et al. (2019) Acute Community-Acquired Bacterial Meningitis: Update on Clinical Presentation and Prognostic factors. New Microbiologica 41(4): 81-87	- Study design does not meet inclusion criteria
Geyik, M. F., Kokoglu, O. F., Hosoglu, S. et al. (2002) Acute bacterial meningitis as a complication of otitis media and related mortality factors. Yonsei Medical Journal 43(5): 573-8	- Study from low or middle income country
Ghotbi, F. and Shiva, F. (2009) An assessment of the necessity of lumbar puncture in children with seizure and fever. JPMA - Journal of the Pakistan Medical Association 59(5): 292-5	- Study from low or middle income country
Grimwood, K., Anderson, P., Anderson, V. et al. (2000) Twelve year outcomes following bacterial meningitis: further evidence for persisting effects. Archives of Disease in Childhood 83(2): 111-6	- Same participants and data as Anderson 2004 and Grimwood 1995, which are already included
Gronhoj, M. H., Sejbaek, T., Hansen, R. W. et al. (2021) Serum levels of neurofilament light chain, neuron-specific enolase and S100 calcium-binding protein B during acute bacterial meningitis: a prospective cohort study. Infectious Diseases 53(6): 409-419	- Study design does not meet inclusion criteria *No comparison for outcomes of interest between those with bacterial meningitis and the healthy controls*
Halket, S., de Louvois, J., Holt, D. E. et al. (2003) Long term follow up after meningitis in infancy: behaviour of teenagers. Archives of Disease in Childhood 88(5): 395-8	- Same participants and data as de Louvois 2007 and Bedford 2001, which are already included
Horvath-Puho, E., Snoek, L., van Kassel, M. N. et al. (2021) Every Country, Every Woman, Every Child; Group B Streptococcal Disease Worldwide Prematurity modifies the risk of long-term neurodevelopmental impairments after invasive Group B Streptococcus infections during infancy in Denmark and the Netherlands. Clinical Infectious Diseases 24: 24	- Population does not meet inclusion criteria
Horvath-Puho, E., van Kassel, M. N., Goncalves, B. P. et al. (2021) Mortality, neurodevelopmental impairments, and economic outcomes after invasive group B streptococcal disease in early infancy in Denmark and the Netherlands: a national matched cohort study. The Lancet Child & Adolescent Health 5(6): 398-407	- Population does not meet inclusion criteria *Group B streptococcal disease*
Hosoglu, S., Ayaz, C., Geyik, M. F. et al. (1997) Acute bacterial meningitis in adults: analysis of 218 episodes. Irish Journal of Medical Science 166(4): 231-4	- Study from low or middle income country
Huang, C. C., Chang, Y. C., Chow, N. H. et al. (1997) Level of transforming growth factor beta 1 is elevated in cerebrospinal fluid of children with acute bacterial meningitis. Journal of Neurology	- Comparison does not meet inclusion criteria *Comparison group is not healthy cohort*

Study	Code [Reason]
244(10): 634-8	
Hughes, G. J., Wright, L. B., Chapman, K. E. et al. (2016) Serotype-specific differences in short- and longer-term mortality following invasive pneumococcal disease. Epidemiology & Infection 144(12): 2654-69	- Study design does not meet inclusion criteria
Hugosson, S., Silfverdal, S. A., Garpenholt, O. et al. (1995) INVASIVE HAEMOPHILUS-INFLUENZAE DISEASE - EPIDEMIOLOGY AND CLINICAL SPECTRUM BEFORE LARGE-SCALE HAEMOPHILUS-INFLUENZAE TYPE-B VACCINATION. SCANDINAVIAN JOURNAL OF INFECTIOUS DISEASES 27(1): 63-67	- Study design does not meet inclusion criteria
Isaacson, J. E., Hasenstab, M. S., Wohl, D. L. et al. (1996) Learning disability in children with postmeningitic cochlear implants. Archives of Otolaryngology -- Head & Neck Surgery 122(9): 929-36	- Comparison does not meet inclusion criteria
Jacob, L., Koyanagi, A., Haro, J. M. et al. (2021) Association between inflammatory central nervous system diseases and epilepsy: A retrospective cohort study of 4252 patients in Germany. Epilepsy & Behavior 117: 107879	- Population does not meet inclusion criteria *People with encephalitis, meningitis or brain abscess, and proportion of people with meningitis not reported*
Jatto, M. E., Adeyemo, A. A., Ogunkeyede, S. A. et al. (2020) Pediatric Hearing Thresholds Post-bacterial Meningitis. Frontiers in Surgery 7: 36	- Study from low or middle income country
Jiang, H. Y., Zhang, X., Pan, L. Y. et al. (2020) Childhood infection and subsequent risk of psychotic disorders in adults: A systematic review and meta-analysis. Asian Journal of Psychiatry 54 (no pagination)	- Population does not meet inclusion criteria
Jit, M. (2010) The risk of sequelae due to pneumococcal meningitis in high-income countries: a systematic review and meta-analysis. Journal of Infection 61(2): 114-24	- Comparison does not meet inclusion criteria *No comparison between pneumococcal meningitis and healthy cohort*
Johansson Kostenniemi, U., Bazan, A., Karlsson, L. et al. (2021) Psychiatric Disabilities and Other Long-term Consequences of Childhood Bacterial Meningitis. Pediatric Infectious Disease Journal 40(1): 26-31	- Study design does not meet inclusion criteria
Jung, Y. J. (2021) Bacterial meningitis in very low birthweight infants in the Korean Neonatal Network 2013-2016. Pediatrics International 15: 15	- Comparison does not meet inclusion criteria
Kadambari, S., Trotter, C. L., Heath, P. T. et al. (2021) Group B Streptococcal Disease in England (1998 - 2017): A Population-based Observational Study. Clinical Infectious Diseases 72(11): e791-e798	- Population does not meet inclusion criteria

Study	Code [Reason]
Kang, C. I., Song, J. H., Kim, S. H. et al. (2013) Association of levofloxacin resistance with mortality in adult patients with invasive pneumococcal diseases: a post hoc analysis of a prospective cohort. Infection 41(1): 151-7	- 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
Kaplan, S. L., Smith, E. O., Wills, C. et al. (1986) Association between preadmission oral antibiotic therapy and cerebrospinal fluid findings and sequelae caused by Haemophilus influenzae type b meningitis. Pediatric Infectious Disease 5(6): 626-32	- Comparison does not meet inclusion criteria
Khandaker, G. M., Stochl, J., Zammit, S. et al. (2015) A population-based prospective birth cohort study of childhood neurocognitive and psychological functioning in healthy survivors of early life meningitis. Annals of Epidemiology 25(4): 236-42	- Population does not meet inclusion criteria *The study did not specify how many participants had bacterial meningitis*
Kim, B. G.; Jang, M. S.; Kim, J. (2021) Epidemiology of Pediatric Meningitis in South Korea From 2010 to 2018: A Population-based Retrospective Cohort Study. Pediatric Infectious Disease Journal 40(10): 885-891	- Study design does not meet inclusion criteria
Kimia, A., Ben-Joseph, E. P., Rudloe, T. et al. (2010) Yield of lumbar puncture among children who present with their first complex febrile seizure. Pediatrics 126(1): 62-9	- Study design does not meet inclusion criteria
Kirkham, F. J. (2017) Neurocognitive outcomes for acute global acquired brain injury in children. Current Opinion in Neurology 30(2): 148-155	- Study design does not meet inclusion criteria
Kjersem, H., Bohr, V., Rasmussen, N. et al. (1986) Mortality in the years following bacterial meningitis. Infection 14(2): 55-9	- Insufficient presentation of results *Insufficient information about the number of people and events in the general population*
Klinger, G., Chin, C. N., Beyene, J. et al. (2000) Predicting the outcome of neonatal bacterial meningitis. Pediatrics 106(3): 477-82	- Study design does not meet inclusion criteria
Kloek, A. T., Seron, M. V., Schmand, B. et al. (2021) Individual responsiveness of macrophage migration inhibitory factor predicts long-term cognitive impairment after bacterial meningitis. Acta Neuropathologica Communications 9(1): 4	- Same participants and data as Kloek 2020, which is already included
Kohli-Lynch, M., Russell, N. J., Seale, A. C. et al. (2017) Neurodevelopmental Impairment in Children After Group B Streptococcal Disease Worldwide: Systematic Review and Meta-analyses. Clinical Infectious Diseases 65(suppl2):	- Study design does not meet inclusion criteria *Non comparative study*

Study	Code [Reason]
S190-S199	
Koomen, I., Grobbee, D. E., Roord, J. J. et al. (2003) Hearing loss at school age in survivors of bacterial meningitis: assessment, incidence, and prediction. Pediatrics 112(5): 1049-53	- Comparison does not meet inclusion criteria *Comparison group is not healthy cohort*
Koomen, I., Raat, H., Jennekens-Schinkel, A. et al. (2005) Academic and behavioral limitations and health-related quality of life in school-age survivors of bacterial meningitis. Quality of Life Research 14(6): 1563-72	- Insufficient presentation of results *Continuous outcomes but not proportion of participants with outcomes of interest reported*
Legood, R., Coen, P. G., Knox, K. et al. (2009) Health related quality of life in survivors of pneumococcal meningitis. Acta Paediatrica 98(3): 543-7	- Insufficient presentation of results *Continuous outcomes but not proportion of participants with outcomes of interest reported*
Lepur, D.; Kutlesa, M.; Barsic, B. (2011) Prospective observational cohort study of cerebrovascular CO2 reactivity in patients with inflammatory CNS diseases. European Journal of Clinical Microbiology & Infectious Diseases 30(8): 989-96	- Insufficient presentation of results *Continuous outcomes but not proportion of participants with outcomes of interest reported*
Lesnakova, A., Holeckova, K., Kolenova, A. et al. (2007) Bacterial meningitis after sinusitis and otitis media: ear, nose, throat infections are still the commonest risk factors for the community acquired meningitis. Neuroendocrinology Letters 28suppl3: 14-5	- Study design does not meet inclusion criteria
Letson, G. W., Gellin, B. G., Bulkow, L. R. et al. (1992) Severity and frequency of sequelae of bacterial meningitis in Alaska Native infants. Correlation with a scoring system for severity of sequelae. American Journal of Diseases of Children 146(5): 560-6	- Comparison does not meet inclusion criteria
Lopes-Junior, L. C.; Rosa, M. A. D. R. D. P.; Lima, R. A. G. D. (2018) Psychological and Psychiatric Outcomes Following PICU Admission: A Systematic Review of Cohort Studies. Pediatric Critical Care Medicine 19(1): e58-e67	- Population 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	- Study design does not meet inclusion criteria
Meert, Kathleen L., Reeder, Ron, Maddux, Aline B. et al. (2020) Trajectories and Risk Factors for Altered Physical and Psychosocial Health-Related Quality of Life After Pediatric Community-Acquired Septic Shock*. PEDIATRIC CRITICAL CARE MEDICINE 21(10): 869-878	- Population does not meet inclusion criteria
Merkelbach, S., Sittinger, H., Schweizer, I. et al. (2000) Cognitive outcome after bacterial	- No outcomes of interest *Continuous outcomes reported 2.5 years after*

Study	Code [Reason]
meningitis. Acta Neurologica Scandinavica 102(2): 118-23	*illness*
Metan, G., Hayran, M., Hascelik, G. et al. (2006) Which patient is a candidate for empirical therapy against Stenotrophomonas maltophilia bacteraemia? An analysis of associated risk factors in a tertiary care hospital. Scandinavian Journal of Infectious Diseases 38(67): 527-31	- Population does not meet inclusion criteria
Miedzinska, Magdalena, Hnatyszyn, Grazyna, Konefal, Halina et al. (2012) Meningitis and chosen complications of neonatal period in preterm neonates born to single or multiple pregnancies. GINEKOLOGIA POLSKA 83(3): 202-208	- Non-English language article
Mulder, C. J. and Zanen, H. C. (1986) Listeria monocytogenes neonatal meningitis in The Netherlands. European Journal of Pediatrics 145(12): 60-2	- Study design does not meet inclusion criteria
Mulder, C. J. and Zanen, H. C. (1984) A study of 280 cases of neonatal meningitis in The Netherlands. Journal of Infection 9(2): 177-84	- Study design does not meet inclusion criteria
Mwaniki, M. K., Atieno, M., Lawn, J. E. et al. (2012) Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: A systematic review. The Lancet 379(9814): 445-452	- Study design does not meet inclusion criteria *Non-comparative data*
Nelson, G. E., Pondo, T., Toews, K. A. et al. (2016) Epidemiology of Invasive Group A Streptococcal Infections in the United States, 2005-2012. Clinical Infectious Diseases 63(4): 478-86	- Study design does not meet inclusion criteria
Neufeld, M. Y., Treves, T. A., Chistik, V. et al. (1999) Postmeningitis headache. Headache 39(2): 132-4	- Population does not meet inclusion criteria *Only 24% had bacterial meningitis and 76% had viral meningitis.*
Offringa, M., Beishuizen, A., Derksen-Lubsen, G. et al. (1992) Seizures and fever: can we rule out meningitis on clinical grounds alone?. Clinical Pediatrics 31(9): 514-22	- Study design does not meet inclusion criteria *Study about recognising meningitis, but not long-term complications*
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	- Comparison does not meet inclusion criteria
Pedersen, E. M. J., Kohler-Forsberg, O., Nordentoft, M. et al. (2020) Infections of the central nervous system as a risk factor for mental disorders and cognitive impairment: A nationwide register-based study. Brain, Behavior, & Immunity 88: 668-674	- Population does not meet inclusion criteria *Results not reported separately for those with bacterial meningitis and proportion of those with bacterial meningitis not reported*

Study	Code [Reason]
Petersen, H., Patel, M., Ingason, E. F. et al. (2014) Long-term effects from bacterial meningitis in childhood and adolescence on postural control. PLoS ONE [Electronic Resource] 9(11): e112016	- Insufficient presentation of results *Outcomes are continuous apart from hearing impairment which has no comparative data*
Polat, T. B., Cetinkaya, F., Caliskan, M. et al. (2010) Assessment of hippocampal volumes in infants with a history of bacterial meningitis. Gazi Medical Journal 21(1): 34-37	- Study from low or middle income country
Rayanakorn, A., Goh, B. H., Lee, L. H. et al. (2018) Risk factors for Streptococcus suis infection: A systematic review and meta-analysis. Scientific Reports 8(1): 13358	- Study from low or middle income country
Richardson, M. P., Reid, A., Williamson, T. J. et al. (1997) Acute otitis media and otitis media with effusion in children with bacterial meningitis. Journal of Laryngology & Otology 111(10): 913-6	- Insufficient presentation of results *No comparative data available for outcomes of interest*
Ritchi, L., Jennekens-Schinkel, A., van Schooneveld, M. et al. (2008) Behaviour is not really at risk after surviving meningitis in childhood. Acta Paediatrica 97(4): 438-41	- Insufficient presentation of results *Continuous outcomes reported*
Robertson, F. C., Lepard, J. R., Mekary, R. A. et al. (2019) Epidemiology of central nervous system infectious diseases: A meta-analysis and systematic review with implications for neurosurgeons worldwide. Journal of Neurosurgery 130(4): 1107-1126	- No outcomes of interest
Rodenburg-Vlot, M. B. A., Ruytjens, L., Oostenbrink, R. et al. (2018) Repeated Audiometry After Bacterial Meningitis: Consequences for Future Management. Otology & Neurotology 39(5): e301-e306	- Comparison does not meet inclusion criteria *Comparison between cohorts with meningitis*
Rodenburg-Vlot, M. B., Ruytjens, L., Oostenbrink, R. et al. (2016) Systematic Review: Incidence and Course of Hearing Loss Caused by Bacterial Meningitis: In Search of an Optimal Timed Audiological Follow-up. Otology & Neurotology 37(1): 1-8	- Study design does not meet inclusion criteria *Non-comparative data reported*
Roine, I., Pelkonen, T., Bernardino, L. et al. (2015) Ataxia and Its Association with Hearing Impairment in Childhood Bacterial Meningitis. Pediatric Infectious Disease Journal 34(8): 809-13	- Study design does not meet inclusion criteria
Samanta, S., Farrer, K., Breathnach, A. et al. (2011) Risk factors for late onset gram-negative infections: A case-control study. Archives of Disease in Childhood: Fetal and Neonatal Edition 96(1): F15-F18	- Population does not meet inclusion criteria
Saxena, M., Young, P., Pilcher, D. et al. (2015) Early temperature and mortality in critically ill	- Population does not meet inclusion criteria

Study	Code [Reason]
patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Medicine. 03	
Schieveld, J. N. M.; van Tuijl, S.; Pikhard, T. (2013) On Nontraumatic Brain Injury in Pediatric Critical Illness, Neuropsychologic Short-Term Outcome, Delirium, and Resilience. CRITICAL CARE MEDICINE 41(4): 1160-1161	- Study design does not meet inclusion criteria
Schlesinger, L. S.; Ross, S. C.; Schaberg, D. R. (1987) Staphylococcus aureus meningitis: A broad-based epidemiologic study. Medicine 66(2): 148-156	- Study design 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	- No outcomes of interest *Continuous outcomes reported*
Schmidt, H., Cohrs, S., Heinemann, T. et al. (2006) Sleep disorders are long-term sequelae of both bacterial and viral meningitis. JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY 77(4): 554-558	- No outcomes of interest *Continuous outcomes reported*
Schmitt, B. (2004) Neurological sequelae after bacterial meningitis. MONATSSCHRIFT KINDERHEILKUNDE 152(4): 391-395	- Non-English language article
Selz, P. A., Girardi, M., Konrad, H. R. et al. (1996) Vestibular deficits in deaf children. Otolaryngology - Head & Neck Surgery 115(1): 70-7	- Population does not meet inclusion criteria *The study did not specify whether participants had bacterial meningitis, and continuous outcomes reported*
Seminog, O. O. and Goldacre, M. J. (2013) Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. Thorax 68(2): 171-6	- Population does not meet inclusion criteria
Sewell, Elizabeth; Roberts, Jessica; Mukhopadhyay, Sagori (2021) Association of Infection in Neonates and Long-Term Neurodevelopmental Outcome. CLINICS IN PERINATOLOGY 48(2): 251-261	- Study design does not meet inclusion criteria
Silkes, E. D. and Chabot, J. (1985) PROGRESSIVE HEARING-LOSS FOLLOWING HEMOPHILUS-INFLUENZAE MENINGITIS. INTERNATIONAL JOURNAL OF PEDIATRIC OTORHINOLARYNGOLOGY 9(3): 249-256	- 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
Stoll, B. J., Hansen, N. I., Adams-Chapman, I. et	- Population does not meet inclusion criteria

Study	Code [Reason]
al. (2004) Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 292(19): 2357-65	*The study did not specify whether participants had bacterial meningitis*
Stoll, B. J., Hansen, N., Fanaroff, A. A. et al. (2004) To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. Pediatrics 113(5): 1181-6	- Population does not meet inclusion criteria
Streharova, A., Krcmery, V., Kisac, P. et al. (2007) Predictors of inferior outcome in community acquired bacterial meningitis. Neuroendocrinology Letters 28suppl3: 2-4	- 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
Sumpter, R., Brunklaus, A., McWilliam, R. et al. (2011) Health-related quality-of-life and behavioural outcome in survivors of childhood meningitis. Brain Injury 25(1314): 1288-95	- Study design does not meet inclusion criteria
Tagarro, A., Bote, P., Sanchez, A. et al. (2016) Complications of Pneumococcal Bacteremia After Thirteen-valent Conjugate Vaccine Withdrawal. Pediatric Infectious Disease Journal 35(12): 1281-1287	- Study design does not meet inclusion criteria
Tarvij Eslami, S., Nassirian, H., Mojgan, B. M. et al. (2012) Comparison of cerebrospinal fluid in newborns and in infants <= 2 months old with or without meningitis. Pediatrics International 54(3): 336-40	- Study from low or middle income country
Taylor, H. G.; Barry, C. T.; Schatschneider, C. (1993) SCHOOL-AGE CONSEQUENCES OF HAEMOPHILUS-INFLUENZAE TYPE-B MENINGITIS. JOURNAL OF CLINICAL CHILD PSYCHOLOGY 22(2): 196-206	- Same participants and data as Taylor 1990, which is already included
Taylor, H. G., Michaels, R. H., Mazur, P. M. et al. (1984) Intellectual, neuropsychological, and achievement outcomes in children six to eight years after recovery from Haemophilus influenzae meningitis. Pediatrics 74(2): 198-205	- Insufficient presentation of results *Continuous outcomes but not proportion of participants with outcomes of interest reported*
Taylor, H. G., Schatschneider, C., Petrill, S. et al. (1996) Executive dysfunction in children with early brain disease: Outcomes post Haemophilus influenzae meningitis. DEVELOPMENTAL NEUROPSYCHOLOGY 12(1): 35-51	- Study design does not meet inclusion criteria *A validation study for tests of executive function*
Teixeira, D. C., Diniz, L. M. O., Guimaraes, N. S. et al. (2020) Risk factors associated with the outcomes of pediatric bacterial meningitis: a	- Study design does not meet inclusion criteria

Study	Code [Reason]
systematic review. Jornal de Pediatria 96(2): 159-167	
Tubiana, S., Varon, E., Biron, C. et al. (2020) Community-acquired bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort. Clinical Microbiology & Infection 26(9): 1192-1200	- Study design does not meet inclusion criteria
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	- Study design does not meet inclusion criteria
Tunkel, A. R.; Wispelwey, B.; Scheld, W. M. (1990) Bacterial meningitis: recent advances in pathophysiology and treatment. Annals of Internal Medicine 112(8): 610-23	- Study design 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	- Insufficient presentation of results *Continuous outcomes but not proportion of participants with outcomes of interest reported*
van Vliet, E. O., de Kieviet, J. F., Oosterlaan, J. et al. (2013) Perinatal infections and neurodevelopmental outcome in very preterm and very low-birth-weight infants: a meta-analysis. JAMA pediatrics 167(7): 662-8	- Population does not meet inclusion criteria *Did not specify whether participants had bacterial meningitis*
Wald, E. R., Bergman, I., Taylor, H. G. et al. (1986) Long-term outcome of group B streptococcal meningitis. Pediatrics 77(2): 217-21	- Conference abstract.
Wang, H. C., Lau, C. I., Lin, C. C. et al. (2016) Group a streptococcal infections are associated with increased risk of pediatric neuropsychiatric disorders: A Taiwanese population-based cohort study. Journal of Clinical Psychiatry 77(7): e848-e854	- Population does not meet inclusion criteria
Yost, G. C., Kaplan, A. M., Bustamante, R. et al. (1986) Bacterial meningitis in Arizona American Indian children. American Journal of Diseases of Children 140(9): 943-6	- Study design does not meet inclusion criteria
Zielinski, A., Kwon, C. B., Tomaszunas-Blaszczykl, J. et al. (2003) Risk of Haemophilus influenzae type b meningitis in Polish children varies directly with number of siblings: Possible implications for vaccination strategies. European Journal of Epidemiology 18(9): 917-922	- Study design does not meet inclusion criteria

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

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

Research question

What are the long-term outcomes after bacterial meningitis in infancy?

Why this is important

Neonatal bacterial infections (NDI) have long been recognised as an important cause of acute morbidity and mortality, but long-term neurodevelopmental consequences are not comprehensively described and there are no recent studies.

Quantifying the risks of NDI is important to allow appropriate counselling and follow-up of those at risk and to prioritise treatment and prevention strategies. Early identification of impairment and institution of appropriate interventions has been shown to improve the outcomes of affected babies, including motor, cognitive, and hearing outcomes.

Knowledge of the neurodevelopmental burden associated with infections may also justify consideration of new management strategies, including new antibiotics or adjunctive therapies, as well as prevention strategies (including vaccination).

Table 3: Research recommendation rationale

Research question	What are the long-term outcomes after bacterial meningitis in infancy?
Why is this needed	
Importance to 'patients' or the population	To allow appropriate counselling and follow-up of those at risk and to prioritise treatment and prevention strategies
Relevance to NICE guidance	This would allow more specific recommendations on follow-up to be made
Relevance to the NHS	Neurodevelopmental sequelae after infant meningitis are common and have major healthcare and cost implications
National priorities	This does not align with specific NHS priorities, but may aid earlier identification and more effective management of long-term complications
Current evidence base	Only 1 eligible study on neonates was identified and this study was not recent
Equality	Bacterial meningitis in infants is more common in certain ethnic groups and in families of lower socioeconomic background
Feasibility	Various validated neurodevelopmental assessments are available
Other comments	None

Table 4: Research recommendation modified PICO table

Criterion	Explanation
Population	Neonates with confirmed bacterial meningitis

Criterion	Explanation
Prognostic factors	Bacterial meningitis
Comparison	No bacterial meningitis (healthy cohort)
Outcomes	Neurodevelopmental and audiological impairments (assessed with validated neurodevelopmental tools)
Study design	Prospective cohort study
Timeframe	5-10 years
Additional information	The older the age at assessment the better the findings will reflect school performance