WHO guidelines on meningitis diagnosis, treatment and care

Web Annex A. Quantitative evidence reports

World Health Organization

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Contents

1. Initial cerebrospinal fluid investigations

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Abbreviations

AM	aseptic meningitis
AUC	area under the receiver-operating-characteristics curve
BM	bacterial meningitis
CI	confidence interval
CNS	central nervous system
CSF	cerebrospinal fluid
ED	emergency department
EVM	enteroviral meningitis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Classification of Diseases
LR+	positive likelihood ratio
LR−	negative likelihood ratio
NA	not applicable
NPV	negative predictive value
NR	not reported
RT-PCR	real-time polymerase chain reaction
PCR	polymerase chain reaction
PPV	positive predictive value
VM	viral meningitis
WBC	white blood cell
WHO	World Health Organization

1. Background

Acute meningitis is a life-threatening condition that requires timely and accurate diagnosis in order to initiate appropriate patient management. Meningitis can be caused by bacteria, viruses, fungi or parasites. If the cause is bacterial, prompt initiation of appropriate antibiotics is needed to prevent severe complications and reduce mortality. Typical clinical characteristics, such as headache, neck stiffness, fever and an altered mental state, are only present in 40–50% of patients with suspected meningitis, often posing diagnostic dilemmas *(1, 2)*. Lumbar puncture is necessary to obtain cerebrospinal fluid (CSF) and perform CSF examination *(3)*. Culture and molecular tests allow for pathogen identification and are generally regarded as the reference standard for confirming the microbiological diagnosis of acute meningitis *(3)*. However, in order to inform timely clinical decisions and guide antibiotic treatment, additional investigations with faster turn-around times and rapidly available results are normally conducted on CSF samples, including Gram stain, cellularity (cell count and differential), protein, glucose and lactate tests *(4)*. These investigations play a crucial role in differentiating acute bacterial meningitis from other forms of acute meningitis, including viral meningitis. Moreover, culture and/or molecular tests may not be routinely or readily available, accessible or affordable, especially in resource-limited settings, further emphasizing the importance of additional CSF investigations in the diagnostic and treatment approach to patients with suspected meningitis.

As part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, this systematic review was conducted in conjunction with two other systematic reviews addressing the research questions on the diagnostic performance of CSF polymerase chain reaction (PCR) and peripheral blood markers (reports 2a and 3 in this web annex). A unified search strategy was developed for this purpose. Here in this report, only the results specifically related to initial CSF investigations (i.e. Gram stain, cellularity, protein, glucose and lactate tests) are presented.

2. Methodology

Initial CSF investigations (i.e. Gram stain, cellularity, protein, glucose and lactate) for the diagnosis of bacterial meningitis were assessed in the review carried out by van de Beek et al. for *Nature Reviews Disease Primers (4)* and in the ESCMID (European Society for Clinical Microbiology and Infectious Diseases) guideline, developed by another team led by van de Beek *(5)*, both of which were published in 2016. Since these reviews were of high quality and covered the literature on acute bacterial meningitis up to 2014, this report summarizes the data on initial CSF testing from 2014 onwards, which were systematically searched and reviewed. Additionally, the evidence from before 2014 was reviewed and graded, largely on the basis of reviews conducted as part of the preparation of the guidelines issued by ESCMID *(7)*.

2.1 Research question and study design

What is the diagnostic performance of CSF testing (Gram stain, leukocyte count and differential, glucose, total protein, lactate) in cases of suspected acute meningitis?

Population: Suspected cases of acute meningitis (adults and children > 1 month of age).

Index test/Intervention: CSF testing, including Gram stain, leukocyte count and differential (neutrophils, lymphocytes, monocytes), glucose, total protein and lactate tests.

Reference standard/comparator: Consensus diagnosis[1]

Outcomes

Critical outcomes (as prioritized by the Guideline Development Group):

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Likelihood ratios.

Other outcomes: Area under-the receiver-operating-characteristics curve (AUC)

Study designs: Cross-sectional and case–control studies. Case reports or case series were excluded.

2.2 Eligible studies

Published language: Studies published in English, French, German, Italian, Portuguese and Spanish were considered for inclusion. For studies in other languages, existing networks within WHO and Cochrane were used for support with screening and/or translation. Studies in Chinese and Korean were excluded.

Exclusion criteria: The following groups of patients were excluded:

- those with tuberculous meningitis;
- those with hospital-acquired, nosocomial and health-care-associated meningitis;
- those with subacute and chronic meningitis;
- newborns (0–28 days) with meningitis;
- those with non-infectious meningitis (e.g. meningitis caused by drugs, malignancy, autoimmune diseases).

Subgroups: None considered.

[1] Consensus diagnosis defined as clinical characteristics (including peripheral white blood cell (WBC) count, C-reactive protein, procalcitonin), blood culture, CSF culture and/or CSF PCR.

2.3 Search strategy

One comprehensive search strategy was developed to identify relevant studies for three research questions – addressing the diagnostic performance of initial CSF investigations, CSF PCR and peripheral blood markers (covered in this report and reports 2a and 3 in this web annex). The following databases were searched for articles published up to the date of the literature search: PubMed, Embase and the Cochrane Library.

The exact search terms can be found in Appendix 1. Search strategy used to identify .

The search was conducted in English on 26 January 2024.

2.4 Selection of studies

The three authors independently screened all the titles and abstracts (NSG, SO and MCB) and assessed their eligibility according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion. The full text of articles found to be potentially relevant on the basis of their titles and abstracts was retrieved and examined in light of the same inclusion criteria by two reviewers independently. Any disagreements regarding the results of the full text screening were resolved by discussion.

Rayyan was used for reference screening, title, abstract and full-text selection.

2.5 Data extraction and management

Data extraction was performed by two authors (NSG and SO) and any uncertainties were discussed with the other author (MCB). The following categories of data were extracted:

- publication year and author(s);
- study type and setting;
- population, intervention, comparator and outcome(s);
- characteristics of patients included (sex, age category, total no. of cases, total no. of non-cases, definitions of disease categories);
- outcomes and results.

2.6 Assessment of risk of bias in studies included in the review

The quality of the studies included has been assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies, by one author and will be checked by a second author. The specific categories offered by the QUADAS-2 tool were tailored to the research questions.

2.7 Data synthesis

Where feasible (with at least two contributing studies and homogeneous data), meta-analyses were conducted, using a random-effects model for proportions to provide pooled estimates for sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). All meta-analyses were conducted using the R software packages "meta" and "metafor". Where meta-analysis was not feasible, ranges and medians were provided to summarize the findings. Data on NPV and PPV were extracted and included in the meta-analysis of non-case control studies only, because measures were considered highly dependent on prevalence. If multiple cut-offs were reported by one article, one cut-off was included for meta-analysis to prevent dependent results. The choice of this cut-off was based on clinical relevance.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was tailored to the research questions. The overall certainty of the evidence was downgraded for imprecision if the confidence interval (CI) of the pooled estimate results was very wide, or in cases of a lower CI boundary (below 60%).

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No subgroup analysis was conducted.

2.10 Sensitivity analysis

No sensitivity analysis was conducted.

2.11 Deviations from the review protocol

There were no protocol deviations.

3. Results

3.1 Studies identified by the search process

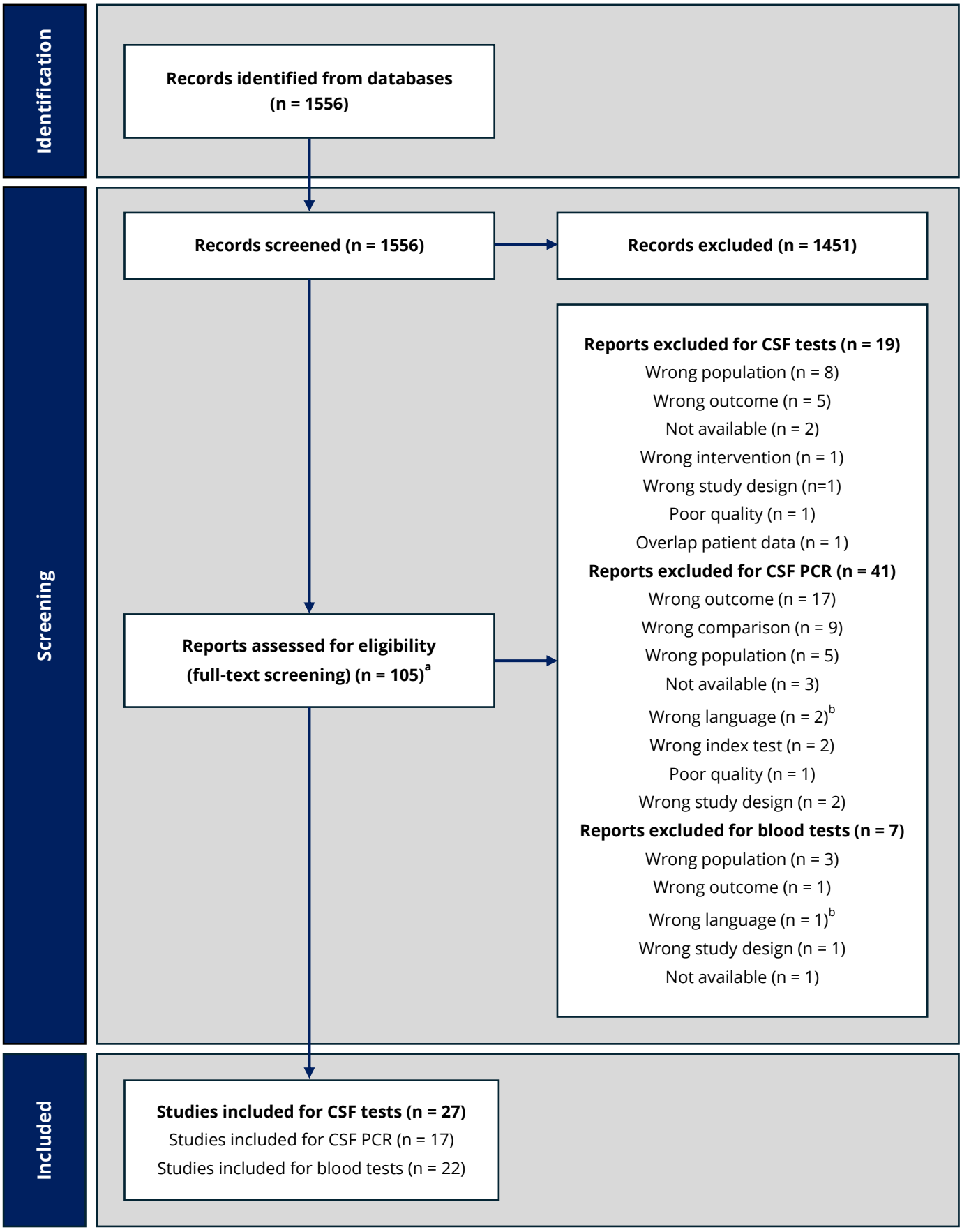
Figure WA1.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review. A total of 1556 records were retrieved for the three research questions, of which 1451 were excluded on the basis of their title and abstract. The search strategy is provided in Appendix 1.

Overall, 105 articles were screened for full-text eligibility. For initial CSF testing, 19 articles were excluded, and a total of 27 studies were included.

3.1.1 Studies included in the review

The characteristics of the included studies are presented in Table WA1.1, by index test.

Fig. WA1.1 PRISMA flow diagram for the systematic review



[a] Some studies were included for more than one research question; therefore, the number of reports excluded per research question is not the same as the total number of reports screened for full text minus all studies included per research question. [b] Studies in Chinese (n = 2) and Korean (n = 1) were excluded.

Table WA1.1a Characteristics of studies included in the GRADE evidence profiles – Index test: CSF Gram stain

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
van de Beek (2004), the Kingdom of the Netherlands *(2)*	Prospective cohort	Low	Adult patients (≥ 16 years) with a final diagnosis of BM	652	Positive CSF culture	Sens
Bohr (1983), Denmark *(6)*	Cross-sectional cohort	Unclear	Patients of all ages admitted with a final diagnosis of BM	650	Positive CSF culture or blood culture or culture from other site	Sens
Nigrovic (2008), the United States of America (USA) *(7)*	Cross-sectional cohort	High	All children (29 days to 19 years) who presented to the ED with BM	225	Positive CSF culture, or positive blood culture/antigen detection and > 10 cells/mm^3 in the CSF	Sens
Shameem (2008), India *(8)*	Prospective cohort	Low	All children with a final diagnosis of BM	204	Positive CSF culture	Sens
Sigurdardottir (1997), Iceland *(9)*	Cross-sectional cohort	High	All adult patients (≥ 16 years) with a final diagnosis of BM	100	Clinical picture of meningitis and positive CSF culture, or positive blood culture and neutrophilic pleocytosis, antigen detection	Sens

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Taniguchi (2020), Japan *(10)*	Case-control study	Unclear	All adult patients (> 15 years) admitted and finally diagnosed with BM or AM[a] (BM vs AM)	131 (34, 97)	Clinically evident acute meningitis and positive routine bacterial culture of CSF	Sens, Spec, LR+, LR−, AUC

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CSF: cerebrospinal fluid; ED: emergency department; LR−: negative likelihood ratio; LR+: positive likelihood ratio; Sens: sensitivity; Spec: specificity.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA1.1b Characteristics of studies included in the GRADE evidence profiles – Index test: CSF leukocyte count

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Alnomasy (2021), Saudi Arabia *(11)*	Case–control	High	Adult patients with suspected meningitis based on clinical features (BM vs VM)	75 (38, 34)	Positive RT-PCR	Sens, Spec, LR-, AUC
Babenko (2021), Kazakhstan *(12)*	Case–control	High	Children aged 1 month to 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids CSF or blood or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids in CSF or blood	Sens, Spec, LR+, LR−
Chaudhary (2018), Nepal *(13)*	Cross-sectional cohort	High	Children with suspected meningitis (BM vs non-BM)	50 (22,28)	Positive CSF culture or CSF Gram stain and abnormal CSF findings	Sens, Spec, LR+, LR−, AUC
Domingues (2019), Brazil *(14)*	Case–control	High	Patients with suspected acute meningitis (BM vs EVM)	1187 (662, 525)	Bacterioscopy, bacterial antigen test, latex agglutination	AUC
Dubos (2008), France *(15)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for BM or AM and had measurements of the main inflammatory markers	198 (96, 102)	CSF WBC count ≥ 7/µl and documented bacterial infection in CSF (direct examination, culture, latex	Sens, Spec, LR+, LR-

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
			(including procalcitonin) in blood and in the ED (BM vs AM)		agglutination or PCR) or blood culture	
Giulieri (2015), Switzerland *(16)*	Case–control	Low	Adult patients with microbiologically proven acute meningitis (BM vs VM)	45 (18,27)	Positive Gram stain, culture or PCR in CSF and/or positive blood culture with clinical symptoms and CSF pleocytosis (> 4 cells/mm^3)	Sens, Spec, LR+, LR−
Gowin (2016), Poland *(17)*	Case–control	High	Children hospitalized with clinical suspicion of meningitis based on clinical symptoms and inflammatory changes in CSF (BM vs AM[a])	129 (64,64)	NR. Assumed: ICD-10 code-based clinical diagnosis	Sens, Spec, LR+, LR−
Kalchev (2021), Bulgaria *(18)*	Prospective cohort	Unclear	Patients of all ages with clinical evidence of acute CNS infection based on clinical signs and abnormal CSF findings with presence of at least 1 ml CSF and serum (BM vs non-BM)	80 (21, 59)	Microbiological analysis	AUC
Morales-Casado (2017), Spain *(19)*	Prospective cohort	Low	Adult patients aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53,101)	Positive CSF culture or CSF antigen test	AUC

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Pormohammad (2019), Islamic Republic of Iran *(20)*	Case–control	Low	Children aged < 16 years with suspected meningitis based on clinical criteria (BM vs AM[a])	62 (43, 19)	Combination of clinical and laboratory tests (Gram stain and culture of blood and CSF)	Sens, Spec, LR+, LR−
Sanaei Dashti (2017), Islamic Republic of Iran *(21)*	Case–control	Low	Children aged 28 days to 14 years with suspected meningitis based on clinical symptoms (BM vs VM)	50 (12,38)	Definitive BM: positive CSF Gram stain, culture or PCR Presumed BM: clinical symptoms with at least 2 of the following: CSF protein ≥ 80 mg/dl, glucose < 40 mg/dl, WBC ≥ 300/mm^3 and/or CSF neutrophil predominancy	Sens, Spec, LR+, LR−
Sormunen (1999), Finland *(22)*	Case–control	Low	Children aged 3 months to 15 years with a positive bacterial CSF culture and negative Gram stain, and children with viral meningitis (BM vs VM)	237 (55,182)	Positive CSF culture	Sens, Spec, LR+, LR−
Staal (2024), the Kingdom of the Netherlands *(23)*	Prospective cohort	Low	Adult patients aged ≥ 16 years, suspected of a CNS infection, who underwent a diagnostic lumbar puncture and had a CSF leukocyte count ≥ 5 cells/mm^3 (BM vs non-BM)	310 (117, 193)	Microbiological evidence of bacteria by culture, Gram stain, PCR or other microbiological test of cerebrospinal fluid, or expert opinion in case	Sens, Spec, LR+, LR−, NPV, PPV, AUC

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
					of > 4 CSF leukocytes/ml without bacteria identified	
Tamune (2014), Japan *(24)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15,119)	Positive CSF culture	Sens, Spec, LR+, LR−
Taniguchi (2020), Japan *(10)*	Case–control	Unclear	Adult patients aged > 15 years admitted and finally diagnosed with BM or AM (BM vs AM[a])	131 (34,97)	Positive CSF culture and clinical signs and symptoms	Sens, Spec, LR+, LR−, AUC
Wang (2022), China *(25)*	Case–control	Low	Children aged > 1 month with a clinical diagnosis of infectious meningitis (BM vs VM)	348 (112,236)	Any of the following: (i) positive CSF or blood culture; (ii) positive Gram stain; (iii) CSF total leukocyte count 1000/mm^3, and any of the following: (i) CSF neutrophil > 1/mm^3, (ii) CSF glucose < 50% of serum glucose, (iii) CSF protein > 50 mg/dl	AUC

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CSF: cerebrospinal fluid; ED: emergency department; EVM: enteroviral meningitis; ICD: International Classification of Diseases; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RT-PCR: real-time polymerase chain reaction; Sens: sensitivity; Spec: specificity; VM: viral meningitis; WBC: white blood cell.
[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA.1.1c Characteristics of studies included in the GRADE evidence profiles – Index test: CSF leukocyte differential

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Chaudhary (2018), Nepal *(13)*	Cross-sectional cohort	High	Children with suspected meningitis (BM vs non-BM)	50 (22, 28)	Positive CSF culture or CSF Gram stain and abnormal CSF findings	Sens, Spec, LR+, LR−, AUC
Babenko (2021), Kazakhstan *(12)*	Case–control	High	Children aged 1 month to 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids in CSF or blood	Sens, Spec, LR+, LR−
Dubos (2008), France *(15)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for BM or AM and had measurements of the main inflammatory markers (including procalcitonin) in blood and in the ED (BM vs AM)	184 (95, 89)	CSF WBC count ≥ 7/µl and documented bacterial infection in CSF (direct examination, culture, latex agglutination, or PCR) or blood culture	Sens, Spec, LR+, LR−, AUC
Fouad (2014), Egypt *(26)*	Prospective cohort	Unclear	Patients of all ages with acute meningitis (BM vs non-BM)	623 (457, 166)	Positive CSF culture or positive blood culture with concurrent meningitis	Sens, Spec, LR+, LR−, PPV, NPV

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Giulieri (2015), Switzerland *(16)*	Case–control	Low	Adult patients with microbiologically proven acute meningitis (BM vs VM)	45 (18, 27)	Positive Gram stain, culture or PCR in CSF and/or positive blood culture with clinical symptoms and CSF pleocytosis (> 4 cells/mm^3)	Sens, Spec, LR+, LR−
Mentis (2016), Greece *(27)*	Case–control	Low	Patients of all ages with suspected community-acquired meningitis (BM vs VM)	4339 (1758, 2581)	Positive CSF Gram stain, latex agglutination test, conventional bacterial procedures or multiplex PCR	Sens, Spec, LR+, LR−, AUC
Morales Casado (2017), Spain *(19)*	Prospective cohort	Low	Adult patients aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53, 101)	Positive CSF culture or antigen test	AUC
Pormohammad (2019), Islamic Republic of Iran *(20)*	Case–control	Low	Children aged < 16 years with suspected meningitis based on clinical criteria (BM vs AM[a])	62 (43, 19)	Combination of clinical and laboratory tests (Gram stain and culture of blood and CSF)	Sens, Spec, LR+, LR−
Sanaei Dashti (2017), Islamic Republic of Iran *(21)*	Case–control	Low	Children aged 28 days – 14 years with suspected meningitis based on clinical symptoms (BM vs VM)	50 (12, 38)	Definitive BM: positive CSF Gram stain, culture or PCR Presumed BM: clinical symptoms with at least	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
					2 of following: CSF protein ≥ 80 mg/dl, glucose < 40 mg/dl, WBC ≥ 300/mm^3, and/or CSF neutrophil predominancy	
Staal (2024), the Kingdom of the Netherlands *(23)*	Prospective cohort	Low	Adult patients aged ≥ 16 years, suspected of a CNS infection, who underwent a diagnostic lumbar puncture and had a CSF leukocyte count ≥ 5 cells/mm^3 (BM vs non-BM)	310 (117, 193)	Microbiological evidence of bacteria by culture, gram stain, PCR or other microbiological test of cerebrospinal fluid, or expert opinion in case of > 4 CSF leukocytes/ml without bacteria identified.	Sens, Spec, LR+, LR-, NPV, PPV, AUC
Tamune (2014), Japan *(24)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15, 119)	Positive CSF culture	Sens, Spec, LR+, LR−
Taniguchi (2020), Japan *(10)*	Case–control	Unclear	All adult patients aged > 15 years admitted and finally diagnosed with BM or AM (BM vs AM[a])	131 (34, 97)	Positive CSF culture and clinical signs and symptoms	Sens, Spec, LR+, LR−, AUC
Wang (2022), China *(25)*	Case–control	Low	Children aged > 1 month with a clinical diagnosis of infectious meningitis (BM vs VM)	348 (112, 236)	Any of the following: (i) positive CSF or blood culture; (ii) positive	AUC

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
					Gram stain; (iii) CSF total leukocyte count > 1000/mm^3, and any of the following: (i) CSF neutrophil > 1/mm^3, (ii) CSF glucose < 50% of serum glucose, (iii) CSF protein > 50 mg/dl	

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CNS: central nervous system; CSF: cerebrospinal fluid; ED: emergency department; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; NR: not reported; PCR: polymerase chain reaction; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; VM: viral meningitis; WBC: white blood cell.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA1.1d Characteristics of studies included in the GRADE evidence profiles – Index test: CSF glucose and CSF/blood glucose ratio

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Alnomasy (2021), Saudi Arabia *(11)*	Case–control	High	Adult patients with suspected meningitis based on clinical features (BM vs VM)	75 (38, 34)	Positive RT-PCR	Sens, Spec, LR+, LR−, AUC
Babenko (2021), Kazakhstan *(12)*	Case–control	High	Children aged 1 month to 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids in CSF or blood	Sens, Spec, LR+, LR−
Domingues (2019), Brazil *(14)*	Case–control	High	Patients with suspected acute meningitis (BM vs EVM)	1187 (662, 525)	Bacterioscopy, bacterial antigen test, latex agglutination	AUC
Dubos (2008), France *(15)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for BM or AM and had measurements of the main inflammatory markers (including procalcitonin) in blood and in the ED (BM vs AM)	195 (96, 99)	CSF WBC count ≥ 7/µl and documented bacterial infection in CSF (direct examination, culture, latex agglutination or PCR) or blood culture	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Fouad (2014), Egypt *(26)*	Prospective cohort	Unclear	Patients of all ages with acute meningitis (BM vs non-BM)	623 (457,166)	Positive CSF culture or positive blood culture with concurrent meningitis	Sens, Spec, LR+, LR−, PPV, NPV
Gowin (2016), Poland *(17)*	Case–control	High	Children hospitalized with clinical suspicion of meningitis based on clinical symptoms and inflammatory changes in CSF (BM vs AM[a])	129 (64, 64)	NR. Assumed: ICD-10 code clinical diagnosis	Sens, Spec, LR+, LR−
Kalchev (2021), Bulgaria *(18)*	Prospective cohort	Unclear	Patients of all ages with clinical evidence of acute CNS infection based on clinical signs and abnormal CSF findings with presence of at least 1 ml CSF and serum (BM vs non-BM)	80 (21, 59)	Microbiological analysis	AUC
Pormohammad (2019), Islamic Republic of Iran *(20)*	Case–control	Low	Children aged < 16 years with suspected meningitis based on clinical criteria (BM vs AM[a])	62 (43, 19)	Combination of clinical and laboratory tests (Gram stain and culture of blood and CSF)	Sens, Spec, LR+, LR−,
Sormunen (1999), Finland *(22)*	Case–control	Low	Children aged 3 months to 15 years with a positive bacterial CSF culture and negative Gram stain, and children with viral meningitis (BM vs VM)	237 (55,182)	Positive CSF culture	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Tamune (2014), Japan *(24)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15, 119)	Positive CSF culture	Sens, Spec, LR+, LR−
Viallon (1999), France *(28)*	Case–control	High	Adult patients admitted to an ED for suspected acute meningitis (unclear comparison)	80 (23, 57)	Definitive in case of a positive CSF culture or Gram staining, probable in case of cloudy CSF, CSF leukocyte count > 1500 cells/mm^3, > 50% granulocytes, CSF/blood glucose ratio < 0.4, CSF protein > 2 g/L; if there was improvement in CSF parameters after 48 hours of antibiotics and if the discharge diagnosis was a bacterial pretreated meningitis.	Sens, Spec, LR+, LR−
Wang (2022), China *(25)*	Case–control	Low	Children aged > 1 month with a clinical diagnosis of infectious meningitis (BM vs VM)	348 (112, 236)	Any of the following: (i) positive CSF or blood culture; (ii) positive Gram stain; (iii) CSF total leukocyte count > 1000/mm^3, and any of the following:	AUC

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
					(i) CSF neutrophil > 1/mm^3, (ii) CSF glucose < 50% of serum glucose, (iii) CSF protein > 50 mg/dl	

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CNS: central nervous system; CSF: cerebrospinal fluid; EVM: enteroviral meningitis; ICD: International Classification of Diseases; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RT-PCR: real-time polymerase chain reaction; Sens: sensitivity; Spec: specificity; VM: viral meningitis.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA1.1e Characteristics of studies included in the GRADE evidence profiles – Index test: CSF protein

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Alnomasy (2021), Saudi Arabia *(11)*	Case–control	High	Adult patients with suspected meningitis based on clinical features (BM vs VM)	75 (38, 34)	Positive RT-PCR	Sens, Spec, LR+, LR−, AUC
Babenko (2021), Kazakhstan *(12)*	Case–control	High	Children aged 1 month – 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids CSF or blood	Sens, Spec, LR+, LR−
Chaudhary (2018), Nepal *(13)*	Cross-sectional	High	Children with suspected meningitis (BM vs non-BM)	50 (22, 28)	Positive CSF culture or CSF Gram stain and abnormal CSF findings	Sens, Spec, LR+, LR−, AUC
Domingues (2019), Brazil *(14)*	Case–control	High	Patients with suspected acute meningitis (BM vs EVM)	1187 (662, 525)	Bacterioscopy, bacterial antigen test, latex agglutination	AUC
Dubos (2008), France *(15)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for BM or AM and had measurements of the main inflammatory markers (including procalcitonin) in blood and in the ED (BM vs AM)	195 (95, 100)	CSF WBC count ≥ 7/µl and documented bacterial infection in CSF (direct examination, culture, latex agglutination, or PCR) or blood culture	Sens, Spec, LR+, LR−, AUC

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Fouad (2014), Egypt *(26)*	Prospective cohort	Unclear	Patients of all ages with acute meningitis (BM vs non-BM)	623 (457, 166)	Positive CSF culture or positive blood culture with concurrent meningitis	Sens, Spec, LR+, LR−, PPV, NPV
Giulieri (2015), Switzerland *(16)*	Case–control	Low	Adult patients with microbiologically proven acute meningitis (BM vs VM)	45 (18, 27)	Positive Gram stain, culture or PCR in the CSF and/or positive blood culture with clinical symptoms and CSF pleocytosis (> 4 cells/mm^3)	Sens, Spec, LR+, LR−
Gowin (2016), Poland *(17)*	Case–control	High	Children hospitalized with clinical suspicion of meningitis based on clinical symptoms and inflammatory changes in CSF (BM vs AM[a])	129 (64, 64)	NR. Assumed: ICD-10 code clinical diagnosis	Sens, Spec, LR+, LR−
Kalchev (2021), Bulgaria *(18)*	Prospective cohort	Unclear	Patients of all ages with clinical evidence of acute CNS infection based on clinical signs and abnormal CSF findings with presence of at least 1 ml CSF and serum (BM vs non-BM)	80 (21, 59)	Microbiological analysis	AUC

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Morales Casado (2017), Spain *(19)*	Prospective cohort	Low	Adult patients aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53, 101)	Positive CSF culture or CSF antigen test	AUC
Pormohammad (2019), Islamic Republic of Iran *(20)*	Case–control	Low	Children aged < 16 years with suspected meningitis based on clinical criteria (BM vs AM[a])	62 (43, 19)	Combination of clinical and laboratory tests (Gram stain and culture of blood and CSF)	Sens, Spec, LR+, LR−
Sormunen (1999), Finland *(22)*	Case–control	Low	Children aged 3 months to 15 years with a positive bacterial CSF culture and negative Gram stain, and children with viral meningitis (BM vs VM)	237 (55,182)	Positive CSF culture	Sens, Spec, LR+, LR−
Tamune (2014), Japan *(24)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15, 119)	Positive CSF culture	Sens, Spec, LR+, LR−
Taniguchi (2020), Japan *(10)*	Case–control	Unclear	Adult patients aged > 15 years admitted and finally diagnosed with BM or AM (BM vs AM[a])	131 (34, 97)	Positive CSF culture and clinical signs and symptoms	Sens, Spec, LR+, LR−AUC
Viallon (1999), France *(28)*	Case–control	High	Adult patients admitted to an ED for suspected acute meningitis (unclear comparison)	80 (23, 57)	Definitive in case of a positive CSF culture or Gram staining, probable in case of cloudy CSF, CSF leukocyte count > 1500	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
					cells/mm^3, > 50% granulocytes, CSF/blood glucose ratio < 0.4, CSF protein > 2 g/L; if there was improvement in CSF parameters after 48 hours of antibiotics and if the discharge diagnosis was a bacterial pretreated meningitis.	
Wang (2022), China *(25)*	Case–control	Low	Children aged > 1 month with a clinical diagnosis of infectious meningitis (BM vs VM)	348 (112, 236)	Any of the following: (i) positive CSF or blood culture; (ii) positive Gram stain; (iii) CSF total leukocyte count > 1000/mm^3, and any of the following: (i) CSF neutrophil > 1/mm^3, (ii) CSF glucose < 50% of serum glucose, (iii) CSF protein > 50 mg/dl	AUC

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CNS: central nervous system; CSF: cerebrospinal fluid; EVM: enteroviral meningitis; ICD: International Classification of Diseases; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RT-PCR: real-time polymerase chain reaction; Sens: sensitivity; Spec: specificity; VM: viral meningitis; WBC: white blood cell.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA1.1f Characteristics of studies included in the GRADE evidence profiles – Index test: CSF lactate

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Domingues (2019), Brazil *(14)*	Case-control	High	Patients with suspected acute meningitis (BM vs EVM)	1187 (662, 525)	Bacterioscopy, bacterial antigen test, latex agglutination	AUC
Giulieri (2015), Switzerland *(16)*	Case-control	Low	Adult patients with microbiologically proven acute meningitis (BM vs VM)	45 (18, 27)	Positive Gram stain, culture or PCR in CSF and/or positive blood culture with clinical symptoms and CSF pleocytosis (> 4 cells/mm^3)	Sens, Spec, LR+, LR−
Mekitarian Filho (2014), Brazil *(29)*	Case-control	Low	Children aged 1 month – 15 years with clinical findings of meningitis and CSF elevated leukocytes in whom CSF lactate and CSF culture were performed (BM vs AM[a])	451 (40, 411)	Positive CSF culture or CSF pleocytosis with a positive blood culture for a bacterial pathogen	Sens, Spec, LR+, LR−, AUC
Morales-Casado (2017), Spain *(19)*	Prospective cohort	Low	Adult patients aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53, 101)	Positive CSF culture or CSF antigen test	Sens, Spec, LR+, LR−, AUC
Nasir (2020), Pakistan *(30)*	Cross-sectional	Low	Children with clinical diagnosis of acute suspected meningitis (culture-positive BM vs culture-negative BM)	250 (19, 231)	Positive CSF culture	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (Intervention, Control)	Reference standard	Outcomes available
Nazir (2018), India *(31)*	Case-control	Low	Children with clinical findings of meningitis (BM vs VM)	216 (60, 156)	Positive CSF or blood culture, or positive CSF Gram stain, or CSF leukocytes > 1000/mm^3 with any of following: CSF neutrophils > 1mm^3, CSF glucose < 50% of serum glucose, CSF protein > 50 mg/dl	Sens, Spec, LR+, LR−, AUC
Sanaei Dashti (2017), Islamic Republic of Iran *(21)*	Case-control	Low	Children aged 28 days – 14 years with suspected meningitis based on clinical symptoms (BM vs VM)	50 (12, 38)	Definitive BM: positive CSF Gram stain, culture or PCR Presumed BM: clinical symptoms with at least 2 of following: CSF protein ≥ 80 mg/dl, glucose < 40 mg/dl, WBC ≥ 300/mm^3 and/or CSF neutrophil predominancy	Sens, Spec, LR+, LR−

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CSF: cerebrospinal fluid; ED: emergency department; EVM: enteroviral meningitis; ICD: International Classification of Diseases; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; RT-PCR: real-time polymerase chain reaction; Sens: sensitivity; Spec: specificity; VM: viral meningitis.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

3.1.2 Studies excluded from the review

The following studies were excluded from the review: Mentis, Kyprianou *(27),* Abuhayyeh, Al Droubi, Al-Nusair, Malkawi, Haddad, Abed Alfattah et al. *(32),* Aggarwal, Kumar, Avasthi and Soni *(33),* Arafa, Gabr, Kamel, ElMasry and Fahim *(34),* Arora, Abhilash, Mitra, Hazra, Gunasekharan and Yesudass *(35),* Baud, Vitt, Robbins, Wabl, Wilson, Chow et al. *(36),* Buch, Bodilsen, Knudsen, Larsen, Helweg-Larsen, Storgaard et al. *(37),* Caragheorgheopol, Țucureanu, Lazăr, Florescu, Lazăr and Caraş *(38),* Chonmaitree, Menegus and Powell *(39),* de Almeida, Furlan, Cretella, Lapinski, Nogueira, Cogo et al. *(40),* de Almeida, Nogueira, Raboni and Vidal *(41),* Maillet, De Broucker, Mailles, Bouzat and Stahl *(42),* Manning, Laman, Mare, Hwaiwhanje, Siba and Davis *(43),* McLaughlin, Lamb and Gaensbauer *(44),* Metrou and Crain *(45),* Obaro *(46),* Wong, Schlaggar, Buller, Storch and Landt *(47),* Yadav, Singh, Juneja, Goel, Kataria and Beniwal *(48),* Yadhav Ml *(49)*.

3.1.3 Studies with additional evidence

The following study contained additional evidence: Sakushima, Hayashino, Kawaguchi, Jackson and Fukuhara *(50)*.

3.2 Narrative description of diagnostic performance evidence

3.2.1 Parameter 1: CSF Gram stain

Overall, six studies were found, including three involving adults, two involving children and one involving patients of all ages. References standards varied and included either a positive CSF culture or a combination of a positive blood culture, elevated CSF leukocytes, positive latex agglutination test and clinical symptoms consistent with meningitis.

- The sensitivity pooled across the six studies (1962 participants) was 85% (95% CI 55–96, I^2 =99%, P = <0.0001). The certainty of the evidence was high (GRADE evidence profile).
- Data on specificity, LR+, LR− and AUC were reported in one study consisting of 131 participants. Specificity was 99% (95% CI NR), LR+ 91.2 (95% CI NR), LR− 0.09 (95% CI NR) and the AUC 0.95 (95% CI 0.9–1.0). The certainty of the evidence was moderate for all reported outcomes (GRADE evidence profile).
- Evidence suggests that CSF Gram stain has moderate to high sensitivity and it is likely to have very high specificity.
- Additional evidence indicates that CSF Gram stain has very high specificity (almost 100% if the hospital's infrastructure and the experience of the assessor are optimal) and that sensitivity varies greatly depending on the pathogen (93% for *Streptococcus pneumoniae,* 30–89% for *Neisseria meningitidis*, 25–65% for *Haemophilus influenzae* type b (Hib), 10–25% for *Listeria monocytogenes,* 80–90% for *Streptococcus agalactiae,*

20–44% for *Staphylococcus aureus,* 66–73% for *Streptococcus pyogenes,* 50% for *Streptococcus suis*). The aggregate diagnostic yield of CSF Gram stain is 90% in pneumococcal meningitis, 70–90% in meningococcal meningitis, 50% in *H. influenzae* meningitis, and 25–35% in *L. monocytogenes* meningitis. As reported in a Danish study involving 481 children, the yield decreased slightly (from 56% to 52%) if the patient received the antibiotic therapy before lumbar puncture was performed.

3.2.2 Parameter 2: CSF leukocyte count

Overall, 16 studies were found, including five involving adults, eight involving children and one involving patients of all ages (two studies did not report the age of the population). Reference standards varied greatly between studies, including combinations of the following: positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive PCR for bacterial and/or viral pathogens, International Classification of Diseases, 10th revision (ICD-10) code-based and clinical diagnosis (Table WA1.2).

- The sensitivity pooled across 12 studies (1634 participants) was 77% (95% CI 74–81%, I^2 = 26%, P = 0.19). The certainty of the evidence was high (GRADE evidence profile).
- The specificity pooled across 12 studies (1634 participants) was 83% (95% CI 75–92%, I^2 = 93%, P < 0.01). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in one study, conducted in the Kingdom of the Netherlands between 2012 and 2017. PPV was 86% (95% CI 80–92) and NPV was 94% (95% CI 93–96).
- Median AUC across eight studies (2332 participants) was 0.86 (range 0.56–0.94). The certainty of the evidence was high (GRADE evidence profile).
- Median LR+ across 12 studies (1634 participants) was 6.39 (range 1.45–64) and median LR− across 12 studies (1634 participants) was 0.28 (range 0.21–0.73). The certainty of the evidence was high (GRADE evidence profile).
- Evidence suggests that CSF leukocytes have been shown to have moderate sensitivity and moderate to high specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.3 Parameter 3: CSF neutrophils (absolute count or %)

Overall, 10 studies on CSF neutrophil absolute count or percentage were found, including two studies involving adults, five studies involving children and two studies involving patients of all ages (one study did not report the age of the population). Reference standards varied greatly between studies, including combinations of the following: positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive PCR tests and clinical

diagnosis (Table WA1.2).

- The sensitivity pooled across the 10 studies (6013 participants) was 82% (95% CI 70–94%, I^2 = 97%, P < 0.01). The certainty of the evidence was moderate (GRADE evidence profile).
- The specificity pooled across 10 studies (6013 participants) was 84% (95% CI 77–90%, I^2 =89%, P < 0.01). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in two studies, one conducted in Egypt (623 participants) and one in the Kingdom of the Netherlands (310 participants). PPV was reported as 89% (95% CI NR) and 72% (95% CI 66–78) and NPV was reported as 48% (95% CI NR) and 97% (95% CI 96–99). The certainty of the evidence was moderate for each of these outcomes (GRADE evidence profile).
- Median AUC across four studies (4853 participants) was 0.90 (range 0.66–0.97). The certainty of the evidence was high (GRADE evidence profile).
- Median LR+ across 10 studies (6013 participants) was 3.58 (range 2.28–9.1) and median LR− was 0.17 (range 0–0.83). The certainty of the evidence was high (GRADE evidence profile).
- Evidence suggests that CSF neutrophils are likely to have moderate to high sensitivity and high specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.4 Parameter 4: CSF mononuclear cells (absolute count or %)

Overall, two studies on CSF mononuclear absolute cell count or percentage were found, including one involving adults and one that did not report the age of the population. Reference standards included a positive CSF culture in one study and a positive CSF culture and clinical signs and symptoms of acute meningitis in the other (Table WA1.2).

- The sensitivity pooled across the two studies (265 participants) was 64.0% (95% CI 19.7–100%, I^2 = 90.4%, P < 0.05). The certainty of the evidence was moderate (GRADE evidence profile).
- The specificity pooled across the two studies (265 participants) was 88.4% (95% CI 79.7–97.1%, I^2 = 74.8%, P < 0.0001). The certainty of evidence was moderate (GRADE evidence profile).
- Data on PPV and NPV were not reported.
- In one study (131 participants), LR+ was 5.1 (95% CI NR) and LR− was 0.18 (95% CI NR). The certainty of evidence was moderate for both outcomes (GRADE evidence profile).
- Data on the AUC were reported in one study (131 participants) and showed an AUC of 0.84 (95% CI 0.77-0.91). The certainty of the evidence was moderate (GRADE evidence profile).

- Evidence suggests that CSF mononuclear cells were likely to have moderate to low sensitivity and moderate to high specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.5.5 Parameter 5: CSF neutrophil-to-lymphocyte ratio

Overall, two studies on CSF neutrophil-to-lymphocyte ratio were found, including one study involving patients of all ages, and another involving children > 1 month of age. The reference standard in the first study was a positive CSF Gram stain, a positive latex agglutination test, positive conventional bacterial cultures or a positive multiplex PCR. The reference standard in the second study was any of the following: positive CSF or blood culture, positive Gram stain, or elevated CSF leukocyte count with other typical CSF abnormalities of neutrophils, glucose and protein (Table WA1.2).

- The sensitivity pooled across the two studies (4687 participants) was 86.8% (95% CI 81.7–91.9% I^2 = 70.0%, P < 0.0001). The certainty of evidence was high (GRADE evidence profile).
- The specificity pooled across the two studies (4687 participants) was 78.1% (95% CI 73.9–82.3%, I^2 =59.2%, P < 0.0001). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were not reported.
- LR+ was reported in two studies (4687 participants) and was 4.16 (95% CI NR) and 3.60 (95% CI NR), respectively, with an overall high certainty of evidence. LR– was reported in two studies (4687 participants) and was 0.19 (95% CI NR) and 0.13 (95% CI NR), respectively, with a overall high certainty of evidence (GRADE evidence profile).
- Data on the AUC were reported in two studies (4687 participants), with AUCs of 0.90 (95% CI 0.88–0.90) and 0.91 (95% CI 0.87–0.95) with an overall high certainty of evidence.
- Evidence suggests that the CSF neutrophil-to-lymphocyte ratio has moderate to high sensitivity and moderate specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.6 Parameter 6: CSF glucose

A total of 10 studies on CSF glucose were found, with five involving children, one involving adults and two studies involving patients of all ages (while two studies did not report the age category). Reference standards varied greatly between studies, including combinations of the following: positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive PCR test for bacterial and/or viral pathogens, ICD-10 code-based and clinical diagnosis (Table WA1.2).

- The sensitivity pooled across eight studies (3336 participants) was 66% (95% CI 52–79%, I^2 = 95%, P < 0.01). The certainty of the evidence was low (GRADE evidence profile).
- The specificity pooled across eight studies (3336 participants) was 85% (95% CI 72–98%, I^2 = 97%, P < 0.01). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in one study that was conducted in Egypt in 2014 and included 623 participants of all ages with acute meningitis. This study reported a PPV of 89% (95% CI NR) and NPV of 37% (95% CI NR). The certainty of the evidence was moderate for both PPV and NPV (GRADE evidence profile).
- Median LR+ across eight studies (3336 participants) was 10.49 (range 1.13–16.63) with high certainty of evidence. Median LR− across eight studies (3336 participants) was 0.38 (range 0.16–0.83) with high certainty of evidence.
- Data on AUC were reported in four studies (1690 participants), with median AUC of 0.93 (range 0.23–0.97). The certainty of the evidence was low (GRADE evidence profile).
- Evidence suggests that CSF glucose level may have moderate to low sensitivity and it has moderate to high specificity for diagnosis of acute bacterial meningitis in a population of patients with suspected acute meningitis.

3.2.7 Parameter 7: CSF/blood glucose ratio

A total of eight studies on CSF/blood glucose ratio were found, with two studies involving children, four involving adults, and one involving patients of all ages (while one study did not report the age category). Reference standards varied between studies, including combinations of the following: positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive PCR tests for bacterial and/or viral pathogens, ICD-10 code-based and clinical diagnosis (Table WA1.2).

- The sensitivity pooled across six studies (488 participants) was 88% (95% CI 83–93, I^2 = 4%, P = 0.39). The certainty of the evidence was high (GRADE evidence profile).
- The specificity pooled across six studies (488 participants) was 78% (95% CI 52–100%, I^2 = 97%, P < 0.01). The certainty of the evidence was moderate (GRADE evidence profile).
- Data on PPV and NPV were not reported.
- Median LR+ across six studies (488 participants) was 5 (range 1.07–60) with an overall high certainty of evidence. Median LR− across six studies (488 participants) was 0.21 (range 0.08–0.60) with an overall high certainty of evidence.

- Median AUC across five studies (463 participants) was 0.81 (range 0.54–0.92) with an overall moderate certainty of the evidence (GRADE evidence profile).
- Evidence suggests that a low CSF/blood ratio has moderate to high sensitivity, and it is likely to have moderate specificity for diagnosis of acute bacterial meningitis in a population of patients with suspected acute meningitis.

3.2.8 Parameter 8: CSF total protein

A total of 16 studies were found, with seven studies involving children, five involving adults and two involving patients of all ages (while two studies did not report the age category). Reference standards varied greatly between studies, including combinations of the following: positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive PCR tests for bacterial and/or viral pathogens, ICD-10 code-based and clinical diagnosis (Table WA1.2).

- The sensitivity pooled across 12 studies (1974 participants) was 86% (95% CI 80–92%, I^2 = 84%, P < 0.01). The certainty of evidence was high (GRADE evidence profile).
- The specificity pooled across 12 studies (1974 participants) was 79% (95% CI 70–88%, I^2 = 95%, P < 0.01). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in one study that was conducted in Egypt in 2014 and included 623 participants of all ages with acute meningitis. The PPV was 84% (95% CI NR) and NPV was 60% (95% CI NR). The overall certainty of the evidence was moderate (GRADE evidence profile).
- Median LR+ across 12 studies (1974 participants) was 3.75 (range 1.65–16.95), with overall high certainty of evidence. Median LR− across 12 studies (1974 participants) was 0.18 (range 0–0.54), with overall high certainty of the evidence.
- Median AUC across seven studies (2022 participants) was 0.89 (range 0.77–1.00), with an overall high certainty of evidence (GRADE evidence profile).
- Evidence suggests CSF protein has moderate to high sensitivity and moderate specificity for diagnosis of acute bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.9 Parameter 9: CSF lactate

A total of seven studies were found, with four studies involving children and two involving adults (while one study did not report the age category). Reference standards varied between studies, including combinations of the following: positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive PCR tests for bacterial and/or viral pathogens, and clinical diagnosis (Table WA1.2).

- The sensitivity pooled across six studies (1166 participants) was 94% (95% CI 91–98%, I^2 = 0.0%, P < 0.0001). The certainty of the evidence was high (GRADE evidence profile).
- The specificity pooled across six studies (1166 participants) was 86% (95% CI 74–98%, I^2 = 98%, P < 0.0001). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in one study conducted in Spain in 2017, including 154 participants aged >15 years diagnosed with acute meningitis at the emergency department. The PPV was 91% (95% CI 79–98%) and NPV was 86% (95% CI 72–97%), with overall moderate certainty of evidence (GRADE evidence profile).
- Median LR+ across six studies (1166 participants) was 5.53 (range 2.54–10.1) with an overall high certainty of evidence. Median LR− across six studies (1166 participants) was 0.05 (range 0–0.13) with an overall high certainty of evidence.
- Median AUC across four studies (2008 participants) was 0.95 (range 0.94–0.98), with an overall high certainty of evidence (GRADE evidence profile).
- Evidence suggests that CSF lactate has moderate to high sensitivity and moderate specificity for diagnosis of acute bacterial meningitis in a population of patients with acute suspected meningitis.
- Additional evidence from a meta-analysis performed on the diagnostic use of CSF lactate in the differentiation of bacterial meningitis versus other types of meningitis showed high diagnostic accuracy of CSF lactate. This meta-analysis included 33 studies with 1885 patients (adults and children). This meta-analysis showed a pooled sensitivity of 93% (95% CI 89–96%), pooled specificity of 96% (95% CI 93–98%), pooled LR+ of 22.9 (95% CI 12.6–41.9) and a pooled LR− of 0.07 (95% CI 0.05–0.12). In patients receiving antibiotic treatment prior to lumbar puncture, CSF lactate concentration had a lower sensitivity (49%) compared to those not receiving antibiotic treatment before lumbar puncture (98%). As a result, the conclusions across the two bodies of evidence (previous meta-analysis and current meta-analysis) are consistent and show excellent sensitivity and good specificity of CSF lactate for diagnosing acute bacterial meningitis in a population of patients with acute suspected meningitis.

3.3 GRADE evidence profile

Table WA1.2 presents the GRADE evidence profiles for this review, by parameter.

Table WA1.2a GRADE evidence profiles – Parameter 1: CSF Gram stain

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	6	1962	NA	76 (57–100)	85 (95% CI 55–96, I^2 = 99%, P < 0.0001)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Spec, %	1	131	NA	99% (95% CI NR)	Not serious	Not serious	Serious [a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	NA	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
NPV, %	NA	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
LR+	1	131	NA	91.2 (95% CI NR)	NA	Not serious	Serious [a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	1	131	NA	0.09 (95% CI NR)	NA	Not serious	Serious [a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC	1	131	NA	0.95 (95% CI 0.9–1.0)	NA	Not serious	Serious [a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate	

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

[a] Number of studies is small.

Table WA1.2b GRADE evidence profiles – Parameter 2: CSF leukocyte count

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	12	1634	10–992 cells/mm^3	79 (55–82)	77% (95% CI 74–81%, I^2 = 26%, P = 0.19)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Spec, %	12	1634	10–992 cells/mm^3	88 (59–100)	83% (95% CI 75–92%, I^2 = 93%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
NPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
LR+	12	1634	10–992 cells/mm^3	6.39 (1.45–64)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
LR−	12	1634	10–992 cells/mm^3	0.28 (0.21–0.73)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	8	2332	NA	0.86 (0.56–0.94)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Table WA1.2c GRADE evidence profiles – Parameter 3: CSF neutrophils (absolute count or %)

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	10	6013	64–299 cells/mm^3, 50—85%	87 (27–100)	82% (95% CI 70–94%, I^2 = 97%, P < 0.01)	Not serious	Not serious	Serious[a]	Not serious	Not serious	⊕⊕⊕◯ Moderate
Spec, %	10	6013	64-299 cells/mm^3, 50–85%	86 (61–100)	84% (95% CI 77–90%, I^2 = 89%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	2	1341	50%, 82 cells/mm^3	89 (95% CI NR), 72% (95% CI 66–78)	NA	Not serious	Serious[b]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	2	1341	50%, 82 cells/mm^3	48 (95% CI NR), 97% (95% CI 96–99)	NA	Not serious	Serious[b]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	10	6013	64–299 cells/mm^3, 50–85%	3.58 (2.28–9.1)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
LR−	10	6013	64–299 cells/mm^3, 50–85%	0.17 (0–0.83)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	4	4853	NA	0.90 (0.66–0.97)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

[a] One study showed unexplained exceptionally low results.

[b] Number of studies is small.

Table WA1.2d GRADE evidence profiles – Parameter 4: CSF mononuclear cells (absolute count or %)

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	2	265	320 cells/mm^3, 20%	40 (95% CI NR), 85 (95% CI NR)	64% (95% CI 20–100%, I^2 = 90%, P = < 0.05)	Not serious	Very serious[a,b]	NA	Not serious	Not serious	⊕⊕◯◯ Low
Spec, %	2	265	320 cells/mm^3, 20%	83 (95% CI NR), 92 (95% CI NR)	88.4% (95% CI 80–97%, I^2 = 75%, P < 0.0001)	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
NPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
LR+	1	131	20%	5.1 (95% CI NR)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR-	1	131	20%	0.18 (95% CI NR)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
AUC	1	131	NA	0.84 (95% CI 0.77–0.91)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

[a] Total cumulative study population is low; [b] number of studies is small.

Table WA1.2e GRADE evidence profiles – Parameter 5: CSF neutrophil-to-lymphocyte ratio

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	2	4687	0.68, 2	85 (95% CI NR), 90 (95% CI NR)	87% (95% CI 82–92% I^2 = 70.0%, *P* < 0.0001)	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
Spec, %	2	4687	0.68, 2	75 (95% CI NR), 80 (95% CI NR)	78.1% (95% CI 74–82%, I^2 = 59%, *P* < 0.0001)	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
NPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
LR+	2	4687	0.68, 2	4.16 (95% CI NR), 3.60 (95% CI NR)	NA	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
LR-	2	4687	0.68, 2	0.19 (95% CI NR), 0.13 (95% CI NR)	NA	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High

AUC	2	4687	NA	0.90 (95% CI 0.88-0.90), 0.91 (95% CI 0.87–0.95)	NA	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Table WA1.2f GRADE evidence profiles – Parameter 6: CSF glucose

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	8	3336	39–196 mg/dl	69 (31-85)	66% (95% CI 52–79%, I^2 = 95%, P < 0.01)	Not serious	Serious[d]	Serious[b]	Not serious	Not serious	⊕⊕◯◯ Low
Spec, %	8	3336	39–196 mg/dl	93 (73-100)	85% (95% CI 72–98%, I^2 = 97%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	1	623	45 mg/dl	89 (95% CI NR)	NA	Not serious	Serious[c]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	1	623	45 mg/dl	37 (95% CI NR)	NA	Not serious	Serious[c]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	8	3336	39–196 mg/dl	10.49 (1.13-16.63)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
LR–	8	3336	39–196 mg/dl	0.38 (0.16–0.83)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	4	1690	NA	0.93 (0.23–0.97)	NA	Serious[a]	Not serious	Serious[b]	Not serious	Not serious	⊕⊕◯◯ Low

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

[b] number of studies is small.

[c] Total cumulative study population is low and number of studies is small.

[d] Wide CI with lower boundary close to 50.

Table WA1.2g GRADE evidence profiles – Parameter 7: CSF-to-blood glucose ratio

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sens, %	6	488	0.33–0.60	88 (78–93)	88% (95% CI 83–93%, I^2 = 4%, P = 0.39)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Spec, %	6	488	0.33–0.60	88 (15–100)	78% (95% CI 52–100%, I^2 = 97%, P < 0.01)	Not serious	Serious[d]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
NPV, %	0	0	NA	NA	NA	NA	NA	NA	NA	Not serious	NA
LR+	6	488	0.33–0.60	5 (1.07–60)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
LR−	6	488	0.33–0.60	0.21 (0.08–0.60)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	5	463	NA	0.81 (0.54–0.92)	NA	Not serious	Not serious	Serious[b]	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA: not applicable; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

[a] High risk of bias in 2/4 studies.

[b] One study showed unexplained exceptionally low results.

[c] Total cumulative study population is low and number of studies is small.
[d] Wide CI with lower boundary close to 50.

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Appendix WB.I.A1

Search strategy used to identify primary studies

Table WB.I.A1.1 Database: Embase (Elsevier) (https://www.embase.com/#advancedSearch/), searched on 13 February 2024

2. (a). Diagnostic performance of cerebrospinal fluid molecular testing (Singleplex PCR)

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Abbreviations

AM	aseptic meningitis
AUC	area under the receiver-operating-characteristics curve
BM	bacterial meningitis
CI	confidence interval
CNS	central nervous system
CSF	cerebrospinal fluid
EV	enterovirus
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
GRADE	Grading of Recommendations Assessment, Development and Evaluation
NR	not reported
PCR	polymerase chain reaction
PICO	population, intervention, comparator and outcome(s)
VM	viral meningitis
WBC	white blood cell

1. Background

Acute meningitis is a life-threatening medical emergency that needs timely and accurate diagnosis if appropriate patient management is to be initiated. Meningitis can be caused by bacteria, viruses, fungi or parasites. Prompt initiation of appropriate antibiotics is needed to prevent severe complications and reduce mortality if the cause is bacterial. Typical clinical characteristics, such as headache, neck stiffness, fever, and an altered mental state are only present in 40–50% of patients with suspected meningitis, often posing diagnostic dilemmas *(1-3)*. Lumbar puncture is necessary to obtain cerebrospinal fluid (CSF) and perform CSF examination *(2)*. Polymerase chain reaction (PCR) testing of CSF has emerged as a quick and highly specific diagnostic tool for identifying specific bacterial and viral pathogens responsible for meningitis. Where available, molecular testing allows for pathogen identification (both bacteria and viruses) and is often used as the confirmatory test for bacterial meningitis diagnosis (alongside culture) *(2)*. The diagnostic accuracy of PCR in cerebrospinal fluid has been primarily studied for *S. pneumoniae*, *N. meningitidis* and *H. influenzae*, and was found to be nearly 95–100% in the case of culture-positive bacterial meningitis *(3)*. The increasing availability and use of nucleic acid amplification tests have revolutionized the diagnostic approach to meningitis. Nonetheless, in spite of significant advancements in test design, some limitations in diagnostic accuracy remain, highlighting the importance of having evidence-based recommendations on the of molecular tests in clinical settings.

As part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, this systematic review was conducted in conjunction with two other systematic reviews addressing the research questions on the diagnostic performance of initial CSF investigations and peripheral blood markers (reports 1 and 3 in this web annex). A unified search strategy was developed for this purpose. Here in this report, only the results specifically related to CSF PCR are presented.

2. Methodology

CSF PCR for the diagnosis of bacterial meningitis was addressed in the review carried out by van de Beek et al. for *Nature Reviews Disease Primers (4)*, and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline by van de Beek et al. *(5)*, both published in 2016. Since these reviews were of high quality and covered the literature on acute bacterial meningitis up to 2014, this report summarizes the data on initial CSF testing that were systematically searched and reviewed from 2014 onwards. Additionally, the evidence from before 2014 was reviewed and graded, largely on the basis of reviews conducted as part of the ESCMID guideline *(5)*.

2.1 Research question and study design

What is the diagnostic performance of CSF PCR in cases of suspected acute meningitis?

Population: Suspected cases of acute meningitis (adults and children > 1 month of age).

Index test/Intervention: CSF PCR

Reference standard/comparator: Consensus diagnosis[3]

Outcomes:

Critical outcomes (as prioritized by the Guideline Development Group):

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Likelihood ratios

Other outcomes: Area under the receiver-operating-characteristics curve (AUC)

Study designs: Cross-sectional and case-controlled studies. Case reports or case series were excluded.

2.2 Eligible studies

Published language: Studies published in languages English, French, German, Italian, Portuguese and Spanish were considered for inclusion. For studies in other languages, existing networks within WHO and Cochrane were used for support with screening and/or translation. Studies in Chinese and Korean were excluded.

Exclusion criteria: The following groups of patients were excluded:

[3] Consensus diagnosis defined as clinical characteristics (including peripheral white blood cell count, C-reactive protein, procalcitonin), blood culture, CSF culture and/or CSF PCR.

- those with tuberculous meningitis;
- those with hospital-acquired, nosocomial and health-care-associated meningitis;
- those with subacute and chronic meningitis;
- newborns (0–28 days) with meningitis;
- those with non-infectious meningitis (e.g. meningitis caused by drugs, malignancy, autoimmune diseases).

Subgroups: None considered.

2.3 Search strategy

One comprehensive search strategy was developed to identify relevant studies for three research questions – addressing the diagnostic performance of initial CSF investigations, CSF PCR and peripheral blood tests (covered in this report and reports 1 and 3 in this web annex). The following databases were searched for articles published up to the date of the literature search: PubMed, Embase and the Cochrane Library.

The exact search terms can be found in Appendix 1. Search strategy used to identify .

The search was conducted in English language on 26 January 2024.

2.4 Selection of studies

The authors independently screened all titles and abstracts (NSG and MCB) and assessed their eligibility according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion. The full text of articles found to be potentially relevant on the basis of their titles and abstracts was retrieved and examined in light of the same inclusion criteria, by the two authors independently. Any disagreements regarding the results of the full-text screening were resolved by discussion.

Rayyan was used for reference screening, title, abstract and full-text selection.

2.5 Data extraction and management

Data extraction was performed by one author (NSG) and any uncertainties were discussed with the second author (MCB). The following categories of data were extracted:

- publication year and author(s);
- study type and setting;
- population, intervention, comparator and outcome(s);
- Characteristics of patients included (sex, age category, total no. of cases, total no. of non-cases, definitions of disease categories);
- outcomes and results.

2.6 Assessment of risk of bias in studies included in the review

The quality of the studies included has been assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies, by one author and will be checked by the other. The specific categories offered by the QUADAS-2 tool were tailored to the research questions.

2.7 Data synthesis

Where feasible (with at least two contributing studies and homogeneous data), meta-analyses were conducted, using a random-effects model for proportions to provide pooled estimates for sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). All meta-analyses were conducted using the R software packages "meta" and "metafor". Where meta-analysis was not feasible, ranges and medians were provided to summarize the findings. Data on NPV and PPV were extracted and included in the meta-analysis of non-case control studies only, because these measures are considered highly dependent on prevalence. If multiple cut-offs were reported by one article, one cut-off was included for meta-analysis to prevent dependent results. The choice of this cut-off was based on clinical relevance.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was tailored to the research questions. The overall certainty of evidence was downgraded for imprecision if the confidence interval (CI) of the pooled estimate results was very wide, or in cases of a lower CI boundary (below 60%).

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No sub-group analysis was conducted.

2.10 Sensitivity analysis

No sensitivity analysis was conducted.

2.11 Deviations from the review protocol

There were no deviations from the protocol.

3. Results

3.1 Studies identified by the search process

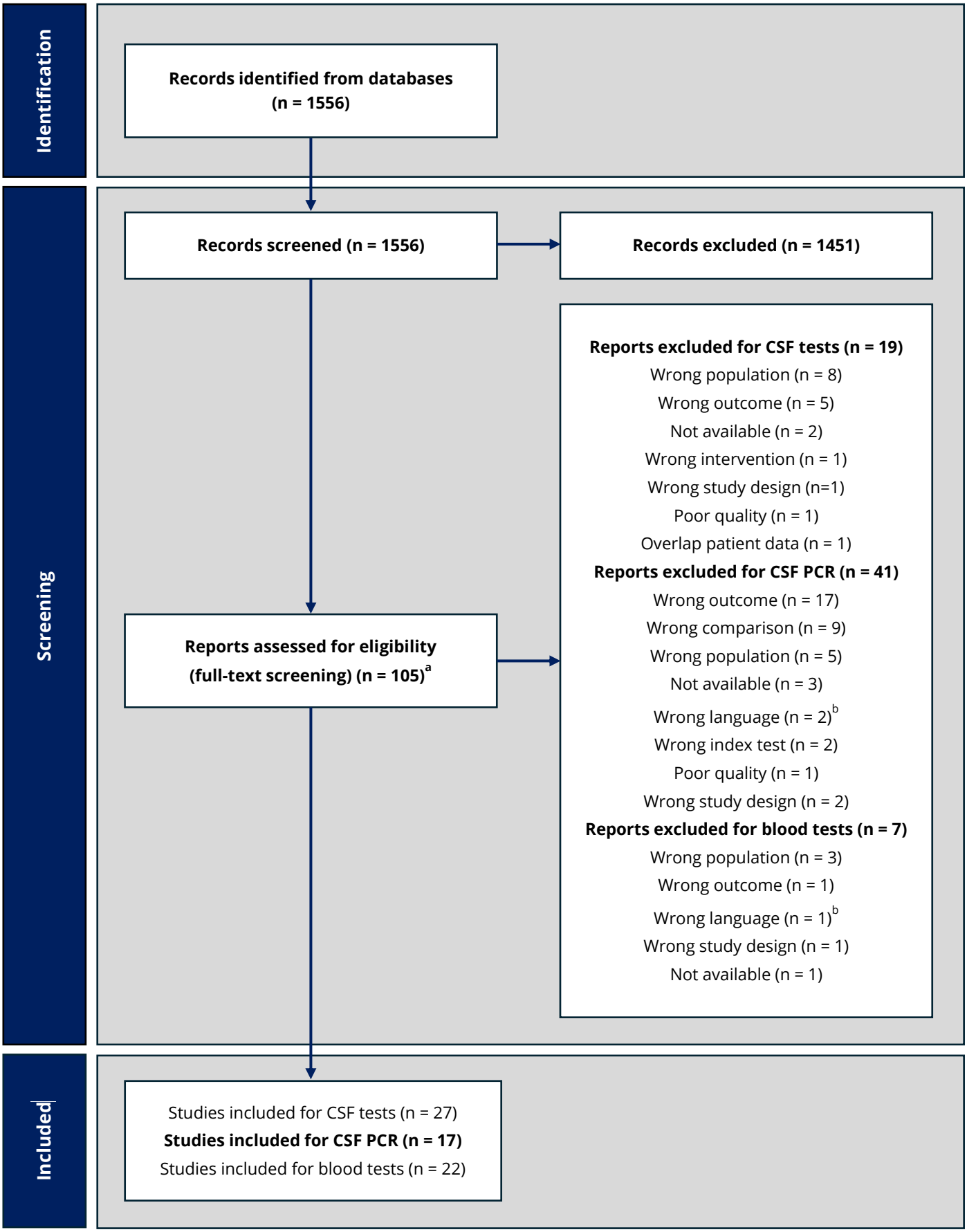
Figure WA2a.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review. A total of 1556 records were retrieved for the three research questions, of which 1451 were excluded on the basis of their title and abstract. The search strategy is provided in Appendix 1.

Overall, 105 articles were screened for full-text eligibility. For CSF PCR, 41 studies were excluded *(6-46)* and a total of 17 studies were included *(47-63)*.

3.1.1 Studies included in the review

The characteristics of the included studies are presented in Table WA2a.1, by intervention.

Fig. WA2a.1 PRISMA flow diagram for the systematic review



[a] Some studies were included for more than one research question; therefore, the number of reports excluded per research question is not the same as the total number of reports screened for full text minus all studies included per research question. [b] Studies in Chinese (n = 2) and Korean (n = 1) were excluded.

Table WA2a.1a Characteristics of studies included in the GRADE evidence profiles – Intervention: CSF PCR enterovirus

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Buxbaum (2011), Germany *(49)*	Retrospective cohort	Low	Children aged 1 month–17 years with clinically suspected VM	45 (19, 26)	Positive CSF viral culture	Sens, Spec, PPV, NPV, LR+, LR−
Carroll (2000), USA *(50)*	Prospective cohort	Low	Patients of all ages in which CSF samples submitted for EV detection were evaluated by both culture and PCR EV	461 (77, 384)	Positive CSF viral culture or abnormal CSF parameters (WBC > 10 cells/mm^3, glucose < 40 mg/dl, protein > 40 mg/dl) and a clinical presentation consistent with meningitis or encephalitis	Sens, Spec, PPV, NPV, LR+, LR−
De Crom (2012), the Kingdom of the Netherlands *(51)*	Retrospective cohort	Unclear	Patients of all ages with suspected meningitis	116 (10, 106)	Positive CSF viral culture	Sens, Spec, PPV, NPV, LR+, LR−
Furione (1993), Italy *(52)*	NR	High	Patients of all ages with AM[a]	32 (10, 22)	Positive CSF viral culture	Sens, Spec, LR+, LR−
Guney (1999), Türkiye *(53)*	Retrospective cohort	Low	Children with suspected AM based on clinical signs and pleocytosis	68 (36, 32)	Positive CSF viral culture	Sens, Spec, PPV, NPV, LR+, LR−
Hadziyannis (2021), USA *(54)*	NR	High	Patients with possible VM	38 (9, 29)	Positive CSF viral culture	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Jacques (2005), France *(55)*	Retrospective cohort	Low	Patients of all ages hospitalized with AM, negative CSF culture and Gram stain and typical CSF abnormalities for AM	54 (28, 26)	Positive CSF viral culture	Sens, Spec, LR+, LR−
Rotbart (1990), USA *(59)*	Prospective cohort	Low	Children in whom a lumbar puncture was performed	20 (9, 11)	Positive CSF viral culture	Sens, Spec, LR+, LR−
Rotbart (1994), USA *(60)*	NR	High	NR	114 (35, 79)	Positive CSF viral culture and clinical diagnosis of EV meningitis	Sens, Spec, LR+, LR−
Tanel (1996), USA *(61)*	Prospective cohort	Low	Children who underwent a lumbar puncture for evaluation of possible meningitis	81 (9, 72)	Positive CSF viral culture or positive culture for EV at any site (CSF, throat, rectum)	Sens, Spec, PPV, NPV, LR+, LR−
Thoren (2002), Sweden *(62)*	NR	Unclear	Patients of all ages with suspected VM	27 (6, 21)	Combination of CSF abnormalities (not specified) with at least one positive test (CSF culture, serology, viral culture throat, viral culture stool)	Sens, Spec, LR+, LR−
Verstrepen (2002), Belgium *(63)*	Retrospective cohort	High	Patients of all ages with suspected viral meningitis	251 (51, 149)	Clinical diagnosis of viral or aseptic meningitis based on	Sens, Spec, LR+, LR−

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
					patient reports (not further specified)	

AM: aseptic meningitis; BM: bacterial meningitis; CSF: cerebrospinal fluid; EV: enterovirus; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio, LR+: positive likelihood ratio; NR: not reported; PCR: polymerase chain reaction; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; VM: viral meningitis; WBC: white blood cell count.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA2a.1b Characteristics of studies included in the GRADE evidence profiles – Intervention: CSF PCR *Borrelia burgdorferi*

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Avery (2005), USA *(48)*	Retrospective cohort	Low	Children aged > 2 years in which Lyme serology and Lyme CSF PCR was performed during the same hospital encounter, with documented meningitis (CSF WBC > 8 cells/mm^3) and no positive CSF Gram stain	108 (20, 88)	Patients with meningitis who met the Centers for Disease Control and Prevention criteria for Lyme disease (erythema migrans observed by a physician and/or positive serology including Western blot confirmation)	Sens, Spec, PPV, NPV, LR+, LR−

CSF: cerebrospinal fluid; NPV: negative predictive value; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PCR: polymerase chain reaction; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; WBC: white blood cell count.

Table WA2a.1c Characteristics of studies included in the GRADE evidence profiles – Intervention: CSF PCR *Streptococcus pneumoniae*

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Alqayoudhi (2017), Ireland *(47)*	Retrospective cohort	Low	Children aged < 16 years who had a CSF sample tested for *Streptococcus pneumonia*	2006 (16, 1990)	Positive CSF culture	Sens, Spec, PPV, NPV, LR+, LR−, AUC
Parent du Châtelet (2005), France *(58)*	Retrospective and prospective cohort	Low	Patients of all ages with a clinical definition of meningitis	434 (34, 400)	Positive CSF culture	Sens, Spec, PPV, NPV, LR+, LR−

SF: cerebrospinal fluid; NPV: negative predictive value; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PCR: polymerase chain reaction; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; WBC: white blood cell count.

Table WA2a.1d Characteristics of studies included in the GRADE evidence profiles – Intervention: CSF PCR *Neisseria meningitidis*

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Ni (1992), United Kingdom of Great Britain and Northern Ireland *(57)*	not reported	High	Patients of all ages with proven meningococcal meningitis	50 (11, 39)	Positive CSF culture or positive Gram stain	Sens, Spec, PPV, NPV, LR+, LR−
Parent du Châtelet (2005), France *(58)*	Retrospective and prospective cohort	Low	Patients of all ages with a clinical definition of meningitis	434 (34, 400)	Positive CSF culture	Sens, Spec, PPV, NPV, LR+, LR−

CSF: cerebrospinal fluid; CSF: cerebrospinal fluid; LR–: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Table WA2a.1e Characteristics of studies included in the GRADE evidence profiles – Intervention: CSF PCR *Haemophilus influenzae* type b

Lead author (Year), Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Parent du Châtelet (2005), France *(58)*	Retrospective and prospective cohort	Low	Patients of all ages with a clinical definition of meningitis	434 (34, 400)	Positive CSF culture	Sens, Spec, PPV, NPV, LR+, LR−

CSF: cerebrospinal fluid; CSF: cerebrospinal fluid; LR–: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Table WA2a.1f Characteristics of studies included in the GRADE evidence profiles – Intervention: CSF PCR *Listeria monocytogenes*

Lead author (Year) Country	Study design	Overall risk of bias	Population	Sample size (cases, non-cases)	Reference standard	Outcomes available
Le Monnier (2011), France *(56)*	Prospective cohort	Low	Patients of all ages suspected of having CNS listeriosis	24 (9, 15)	Positive CSF culture	Sens, Spec, PPV, NPV, LR+, LR−

CSF: cerebrospinal fluid; CNS: central nervous system; CSF: cerebrospinal fluid; LR–: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

3.1.2 Studies excluded from the review

The following studies were excluded from the review: Commun Dis Rep CDR Wkly *(6),* Ahmet, Stanier *(7),* Almeida-Silva, Almeida *(8),* Arafa, Gabr *(9),* Benschop, Molenkamp *(10),* Bergström *(11),* Brisbarre, Plumet *(12),* Chesky, Scalco *(13),* Chye, Lin *(14),* Cordey, Sahli *(15),* Fernández-San José, Moraga-Llop *(16),* Fevola, Kuivanen *(17),* Franzen-Röhl, Tiveljung-Lindell *(18),* Glimåker, Johansson *(19),* Guiducci, Moriondo *(20),* Haag, Locher *(21),* Hasanuzzaman, Saha *(22),* Hayes, Nguyen *(23),* Hong, Kang *(24),* Hymas, Aldous *(25),* Kost, Rogers *(26),* Kupila, Vuorinen *(27),* Law and Tsang *(28),* Leitch, Harvala *(29),* Li, Chen *(30),* Lina, Pozzetto *(31),* Metzger, Terletskaia-Ladwig *(32),* Moayedi, Nejatizadeh *(33),* Obaro *(34),* Pedersen, Kragh *(35),* Pena, Bolaños *(36),* Petitjean, Vabret *(37),* Pillet, Billaud *(38),* Poggio, Rodriguez *(39),* Pozo, Casas *(40),* Rabenau, Clarici *(41),* Schlesinger, Sawyer *(42),* Sears, Qvarnstrom *(43),* Song, Kim *(44),* Tuerlinckx and Bodart *(45),* Usuku, Noguchi *(46)*.

3.2 Narrative description of diagnostic performance evidence

3.2.1 Parameter 1: CSF PCR enterovirus

Overall, 12 studies were found, including four studies involving children, six studies involving patients of all ages and one study involving adults (two studies did not report the age category). The reference standard was a positive viral CSF culture in six studies, and a positive viral CSF culture in combination with one of the following in the other six studies: abnormal CSF parameters (cell count, protein, glucose), positive serology, clinical symptoms, serum antibodies or a positive PCR in throat or rectum samples. One study used clinical diagnosis based on patients' reports only as a reference standard.

- The sensitivity pooled across 12 studies (1256 participants) was 89% (95% CI 81–96, I^2 = 73%, $P < 0.01$). The overall certainty of the evidence was high.
- The specificity pooled across 12 studies (1256 participants) was 79% (95% CI 68–91, I^2 = 91%, $P < 0.01$) The overall certainty of the evidence was high.
- Data on PPV and NPV were reported in five studies including patients in 2011 in Germany, in 2000 in the USA, in 2012 in the Kingdom of the Netherlands, in 1999 in Türkiye and in 1994 in the USA. The pooled PPV across five studies (771 participants) was 72% (95% CI 46–97, I^2 = 95%, $P < 0.01$). The overall certainty of the evidence was low. The pooled NPV across five studies (771 participants) was 94 (95% CI 87–100), I^2 = 75%, $P < 0.01$). The overall certainty of the evidence was moderate for NPV.
- Data on LR+ and LR− were reported in 12 studies (1256 participants), with median LR+ of 2.90 (range 1.29–164.33) and median LR− of 0.19 (range 0–0.69). The overall certainty of the evidence was high for LR+ and LR−. Data on the AUC were not reported.

3.2.2 Parameter 2: CSF PCR *Borrelia burgdorferi*

One study was found which included 108 children (aged > 2 years) in which Lyme serology and Lyme CSF PCR were performed, CSF Gram stain was negative and meningitis was documented. The reference standard was the criteria of the United States Centers for Disease Control and Prevention (CDC) for Lyme disease (erythema migrans observed by a physician and/or positive serology including Western blot confirmation).

Sensitivity was 5% (95% CI 0–25), specificity 99% (95% CI 93–99), PPV 50% (95% CI NR), NPV 82% (95% CI NR), LR+ 4.17 (95% CI NR), LR− was 0.96 (95% CI NR) and AUC NR. The certainty of the evidence was moderate for all reported outcomes.

3.2.3 Parameter 3: CSF PCR *Streptococcus pneumoniae*

Two studies were found involving 2006 children (aged < 16 years) who had a CSF sample tested for *Streptococcus pneumoniae* and 434 patients of all ages with a clinical definition of meningitis. The reference standard was a positive CSF culture in both studies.

- The sensitivity pooled across two studies (2440 participants) was 90% (95% CI 70–100, I^2 = 85%, *P* = 0.01). The overall certainty of the evidence was high.
- The specificity pooled across the two studies (2440 participants) was 97% (95% CI 93–100, I^2 = 92%, *P* < 0.01). The overall certainty of the evidence was high.
- Data on PPV and NPV were reported in one study conducted in Ireland in 2007. The PPV was 36% (95% CI 22–52) and the NPV was 100 (95% CI 99–100). The overall certainty of the evidence was low for PPV and moderate for NPV.
- The LR+ reported in the two studies (2440 participants) was 71.1 (95% CI NR) and 15.8 (95% CI NR). The LR− across the two studies (2440 participants) was 0.0 (95% CI NR) and 0.22 (95% CI NR). The overall certainty of the evidence for LR+ and LR− was high.
- Data on AUC were reported in one study and were 0.99 (95% CI 99–100). The overall certainty of the evidence was moderate.

3.2.4 Parameter 4: CSF PCR *Neisseria meningitidis*

Two studies were found involving 50 patients of all ages with proven meningococcal meningitis and 434 patients of all ages with a clinical definition of meningitis. The reference standard was a positive CSF culture/positive Gram stain in one study, and a positive CSF culture in the other.

- The sensitivity pooled across the two studies (484 participants) was 95% (95% CI 91–99, I^2 = 0%, *P* = 0.62). The overall certainty of the evidence was moderate.
- The specificity pooled across two studies (484 participants) was 94% (95% CI 92–97, I^2 = 4%, *P* = 0.31). The overall certainty of the evidence was moderate.

- Data on PPV and NPV were reported in the study conducted in the United Kingdom in 1992 and in the study conducted in France in 2005. The PPV pooled across the two studies (484 participants) was 81% (95% CI 74–88, I^2 = 0%, *P* = 0.41). The NPV pooled across the two studies (484 participants) was 99% (95% CI 98–100, I^2=0%, *P* = 0.57). The overall certainty of the evidence for PPV and NPV was moderate.
- The LR+ reported in the two studies (484 participants) was 19 (95% CI NR) and 9.1 (95% CI NR). The LR− reported in the two studies (484 participants) was 0.05 (95% CI NR) and 0.1 (95% CI NR). The overall certainty of evidence for LR+ and LR− was moderate.
- Data on AUC were not reported.

3.2.5 Parameter 5: CSF PCR *Haemophilus influenzae* type b

One study was found involving 434 patients of all ages with a clinical definition of meningitis. The reference standard was a positive CSF culture.

- The sensitivity was 81% (95% CI NR) and the overall certainty of the evidence was moderate.
- The specificity was 97% (95% CI NR) and the overall certainty of the evidence was moderate.
- Data on NPV and PPV were reported in this one study, conducted in France in 2005. The PPV was 54% (95% CI NR) and the NPV was 99% (95% CI NR). The overall certainty of the evidence for PPV and NPV was moderate.
- The LR+ was 27 (95% CI NR). The overall certainty of the evidence was moderate.
- The LR− was 0.20 (95% CI NR). The overall certainty of the evidence was moderate.
- Data on AUC were not reported.

3.2.6 Parameter 6: CSF PCR *Listeria monocytogenes*

One study was found involving 24 patients of all ages suspected of having central nervous system listeriosis. The reference standard was a positive CSF culture.

- The sensitivity was 100% (95% CI NR) and the overall certainty of the evidence was moderate.
- The specificity was 67% (95% CI NR) and the overall certainty of the evidence was moderate.
- Data on NPV and PPV were reported in this one study, conducted in France in 2011. The PPV was 64% (95% CI NR) and the NPV was 100% (95% CI NR). The overall certainty of the evidence was low for PPV and moderate for NPV.
- The LR+ was 3.03 (95% CI NR). The overall certainty of the evidence was moderate.

- The LR− was 0 (95% CI NR). The overall certainty of the evidence was moderate.
- Data on AUC were not reported.

3.3 GRADE evidence profiles

Table WA2a.2 presents the GRADE evidence profiles for this review, by parameter.

Table WA2a.2a GRADE evidence profiles – Parameter: CSF PCR enterovirus

Summary of evidence					Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	12	1256	85 (57–100)	89 (95% CI 81–96, I^2 = 73%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Specificity, %	12	1256	76 (48–100)	79 (95% CI 68–91, I^2 = 91%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	5	771	74 (29–100)	72 (95% CI 46–97, I^2 = 95%, P < 0.01)	Not serious	Serious[a]	Serious[a]	Not serious	Not serious	⊕⊕◯◯ Low
NPV, %	5	771	97 (70–99)	94 (95% CI 87–100), I^2 = 75%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High

LR+	12	1256	2.90 (1.29–164.33)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
LR−	12	1256	0.19 (0–0.69)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV: positive predictive value.

[a] Wide confidence interval and lower boundary < 60%.

[b] One study showed unexplained exceptionally low results.

Table WA2a.2b GRADE evidence profiles – Parameter: CSF PCR *Borrelia burgdorferi*

Summary of evidence					Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	1	108	5 (95% CI 0–25)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
Specificity, %	1	108	99 (95% CI 93–99)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	1	108	50 (95% CI NR)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	1	108	82 (95% CI NR)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	1	108	4.17 (95% CI NR)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	1	108	0.96 (95% CI NR)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
AUC	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC: area-under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV: positive predictive value.

[a] Total cumulative study population is low and number of studies is small.

Table WA2a.2c GRADE evidence profiles – Parameter: CSF PCR *Streptococcus pneumoniae*

Summary of evidence					Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	2	2440	100 (95% CI 79–100), 79% (95% CI NR)	90 (95% CI 70–100, I^2 = 85%, P = 0.01)	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
Specificity, %	2	2440	99 (95% CI 98–99), 94% (95% CI NR)	97 (95% CI 93–100, I^2 = 92%, P < 0.01)	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	1	2006	36 (95% CI 22–52)	NA	Not serious	Serious[a,b]	NA	Not serious	Not serious	⊕⊕◯◯ Low
NPV, %	1	2006	100 (95% CI 99–100)	NA	Not serious	Serious[a]	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	2	2440	71.1 (95% CI NR), 15.8 (95% CI NR)	NA	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
LR−	2	2440	0.0 (95% CI NR), 0.22	NA	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	1	2006	0.99 (95% CI 99–100)	NA	Not serious	Not serious	NA	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV: positive predictive value.

[a] Total number of studies is small.

[b] Lower boundary of confidence interval < 60%.

Table WA2a.2d GRADE evidence profiles – Parameter: CSF PCR *Neisseria meningitidis*

Summary of evidence					Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	2	484	95 (95% CI NR), 91 (95% CI NR)	95 (95% CI 91–99, I^2 = 0%, *P* = 0.62)	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Specificity, %	2	484	95 (95% CI NR), 90 (95% CI NR)	94 (95% CI 92–97, I^2 = 4%, *P* = 0.31)	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	2	484	82 (95% CI NR), 71 (95% CI NR)	81 (95% CI 74–88, I^2 = 0%, *P* = 0.41)	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	2	484	99 (95% CI NR), 97 (95% CI NR)	99 (95% CI 98–100, I^2 = 0%, *P* = 0.57)	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	2	484	19 (95% CI NR), 9.1 (95% CI NR)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	2	484	0.05 (95% CI NR), 0.1 (95% CI NR)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC: area-under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV: positive predictive value.

[a] High risk of bias in 1 or 2 studies.

Table WA2a.2e GRADE evidence profiles – Parameter: CSF PCR *Haemophilus influenzae* type b

Summary of evidence					Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	1	434	81 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Specificity, %	1	434	97 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	1	434	54 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	1	434	99 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	1	434	27 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	1	434	0.20 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
AUC	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV: positive predictive value.

[a] Total number of studies is small.

Table WA2a.2f GRADE evidence profiles – Parameter: CSF PCR *Listeria monocytogenes*

Summary of evidence					Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	1	24	100 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Specificity, %	1	24	67 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
PPV, %	1	24	64 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
NPV, %	1	24	100 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	1	24	3.03 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	1	24	0 (95% CI NR)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
AUC	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC: area under the receiver-operating-characteristics curve; CI: confidence interval; CSF: cerebrospinal fluid; NA: not applicable; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV = positive predictive value.

[a] Total cumulative study population is low and number of studies is small.

3.4 Additional evidence not reported in GRADE evidence profiles

Additional evidence from reviews from the ESCMID guidelines summarizing evidence in the period up to 2014 are presented in section 3.2.

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Appendix 1. Search strategy used to identify primary studies

This search covers three research questions, as explained in section 2.3.

Table WA2.A1.1 Database: Ovid MEDLINE, 1946 to 26 January 2024

No.	Searches	Results
1	meningiti*.ti,ab,kf. or exp meningitis/	90 289
2	Polymerase Chain Reaction/	250 656
3	(((DNA or RNA or nucleic-acid or gene) adj2 amplification) or PCR or "polymerase chain reaction" or ddpcr or qpcr or RT-PCR or rtpcr or NAT).ti,ab,kf.	854 020
4	2 or 3	947 412
5	C-Reactive Protein/ or Procalcitonin/ or exp Leukocyte Count/	156 743
6	((c-reactive adj protein) or crp or wbc or (white-blood adj cell) or procalcitonin or leukocyte* or neutrophil* or lymphocyte* or monocyte*).ti,ab,kf.	866 569
7	5 or 6	926 367
8	exp Bacterial Typing Techniques/ or gram-negative bacteria/ or gram-positive bacteria/ or exp Leukocytes/ or exp Leukocyte Count/ or Glucose/ or exp Lactates/ or Proteins/ or exp Cerebrospinal Fluid Proteins/ or exp Albumins/ or Cell Culture Techniques/ or exp Virus Cultivation/	1 666 250
9	((gram adj2 stain*) or ((viral or virus) adj3 (cultivation* or culture* or plaque)) or leukocyt* or neutrophil* or lymphocyte* or monocyte* or glucose or lactate* or protein* or albumin* or culture).ti,ab,kf.	5 335 465
10	8 or 9	5 953 596
11	Spinal Puncture/ or exp Cerebrospinal Fluid/	25 691
12	(((lumbar or spinal or cerebrospinal) adj3 (fluid or puncture or tap)) or csf).ti,ab,kf.	184 831
13	11 or 12	191 328
14	10 and 13	69 651
15	4 or 7 or 14	1 860 585

16	1 and 15	14 752
17	"sensitivity and specificity"/ or "mass screening"/ or "reference values"/ or "false positive reactions"/ or "false negative reactions"/ or (specificit* or screening or false positive* or false negative* or accuracy or predictive value* or reference value* or roc* or likelihood ratio*).tw.	2 308 396
18	16 and 17	2 332
19	exp animals/ not humans/	5 190 821
20	18 not 19	2 250
21	exp Meningitis, Bacterial/	25 915
22	(((bacterial or meningococcal or pneumococcal or Neisseria or meningitides or Streptococcus or pneumoniae or Haemophilus or Hib or influenzae or Listeria or monocytogenes or Escherichia or coli or agalactiae or pyogenes or Staphylococcus or aureus or Cryptococcus or neoformans) adj5 meningiti*) or (meningococcal adj2 disease)).ti,ab.	26 122
23	21 or 22	40 727
24	4 or 14	1 011 671
25	23 and 24	5 800
26	17 and 25	1 219
27	limit 26 to yr="1946 - 2013"	747
28	20 not 27	1 526

2. (b). Diagnostic performance of cerebrospinal fluid molecular testing (Multiplex PCR)

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Abbreviations

CI	confidence interval
CSF	cerebrospinal fluid
DTA	differential thermal analysis
FAME	FilmArray meningitis/encephalitis
GBS	Group B streptococcus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IQR	interquartile range
NICE	National Institute for Health and Care Excellence
PCR	polymerase chain reaction
WHO	World Health Organization

1. Background

Acute meningitis is a life-threatening medical emergency that needs timely and accurate diagnosis if appropriate patient management is to be initiated. Meningitis can be caused by bacteria, viruses, fungi or parasites. Prompt initiation of appropriate antibiotics is needed to prevent severe complications and reduce mortality if the cause is bacterial. Typical clinical characteristics, such as headache, neck stiffness, fever, and an altered mental state are only present in 40–50% of patients with suspected meningitis, often posing diagnostic dilemmas *(1-3)*. Lumbar puncture is necessary to obtain cerebrospinal fluid (CSF) and perform CSF examination *(2)*. Polymerase chain reaction (PCR) testing of CSF has emerged as a quick and highly specific diagnostic tool for identifying specific bacterial and viral pathogens responsible for meningitis. Where available, molecular testing allows for pathogen identification (both bacteria and viruses) and is often used as the confirmatory test for bacterial meningitis diagnosis (alongside culture) *(2)*. The diagnostic accuracy of PCR in cerebrospinal fluid has been primarily studied for *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*, and was found to be nearly 95–100% in the case of culture-positive bacterial meningitis *(3)*. Moreover, molecular assays allowing simultaneous diagnosis of multiple microorganisms using multiplex PCR have been increasingly adopted. However, these molecular panels have variable diagnostic performance across different microorganisms and do not allow for antibiotic susceptibility testing *(4)*.

The increasing availability and use of nucleic acid amplification tests, including individual and panel-based (multiplex) tests, have revolutionized the diagnostic approach to meningitis. Nonetheless, in spite of significant advancements in test design, some limitations in diagnostic accuracy remain, highlighting the importance of having evidence-based recommendations on the of molecular tests in clinical settings.

2. Methodology

Studies assessing the diagnostic performance of multiplex PCR were extracted from the evidence review on the diagnosis of suspected bacterial meningitis using CSF parameters performed by the National Institute for Health and Care Excellence (NICE) guideline on "Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management" *(5)*. The guideline provides a detailed description of the methods used for this evidence review *(6)*.

2.1 Research question and study design

What is the diagnostic performance of multiplex CSF PCR in cases of suspected acute meningitis?

Population: Suspected cases of acute meningitis (adults and children > 1 month of age).

Index test/Intervention: Multiplex CSF PCR

Reference standard/comparator: Consensus diagnosis[4]

Outcomes:

Critical outcomes (as prioritized by the Guideline Development Group):

- Sensitivity
- Specificity

Study designs: Cross-sectional and case-controlled studies. Case reports or case series were excluded.

2.2 Eligible studies

Published language: Only studies in the English language were considered.

Exclusion criteria: The following groups of patients were excluded:

- those with tuberculous meningitis;
- those with hospital-acquired, nosocomial and health-care-associated meningitis;
- those with subacute and chronic meningitis;
- newborns (0–28 days) with meningitis;
- patients with non-infectious meningitis (e.g. meningitis caused by drugs, malignancy, autoimmune diseases).

Subgroups: None considered.

[4] Consensus diagnosis defined as clinical characteristics (including peripheral white blood cell count, C-reactive protein, procalcitonin), blood culture, CSF culture and/or CSF PCR.

2.3 Search strategy

We searched for relevant studies in the "Evidence review for investigating and diagnosing suspected bacterial meningitis with cerebrospinal fluid parameters" performed for the NICE guideline on "Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management" *(5, 6)*.

The search was performed on 9 April 2024.

2.4 Selection of studies

Two of the authors independently screened all titles and abstracts (FV and AM) and assessed their eligibility according to the inclusion and exclusion criteria. Any disagreements between the authors were resolved by discussion. The full text of articles found to be potentially relevant on the basis of their titles and abstracts was retrieved and examined in light of the same inclusion criteria, by those two authors independently. Any disagreements regarding the results of the full-text screening were resolved by discussion.

Multiplex PCR was defined as a single assay able to identify two or more microorganisms simultaneously. Studies using broad-range 16s PCR were excluded.

2.5 Data extraction and management

Data extraction was performed by one author (FV) and any uncertainties were discussed with a second author (AM). The following categories of data were extracted:

- publication year and author(s);
- study type and setting;
- population, intervention, comparison and outcome;
- characteristics of the patients included (sex, age category, total no. of cases, total no. of non-cases, definitions of disease categories);
- outcomes and results.

2.6 Assessment of risk of bias in studies included in the review

The quality of the studies included was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies, by one author and checked by a second author. The specific categories offered by the QUADAS-2 tool were tailored to our research questions.

2.7 Data synthesis

Where at least two contributing studies and homogeneous data were available, we conducted meta-analyses, using a random-effects model for proportions to provide

pooled estimates for sensitivity and specificity. All meta-analyses were conducted using the R software packages “meta” and “metafor”.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments were tailored to our research questions. The overall certainty of evidence was downgraded for imprecision if the confidence interval (CI) of the pooled estimate results was very wide, or in case of a lower CI boundary (below 60%).

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

We did not conduct any subgroup analysis.

2.10 Sensitivity analysis

We did not conduct any sensitivity analysis.

2.11 Deviations from the review protocol

There were no deviations from the protocol.

3.1 Studies identified by the search process

All 70 studies included in the "NICE Evidence review for investigating and diagnosing suspected bacterial meningitis with cerebrospinal fluid parameters" *(6)* were assessed and eleven studies were finally included in the review.

3.1.1 Studies included in the review

The characteristics of the included studies are reported in Table WA2b.1.

Table WA2b.1a Characteristics of included studies – Intervention: CSF multiplex PCR for diagnosis of acute meningitis caused by *Streptococcus pneumoniae*

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boudet (2019), France *(7)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *Neisseria meningitidis* • for *Streptococcus pneumoniae* • for *Haemophilus influenzae* • for Group B streptococcus (GBS) • for Gram-negative bacilli (*Escherichia coli*)	Children and adults with suspected meningitis Age (mean [range]): 44 years (1 day to 98 years); N = 556 adult (mean 52.9 years, range 18–98 years); N = 152 children (mean 3.3 years, range 1 day to 17 years) Sex (%): 53.4 male: 46.6 female	N = 708	CSF bacterial culture	Sensitivity	Very serious
						Specificity	Very serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boving (2009), Denmark *(8)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (PCR-Luminex assay): • for *N. meningitidis* • for *S. pneumoniae* • for Gram-negative bacilli (*E. coli*) • for *Listeria monocytogenes*	Patients with suspected meningitis Ages of participants not reported	N = 1187 n = 1031 suspected bacterial meningitis n = 156 suspected viral meningitis	CSF microscopy, CSF bacterial culture, PCR or blood culture	Sensitivity	Serious
						Specificity	Serious
Chiba (2009), Japan *(9)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*)	Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings and blood exam	N = 168	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
		• for *L. monocytogenes*	Ages of participants not reported				
Deutch (2008), Denmark *(10)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *N. meningitidis* • for *S. pneumoniae*	Adults and children with suspected meningitis Age in years (mean [range]): 40 (0–97)	N = 1015 samples from 994 patients n = 35 bacterial meningitis	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious
Ena (2021), Spain *(11)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for *L. monocytogenes*	Adults with suspected meningoencephalitis Age in years (median [IQR]): bacterial or fungal aetiology 57 (20–77), unknown etiology 45 (13–73), viral	N = 46 n = 12 meningitis/ encephalitis of bacterial etiology n = 11 meningitis/ encephalitis of viral etiology	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
			aetiology 13 (0.06–69)	n = 1 meningitis/ encephalitis of fungal etiology n = 22 meningitis/ encephalitis of unknown etiology			
Leber (2016), USA *(12)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for all included bacteria • for *S. pneumoniae* • for *H. influenzae* • for Gram-negative bacilli (*E. coli*)	Adults and children with suspected meningitis Age in years (n): 921 adults ≥ 18 years, 639 children < 18 years Sex (n): 797 males and 763 females	N = 1560 n = 8 bacterial meningitis n = 95 viral meningitis n = 1 fungal meningitis n = 1456 non-meningitis	CSF bacterial culture	Sensitivity Specificity	Not serious Not serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Leli (2019), Italy *(13)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for GBS • for *L. monocytogenes*	Adults with suspected meningitis Age in years (median [IQR]): 60 (41.5–71)	N = 109 n = 14 bacterial meningitis n = 9 viral meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious
Vincent (2020), France *(14)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*)	Adults and children with suspected meningitis Age (n): n = 815 adults (> 18 years old), n = 309 children (≤ 18 years old)	N = 1124 n = 14 culture-confirmed bacterial meningitis n = 1110 without culture-confirmed bacterial meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Wagner (2018), Switzerland *(15)*	Prospective single-gate cross-sectional DTA study	Multiplex LightMix RT-PCR: • for *S. pneumoniae* • for other bacteria	Patients with suspected meningitis Ages of participants not reported.	N = 220 n = 20 bacterial meningitis n = 200 without bacterial meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

CSF: cerebrospinal fluid; DTA: differential thermal analysis; FAME: FilmArray meningitis/encephalitis; GBS: Group B streptococcus; IQR: interquartile range; PCR: polymerase chain reaction; RT-PCR: real-time PCR.

Table WA2b.1b Characteristics of included studies – Intervention: CSF multiplex PCR for diagnosis of acute meningitis caused by *Neisseria meningitidis*

Lead author (Year), Country	Study design	Index tests	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boudet (2019), France *(7)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for Group B streptococcus (GBS) • for Gram-negative bacilli (*E. coli*)	Children and adults with suspected meningitis Age (mean[range]): 44 years (1 day–98 years); n = 556 adult (mean 52.9 years, range 18–98 years); n = 152 children (mean 3.3 years, range 1 day–17 years) Sex (%): 53.4 male: 46.6 female	N = 708	CSF bacterial culture	Sensitivity	Very serious
						Specificity	Very serious

Lead author (Year), Country	Study design	Index tests	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boving (2009), Denmark *(8)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (PCR-Luminex assay): • for *N. meningitidis* • for *S. pneumoniae* • for Gram-negative bacilli (*E. coli*) • for *L. monocytogenes*	Patients with suspected meningitis Ages of participants not reported	N = 1187 n = 1031 suspected bacterial meningitis n = 156 suspected viral meningitis	CSF microscopy, CSF bacterial culture, PCR, or blood culture	Sensitivity	Serious
						Specificity	Serious
Deutch (2008), Denmark *(10)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *N. meningitidis* • for *S. pneumoniae*	Adults and children with suspected meningitis Age in years (mean [range]): 40 (0–97)	N = 1015 samples from 994 patients n = 35 bacterial meningitis	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index tests	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Ena (2021), Spain *(11)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for *L. monocytogenes*	Adults with suspected meningoencephalitis Age in years (median [IQR]): bacterial or fungal aetiology 57 (20–77), unknown aetiology 45 (13–73), viral etiology 13 (0.06–69)	N = 46 n = 12 meningitis/ encephalitis of bacterial etiology N = 11 meningitis/ encephalitis of viral etiology n = 1 meningitis/ encephalitis of fungal etiology n = 22 meningitis/ encephalitis of unknown etiology	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index tests	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Leli (2019), Italy *(13)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for GBS • for *L. monocytogenes*	Adults with suspected meningitis Age in years (median [IQR]): 60 (41.5–71)	N = 109 n = 14 bacterial meningitis n = 9 viral meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious
Seward (2000), United Kingdom *(16)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR: • for *N. meningitidis* • for other bacteria	Patients with suspected meningitis Ages of participants not reported	N = 294 n = 25 bacterial meningitis n = meningococcal n = 269 without bacterial meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

Lead author (Year), Country	Study design	Index tests	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Vincent (2020), France *(14)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*)	Adults and children with suspected meningitis Age (n): n = 815 adults (> 18 years old), n = 309 children (≤ 18 years old)	N = 1124 n = 14 culture-confirmed bacterial meningitis n = 1110 without culture-confirmed bacterial meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

CSF: cerebrospinal fluid; DTA: differential thermal analysis; FAME: FilmArray meningitis/encephalitis; GBS: Group B streptococcus; IQR: interquartile range; PCR: polymerase chain reaction.

Table WA2b.1c Characteristics of included studies – Intervention: CSF multiplex PCR for diagnosis of acute meningitis caused by *Haemophilus influenzae* type b

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boudet (2019), France *(7)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for Group B streptococcus (GBS) • for Gram-negative bacilli (*E. coli*)	Children and adults with suspected meningitis Age (mean [range]): 44 years (1 day–98 years); n = 556 adult [mean 52.9 years, range 18–98 years]; n = 152 children [mean 3.3 years, range 1 day–17 years])	N = 708	CSF bacterial culture	Sensitivity	Very serious
						Specificity	Very serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
			Sex (%): 53.4 male: 46.6 female				
Chiba (2009), Japan *(9)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*) • for *L. monocytogenes*	Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings and blood exam Ages of participants not reported	N = 168	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Leber (2016), USA *(12)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *S. pneumoniae* • for *H. influenzae* • for Gram-negative bacilli (*E. coli*)	Adults and children with suspected meningitis Age in years (n): 921 adults ≥ 18 years, 639 children < 18 years Sex (n): 797 males and 763 females	N = 1560 n = 8 bacterial meningitis n = 95 viral meningitis n = 1 fungal meningitis n = 1456 non-meningitis	CSF bacterial culture	Sensitivity Specificity	Not serious Not serious
Vincent (2020), France *(14)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* for *S. pneumoniae* • for *H. influenzae* • for GBS	Adults and children with suspected meningitis Age (n): n = 815 adults (> 18 years old), n = 309 children (≤ 18 years old)	N = 1124 n = 14 culture-confirmed bacterial meningitis n = 1110 without culture-	CSF bacterial culture	Sensitivity Specificity	Not serious Not serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
		• for Gram-negative bacilli (*E. coli*)		confirmed bacterial meningitis			
Xirogianni (2009), Greece *(17)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR: • for *H. influenzae* • for Gram-negative bacilli (*P. aeruginosa*)	Patients with suspected meningitis Ages of participants not reported.	N = 262 n = 20 bacterial meningitis n = 16 viral meningitis n = 226 non-meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

CSF: cerebrospinal fluid; DTA: differential thermal analysis; FAME: FilmArray meningitis/encephalitis; GBS: Group B streptococcus; IQR: interquartile range; PCR: polymerase chain reaction.

Table WA2b.1d Characteristics of included studies – Intervention: CSF multiplex PCR for diagnosis of acute meningitis caused by *Listeria monocytogenes*

Lead author (Year), Country	Study design	Index test	Population	Sample size (Intervention, control)	Reference standard	Outcomes available	Risk of bias
Boving (2009), Denmark *(8)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (PCR-Luminex assay): • for *N. meningitidis* • for *S. pneumoniae* • for Gram-negative bacilli (*E. coli*) • for *L. monocytogenes*	Patients with suspected meningitis Ages of participants not reported	N = 1187 n = 1031 suspected bacterial meningitis n = 156 suspected viral meningitis	CSF microscopy, CSF bacterial culture, PCR, or blood culture	Sensitivity	Serious
						Specificity	Serious
Chiba (2009), Japan *(9)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *S. pneumoniae* • for *H. influenzae* • for Group B streptococcus (GBS)	Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings, and blood exam	N = 168	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index test	Population	Sample size (Intervention, control)	Reference standard	Outcomes available	Risk of bias
		• for Gram-negative bacilli (*E. coli*) • for *L. monocytogenes*	Ages of participants not reported				
Ena (2021), Spain *(11)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for *L. monocytogenes*	Adults with suspected meningoencephalitis Age in years (median [IQR]): bacterial or fungal etiology 57 (20–77), unknown aetiology 45 (13–73), viral etiology 13 (0.06–69)	N = 46 n = 12 meningitis/ encephalitis of bacterial etiology n = 11 meningitis/encephalitis of viral etiology n=1 meningitis/ encephalitis of fungal etiology	CSF bacterial culture	Sensitivity Specificity	Serious Serious

Lead author (Year), Country	Study design	Index test	Population	Sample size (Intervention, control)	Reference standard	Outcomes available	Risk of bias
				n = 22 meningitis/ encephalitis of unknown etiology			
Leli (2019), Italy *(13)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for GBS • for *L. monocytogenes*	Adults with suspected meningitis Age in years (median [IQR]): 60 (41.5–71)	N = 109 n = 14 bacterial meningitis n = 9 viral meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

CSF: cerebrospinal fluid; DTA: differential thermal analysis; FAME: FilmArray meningitis/encephalitis; GBS: Group B streptococcus; IQR: interquartile range; PCR: polymerase chain reaction.

Table WA2b.1e Characteristics of included studies – Intervention: CSF multiplex PCR for diagnosis of acute meningitis caused by *Streptococcus agalactiae* (Group B *Streptococcus*)

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boudet (2019), France *(7)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for Group B streptococcus (GBS) • for Gram-negative bacilli (*E. coli*)	Children and adults with suspected meningitis Age (mean[range]): 44 years (1 day–98 years); n = 556 adult (mean 52.9 years, range 18–98 years); n = 152 children (mean 3.3 years, range 1 day–17 years) Sex (%): 53.4 male: 46.6 female	N = 708	CSF bacterial culture	Sensitivity	Very serious
						Specificity	Very serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Chiba (2009), Japan *(9)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*) • for *L. monocytogenes*	Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings and blood exam Ages of participants not reported	N = 168	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious
Leli (2019), Italy *(13)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for GBS • for *L. monocytogenes*	Adults with suspected meningitis Age in years (median [IQR]): 60 (41.5–71)	N = 109 n = 14 bacterial meningitis n = 9 viral meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Vincent (2020), France *(14)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*)	Adults and children with suspected meningitis Age (n): n = 815 adults (> 18 years old), n = 309 children (≤ 18 years old)	N = 1124 n = 14 culture-confirmed bacterial meningitis n = 1110 without culture-confirmed bacterial meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

CSF: cerebrospinal fluid; DTA: differential thermal analysis; FAME: FilmArray meningitis/encephalitis; GBS: Group B streptococcus; IQR: interquartile range; PCR: polymerase chain reaction.

Table WA2b.1f Characteristics of included studies – Intervention: CSF multiplex PCR for diagnosis of acute meningitis caused by *Escherichia coli*

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boudet (2019), France *(7)*	Retrospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for *N. meningitidis* • for *S. pneumoniae* • for *H. influenzae* • for Group B streptococcus (GBS) • for Gram-negative bacilli (*E. coli*)	Children and adults with suspected meningitis Age (mean [range]): 44 years (1 day–98 years); n = 556 adult [mean 52.9 years, range 18–98 years]; n = 152 children [mean 3.3 years, range 1 day–17 years]) Sex (%): 53.4 male: 46.6 female	N = 708	CSF bacterial culture	Sensitivity	Very serious
						Specificity	Very serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
Boving (2009), Denmark *(8)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (PCR-Luminex assay): • for *N. meningitidis* • for *S. pneumoniae* • for Gram-negative bacilli (*E. coli*) • for *L. monocytogenes*	Patients with suspected meningitis Ages of participants not reported	N = 1187 n = 1031 suspected bacterial meningitis n = 156 suspected viral meningitis	CSF microscopy, CSF bacterial culture, PCR or blood culture	Sensitivity	Serious
						Specificity	Serious
Chiba, (2009), Japan *(9)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR: • for *S. pneumoniae* • for *H. influenzae* • for GBS • for Gram-negative bacilli (*E. coli*)	Patients with suspected bacterial meningitis, based on clinical symptoms, CSF findings and blood exam	N = 168	CSF bacterial culture	Sensitivity	Serious
						Specificity	Serious

Lead author (Year), Country	Study design	Index test	Population	Sample size	Reference standard	Outcomes available	Risk of bias
		• for *L. monocytogenes*	Ages of participants not reported				
Leber, (2016), USA *(12)*	Prospective single-gate cross-sectional DTA study	Multiplex PCR (FAME panel): • for all included bacteria • for *S. pneumoniae* • for *H. influenzae* • for Gram-negative bacilli (*E. coli*)	Adults and children with suspected meningitis Age in years (n): 921 adults ≥ 18 years, 639 children < 18 years Sex (n): 797 males and 763 females	N = 1560 n = 8 bacterial meningitis n = 95 viral meningitis n = 1 fungal meningitis n = 1456 non-meningitis	CSF bacterial culture	Sensitivity	Not serious
						Specificity	Not serious

CSF: cerebrospinal fluid; DTA: differential thermal analysis; FAME: FilmArray meningitis/encephalitis; GBS: Group B streptococcus; IQR: interquartile range; PCR: polymerase chain reaction.

3.1.2 Excluded studies

Excluded studies and reason for exclusion are reported in Table WA2b.2.

Table WA2b.2 Excluded studies and reasons for exclusion

Study: Lead author, year	Reason for exclusion
Abdeldaim, 2010 *(18)*	Wrong index test
Agueda, 2013 *(19)*	Wrong index test
Alqayoudhi, 2017 *(20)*	Wrong index test
Ansong, 2009 *(21)*	Wrong index test
Arora, 2017 *(22)*	Wrong index test
Balamuth, 2021 *(23)*	Wrong index test
BenGershom, 1986 *(24)*	Wrong index test
Benjamin, 1984 *(25)*	Wrong index test
Bonadio, 1989 *(26)*	Wrong index test
Bonsu, 2003 *(27)*	Wrong index test
Bonsu, 2005 *(28)*	Wrong index test
Bonsu, 2008 *(29)*	Wrong index test
Bortolussi, 1982 *(30)*	Wrong index test
Brizzi, 2012 *(31)*	Wrong index test
Bryant, 2004 *(32)*	Wrong index test
Buch, 2018 *(33)*	Wrong index test
Corrall, 1981 *(34)*	Wrong index test
D'Inzeo, 2020 *(35)*	Wrong index test
Dastych, 2015 *(36)*	Wrong index test
De Cauwer, 2007 *(37)*	Wrong index test

Deutch, 2006 *(38)*	Wrong index test
Dubos, 2006 *(39)*	Wrong index test
Dubos, 2008 *(40)*	Wrong index test
Dunbar, 1998 *(41)*	Wrong index test
Esparcia, 2011 *(42)*	Wrong index test
Favaro, 2013 *(43)*	Wrong index test
Freedman, 2001 *(44)*	Wrong index test
Garges, 2006 *(45)*	Wrong index test
Giulieri, 2015 *(46)*	Wrong index test
Jorgensen, 1978 *(47)*	Wrong index test
Kennedy, 2007 *(48)*	Wrong index test
Khurana, 1987 *(49)*	Wrong index test
Kim, 2012 *(50)*	Wrong index test
Kleine, 2003 *(51)*	Wrong index test
Kotilainen, 1998 *(52)*	Wrong index test
La Scolea Jr, 1984 *(53)*	Wrong index test
Lee 2015, *(54)*	Wrong index test
Leitner, 2016 *(55)*	Wrong index test
Lindquist, 1988 *(56)*	Wrong index test
Meyer, 2014 *(57)*	Wrong index test
Morrissey, 2017 *(58)*	Wrong index test
Nabower, 2019 *(59)*	Wrong index test
Negrini, 2000 *(60)*	Wrong index test
Nelson, 1986 *(61)*	Wrong index test
Neuman, 2008 *(62)*	Wrong index test

Pfefferle, 2020 *(63)*	Wrong index test
Poppert, 2005 *(64)*	Wrong index test
Porritt, 2000 *(65)*	Wrong index test
Ray, 2007 *(66)*	Wrong index test
Richardson, 2003 *(67)*	Wrong index test
Rothman, 2010 *(68)*	Wrong index test
Schuurman, 2004 *(69)*	Wrong index test
Seward, 2000 *(70)*	Wrong index test
Sormunen, 1999 *(71)*	Wrong index test
Viallon, 2011 *(72)*	Wrong index test
Welinder-Olsson, 2007 *(73)*	Wrong index test
White, 2012 *(74)*	Wrong index test

3.3 Narrative description of diagnostic performance evidence

3.3.1 Parameter 1: CSF multiplex PCR *Streptococcus pneumoniae*

Nine studies were found involving 6137 patients who had a CSF sample tested for *S. pneumoniae* as part of a multiplex PCR panel. Five studies used the multiplex PCR FilmArray meningitis/encephalitis (FAME) panel. The reference standard was CSF bacterial culture in eight studies and a combination of CSF microscopy, CSF bacterial culture, PCR and blood culture in one study.

- Low certainty evidence suggests that CSF multiplex PCR may have very high sensitivity (9 studies/6137 patients; pooled effect: 98%, 95% CI 93–100%).
- Moderate certainty evidence suggests that CSF multiplex PCR is likely to have very high specificity (9 studies/6,137 patients; pooled effect: 99%, 95% CI 99–100%).

3.3.2 Parameter 2: CSF multiplex PCR *Neisseria meningitidis*

Seven studies were found involving 4483 patients who had a CSF sample tested for *N. meningitidis* as part of a multiplex PCR panel. Four studies used the multiplex PCR FAME panel. The reference standard was CSF bacterial culture in six studies and a combination CSF microscopy, CSF bacterial culture, PCR and blood culture in one study.

- Low certainty evidence suggests that CSF multiplex PCR may have very high sensitivity (7 studies/4483 patients; pooled effect: 99%, 95% CI 91–100%).
- Moderate certainty evidence suggests that CSF multiplex PCR is likely to have very high specificity (7 studies/4483 patients; pooled effect: 100%, 95% CI 100–100%).

3.3.3 Parameter 3: CSF multiplex PCR *Haemophilus influenzae* type b

Five studies were found involving 3822 patients who had a CSF sample tested for *Haemophilus influenzae* type b (Hib) as part of a multiplex PCR panel. Three studies used the multiplex PCR FAME panel. The reference standard was CSF bacterial culture in all studies.

- Low certainty evidence suggests that CSF multiplex PCR may have very high sensitivity (5 studies/3822 patients; pooled effect: 100%, 95% CI 97–100%).
- Moderate certainty evidence suggests that CSF multiplex PCR is likely to have very high specificity (5 studies/3822 patients; pooled effect: 96%, 95% CI 87–100%).

3.3.4 Parameter 4: CSF multiplex PCR *Listeria monocytogenes*

Five studies were found involving 1510 patients who had a CSF sample tested for *L. monocytogenes* as part of a multiplex PCR panel. Two studies used the multiplex PCR FAME panel. The reference standard was CSF bacterial culture in three studies and a combination of CSF microscopy, CSF bacterial culture, PCR and blood culture in one study.

- Low certainty evidence suggests that CSF multiplex PCR may have very high sensitivity (4 studies/1510 patients; pooled effect: 100%, 95% CI 70–100%).
- Moderate certainty evidence suggests that CSF multiplex PCR is likely to have very high specificity (4 studies/1510 patients; pooled effect: 100%, 95% CI 100–100%).

3.3.5 Parameter 5: CSF multiplex PCR *Streptococcus agalactiae*

Four studies were found involving 2109 patients who had a CSF sample tested for *S. agalactiae* as part of a multiplex PCR panel. Four studies used the multiplex PCR FAME panel. The reference standard was CSF bacterial culture in all studies.

- Low certainty evidence suggests that CSF multiplex PCR may have very high sensitivity (4 studies/2109 patients; pooled effect: 96%, 95% CI 76–100%).
- Moderate certainty evidence suggests that CSF multiplex PCR likely has very high specificity (4 studies/2109 patients; pooled effect: 100% (95% CI 100–100%).

3.3.6 Parameter 5: CSF multiplex PCR *Escherichia coli*

Four studies were found involving 3623 patients who had CSF sample tested for *E. coli* as part of a multiplex PCR panel. Two studies used the multiplex PCR FAME panel. The reference standard was CSF bacterial culture in three studies and a combination of CSF microscopy, CSF bacterial culture, PCR and blood culture in one study.

- Low certainty evidence suggests that CSF multiplex PCR may have very high sensitivity (4 studies/3623 patients pooled effect: 100%, 95% CI 78–100%).
- Moderate certainty evidence suggests that CSF multiplex PCR is likely to have very high specificity (4 studies/3623 patients; pooled effect: 100% (95% CI 100–100%).

3.3 GRADE evidence profiles

Table WA2b.3 presents the GRADE evidence profiles for this review.

Table WA2b.3 GRADE evidence profiles, by parameter

Summary of evidence				Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Result: pooled estimate**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**	**Overall certainty of evidence**
Parameter: Multiplex CSF PCR: diagnosis of *Streptococcus pneumoniae*									
Sensitivity, %	9	6137	98 (95% CI 93–100)	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	9	6137	99 (95% CI 99–100)	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Parameter: Multiplex CSF PCR: diagnosis of *Neisseria meningitidis*									
Sensitivity, %	7	4483	99 (95% CI 91–100)	Serious[c]	Serious[d]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	7	4483	100 (95% CI 100–100)	Serious[c]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Parameter: Multiplex CSF PCR: diagnosis of *Haemophilus influenzae* type b									

Sensitivity, %	5	3822	100 (95% CI 97–100)	Serious[e]	Serious[f]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	5	3822	96 (95% CI 87–100)	Serious[e]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Parameter: Multiplex CSF PCR: diagnosis of *Listeria monocytogenes*									
Sensitivity, %	4	1510	100 (95% CI 70–100)	Serious[g]	Serious[h]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	4	1510	100 (95% CI 100–100)	Serious[g]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Parameter: Multiplex CSF PCR: diagnosis of *Streptococcus agalactiae*									
Sensitivity, %	4	2109	96 (95% CI 76–100)	Serious[i]	Serious[j]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	4	2109	100 (95% CI 100–100)	Serious[i]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Parameter: Multiplex CSF PCR: diagnosis of *Escherichia coli*									
Sensitivity, %	4	3623	100 (95% CI 78–100)	Serious[k]	Serious[l]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	4	3623	100 (95% CI 100–100)	Serious[k]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate

[a] Five studies in the body of evidence had a serious risk of bias.
[b] Limited number of patients with the disease in the body of evidence.
[c] Four studies in the body of evidence had serious risk of bias.
[d] Limited number of patients with the disease in the body of evidence.

[e] Two studies in the body of evidence had serious risk of bias.
[f] Limited number of patients with the disease in the body of evidence.
[g] Three studies in the body of evidence had serious risk of bias.
[h] Limited number of patients with the disease in the body of evidence.
[i] Two studies in the body of evidence had serious risk of bias.
[j] Limited number of patients with the disease in the body of evidence.
[k] Three studies in the body of evidence had serious risk of bias.
[l] Limited number of patients with the disease in the body of evidence.

4. Research gaps

Most studies were performed in high-income countries. Further evidence is needed to assess the diagnostic performance of Multiplex PCR in low- and middle-income countries.

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3. Blood markers of bacterial infection

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Abbreviations

AM	aseptic meningitis
AUC	area under the receiver-operating-characteristics curve
BM	bacterial meningitis
CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
ED	emergency department
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Classification of Diseases
NA	not applicable
NPV	negative predictive value
NR	not reported
RT	real time
RT-PCR	real-time polymerase chain reaction
PCR	polymerase chain reaction
PPV	positive predictive value
VM	viral meningitis
WBC	white blood cell
WHO	World Health Organization

1. Background

Acute meningitis is a life-threatening medical emergency that needs timely and accurate diagnosis if appropriate patient management is to be initiated. Meningitis can be caused by bacteria, viruses, fungi or parasites. Prompt initiation of appropriate antibiotics is needed to prevent severe complications and reduce mortality if the cause is bacterial. Typical clinical characteristics, such as headache, neck stiffness, fever, and an altered mental state are only present in 40–50% of patients with suspected meningitis, often posing diagnostic dilemmas *(1–3)*. Lumbar puncture is necessary to obtain cerebrospinal fluid (CSF) and perform CSF examination *(2)*. Culture and molecular tests allow for pathogen identification and are generally regarded as the reference standard to confirm microbiological diagnosis of acute meningitis *(2)*. However, in order to inform timely clinical decisions and guide antibiotic treatment, additional investigations with faster turn-around times and rapidly available results are normally performed on blood and CSF samples *(2)*. Specifically, peripheral white blood cell (WBC) count, C-reactive protein (CRP) and procalcitonin are often used as auxiliary tests that may contribute to meningitis diagnosis, including for differentiating bacterial from non-bacterial disease *(2)*.

As part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, this systematic review was conducted in conjunction with two other systematic reviews addressing the research questions on the diagnostic performance of initial CSF investigations and CSF polymerase chain reaction (PCR) (reports 1 and 2a in this web annex). A unified search strategy was developed for this purpose. Here in this report, only the results specifically related to peripheral blood markers (i.e. peripheral WBC count, CRP and procalcitonin) are presented.

2. Methodology

Peripheral blood tests for the diagnosis of bacterial meningitis were addressed in the review carried out by van de Beek et al. for *Nature* Primers *(4)* and in the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline by van de Beek et al. *(5)*, both published in 2016. Since these reviews were of high quality and covered the literature on acute bacterial meningitis up to 2014, this report summarizes the data on CSF testing from 2014 onwards. Additionally, the evidence from before 2014 was reviewed and graded, largely on the basis of reviews conducted as part of the ESCMID guideline *(5)*.

2.1 Research question and study design

What is the diagnostic performance of peripheral blood testing (white blood cell count and differential, CRP, procalcitonin) in cases of suspected acute meningitis?

Population: Suspected cases of acute meningitis (adults and children > 1 month of age).

Index test/Intervention: Peripheral blood testing**,** including white blood cell count and differential, CRP, procalcitonin.

Reference standard/comparator: Consensus diagnosis[6]

Outcomes:

Critical outcomes (as prioritized by the Guideline Development Group):

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Likelihood ratios

Other outcomes: Area under the receiver-operating-characteristics curve (AUC)

Study designs: Cross-sectional and case-controlled studies. Case reports or case series were excluded.

2.2 Eligible studies

Published language: Studies published in English, French, German, Italian, Portuguese and Spanish were considered for inclusion. For studies in other languages, networks within WHO and Cochrane were used for support with screening and/or translation. Studies in Chinese and Korean were excluded.

[6] Consensus diagnosis defined as clinical characteristics (including peripheral white blood cell count, C-reactive protein, procalcitonin), blood culture, CSF culture, and/or CSF PCR.

Exclusion criteria: The following groups of patients were excluded:

- those with tuberculous meningitis;
- those with hospital-acquired, nosocomial and health-care-associated meningitis;
- those with subacute and chronic meningitis;
- newborns (0–28 days) with meningitis;
- those with non-infectious meningitis (e.g. meningitis caused by drugs, malignancy, autoimmune diseases).

Subgroups: None considered.

2.3 Search strategy

One comprehensive search strategy was developed to identify relevant studies for three research questions – addressing the diagnostic performance of initial CSF investigations, CSF PCR and peripheral blood tests (covered in this report and reports 1 and 2a in this web annex). The following databases were searched for articles published up to the date of the literature search: PubMed, Embase and the Cochrane Library.

The exact search terms can be found in Appendix 1. Search strategy used to identify .

The search was conducted in English on 26 January 2024.

2.4 Selection of studies

The two authors (NSG and MCB) screened all titles and abstracts independently and assessed their eligibility according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion. The full text of articles found to be potentially relevant on the basis of their titles and abstracts was retrieved and examined in the light of the same inclusion criteria by the two authors independently. Any disagreements regarding the full-text screening were resolved by discussion.

Rayyan was used for reference screening, title, abstract and full-text selection.

2.5 Data extraction and management

Data extraction was performed by one author (NSG) and any uncertainties were discussed with the second author (MCB). The following categories of data were extracted:

- publication year and author(s);
- study type and setting;
- population, intervention, comparator and outcome(s);
- characteristics of patients included (sex, age category, total number of cases, total number of non-cases, definitions of disease categories);
- outcomes and results.

2.6 Assessment of risk of bias in studies included in the review

The quality of the studies included will be assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool by one author and will be checked by the second author. The specific categories offered by the QUADAS-2 tool were tailored to the research questions.

2.7 Data synthesis

Where feasible (i.e. when there were at least two contributing studies and homogeneous data), meta-analyses were conducted using a random-effects model for proportions to provide pooled estimates for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). All meta-analyses were conducted using the R software packages “meta” and “metafor”. Where meta-analysis was not feasible, ranges and medians were provided to summarize the findings. Data on NPV and PPV were extracted and included in the meta-analysis non-case control studies only, because these measures are considered highly dependent on prevalence.

If multiple cut-offs were reported by one article, one cut-off was included for meta-analysis to prevent dependent results. The choice of this cut-off was based on clinical relevance.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was tailored to the research questions. The overall certainty of the evidence was downgraded for imprecision if the confidence interval (CI) of the pooled estimate results was very wide, or in cases of a lower CI boundary (below 60%).

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No subgroup analysis was conducted.

2.10 Sensitivity analysis

No sensitivity analysis was conducted.

2.11 Deviations from the review protocol

There were no deviations from the protocol.

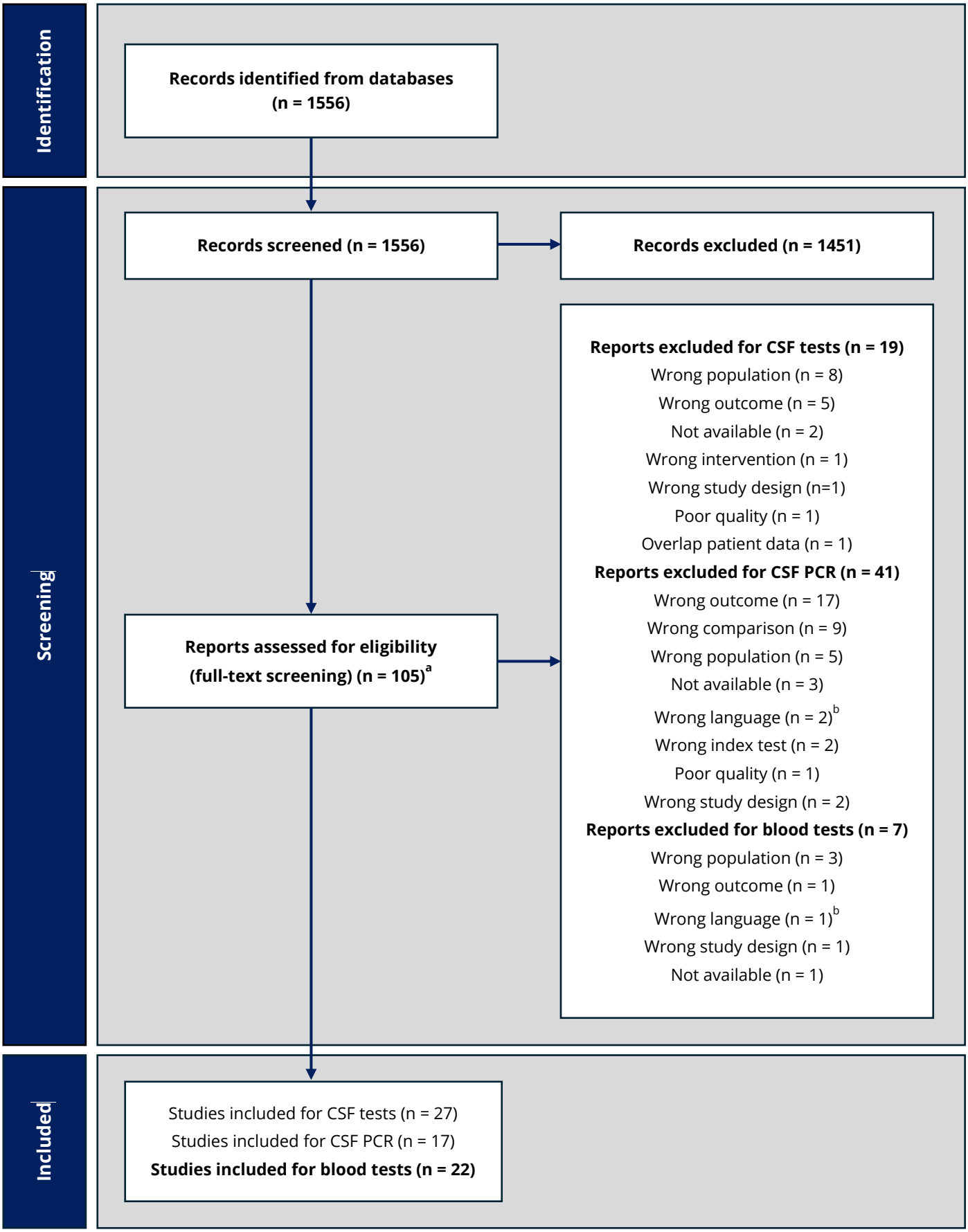
3. Results

3.1 Studies identified by the search process

Figure WA3.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review. A total of 1556 records were retrieved for the three research questions, of which 1451 were excluded on the basis of their title and abstract. The search strategy is provided in Appendix 1.

Overall, 105 articles were screened for full-text eligibility. For peripheral blood testing (the topic of this report), seven articles were excluded *(6)(7)(8)(9)(10)(11)(12)*, and a total of 22 studies were included *(13–34)*.

Fig. WA3.1 PRISMA flow diagram for the systematic review



[a] Some studies were included for more than one research question; therefore, the number of reports excluded per research question is not the same as the total number of reports screened for full text minus all the studies included per research question. [b] Studies in Chinese (n = 2) and Korean (n = 1) were excluded.

3.1.1 Studies included in the review and the GRADE evidence profiles

Ahmed et al. *(13)*, Alnomasy et al. *(14)*, Babenko et al. *(15)*, Chaudhary et al. *(16)*, El Shorbagy et al. *(17)*, Fouad et al. *(18)*, Gowin et al. *(19)*, Kalchev et al. *(20)*, Lembo and Marchant *(21)*, Morales Casado et al. *(22)*, Morales Casado et al. *(23)*, Morales Casado et al. *(24)*, Pormohammad et al. *(25)*, Sanaei Dashti et al. *(26)*, Santotoribio et al. *(27)*, Shen et al. *(28)*, Tamune et al. *(29)*, Taniguchi et al. *(30)*, Umran and Radhi *(31)*, Zhang et al. *(32)*, Dubos et al. *(33)*, Sormunen et al. *(34)*.

Table WA3.1a Characteristics of studies included in this review – Intervention: Peripheral white blood cell count

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Alnomasy (2021), Saudi Arabia *(14)*	Case–control	High	Adult patients with suspected meningitis based on clinical features (BM vs VM)	75 (38, 34)	Positive RT-PCR	Sens, spec, LR+, LR−, AUC
Babenko (2021), Kazakhstan *(15)*	Case–control	High	Children aged 1 month to 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood, or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids CSF or blood	Sens, spec, LR+, LR−
Chaudhary (2018), Nepal *(16)*	Case–control	Low	Children with suspected meningitis (BM vs non-BM)	50 (22, 28)	Positive CSF culture or CSF Gram stain and abnormal CSF findings	Sens, spec, LR+, LR−, AUC
Dubos (2008), France *(33)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for BM or AM and had measurements of the main inflammatory markers (including procalcitonin) in blood (BM vs AM)	198 (96, 102)	CSF WBC count ≥ 7/µl and documented bacterial infection in CSF (direct examination, culture, latex agglutination or PCR) or blood culture	Sens, spec, LR+, LR−

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Fouad (2014), Egypt *(18)*	Prospective cohort	Unclear	Patients of all ages with acute meningitis (BM vs non-BM)	623 (457, 166)	Positive CSF culture or positive blood culture with concurrent meningitis	Sens, spec, LR+, LR−, PPV, NPV
Gowin (2016), Poland *(19)*	Case–control	High	Children hospitalized with clinical suspicion of meningitis based on clinical symptoms and inflammatory changes in CSF (BM vs AM[a])	129 (64, 64)	NR. Assumed: ICD-10 code-based clinical diagnosis	Sens, spec, LR+, LR−
Lembo (1991), USA *(21)*	Prospective cohort	Low	Children with suspected bacterial meningitis or with CSF obtained in case of sepsis work-up in case of age < 2 months (BM vs non-BM)	160 (10, 150)	Positive CSF culture or positive antigen test in CSF combined with positive CSF Gram stain	Sens, spec, LR+, LR−, PPV, NPV
Morales Casado (2016), Spain *(22)*	Case–control	Low	Adults aged > 15 years diagnosed with acute meningitis at the ED (BM vs VM)	98 (38, 33)	Positive CSF culture or CSF antigen test	AUC
Morales Casado (2017), Spain *(23)*	Prospective cohort	Low	Adults aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53, 101)	Positive CSF culture or CSF antigen test	AUC

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Pormohammad (2019), Islamic Republic of Iran *(25)*	Case–control	Low	Children aged < 16 years with suspected meningitis based on clinical criteria (BM vs AM[a])	62 (43, 19)	Combination of clinical and laboratory tests (Gram staining and culture of blood and CSF)	Sens, spec, LR+, LR−
Sormunen (1999), Finland *(34)*	Case–control	Low	Children aged 3 months to 15 years with a positive bacterial CSF culture and negative Gram stain, and children with viral meningitis (BM vs VM)	237 (55, 182)	Positive CSF culture	Sens, spec, LR+, LR−
Tamune (2014), Japan *(29)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15,119)	Positive CSF culture	Sens, spec, LR+, LR−
Taniguchi (2020), Japan *(30)*	Case–control	Unclear	Adults aged > 15 years admitted and finally diagnosed with BM or AM (BM vs AM[a])	131 (34, 97)	Positive CSF culture and clinical signs and symptoms	Sens, spec, LR+, LR−, AUC
Umran (2014), Iraq *(31)*	Case–control	High	Children with clinical suspected meningitis (BM vs non-BM)	45 (29, 16)	Clinical history, CSF protein > 0.2 g/l, CSF/blood glucose ratio < 0.4, CSF leukocyte count	Sens, spec, LR+, LR−, PPV, NPV, AUC

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
					> 1500 cells/mm^3 and neutrophil predominance	

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CSF: cerebrospinal fluid; ED emergency department; ICD: International Classification of Diseases; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PCR: polymerase chain reaction; PPV: positive predictive value; RT-PCR: real-time polymerase chain reaction; Sens: sensitivity; Spec: specificity; VM: viral meningitis.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA3.1b Characteristics of studies included in this review – Intervention: Peripheral neutrophil percentage

Lead author (Year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Babenko (2021), Kazakhstan *(15)*	Case–control	High	Children aged 1 month to 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood, or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids CSF or blood	Sens, spec, LR+, LR−
Tamune (2014), Japan *(29)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15, 119)	Positive CSF culture	Sens, spec, LR+, LR−

BM: bacterial meningitis; CSF: cerebrospinal fluid; NPV: negative predictive value; LR−: negative likelihood ratio; LR+: positive likelihood ratio; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; VM: viral meningitis.

[a] AM was defined as clinically and/or laboratory (pleocytosis) evident meningitis with negative CSF culture.

Table WA3.1c Characteristics of studies included in this review – Intervention: Serum C-reactive protein (CRP)

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Ahmed (2022), Egypt *(13)*	Cross-sectional cohort	High	Children aged 2–18 years with manifestations suggesting meningitis (BM vs VM)	48 (35, 13)	NR. Probably positive CSF culture or abnormal CSF characteristics with clinical manifestations	Sens, spec, LR+, LR−, AUC
Alnomasy (2021), Saudi Arabia *(14)*	Case–control	High	Adults with suspected meningitis based on clinical features (BM vs VM)	75 (38, 34)	Positive RT-PCR	Sens, spec, LR+, LR−, AUC
Babenko (2021), Kazakhstan *(15)*	Case–control	High	Children aged 1 month to 17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood, or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids CSF or blood	Sens, spec, LR+, LR−
Fouad (2014), Egypt *(18)*	Prospective cohort	Unclear	Patients of all ages with acute meningitis (BM vs non-BM)	623 (457,166)	Positive CSF culture or positive blood culture with concurrent meningitis	Sens, spec, LR+, LR−, PPV, NPV

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Dubos (2008), France *(33)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for BM or AM and had measurements of the main inflammatory markers (including procalcitonin) in blood (BM vs AM)	197 (95, 102)	CSF WBC count ≥ 7/µl and documented bacterial infection in CSF (direct examination, culture, latex agglutination, or PCR) or blood culture	Sens, Spec, LR+, LR−
Gowin (2016), Poland *(19)*	Case–control	High	Children hospitalized with clinical suspicion of meningitis based on clinical symptoms and inflammatory changes in CSF (BM vs AM[a])	129 (64,64)	NR. Assumed: ICD-10 code-based clinical diagnosis	Sens, spec, LR+, LR−
Kalchev (2021), Bulgaria *(20)*	Prospective cohort	Unclear	Patients of all ages with clinical evidence of acute central nervous system infection based on clinical signs and abnormal CSF findings with presence of at least 1 ml CSF and serum (BM vs non-BM)	80 (21, 59)	Microbiological analysis (undefined)	AUC
Lembo (1991), USA *(21)*	Prospective cohort	Low	Children with suspected bacterial meningitis or with CSF obtained in case of sepsis workup in case of age < 2 months (BM vs non-BM)	160 (10, 150)	Positive CSF culture or positive antigen test in CSF combined with positive CSF Gram stain	Sens, spec, LR+, LR−, PPV, NPV

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Morales Casado (2016), Spain *(22)*	Case–control	Low	Adults aged > 15 years diagnosed with acute meningitis at the ED (BM vs VM)	98 (38, 33)	Positive CSF culture or CSF antigen test	AUC
Morales Casado (2016), Spain *(24)*	Case–control	Low	Patients of all ages diagnosed with acute meningitis at the ED (BM vs VM)	220 (66, 154)	Positive CSF culture or CSF antigen test	Sens, spec, LR+, LR−
Morales-Casado (2017), Spain *(23)*	Prospective cohort	Low	Adults aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53,101)	Positive CSF culture or CSF antigen test	AUC
Pormohammad (2019), Iran *(25)*	Case–control	Low	Children aged < 16 years with suspected meningitis based on clinical criteria (BM vs AM[a])	62 (43, 19)	Combination of clinical and laboratory tests (Gram staining and culture of blood and CSF)	Sens, spec, LR+, LR−
Sanaei Dashti (2017), Iran *(26)*	Case–control	Low	Children aged 28 days to 14 years with suspected meningitis based on clinical symptoms (BM vs VM)	50 (12, 38)	Definitive BM: positive CSF Gram stain, culture or PCR. Presumed BM: clinical symptoms with at least two of following:	Sens, spec, LR+, LR−

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
					CSF protein ≥ 80 mg/dl, glucose < 40, WBC ≥ 300 cells/mm^3, and or CSF neutrophil predominance	
Santotoribio (2018), Spain *(27)*	Case–control	High	Patients of all ages with a clinical suspicion of acute meningitis (BM vs VM)	30 (18, 12)	Positive CSF culture or symptoms and signs of acute meningitis with CSF neutrophil pleocytosis, elevated protein and lowered glucose	Sens, spec, LR+, LR−, AUC
Sormunen (1999), Finland *(34)*	Case–control	Low	Children aged 3 months to 15 years with a positive bacterial CSF culture and negative Gram stain, and children with viral meningitis (BM vs VM)	237 (55,182)	Positive CSF culture	Sens, spec, LR+, LR−
Tamune (2014), Japan *(29)*	Retrospective cohort	Low	Patients with clinical evidence suggesting meningitis and > 5 cells/mm^3 in CSF (BM vs AM[a])	134 (15, 119)	Positive CSF culture	Sens, spec, LR+, LR−

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Taniguchi (2020), Japan *(30)*	Case–control	Unclear	Adults aged > 15 years admitted and finally diagnosed with BM or AM (BM vs AM[a])	131 (34, 97)	Positive CSF culture and clinical signs and symptoms	Sens, spec, LR+, LR−, AUC
Umran (2014), Iraq *(31)*	Prospective cohort	High	Children with clinical suspected meningitis (BM vs non-BM)	45 (29, 16)	Clinical history, CSF protein > 0.2 g/L, CSF/blood glucose ratio < 0.4, CSF leukocyte count > 1500 cells/mm^3 and neutrophil predominance	Sens, spec, LR+, LR− PPV, NPV, AUC

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CSF: cerebrospinal fluid; ICD: International Classification of Diseases; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; RT-PCR: real-time polymerase chain reaction; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; VM: viral meningitis; WBC: white blood cell.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

Table WA3.1d Characteristics of studies included in this review – Intervention: Serum procalcitonin

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Ahmed (2022), Egypt *(13)*	Case–control	High	Children aged 2–18 years with manifestations suggesting meningitis (BM vs VM)	48 (35, 13)	NR. Probably positive CSF culture or abnormal CSF characteristics with clinical manifestations	Sens, spec, LR+, LR−, AUC
Alnomasy (2021), Saudi Arabia *(14)*	Case–control	High	Children aged 2–18 years with manifestations suggesting meningitis (BM vs VM)	48 (35, 13)	Positive RT-PCR	Sens, spec, LR+, LR−, AUC
Babenko (2021), Kazakhstan *(15)*	Case–control	High	Children aged 1 month–17 years with clinical signs of meningitis and presence of bacterial antigen in CSF, identification of bacterial or viral nucleic acids in CSF or blood, or a positive blood culture (BM vs VM)	216 (123, 146)	Presence of bacterial antigen in CSF or identification of bacterial nucleic acids CSF or blood	Sens, spec, LR+, LR−
Chaudhary (2018), Nepal *(16)*	Case–control	Low	Children with suspected meningitis (BM vs non-BM)	50 (22, 28)	Positive CSF culture or CSF Gram stain and abnormal CSF findings	Sens, spec, LR+, LR−, AUC
Dubos (2008), France *(33)*	Case–control	Low	Children aged 29 days to 18 years who were admitted for	190 (90, 100)	CSF WBC count ≥ 7/µl and	Sens, spec, LR+, LR−

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
			BM or AM and had measurements of the main inflammatory markers (including procalcitonin) in blood (BM vs AM)		documented bacterial infection in CSF (direct examination, culture, latex agglutination or PCR) or blood culture	
El Shorbagy (2018), Egypt *(17)*	Case–control	Low	Children with a suspected meningitis (BM vs AM[a])	40 (24, 16)	Positive CSF culture or negative CSF culture with CSF abnormalities typical for bacteria	Sens, spec, LR+, LR−
Morales Casado (2016), Spain *(22)*	Case–control	Low	Adults aged > 15 years diagnosed with acute meningitis at the ED (BM vs VM)	98 (38, 33)	Positive CSF culture or CSF antigen test	AUC
Morales Casado (2016), Spain *(24)*	Case–control	Low	Patients of all ages diagnosed with acute meningitis at the ED (BM vs VM)	220 (66, 154)	Positive CSF culture or CSF antigen test	Sens, spec, LR+, LR−
Morales Casado (2017), Spain *(23)*	Prospective cohort	Low	Adults aged > 15 years diagnosed with acute meningitis at the ED (BM vs non-BM)	154 (53,101)	Positive CSF culture or CSF antigen test	Sens, spec, LR+, LR-, AUC

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
Sanaei Dashti (2017), Iran *(26)*	Case–control	Low	Children aged 28 days to 14 years of age with suspected meningitis based on clinical symptoms (BM vs VM)	50 (12, 38)	Definitive BM: positive CSF Gram stain, culture or PCR. Presumed BM: clinical symptoms with at least two of following: CSF protein ≥ 80 mg/dl, glucose < 40, WBC ≥ 300 cells/mm^3 and/or CSF neutrophil predominance	Sens, spec, LR+, LR−
Santotoribio (2018), Spain *(27)*	Case–control	High	Patients of all ages with a clinical suspicion of acute meningitis (BM vs VM)	30 (18, 12)	Positive CSF culture or symptoms and signs of acute meningitis with CSF neutrophil pleocytosis, elevated protein and lowered glucose	Sens, spec, LR+, LR−, AUC
Shen (2015), China *(28)*	Prospective cohort	Low	Adult patients with clinical signs of meningitis, no determination of a meningitis pathogen on	120 (45, 75)	Positive CSF culture or Gram stain, with negative CSF-PCR	Sens, spec, LR+, LR−, AUC

Lead author (year), Country	Study design	Overall risk of bias	Population (comparison)	Sample size (intervention, control)	Reference standard	Outcomes available
			admission, and CSF leukocytes > 5 cells/mm^3 (BM vs non-BM)			
Umran (2014), Iraq *(31)*	Prospective cohort	High	Children with clinical suspected meningitis (BM vs non-BM)	45 (29, 16)	Clinical history, CSF protein > 0.2 g/L, CSF/blood glucose ratio < 0.4, CSF leukocyte count > 1500 cells/mm^3 and neutrophil predominance	Sens, spec, LR+, LR−, PPV, NPV, AUC
Zhang (2019), China *(32)*	NR	Low	Children with meningitis-like manifestations (BM vs non-BM)	101 (29, 72)	CSF protein > 100 mg/dL or CSF glucose < 40 mg/dl or CSF leukocyte count > 100 cells/mm^3 with at least 80% neutrophils, identification of bacterial agents in Gram staining, and/or positive CSF culture	Sens, spec, LR+, LR−, AUC

AM: aseptic meningitis; AUC: area under the receiver-operating-characteristics curve; BM: bacterial meningitis; CSF: cerebrospinal fluid; ED: emergency department; NPV: negative predictive value; NR: not reported; LR−: negative likelihood ratio; LR+: positive likelihood ratio; RT-PCR: real-time polymerase chain reaction; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; VM: viral meningitis.

[a] AM was defined as clinically evident meningitis and/or meningitis diagnosed in a laboratory (pleocytosis), with negative CSF culture.

3.1.2 Studies excluded from the review

Alons et al. *(6)*, Hoffmann et al. *(7)*, Jereb et al. *(8)*, Liu et al. *(9)*, Metrou and Crain *(10)*, Obaro *(11)*, Prat et al. *(12)*.

3.2 Narrative description of diagnostic performance evidence

3.2.1 Parameter 1: Peripheral white blood cell count

Overall, 14 studies were found, including four studies involving adults, eight studies involving children and one study involving patients of all ages (one study did not report the age of the population). Reference standards varied between studies, including combinations of the following: a positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, antigen tests, ICD-10 codes, a positive real-time PCR (RT-PCR) and clinical signs and history (Table WA3.1).

- The sensitivity pooled across 12 studies (2057 participants) was 68% (95% CI 59–78%, I^2 = 94%, P < 0.01). The certainty of evidence was low (GRADE evidence profile).
- The specificity pooled across 12 studies (2057 participants) was 74% (95% CI 69–79%, I^2 = 72%, P < 0.01). The certainty of the evidence was low (GRADE evidence profile).
- Data on PPV and NPV were reported in three studies (828 participants): one was conducted in Egypt in 2014, one in the USA in 1991 and one in Iraq in 2014. Two studies involved children with clinically suspected meningitis, one study involved patients of all ages with suspected acute meningitis. The median PPV was 84% (range 7–85%) and the median NPV was 60% (range 35–84%), with overall moderate certainty of evidence for PPV and high for NPV (GRADE evidence profile).
- The LR+ was reported in 12 studies (2057 participants) and the median was 2.71 (range 1.11–4.16). The LR− was reported in 12 studies (2057 participants) and the median was 0.40 (range 0.12–0.94). The overall certainty of the evidence was moderate for LR+ and LR−.
- The AUC was reported in six studies (553 participants), with a median of 0.75 (range 0.68–0.82). The overall certainty of the evidence was moderate (GRADE evidence profile).
- Evidence suggests that the peripheral white blood cell count may have moderate to low sensitivity and moderate specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.2 Parameter 2: Peripheral blood neutrophil count/percentage

A total of two studies were found, including one involving children and one that did not report the age category. Reference standards that were used were a positive CSF culture

in one and the presence of bacterial antigens or bacterial nucleic acids identified in CSF or blood in one.

- The sensitivity pooled across the two studies (350 participants) was 89% (95% CI 84–92%, $I^2 = 0\%$, $P < 0.0001$). The certainty of the evidence was moderate (GRADE evidence profile).
- The specificity pooled across the two studies (350 participants) was 58% (95% CI 33–84%, $I^2 = 95\%$, $P < 0.0001$). The certainty of the evidence was low (GRADE evidence profile).
- Data on the LR+ and LR− were reported in two studies (350 participants): the LR+ was 3.2 (95% CI not reported) in one study and 1.6 (95% CI not reported) in one study. The LR− was 0.13 (95% CI not reported) in one study and 0.27 (95% CI not reported) in one study. The overall certainty of the evidence was moderate for LR+ and LR− (GRADE evidence profile).
- Data on PPV, NPV and AUC were not reported.
- Evidence suggests that the peripheral blood neutrophil count/percentage is likely to have moderate to high sensitivity and may have low specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.3 Parameter 3: Serum C-reactive protein

Overall, 18 studies were found, including four studies involving adults, nine involving children and four involving patients of all ages (one study did not report the age of the population). Reference standards varied between studies, and included combinations of the following: a positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, ICD-10 codes, a positive RT-PCR and clinical diagnosis (Table WA3.1).

- The sensitivity pooled across 15 studies (2354 participants) was 82% (95% CI 74–89%, $I^2 = 92\%$, $P < 0.01$). The certainty of the evidence was high (GRADE evidence profile).
- The specificity pooled across 15 studies (2354 participants) was 84% (95% CI 77–92%, $I^2 = 96\%$, $P < 0.01$). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in three studies (828 participants): one was conducted in Egypt in 2014, one in the USA in 1991 and one in Iraq in 2014. Two studies involved children with clinically suspected meningitis, and one study involved patients of all ages with suspected acute meningitis. The median PPV was 85% (range 11–93%) and the median NPV was 63% (range 54–98%). The overall certainty of the evidence for PPV and NPV was moderate (GRADE evidence profile).
- Data on LR+ and LR− was reported in 15 studies (2354 participants). The median LR+ was 3.33 (range 1.78–36.12) and the median LR− was 0.27 (range 0–0.68). The overall certainty of the evidence was high for LR+ and LR− (GRADE evidence profile).

- Data on AUC was reported in eight studies (661 participants), with a median AUC of 0.76 (range 0.56–0.94). The overall certainty of the evidence was moderate (GRADE evidence profile).
- Evidence suggests that peripheral blood CRP has moderate to high sensitivity and moderate to high specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.2.4 Parameter 4: Serum procalcitonin

Overall, 14 studies were found, including three studies involving adults, nine studies involving children and two studies involving patients of all ages. Reference standards varied between studies, and included combinations of the following: a positive CSF culture, positive Gram stain, positive blood culture, CSF abnormalities of protein, glucose and leukocyte count, positive antigen tests, positive RT-PCR and clinical diagnosis (Table WA3.1).

- The sensitivity pooled across 13 studies (1336 participants) was 87% (95% CI 75–98%, $I^2 = 90\%$, $P < 0.01$). The certainty of the evidence was high (GRADE evidence profile).
- The specificity pooled across 13 studies (1336 participants) was 86% (95% CI 79–93%, $I^2 = 86\%$, $P < 0.01$). The certainty of the evidence was high (GRADE evidence profile).
- Data on PPV and NPV were reported in two studies (199 participants): one was conducted in Iraq in 2014 and involved children with clinically suspected meningitis, and one was conducted in Spain in 2017 and involved patients aged > 15 years diagnosed with acute meningitis at the emergency department. The PPV was 88% (95% CI not reported) in one study and 99% (95% CI 92–100) in one study, with overall moderate certainty of evidence. The NPV was 72% (95% CI not reported) in one study and 91% (95% CI 79–98) in one study, with overall moderate certainty of evidence (GRADE Evidence Profile).
- Data on LR+ and LR− were reported in 13 studies (1336 participants) with a median LR+ of 5.21 (range 1.64–58.24) and a median LR− of 0.05 (range 0−0.80). The overall certainty of the evidence was high for LR+ and LR− (GRADE evidence profile).
- The AUC was reported in 10 studies (937 participants) and the median AUC was 0.95 (range 0.67–1.0). The overall certainty of the evidence was moderate (GRADE evidence profile).
- Evidence suggests that serum procalcitonin has good sensitivity and good specificity for diagnosing bacterial meningitis in a population of patients with acute suspected meningitis.

3.3 GRADE evidence profile

Table WA3.2 presents the GRADE evidence profiles for this review.

Table WA3.2a GRADE evidence profile parameter 1: peripheral white blood cell count

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Impre-cision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	12	2057	3480–15 000 cells/mm^3 (1 NR)	79 (55–82)	68% (95% CI 59–78%, I^2 = 94%, P < 0.01)	Serious[a]	Not serious	Serious[c]	Not serious	Not serious	⊕⊕◯◯ Low
Specificity, %	12	2057	3480–15 000 cells/mm^3 (1 NR)	88 (56–100)	74% (95% CI 69–79%, I^2 = 72%, P < 0.01)	Serious[a]	Not serious	Serious[c]	Not serious	Not serious	⊕⊕◯◯ Low
PPV, %	3	828	10 000–15 000 cells/mm^3 (1 NR)	84 (7–85)	NA	Not serious	Not serious	Serious[d]	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	3	828	10 000–15 000 cells/mm^3 (1 NR)	60 (35–84)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High

LR+	12	2057	3480–15 000 cells/mm^3 (1 NR)	2.71 (1.11–4.16)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	12	2057	3480–15 000 cells/mm^3 (1 NR)	0.40 (0.12–0.94)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
AUC	6	553	NA	0.75 (0.68–0.82)	NA	Serious[b]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC: area under the receiver-operating characteristic curve; CI: confidence interval; LR+: positive likelihood ratio; LR−: negative likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV = positive predictive value.

[a] High risk of bias in 5/12 studies.

[b] High risk of bias in 3/6 studies.

[c] Two studies value ≤ 50%.

[d] One out of three studies very low value.

Table WA3.2b GRADE evidence profile parameter 2: peripheral blood neutrophil count/percentage

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Impre-cision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	2	350	73–83%	91 (95% CI NR), 88 (95% CI NR)	89% (95% CI 84–92%, I^2 = 0%, P < 0.0001)	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
Specificity, %	2	350	73–83%	72 (95% CI NR), 45 (95% CI NR)	58% (95% CI 33–84%, I^2 = 95%, P < 0.0001)	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	⊕⊕◯◯ Low
PPV, %	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NPV, %	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LR+	2	350	73–83%	3.2 (95% CI NR), 1.6 (95% CI NR)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR−	2	350	73–83%	0.13 (95% CI NR), 0.27 (95% CI NR)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
AUC	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

AUC: area under the receiver-operating characteristic curve; CI: confidence interval; LR+: positive likelihood ratio; LR−: negative likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

[a] High risk in 1 out of 2 studies. [b] Confidence interval of pooled result below 50%.

Table WA3.2c GRADE evidence profile parameter 3: serum C-reactive protein

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Impre-cision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	15	2354	10–84 mg/L (1 NR)	80 (42–100)	82% (95% CI 74–89%, I^2 = 92%, P < 0.01).	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Specificity, %	15	2354	10–84 mg/L (1 NR)	83 (55–100)	84% (95% CI 77–92%, I^2 = 95%, P < 0.0001)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	3	828	10 mg/L, 60 mg/L (1 NR)	84.6 (11–93)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	3	828	10 mg/L, 60 mg/L (1 NR)	63.1 (54–98)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	15	2354	10–84 mg/L (1 NR)	3.33 (1.78–36.12)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
LR−	15	2,354	10–84 mg/L (1 NR)	0.27 (0-0.68)	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
AUC	8	661	NA	0.76 (0.56–0.94)	NA	Serious[b]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC: area under the receiver-operating characteristic curve; CI: confidence interval; LR+: positive likelihood ratio; LR–: negative likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

[a] High risk in 1/3 studies and unclear risk in 1/3 studies.

[b] High risk of bias in 4/8 studies.

Table WA3.2d GRADE evidence profile parameter 4: serum procalcitonin

Summary of evidence						Certainty assessment					
Outcome	**No. of studies**	**No. of patients**	**Range cut-offs**	**Result: median (range)**	**Result: pooled estimate**	**Risk of bias**	**Impre-cision**	**Incon-sistency**	**Indirect evidence**	**Publication bias**	**Overall quality of evidence**
Sensitivity, %	13	1336	0.16–5.9 ng/ml (1 NR)	95 (24–100)	87% (95% CI 75–98%, I^2 = 90%, P < 0.01)	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Specificity, %	13	1336	0.16–5.9 ng/ml (1 NR)	85 (59–100)	86% (95% CI 79–93%, I^2 = 86%, P < 0.01).	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
PPV, %	2	199	1 ng/ml (1 NR)	88 (95% CI NR), 99 (95% CI 92–100)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
NPV, %	2	199	1 ng/ml (1 NR)	72 (95% CI NR), 91 (95% CI 79–98)	NA	Not serious	Serious[a]	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate
LR+	13	1336	0.16–5.9 ng/ml (1 NR)	5.21 (1.64–58.24	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
LR−	13	1336	0.16–5.9 ng/ml (1 NR)	0.05 (0–0.80).	NA	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High

AUC	10	937	NA	0.95 (0.67–1.0)	NA	Serious[a]	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕◯ Moderate

AUC: area under the receiver-operating characteristic curve; CI: confidence interval; LR+: positive likelihood ratio; LR−: negative likelihood ratio; NA: not applicable; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

[a] Total cumulative study population is low and number of studies is small.

3.4 Additional evidence not reported in GRADE evidence profiles

There is no additional evidence to report.

3.5 Research gaps

The main research gaps concerning peripheral blood parameters for the diagnosis of acute meningitis in a population of patients with clinically suspected meningitis include the lack of well-designed observational cohort studies, that (i) include all patients with suspected acute meningitis, and (ii) clearly define the characteristics of bacterial meningitis, based not only on a positive CSF culture, but including clinical signs, symptoms and other CSF abnormalities (CSF protein, glucose, leukocyte count) as well. Such study designs would enable reliable calculations of diagnostic accuracy, including PPVs and NPVs. Moreover, novel diagnostics (biomarkers, metagenomics) for acute bacterial meningitis are warranted in order to achieve fast and accurate diagnosis and overcome current problems with diagnostics, such as long turnaround times, especially in low-resource settings.

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Appendix 1. Search strategy used to identify primary studies

This search covers three research questions, as explained in section 2.3.

Table WA3.A1.1 Database: Ovid MEDLINE, 1946 to 26 January 2024

No.	Searches	Results
1	meningiti*.ti,ab,kf. or exp meningitis/	90 289
2	Polymerase Chain Reaction/	250 656
3	(((DNA or RNA or nucleic-acid or gene) adj2 amplification) or PCR or "polymerase chain reaction" or ddpcr or qpcr or RT-PCR or rtpcr or NAT).ti,ab,kf.	854 020
4	2 or 3	947 412
5	C-Reactive Protein/ or Procalcitonin/ or exp Leukocyte Count/	156 743
6	((c-reactive adj protein) or crp or wbc or (white-blood adj cell) or procalcitonin or leukocyte* or neutrophil* or lymphocyte* or monocyte*).ti,ab,kf.	866 569
7	5 or 6	926 367
8	exp Bacterial Typing Techniques/ or gram-negative bacteria/ or gram-positive bacteria/ or exp Leukocytes/ or exp Leukocyte Count/ or Glucose/ or exp Lactates/ or Proteins/ or exp Cerebrospinal Fluid Proteins/ or exp Albumins/ or Cell Culture Techniques/ or exp Virus Cultivation/	1 666 250
9	((gram adj2 stain*) or ((viral or virus) adj3 (cultivation* or culture* or plaque)) or leukocyt* or neutrophil* or lymphocyte* or monocyte* or glucose or lactate* or protein* or albumin* or culture).ti,ab,kf.	5 335 465
10	8 or 9	5 953 596
11	Spinal Puncture/ or exp Cerebrospinal Fluid/	25 691
12	(((lumbar or spinal or cerebrospinal) adj3 (fluid or puncture or tap)) or csf).ti,ab,kf.	184 831
13	11 or 12	191 328
14	10 and 13	69 651
15	4 or 7 or 14	1 860 585

16	1 and 15	14 752
17	"sensitivity and specificity"/ or "mass screening"/ or "reference values"/ or "false positive reactions"/ or "false negative reactions"/ or (specificit* or screening or false positive* or false negative* or accuracy or predictive value* or reference value* or roc* or likelihood ratio*).tw.	2 308 396
18	16 and 17	2 332
19	exp animals/ not humans/	5 190 821
20	18 not 19	2 250
21	exp Meningitis, Bacterial/	25 915
22	(((bacterial or meningococcal or pneumococcal or Neisseria or meningitides or Streptococcus or pneumoniae or Haemophilus or Hib or influenzae or Listeria or monocytogenes or Escherichia or coli or agalactiae or pyogenes or Staphylococcus or aureus or Cryptococcus or neoformans) adj5 meningiti*) or (meningococcal adj2 disease)).ti,ab.	26 122
23	21 or 22	40 727
24	4 or 14	1 011 671
25	23 and 24	5 800
26	17 and 25	1 219
27	limit 26 to yr="1946 - 2013"	747
28	20 not 27	1 526

4. Cranial imaging

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Abbreviations

AST	antimicrobial susceptibility testing
AUC	area under the receiver-operating-characteristics curve
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PCR	polymerase chain reaction
PICO	population, intervention, comparator and outcome(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

1. Background

Acute meningitis is a life-threatening condition that requires timely and accurate diagnosis in order to initiate appropriate patient management. Meningitis can be caused by bacteria, viruses, fungi or parasites. If the cause is bacterial, prompt initiation of appropriate antibiotics is needed to prevent severe complications and reduce mortality. Typical clinical characteristics, such as headache, neck stiffness, fever and an altered mental state, are only present in 40–50% of patients with suspected meningitis, often posing diagnostic dilemmas *(1-3)*. Lumbar puncture is necessary to obtain cerebrospinal fluid (CSF) and perform CSF examination but carries a risk of adverse events, especially when intracranial abnormalities are present *(3)*. In the presence of space-occupying lesions with brain midline shift detected on cranial imaging, it may contribute to cerebral herniation and poor outcome *(2)*. Nonetheless, cranial imaging – e.g. a computed tomography (CT) scan – may not be widely available or accessible, especially in resource-limited settings, which could lead to delays in treatment initiation. Identifying clinical characteristics that can predict the presence of such abnormalities may aid with risk assessment and decision-making regarding lumbar puncture. However, variations exist in clinical practice regarding the use of cranial imaging prior to lumbar puncture, depending on the setting and the resources available.

As part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, this systematic review was conducted to establish which clinical characteristics could be used to identify individuals at risk of cerebral herniation where cranial imaging should be performed or, in the absence of cranial imaging, lumbar puncture would be contraindicated and should be deferred.

2. Methodology

The clinical characteristics that might predict intracranial abnormalities were addressed in the review carried out by van de Beek et al. for *Nature* Primers *(4)* and in the guideline on the diagnosis and treatment of acute bacterial meningitis developed by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) *(5)*, both published in 2016. Since these reviews were of high quality and covered the literature on acute bacterial meningitis up to 2014, this report summarizes the data from 2014 onwards on the clinical characteristics that might predict intracranial abnormalities, systematically searched for and reviewed. Additionally, the evidence from before 2014, based on reviews conducted as part of the ESCMID guideline, was reviewed and summarized in a narrative form (section 3.2).

2.1 Research question and study design

Among cases of suspected acute meningitis, can clinical characteristics be used to predict the presence of intracranial abnormalities associated with increased risk of adverse events secondary to lumbar puncture, as detected using cranial imaging?[8]

Population: Suspected cases of acute meningitis (adults and children > 1 month of age).

Index test/Intervention: Presence of any of the following clinical characteristics: a history of CNS lesions, focal neurological deficits, altered consciousness, new-onset seizures, severe immunocompromised status (e.g. HIV/AIDS infection or immunosuppressive medication after organ transplantation) or signs of increased intracranial pressure (including but not limited to papilledema).

Reference standard/comparator: Intracranial abnormalities associated with adverse events secondary to lumbar puncture, defined as space-occupying lesions with brain shift detected on cranial imaging.

Outcomes:

Critical outcomes (as prioritized by the Guideline Development Group):

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value
- Likelihood ratios.

Other outcomes: Area under the receiver-operating-characteristics curve (AUC).

[8] Intracranial abnormalities associated with increased risk of adverse events secondary to lumbar puncture are defined as space-occupying lesions with brain shift detected on cranial imaging.

Study designs: Cross-sectional and case-controlled studies. Case reports or case series were excluded.

2.2 Eligible studies

Published language: Studies published in English, French, German, Italian, Portuguese and Spanish were considered for inclusion. For studies in other languages, networks within WHO and Cochrane were used for support with screening and/or translation. Studies in Chinese and Korean were excluded.

Exclusion criteria

- The following groups of patients were excluded:
- those with tuberculous meningitis;
- those with hospital-acquired, nosocomial, and health care-associated meningitis;
- those with subacute and chronic meningitis;
- newborns (0–28 days) with meningitis;
- patients with non-infectious meningitis (e.g. meningitis caused by drugs, malignancy or autoimmune diseases).

Subgroups: None considered.

2.3 Search strategy

- One comprehensive search strategy was developed to identify relevant studies. The databases PubMed, Embase and Cochrane Library were searched for articles published up to the present date.
- The exact search terms can be found in Appendix 1. Search strategy used to identify
- The search was conducted in English on the 26 January 2024.

2.4 Selection of studies

The two authors (NSG and MCB) screened all titles and abstracts independently and assessed their eligibility according to the inclusion and exclusion criteria. Any disagreements were resolved by discussion. The full text of the articles found to be potentially relevant on the basis of their titles and abstracts was retrieved and examined in the light of the same inclusion criteria by each author. Any disagreements regarding the full-text screening were resolved by discussion.

Rayyan was used for reference screening, title, abstract and full-text selection.

2.5 Data extraction and management

Data extraction was performed by one author (NSG) and any uncertainties were discussed with the second author (MCB). The following categories of data were extracted:

- publication year and author(s);
- study type and setting;
- population, intervention, comparison and outcome;
- characteristics of patients included (sex, age category, total number of cases, total number of non-cases, definitions of disease categories);
- outcomes and results.

2.6 Assessment of risk of bias in studies included in the review

The quality of the studies included has been assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, by one author and has been checked by the other. The specific categories of the QUADAS-2 tool were tailored to our research questions.

2.7 Data synthesis

Where feasible (i.e. where there were at least two contributing studies and homogeneous data), meta-analyses were conducted, using a random-effects model for proportions to provide pooled estimates for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). All meta-analyses were conducted using the R software packages “meta” and “metafor”. Where meta-analysis was not feasible, ranges and medians were provided to summarize the findings. Data on the NPV and PPV were extracted and included in the meta-analysis of non-case control studies only, because these measures are considered highly dependent on prevalence.

If multiple cut-offs were reported by one article, one cut-off was included for meta-analysis to prevent dependent results. The choice of this cut-off was based on clinical relevance.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The GRADE assessments were tailored to our research questions. The overall certainty of the evidence was downgraded for imprecision if the confidence interval (CI) of the pooled estimate results was very wide, or if the CI boundary was below 60%.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No subgroup analysis was conducted.

2.10 Sensitivity analysis

No sensitivity analysis was conducted.

2.11 Deviations from the review protocol

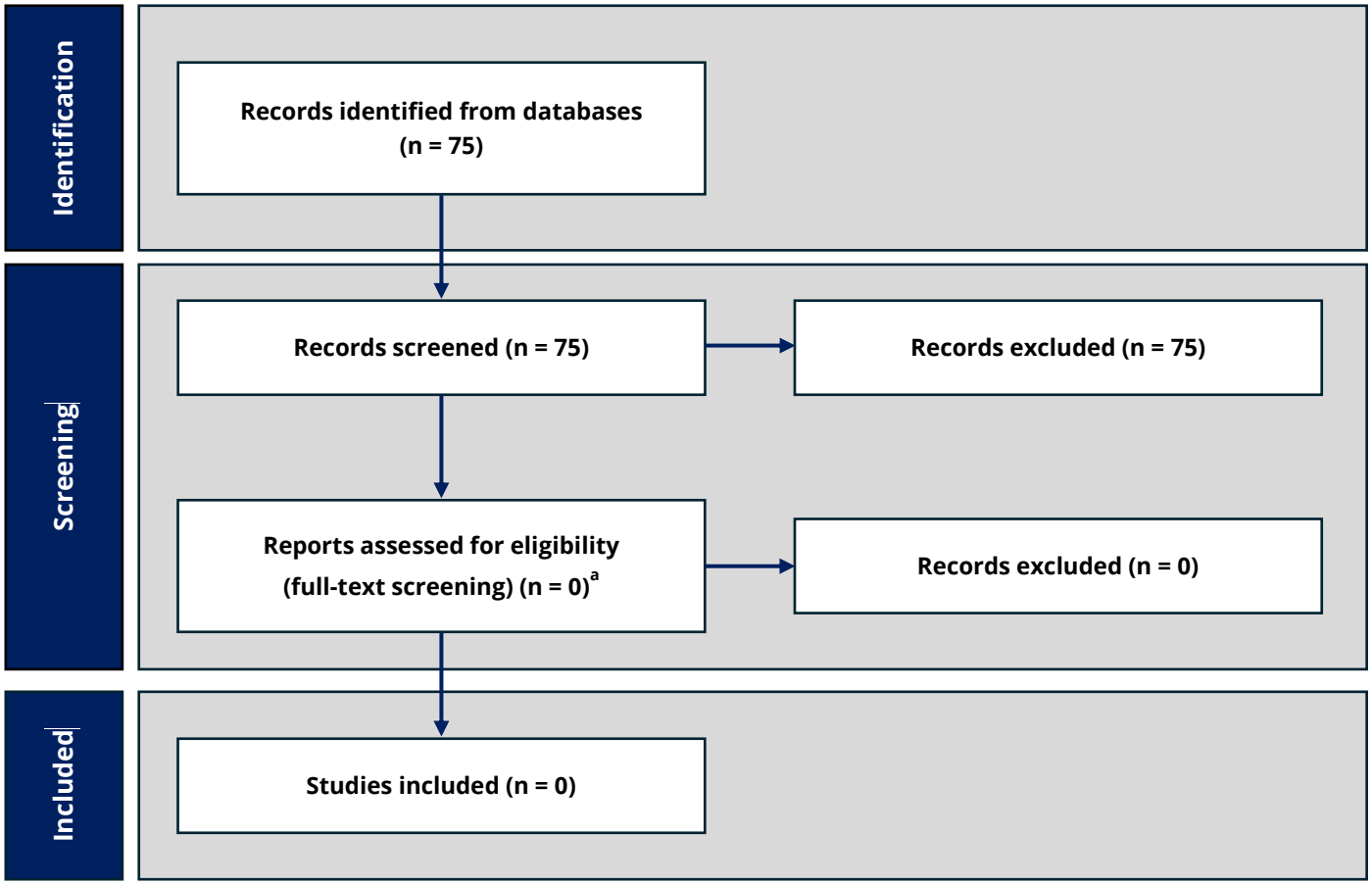
There were no deviations from the protocol.

3. Results

3.1 Studies identified by the search process

Figure WA4.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the review. A total of 75 records were retrieved for the research question, all of which were excluded on the basis of the title and abstract. No articles were screened for full-text eligibility. No articles were included that were published after 2014. A narrative description of one prospective study published before 2014 and included in the ESCMID guidelines is provided.

Fig. WA4.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profiles

None.

3.1.2 Studies excluded from the review (full-text screening)

None.

3.1.3 Studies with additional evidence

Costerus, Brouwer, Bijlsma, Tanck, van der Ende and van de Beek *(6),* Costerus, Lemmens, van de Beek and Brouwer *(7),* Hasbun, Abrahams, Jekel and Quagliarello *(8)*.

3.2 Narrative description of diagnostic performance evidence

Parameter 1: Presence of clinical characteristics that may predict intracranial abnormalities on cranial imaging, which are associated with an increased risk of adverse events following lumbar puncture in suspected acute meningitis cases

- Evidence from before 2014 was retrieved from the ESCMID guideline. It consisted of one retrospective study involving adults aged > 16 years with clinically suspected meningitis who were seen in the emergency department *(8)*. A total of 235 patients were involved and the presence of baseline clinical characteristics associated with an increased likelihood of abnormal findings following a computed tomography (CT) scan of the head were investigated. Among the patients who underwent CT of the head, those who were at least 60 years of age ($P < 0.001$, risk ratio 4.3 [95% CI 2.9–6.4]), those who were immunocompromised ($P = 0.01$, risk ratio 1.8 [95% CI 1.1–2.8]), those who had a history of a CNS disease or condition ($P < 0.001$, risk ratio 4.8 [95% CI 3.3–6.9]), those who had had a seizure within one week before presentation ($P < 0.001$, risk ratio 3.2 [95% CI 2.1–5.0]), those who had an abnormal level of consciousness ($P < 0.001$, risk ratio 3.3 [95% CI 2.2–4.4]), those who were unable to answer two consecutive questions correctly ($P < 0.001$, risk ratio 3.8 [95% CI 2.5–5.8]), those with gaze palsy ($P = 0.003$, risk ratio 3.2 [95% CI 1.9–5.4]), those with abnormal visual fields ($P < 0.001$, risk ratio 4.0 [95% CI 2.7–5.9]), facial palsy ($P < 0.001$, risk ratio 4.9 [95% CI 3.8–6.3]), those with arm drift ($P < 0.001$, risk ratio 4.0 [95% CI 2.7–5.8]), those with leg drift ($P < 0.001$, risk ratio 4.4 [95% CI 3.0–6.5]) or those with abnormal language (i.e. aphasia, dysarthria or extinction, $P < 0.001$, risk ratio 4.3 [95% CI 2.9–6.5]) were significantly more likely to have abnormal findings on their CT scan than patients without these characteristics at baseline.
- Additional evidence on the implementation of such criteria in clinical practice was provided by two studies, published in 2016 and 2020 *(6, 7)*. These studies involved adult patients with suspected CNS infection who underwent CSF examination, and evaluated the adherence to the recommendations in the bacterial meningitis

guidelines published by the Infectious Disease Society of America (IDSA) in 2004 *(9)* and those published by ESCMID in 2016 *(5)*. They showed that the majority of patients with suspected CNS infections presenting to the emergency department received cranial imaging, irrespective of the guideline criteria and thus that adherence to these criteria was consistently poor *(6, 7)*. Moreover, experienced neurologists and neuroradiologists could not reliably assess intracranial abnormalities associated with increased risk of adverse events secondary to a lumbar puncture using cranial imaging.

3.3 Additional evidence not reported in the GRADE evidence profiles

Additional evidence is outlined in the narrative description (see section 3.2).

3.4 Research gaps

The main research needed to determine whether clinical characteristics can be used to predict the presence of intracranial abnormalities associated with an increased risk of adverse events secondary to lumbar puncture, using cranial imaging, among cases of suspected acute meningitis, includes studies investigating this research question in the right study population. To answer this question, all patients with a suspected CNS infection with or without CSF examination should be included. All studies published up to now miss patients in whom lumbar puncture is deferred because of CT abnormalities. Moreover, it is difficult to define outcome (CNS infection) in patients who have not had a CSF examination.

References[9]

1. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. Lancet Infect Dis. 2016;16(3):339-47 (https://doi.org/10.1016/S1473-3099(15)00430-2).
2. van de Beek D, Brouwer MC, Koedel U, Wall EC. Community-acquired bacterial meningitis. Lancet. 2021;398(10306):1171-83 (https://doi.org/10.1016/S0140-6736(21)00883-7).
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9. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39(9):1267-84 (https://doi.org/10.1086/425368).

[9] All references were accessed on 03 January 2025.

Appendix 1. Search strategy used to identify primary studies

This search includes research questions 1–3.

Table WA4.A1.1 Ovid MEDLINE 1946 to January 2024

#	Searches	Results
1	exp Meningitis, Bacterial/	25815
2	Bacterial Meningiti*.ti,ab.	8194
3	((bacterial or meningococcal or pneumococcal or Neisseria or meningitides or Streptococcus or pneumoniae or Haemophilus or Hib or influenzae or Listeria or monocytogenes or Escherichia or coli or agalactiae or pyogenes or Staphylococcus or aureus or Cryptococcus or neoformans) adj5 meningiti*).ti,ab.	23539
4	or/1-3	38623
5	Spinal Puncture/	6803
6	((lumbar or spinal) adj3 (puncture or tap)).tw.	10229
7	exp Cerebrospinal Fluid/	19489
8	spinal fluid.tw.	5620
9	cerebrospinal fluid.tw.	100841
10	CSF.tw.	114630
11	or/5-10	186863
12	4 and 11	9085
13	(ae or de or co).fs.	6812146
14	(safe or safety or side-effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.	2071372
15	13 or 14	8100806
16	12 and 15	3100

17	(CT adj3 (cine or scan* or x?ray* or xray*)).ab,ti.	125135
18	(CT or MDCT).ti.	106248
19	((electron?beam* or comput* or axial) adj3 tomography).ab,ti.	352444
20	tomodensitometry.ab,ti.	661
21	exp Tomography, X-Ray Computed/	494975
22	or/17-21	722171
23	16 and 22	340
24	limit 23 to yr="2014 -Current"	75

5. Timing of empiric antimicrobial treatment

Authors

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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CSF	cerebrospinal fluid
CT	commuted tomography
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
ICU	intensive care unit
MIC	minimum inhibitory concentration
NR	not reported
NRSI	non-randomized study on the effects of an intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
robvis	Risk-Of-Bias VISualization (a tool available as an R package and web app)
RR	risk ratio
WHO	World Health Organization

1. Background

Acute bacterial meningitis is a potentially life-threatening condition requiring immediate recognition and treatment. Despite the development of more effective antibiotics, bacterial meningitis continues to cause high mortality *(1)*.

Immediate administration of antibiotics is critical for patients with suspected acute bacterial meningitis. Early treatment with antibiotics has been shown to decrease mortality rates and neurological sequelae *(1)*. According to a study conducted by Meadow et al., the time from hospital admission to antibiotic administration varied in acute meningitis, with a median duration of 2.0 hours (interquartile ratio 1.25 to 3.33) *(2)*.

To optimize the diagnostic yield, blood and cerebrospinal fluid samples should be obtained for analysis and culture before antibiotic initiation. However, if there is a delay in obtaining the samples, administering antibiotics should still be prioritized over sampling. The choice of antibiotic should be based on the most probable pathogen, local antibiotic resistance patterns, and the drug's ability to penetrate the blood–brain barrier *(3)*.

This evidence synthesis explores the potential association between the timing of antibiotic administration in acute bacterial meningitis and the subsequent risk of death or neurological impairment. Early antibiotic administration could be variously defined as empiric antimicrobial treatment before admission into an inpatient setting (e.g. a hospital or health centre), or before referral, during transport via ambulance, and/or before lumbar puncture and cranial imaging. The recommendation from this evidence synthesis will guide the timing of empiric antibiotic treatment for acute meningitis.

This work was carried out for the development of the *WHO guidelines on meningitis diagnosis, treatment and care*.

2. Methodology

2.1 Research question and study design

Among cases with suspected acute meningitis, should empiric antimicrobial treatment be provided as soon as possible to reduce morbidity and mortality?

Population: Suspected cases of acute meningitis

Intervention: Empiric antimicrobial treatment administered as soon as possible (i.e. empiric antimicrobial treatment administered before admission into an inpatient setting (health centre, hospital), before referral, during transport (ambulance), and/or before lumbar puncture and/or cranial imaging)

Comparator: Delayed empiric antimicrobial treatment (i.e. empiric antimicrobial treatment administered contingent upon admission, referral and/or lumbar puncture and/or cranial imaging results)

Outcomes

Critical outcomes:

- mortality;
- time to resolution of symptoms;
- disease complications (sepsis, disseminated intravascular coagulation, neurological complications, including neurological sequelae).

Important outcomes:

- adverse effects;
- cerebrospinal fluid (CSF) culture-positivity rate;
- blood culture-positivity rate.

Study designs: A systematic review was performed using the primary studies identified by our search strategy. Only randomized controlled trials and prospective cohort studies with a comparator arm were included. The available data from retrospective cohorts relevant to the research question were summarized in the additional evidence (see section 3.3.1).

2.2 Eligible studies

Published language: All relevant studies were included, regardless of language as far as possible. The studies in English were evaluated by the review team. For studies in languages other than English, translated versions were obtained using online software.

Exclusion criteria:

- All non-randomized studies without a comparator (i.e. case reports, case series, and non-randomized studies without a comparator) were excluded.

- Any ongoing trials/studies with outcome data that could not be evaluated were also excluded.

2.3 Search strategy

Searches for primary studies were conducted in Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL) and Clinical trial registry maintained by the United States National Library of Medicine (https://ClinicalTrials.gov/). All databases were searched for studies published from 1946 to November 2023.

2.4 Selection of studies

A preliminary search for systematic reviews relevant to the research question was conducted. One Cochrane systematic review was found, by Sudarsanam et al., which applied to the research question *(4)*. The Cochrane review studied the effectiveness and safety of pre-admission antibiotics versus no pre-admission antibiotics or placebo as well as different pre-admission antibiotic regimens in decreasing mortality, clinical failure and morbidity in people with suspected meningococcal disease. AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) criteria for this study showed the overall confidence was high. This systematic review had not been updated since 2017; thus, the author and the Cochrane group were approached to see if a quick update could be performed. However, this was not deemed feasible in view of time constraints.

Another relevant systematic review was found, which included both prospective and retrospective studies that investigated the association between time to effective antibiotic therapy and clinical outcomes (i.e. death or neurological impairment) in adults with community-acquired bacterial meningitis (Eisen et al. *(5)*). According to the AMSTAR-2 criteria, the overall confidence for this systematic review was critically low as the review did not contain any published protocol or methods, and did not perform a risk of bias assessment for the studies included; no meta-analysis was able to be conducted owing to high heterogeneity.

Hence it was deemed appropriate to perform a new systematic review by focusing our search on the inclusion of primary studies (i.e. randomized controlled trials and prospective cohort studies with a comparator), as specified in our review protocol, which has been published in PROSPERO *(6)*. A search was conducted across the databases mentioned in section 2.3 to identify primary studies relevant to research questions 5–10 (i.e. this report and the next five reports in this web annex) on empiric antimicrobial treatment, the duration of antimicrobial treatment in both epidemic and non-epidemic settings, and post-exposure antimicrobial prophylaxis. The search yielded 15 158 studies. After filtering using the Rayyan tool *(7)*, 1194 duplicate articles were identified. Of these, 208 duplicates were manually removed by the review authors. Subsequently, the remaining 14 950 articles underwent independent screening by the review authors

through Rayyan. After title and abstract screening, 14 880 studies were excluded since they were not relevant to the research questions. Full-text screening was then conducted on 70 articles retrieved from the review authors' institutional libraries and WHO libraries, resulting in the full texts for 64 articles being obtained. However, the remaining six articles were excluded because four of them were clinical trials with unpublished data. Despite attempts to contact the authors, full-text versions of these trials could not be obtained. Additionally, full texts of the other two studies were also unavailable.

After thorough full-text screening, two prospective studies (Kaplan et al. *(8)* and Roznovský et al. *(9)*) were included in the meta-analysis and the rest were not found to be relevant to this research question (i.e. this report). Additional evidence was provided by other technical experts (see section 3.5), and one of these studies was included in the meta-analysis (Auburtin et al. *(10)*). The characteristics of the studies included in the review are given in Table WA5.1, and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram for the search is included in section 3.1 (Fig. WA5.2).

2.5 Data extraction and management

Two of three review authors (JSJ, HA, JM) used a piloted data extraction form to extract data on participant characteristics, disease severity, comorbidity, antimicrobial treatment and administration, and any concurrent treatments given, as well as the outcome measures defined by the research question.

For dichotomous outcomes, the review authors recorded the number of participants who had experienced the event and the number of participants in each treatment group. The number of participants analysed in each arm was recorded and the data used to calculate the number of participants lost to follow-up.

2.6 Assessment of risk of bias in studies included in the review

Two review authors (*JSJ, HA*) assessed the risk of bias for the primary and secondary outcomes using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) *(11)*. The risk of bias assessment was verified by the corresponding authors (*PR, AT*). The results have been reported in a traffic light plot (Fig. WA5.2) and the risk of bias summary created using the robvis tool *(12)*.

2.7 Data synthesis

Data were analysed using Review Manager (RevMan) software *(13)* by two review authors (*JSJ, HA*). When more than one study contributed to the evidence synthesis, data were pooled in meta-analyses using the random-effects model. Dichotomous data are presented and compared using risk ratios (RRs). All results are presented with the corresponding 95% confidence interval (CI).

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the certainty of evidence *(14)*. GRADE is a transparent framework designed for the development and presentation of evidence summaries, offering a systematic approach to formulating clinical practice recommendations. The quality of evidence was assessed for each outcome, and GRADE categorized it into four levels of certainty: very low, low, moderate and high. Certainty in the evidence for each outcome was evaluated across five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. The GRADE levels of certainty are defined below.

Box WA5.1 The certainty of evidence used in GRADE	
High ⨁⨁⨁⨁	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⨁⨁⨁O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⨁⨁OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⨁OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The results of the analysis have been summarized in Table WA5.5 and the summary effect estimates for the outcomes presented.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No subgroup analysis was performed.

2.10 Sensitivity analysis

No sensitivity analysis was performed.

2.11 Deviations from the review protocol

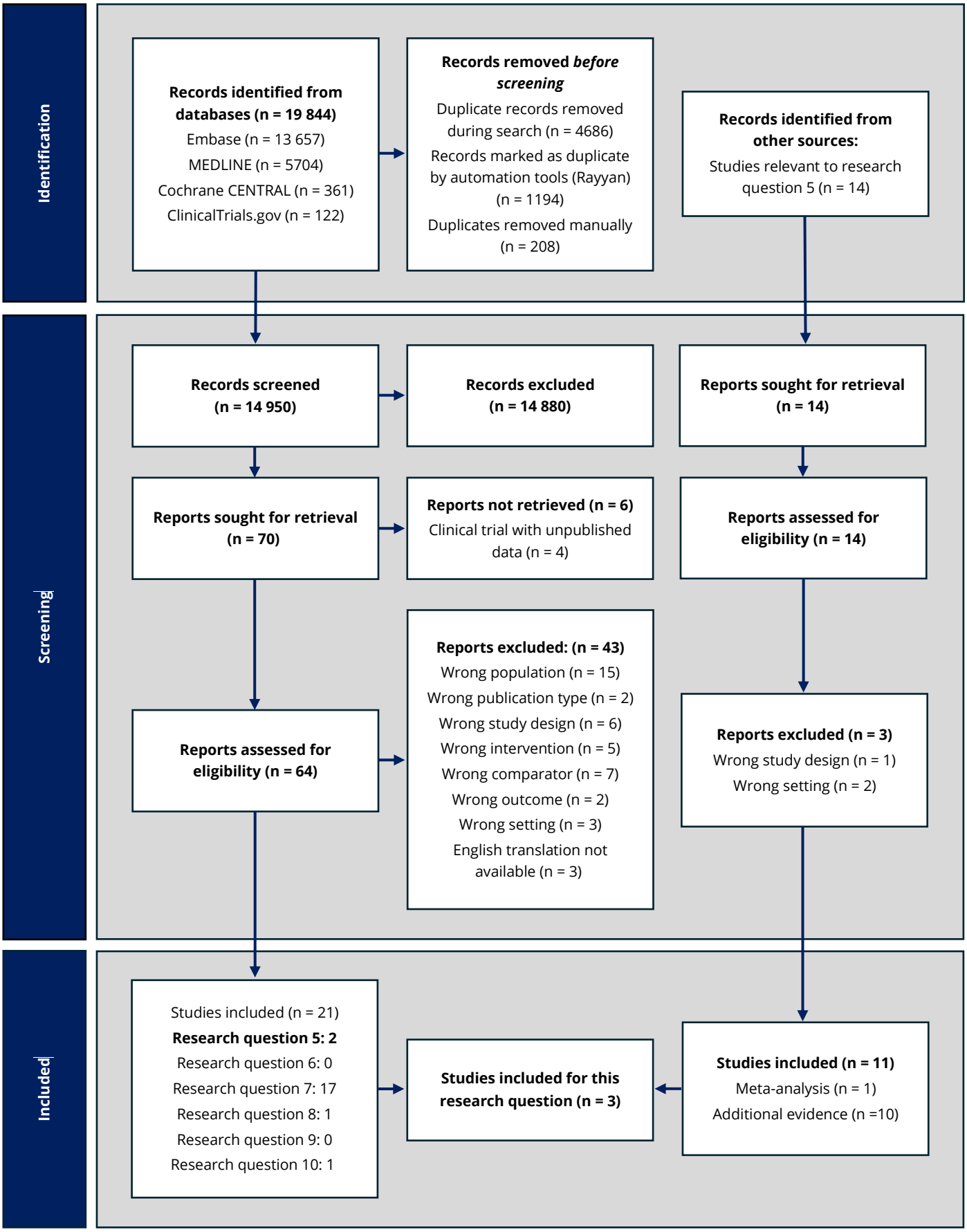
There was no deviation from the review protocol.

3. Results

3.1 Studies identified by the search process

Figure WA5.1 presents the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this systematic review.

Fig. WA5.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profile

Table WA5.1 presents the characteristics of the studies included in the GRADE evidence profile.

Table WA5.1 Characteristics of studies included in the GRADE evidence profile

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention/ control	Control	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
Kaplan (1986), the United States of America (USA) *(8)*	Prospective cohort (post hoc analysis of 2 prospective studies) i. Feigin et al. (1976) *(15)* ii. Lietman et al. (1984) *(16)*	Serious	Antibiotics prior to admission (ampicillin or chloramphenicol or moxalactam)	The first prospective study (enrolment between 1973 and 1977) included children with *H. influenzae* type b (Hib) meningitis. n = 120 The second comparative antibiotic trial (enrolment between 1981 and 1984) included patients with Hib meningitis.	No antibiotic before admission	Mortality sequelae (hearing loss, paresis) Cerebrospinal fluid (CSF) culture-positivity rate Blood culture-positivity rate	Hearing loss – brain stem auditory evoked response	NR

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention/ control	Control	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
				n = 130 Post hoc study: Intervention: 94 Control: 187				
Roznovský (2003), Czech Republic *(9)*	Prospective study	Serious	Patients received at least 1 dose of antibiotics active against *N. meningitidis* within 3 days before admission to regional hospital: Parenteral antibiotics: benzyl penicillin, other penicillins, third-generation cephalosporin, chloramphenicol, penicillins and cephalosporin, aminoglycosides (netilmicin or gentamicin), with penicillin or cephalosporin,	All patients (children and adults) with meningococcal disease (enrolment between 1996 and 2001) Intervention: 116 Control: 48	No antibiotic before admission	Mortality	NR	Mortality within 30 days of admission to hospital

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention/ control	Control	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
			chloramphenicol with penicillin; Oral antibiotics: penicillin or other penicillin antibiotics, cephalosporin, macrolides					
Auburtin (2006), France *(10)*	Prospective multicentre observational study	Serious	For patients infected with a *fully susceptible strain*, initial appropriate therapy includes treatment with one of the following regimens: Amoxicillin at a dose of 150 mg/kg per day Cefotaxime at a dose of 150 mg/kg per day Ceftriaxone at a dose of 70 mg/kg per day	All patients older than 18 years admitted to the ICU with community-acquired pneumococcal meningitis were prospectively evaluated. During the study period, a total of 156 consecutive episodes of pneumococcal meningitis among ICU patients were identified.	No control arm	Mortality Adverse events	NR	Mortality at 3 months after ICU admission

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention/ control	Control	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
			(maximum 4 g per day) For patients infected with *non-susceptible strains with cefotaxime MIC of less than or equal to 0.5 mg/L*, the same drugs are considered adequate, but dosing should be increased: Amoxicillin or cefotaxime at a dose of 200 mg/kg per day Ceftriaxone at a dose of 100 mg/kg per day When the *cefotaxime MIC is greater than 0.5 mg/L*, appropriate therapy includes:					

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention/ control	Control	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
			A combination of cefotaxime or ceftriaxone (at the same dosages as above) Plus either vancomycin at a dose of 40–60 mg/kg per day after a loading dose of 15 mg/kg infused for 1 hour Or rifampin at a dose of 600–1200 mg per day					

CSF: cerebrospinal fluid; ICU: intensive care unit; MIC: minimum inhibitory concentration; NR: not reported.

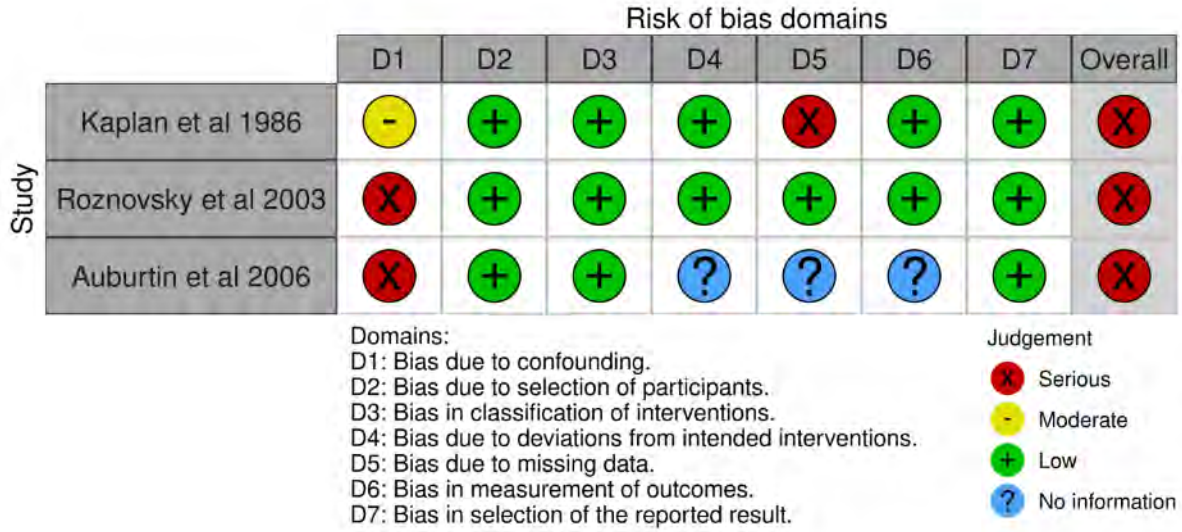
3.1.2 Studies excluded from the review

Table WA5.2 presents the studies excluded from the review, along with the reasons for their exclusion.

Table WA5.2 Excluded studies and reasons for exclusion

Lead author (Year)	Reason for exclusion
Anttilla (1991) *(15)*	Translated full text of this study not retrievable.
Aronin (1998) *(16)*	This study was a bivariate analysis (derivation cohort and validation cohort) based on the presence or absence of adverse events. There were no data on administration of antibiotics either before or after lumbar puncture. It did not fit into the research question inclusion criteria.
Køster-Rasmussen (2008) *(17)*	Exact time to lumbar puncture, imaging and hospital admission in relation to antibiotic administration was not available and hence it was not possible to obtain disaggregated data that would fit the research question.
Lepur (2007) *(18)*	Though 91% of patients received antibiotics within 1 hour of admission, exact time of lumbar puncture was not recorded and disaggregated data of those given antibiotics before or after lumbar puncture were not available. Hence did not fit into the research question inclusion criteria as it was not possible to compare early versus late administration of antibiotics.
Sudarsanam (2017) *(4)*	This was a systematic review conducted in 2017. No RCTs comparing pre-admission vs no pre-admission antibiotics were identified. One RCT comparing ceftriaxone vs long-acting chloramphenicol was included in the review but it did not fit into the research question of this evidence report.

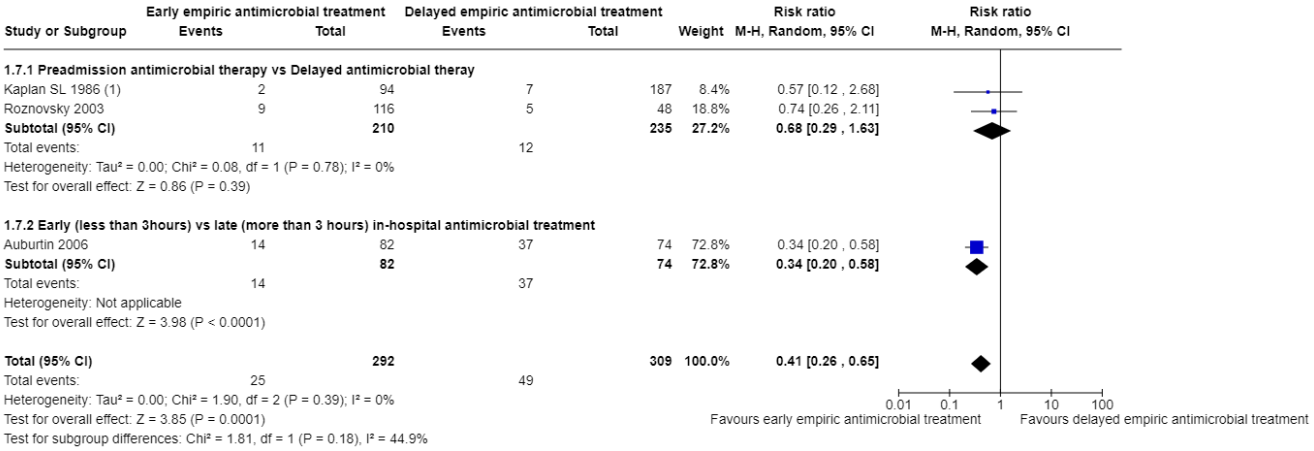
Fig. WA5.2 Risk of bias summary (carried out using robvis tool)



3.2 Forest plots

Forest plots for each outcome are presented below (Figs WA5.3–8).

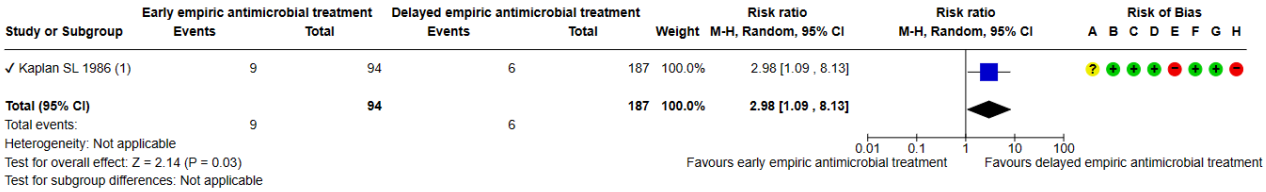
Fig. WA5.3 Mortality forest plot



Footnotes

(1) Intervention :- amoxicillin, chloramphenicol and moxalactam. Comparator :- Either no antibiotic or ineffective antibiotic (penicillin, dicloxacillin and erythromycin)

Fig. WA5.4 Disease complications (hearing loss) forest plot



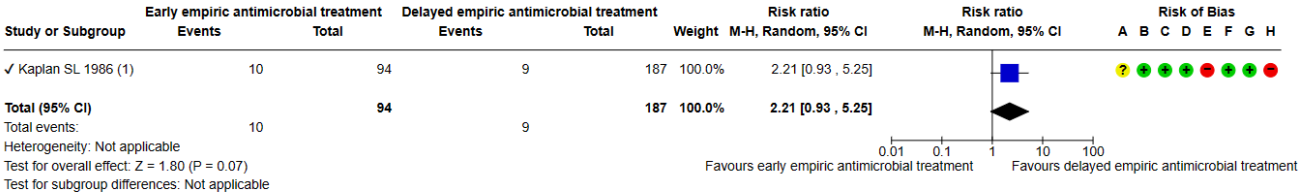
Footnotes

(1) Intervention :- amoxicillin, chloramphenicol and moxalactam. Comparator :- Either no antibiotic or ineffective antibiotic (penicillin, dicloxacillin and erythromycin)

Risk of bias legend

(A) Risk due to confounding
(B) Risk in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviations from intended interventions
(E) Bias due to missing data
(F) Bias in measurements of outcomes
(G) Bias in selection of reported results
(H) Overall risk of bias

Fig. WA5.5 Disease complications (paresis) forest plot



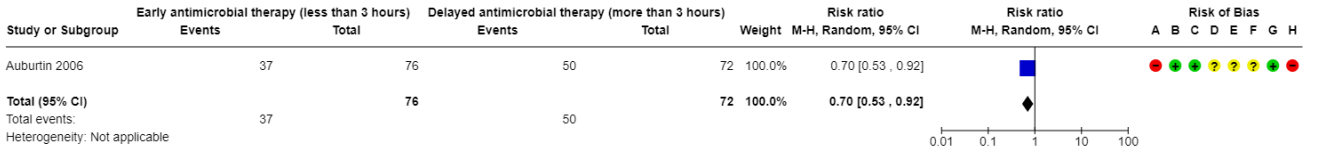
Footnotes

(1) Intervention :- amoxicillin, chloramphenicol and moxalactam. Comparator :- no antibiotic

Risk of bias legend

(A) Risk due to confounding
(B) Risk in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviations from intended interventions
(E) Bias due to missing data
(F) Bias in measurements of outcomes
(G) Bias in selection of reported results
(H) Overall risk of bias

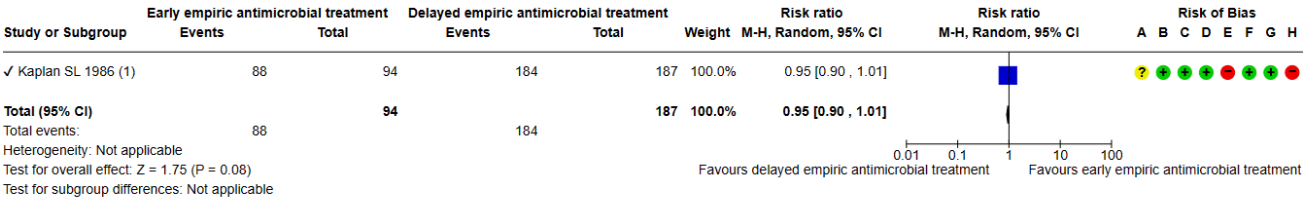
Fig. WA5.6 Adverse events forest plot



Risk of bias legend

(A) Risk due to confounding
(B) Risk in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviations from intended interventions
(E) Bias due to missing data
(F) Bias in measurements of outcomes
(G) Bias in selection of reported results
(H) Overall risk of bias

Fig. WA5.7 CSF culture-positivity rate forest plot



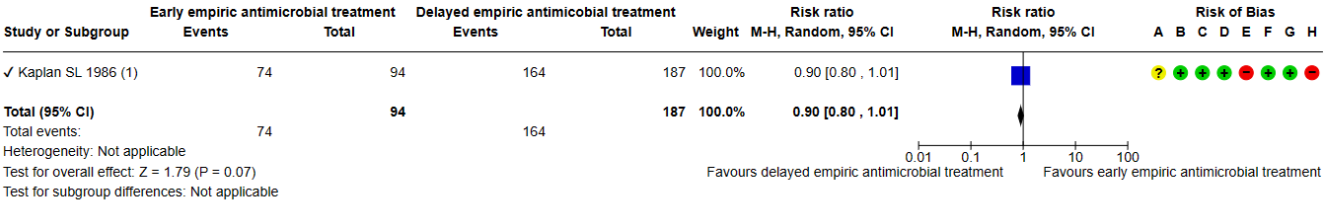
Footnotes

(1) Intervention :- amoxicillin, chloramphenicol and moxalactam. Comparator :- Either no antibiotic or ineffective antibiotic (penicillin, dicloxacillin and erythromycin)

Risk of bias legend

(A) Risk due to confounding
(B) Risk in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviations from intended interventions
(E) Bias due to missing data
(F) Bias in measurements of outcomes
(G) Bias in selection of reported results
(H) Overall risk of bias

Fig. WA5.8 Blood culture-positivity rate forest plot



Footnotes

(1) Intervention :- amoxicillin, chloramphenicol and moxalactam. Comparator :- Either no antibiotic or ineffective antibiotic (penicillin, dicloxacillin and erythromycin)

Risk of bias legend

(A) Risk due to confounding
(B) Risk in selection of participants into the study
(C) Bias in classification of interventions
(D) Bias due to deviations from intended interventions
(E) Bias due to missing data
(F) Bias in measurements of outcomes
(G) Bias in selection of reported results
(H) Overall risk of bias

3.3 GRADE evidence profile

Table WA5.3 Early versus delayed empiric antimicrobial treatment for suspected acute meningitis

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early empiric antimicrobial treatment**	**Delayed empiric antimicrobial treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality												
3 *(8-10)*	Non-randomized studies	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	25/292 (8.6%)	49/309 (15.9%)	RR 0.41 (0.26 to 0.65)	94 fewer per 1000 (from 117 fewer to 56 fewer)	⊕◯◯◯ Very low	Critical
Neurological sequelae – hearing loss												
1 *(8)*	Non-randomized studies	Very serious[d]	Not serious	Not serious	Very serious[e]	None	9/94 (9.6%)	6/187 (3.2%)	RR 2.98 (1.09 to 8.13)	64 more per 1000 (from 3 more to 229 more)	⊕◯◯◯ Very low	Critical
Neurological sequelae (paresis)												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirectness**	**Imprecision**	**Other con-siderations**	**Early empiric antimicrobial treatment**	**Delayed empiric antimicrobial treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 *(8)*	Non-randomized studies	Very serious[d]	Not serious	Not serious	Very serious[f]	None	10/94 (10.6%)	9/187 (4.8%)	RR 2.21 (0.93 to 5.25)	58 more per 1000 (from 3 fewer to 205 more)	⊕◯◯◯ Very low	Important
Adverse events												
1 *(10)*	Non-randomized studies	Very serious[g]	Not serious	Not serious	Serious[c]	None	37/76 (48.7%)	50/72 (69.4%)	RR 0.70 (0.53 to 0.92)	208 fewer per 1000 (from 326 fewer to 56 fewer)	⊕◯◯◯ Very low	Important
CSF culture-positivity rate												
1 *(8)*	Non-randomized studies	Very serious[d]	Not serious	Not serious	Serious[h]	None	88/94 (93.6%)	184/187 (98.4%)	RR 0.95 (0.90 to 1.01)	49 fewer per 1000 (from 98 fewer to 10 more)	⊕◯◯◯ Very low	Important
Blood culture-positivity rate												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirectness**	**Imprecision**	**Other con-siderations**	**Early empiric antimicrobial treatment**	**Delayed empiric antimicrobial treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 *(8)*	Non-randomized studies	Very serious[d]	Not serious	Not serious	Serious[h]	None	74/94 (78.7%)	164/187 (87.7%)	RR 0.90 (0.80 to 1.01)	88 fewer per 1000 (from 175 fewer to 9 more)	⨁◯◯◯ Very low	Important

CI: confidence interval; CSF: cerebrospinal fluid; RR: risk ratio.

[a] Downgraded by two levels for serious risk of bias as all the studies are non-randomized studies of the effects of interventions (NRSIs). Kaplan et al. *(8)* had a serious risk of bias in one domain and moderate in one domain, while Roznovský et al. *(9)* had a serious risk of bias in one domain and Auburtin et al. *(9)* had a serious risk of bias in one domain and no information in 3 domains.

[b] Downgraded by one level for indirectness because the intervention was given at varied time intervals in the three studies, varying from 4 days prior to admission to the emergency room in hospital to within 3 hours of admission to hospital (1 week before admission in Kaplan et al. *(8)*; within 3 days before admission in Roznovský et al. *(9)*; and less than 3 hours of admission in Auburtin et al. *(10)*).

[c] Downgraded by one level for serious imprecision as number of events did not reach optimal information size.

[d] Downgraded by two levels for very serious risk of bias as the study Kaplan et al. *(8)* is an NRSI and had a serious risk of bias in one domain and moderate risk of bias in one domain.

[e] Downgraded by two levels for very serious imprecision as the CIs were very wide, the number of events did not reach optimal information size and the upper and lower limits show mild to very significant harm.

[f] Downgraded by two levels for very serious imprecision as the CIs were very wide, the number of events did not reach optimal information size and the upper limit shows mild benefit and lower limit shows very significant harm

[g] Downgraded by two levels for very serious risk of bias as Auburtin et al. *(10)* is an NRSI and had a serious risk of bias in one domain and no information in three domains.

3.4 Description of intervention effects

All-cause mortality: Very-low-certainty evidence from three non-randomized prospective studies *(8-10)* featuring 601 patients revealed that the effect of empiric antimicrobial treatment administered as soon as possible on all-cause mortality was uncertain (RR 0.41, 95% CI 0.26 to 0.65; I^2 = 44.9%). Among the three studies included, Auburtin et al. *(10)* differed from the other two in that it included early in-hospital empiric antibiotic therapy (≤ 3 hours and > 3 hours). The other two studies included antibiotics given at varying times before admission (median 3 days [0–7 days] in Kaplan et al. *(8)* and within 1–3 days before admission in Roznovský et al.*(9)*). Hence the data from Kaplan et al. *(8)* and Roznovský et al. *(9)* were combined and these data have been presented separately as subgroups.

- *Pre-admission therapy*: Very low certainty evidence from two prospective cohort studies featuring 445 patients showed that the effect of pre-hospital antimicrobial therapy was uncertain (RR 0.68, 95% CI 0.29–1.63).
- *Early in-hospital therapy*: Low certainty evidence from one prospective cohort study featuring 156 adults showed that early in-hospital antimicrobial treatment might reduce mortality (RR 0.34, 95% CI 0.20 to 0.58).

Neurological sequelae – hearing loss: Very-low-certainty evidence in one non-randomized prospective study (Kaplan et al. *(8)*) done on 281 patients revealed that the effect of empiric antimicrobial treatment administered prior to admission (pre-hospital therapy) on the neurological sequela of hearing loss was uncertain (RR 2.98, 95% CI 1.09 to 8.13). A possible explanation for the point estimate favouring the delayed empiric antibiotic group was the delay in admission experienced by patients in the pre-admission antibiotic group – median of 3 days in the intervention (early empiric antimicrobial therapy) arm versus median of 1 day in the comparator (delayed empiric antimicrobial therapy).

Neurological sequelae – paresis: Very-low-certainty evidence in one non-randomized study (Kaplan et al. *(8)*) done on 281 patients revealed that the effect of empiric antimicrobial treatment administered prior to admission (pre-hospital therapy) on the neurological sequela of paresis was uncertain (RR 2.21, 95% CI 0.93 to 5.25). A possible explanation for the point estimate favouring the delayed empiric antibiotic group was the delay in admission experienced by patients in the pre-admission antibiotic group (median of 3 days in the intervention arm versus median of 1 day in the comparator) as detailed above.

Adverse events: Very-low-certainty evidence from one non-randomized prospective study (Auburtin et al. *(10)*) done on 148 patients revealed that the effect of early in-hospital empiric antimicrobial treatment (≤ 3 hours) on adverse events was uncertain (RR 0.70; 95% CI 0.53 to 0.92).

CSF culture-positivity rate: Very-low-certainty evidence in one non-randomized study *(8)* done on 281 patients revealed that the effect of empiric antimicrobial treatment administered prior to admission on CSF culture-positivity rate was uncertain (RR 0.95, 95% CI 0.90 to 1.01).

Blood culture-positivity rate: Very-low-certainty evidence in one non-randomized study (Kaplan et al. *(8)*) done on 281 patients revealed that the effect of empiric antimicrobial treatment administered prior to admission on blood culture-positivity rate was uncertain (0.90, 95% CI 0.80 to 1.01).

3.5 Additional evidence not reported in GRADE evidence profiles

Retrospective studies were not included in the systematic review. However, 10 relevant retrospective studies were identified and summarized as additional evidence. The retrospective cohort studies with a comparator arm are presented in Table WA5.4, and the available outcomes are described in section 3.5.1. The remaining seven studies, which lack a comparator arm, are summarized in section 3.5.2.

Table WA5.4 Characteristics of retrospective cohort studies with comparator group included in additional evidence

Lead author (Year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Exclusion criteria	Inference
Cartwright[a] (1992) *(19)*	Retrospective review	Antibiotic administered before admission	Antibiotic not given before admission	Patients were accepted as having meningococcal disease if: (i) a meningococcus had been isolated from blood or cerebrospinal fluid (CSF); (ii) clinical evidence of meningitis had been accompanied by the presence of Gram negative diplococci in	Evidence of antibiotic treatment before admission was obtained from the general practitioner's referral letter or from the admitting doctor's notes.	Cases were excluded from analysis if the patient had been transferred from another hospital, if the patient had been admitted to hospital as a result of self-referral or developed meningococcal disease while in hospital, or if the final diagnosis was chronic meningococcal sepsis.	

	All cases (n = 340)		Cases of haemorrhagic rash (n = 177)	
Antibiotic	No. survived (%)	No. died (%)	No. survived (%)	No. died (%)
Given	88 (95)	5 (5)	71 (95)	4 (5)
Not given	224 (91)	22 (9)	90 (88)	12 (12)

Lead author (Year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Exclusion criteria	Inference
				CSF; (iii) signs and symptoms of meningitis or septicaemia had been accompanied by haemorrhagic rash.			
Miner (2001) *(20)*	Retrospective chart review	Antibiotic administered in emergency department (ceftriaxone or cefotaxime)	Antibiotics received in clinics or as inpatients	76% of adults and children with community-acquired meningitis received antibiotics in the emergency department (38 adults and 36 children), and the rest received antibiotics in clinics or as inpatients (17 adults and 7 children).	All recovered charts were reviewed to determine the presence of bacterial meningitis, as indicated by a positive CSF culture or a lumbar puncture with a neutrophilic pleocytosis associated with a positive blood culture or CSF antigen test.	169 charts were reviewed; four patients were excluded from data collection. Two were not included owing to insufficient data in the medical record, one because the etiology of the meningitis was *Mycobacterium avium-intracellulare* and the other because it was cryptococcus.	
Strang (1992) *(21)*	Retrospective analysis	Parenteral penicillin given	Antibiotics not given before admission	Patients with *Neisseria meningitidis*	All patients who were admitted to		

Lead author (Year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Exclusion criteria	Inference
		before admission		isolated from blood or CSF, or both, or Gram-negative diplococci had been seen in the CSF, or clinical signs of meningitis or septicaemia had been accompanied by a haemorrhagic rash.	the hospital and who fulfilled the case definition were included in the study.		

[a] Gloucester, Plymouth and Bath health districts have all experienced high rates of meningococcal disease over the past 10 years. Throughout the Gloucester outbreak the staff of the department of public health medicine encouraged local general practitioners to give parenteral benzylpenicillin when meningococcal disease was suspected, before patients were transferred to hospital.

3.5.1 Description of the outcomes

Mortality: All three retrospective studies contributed data to the outcome of all-cause mortality. In the study Cartwright et al. *(19)*, 93 out of 340 patients received antibiotics prior to admission, with the likelihood of getting antibiotics being higher in patients who presented with a rash (38% in patients with rash versus 8% in patients without a rash) suggesting acute meningococcemia with or without meningitis. The study mentioned a 40% reduction in mortality in patients who received pre-admission antibiotics but was not found to be statistically significant (RR 0.60 [95% CI 0.23 to 1. 54]). The agent used as parenteral therapy was not mentioned in the study and the possibility of differential time to admission between the pre-admission antibiotic group and the no antibiotic group was found to be a possible confounding factor, which may have resulted in early admissions and better outcomes in the pre-admission antibiotic group as they were referred by general practitioners. There was possible selective reporting of information.

Strang et al. *(21)* was another study which looked into patients with meningococcal meningitis and compared mortality in patients who received pre-admission parenteral penicillin to those who had not. The study reported a 24% reduction in mortality in the pre-admission group (8/33 in the pre-admission penicillin vs 0/13 in the no pre-admission antibiotics [$P = 0.106$]), but this was statistically insignificant. The numbers in the study were too small to make a conclusive inference.

Miner et al. *(20)* is a study conducted where antibiotics were administered in the emergency department prior to inpatient admission. The study found that 76% of all the children and adults with community-acquired meningitis received antibiotics in the emergency department (cefotaxime or ceftriaxone). Patients admitted to the emergency department received antibiotics significantly more quickly than those treated as hospital inpatients (1.8 hours in the emergency department vs 9 hours in hospital). The mortality rate for adults who did not receive antibiotics in the emergency department was significantly higher than for those receiving emergency department antibiotics (29% vs 7.9%, respectively, $P = 0.003$). The study had small numbers, which may have overestimated the effect.

Table WA5.5 Mortality based on timing of effective antibiotics administration

	Pre-admission antibiotics	Antibiotics after inpatient admission
Cartwright et al. 1992 *(19)*	5/93 (5%)	22/246 (9%)
Miner et al. 2001 *(20)*	0/36 (children) 3/38 (adults) (7%)	1/7 (children) (14%) 6/24 (adults) (25%)
Strang et al. 1992 *(21)*	0/13	8/33 (24%)

CSF culture-positivity rate: Cartwright et al. *(19)* and Strang et al. *(21)* reported data for their CSF culture-positivity rates. In the Cartwright study, patients receiving antibiotics after inpatient admission showed a higher likelihood of positive CSF cultures (62%), compared to those given antibiotics before admission (33%). This suggests a potential impact of antibiotic timing on culture results in the context of hospitalization.

In Strang et al. *(21)*, an organism was identified in 72% of cases. *N. meningitidis* was identified in 47% (7/15) of patients who received antibiotics before admission compared with 84% (26/31) of patients treated after admission.

Table WA5.6 CSF culture-positivity rate based on timing of effective antibiotics administration

	Pre-admission antibiotic	Antibiotics after inpatient admission
Cartwright et al. 1992 *(19)*	33/98 (33%)	154/246 (62%)
Strang et al. 1992 *(21)*	7/15 (47%)	26/31 (84%)

Blood culture-positivity rate: Only one study, Cartwright et al. *(19)*, reported data for blood culture-positivity rate. Blood cultures gave positive results in very few patients given parenteral antibiotics before admission and were positive in half of those not given antibiotics prior to admission.

Table WA5.7 Blood culture-positivity rate based on timing of effective antibiotics administration

	Pre-admission antibiotic	Antibiotics after inpatient admission
Cartwright et al. 1992 *(19)*	4/98 (4%)	111/246 (45%)

3.5.2 Additional studies

Proulx et al. (2005) *(1)* conducted a retrospective cohort study involving 123 cases of acute bacterial meningitis admitted to hospital, revealing a case fatality rate of 13%. They found that patients experiencing delays in antibiotic treatment had a higher mortality rate, and there was an increased risk of severe complications such as sepsis and neurological sequelae among those with delayed antibiotic therapy.

In the study by Kaaresen and Flaegstad (1995) *(22)* involving 92 children with bacterial meningitis, a mortality rate of 4.3% (4 out of 92) and a permanent neurological sequelae rate of 15.2% (14 out of 92) were observed. They identified several risk factors for adverse

outcomes, including duration of symptoms exceeding 48 hours, pre-hospital seizures, peripheral vasoconstriction, low CSF leukocyte count, and admission temperature ≤ 38.0°C. Interestingly, pre-hospital antibiotic therapy showed no significant association with adverse outcomes.

Glimaker et al. (2015) *(23)* evaluated the impact of revised Swedish guidelines on adult bacterial meningitis, using a comparison of mortality rates and sequelae risk. They found that the adoption of revised guidelines, allowing prompt lumbar puncture without prior computed tomography (CT) scan, resulted in lower mortality rates (6.9% vs 11.7%) and reduced sequelae risk (38% vs 49%), indicating the potential benefits of guideline revisions for patient outcomes.

Bretonnière et al. (2015) *(24)* conducted a retrospective cohort study analysing data from five intensive care units (ICUs) over a five-year period (2004–2008) to assess the use of rifampin in the treatment of acute bacterial meningitis. They observed an increase in rifampin use over the study period and found that administration of rifampin within the first 24 hours of hospitalization appeared to be associated with lower ICU survival rates, particularly in patients with pneumococcal meningitis. However, this association did not hold in multivariate analysis, indicating the need for further research to confirm these findings and understand the potential mechanisms underlying the observed effects of rifampin on mortality in ICU patients with bacterial meningitis.

Bodilsen et al. (2016) *(25)* conducted a population-based cohort study in North Denmark from 1998 to 2014 to assess the impact of antibiotic timing on outcomes in community-acquired bacterial meningitis. They found that delays in antibiotic therapy that went beyond six hours of admission to hospital were associated with increased risk of in-hospital mortality and unfavourable outcomes at discharge. Each hour of delay within the first six hours of admission also correlated with higher risks of adverse outcomes. Patients diagnosed after admission experienced more delays and had significantly worse outcomes.

In the cohort study conducted by Bijlsma et al. (2016) *(26)* in the Kingdom of the Netherlands from 2006 to 2014, the authors examined adult cases of community-acquired bacterial meningitis following the introduction of adjunctive dexamethasone treatment and nationwide implementation of paediatric conjugate vaccines. They observed a significant decline in incidence, particularly among pneumococcal serotypes targeted by the vaccine, and in meningococcal meningitis, without evidence of serotype replacement. The overall case fatality rate was 17%, with predictors of unfavourable outcomes being advanced age, absence of otitis or sinusitis, alcoholism, tachycardia, lower score on the Glasgow Coma Scale, cranial nerve palsy, a CSF white cell count lower than 1000 cells per microlitre (µl), a positive blood culture, and a high serum C-reactive protein concentration. Importantly, adjunctive dexamethasone treatment was associated with substantially improved outcomes.

In a study by Bargui et al. (2012) *(27)*, conducted over a 10-year period at a single paediatric centre in France, 101 children surviving bacterial meningitis were examined to

identify predictors of death and long-term neurological deficits. A delay in initiation of antibiotics (hazard ratio [HR] 1.3, 95% CI 1.1–1.7) and hydrocephalus on CT scan (HR 2.6, 95% CI 1.1–6.0) were associated with having one or more long-term neurological deficits highlighting the critical importance of timely antibiotic administration in improving outcomes for children with bacterial meningitis.

4. From evidence to recommendations: summary of findings

Table WA5.5 presents the summary of findings for this review.

Table WA5.5 Summary of findings: Early empiric antimicrobial treatment compared with delayed empiric antimicrobial treatment for suspected acute meningitis

Setting: Before admission into an inpatient setting (health centre, hospital), before referral, during transport (ambulance), and/or before lumbar puncture and/or cranial imaging.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with delayed empiric antimicrobial treatment	Risk with early empiric antimicrobial treatment				
All-cause mortality	159 per 1000	65 per 1000 (41 to 103)	RR 0.41 (0.26 to 0.65)	601 (3 non-randomized studies) (7–9)	⊕◯◯◯ Very low[a,b,c]	The effect of early empiric antimicrobial treatment on all-cause mortality is uncertain.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with delayed empiric antimicrobial treatment	Risk with early empiric antimicrobial treatment				
Neurological sequelae – hearing loss	32 per 1000	96 per 1000 (35 to 261)	RR 2.98 (1.09 to 8.13)	281 (1 non-randomized study) (7)	⊕◯◯◯ Very low[d,e]	The effect of early antimicrobial treatment on hearing loss is uncertain.
Neurological sequelae – paresis	48 per 1000	106 per 1000 (45 to 253)	RR 2.21 (0.93 to 5.25)	281 (1 non-randomized study) (7)	⊕◯◯◯ Very low[d,f]	The effect of early antimicrobial treatment on paresis is uncertain.
Adverse events	694 per 1000	292 per 1000 (146 to 569)	RR 0.70 (0.53 to 0.92)	148 (1 non-randomized study) (9)	⊕◯◯◯ Very low [c,g]	The effect of early empiric antimicrobial treatment on adverse events is uncertain.
CSF culture-positivity rate	984 per 1000	935 per 1000 (886 to 994)	RR 0.95 (0.90 to 1.01)	281 (1 non-randomized study) (7)	⊕◯◯◯ Very low [d,h]	The effect of early empiric antimicrobial treatment on CSF culture-positivity rate is uncertain.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with delayed empiric antimicrobial treatment	Risk with early empiric antimicrobial treatment				
Blood culture-positivity rate	877 per 1000	789 per 1000 (702 to 886)	RR 0.90 (0.80 to 1.01)	281 (1 non-randomized study) (7)	⊕◯◯◯ Very low [d,h]	The effect of early empiric antimicrobial treatment on blood culture-positivity rate is uncertain.

CI: confidence CSF: cerebrospinal fluid; interval; RR: risk ratio.

***** The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[a] Downgraded by two levels for very serious risk of bias as all the studies are non-randomized studies of the effects of interventions (NRSIs). Kaplan et al. *(8)* had a serious risk of bias in one domain and moderate in one domain, Roznovský et al. *(9)* had serious risk of bias in one domain and Auburtin et al. *(10)* had serious risk of bias in one domain and no information on three domains.

[b] Downgraded by one level for indirectness because the intervention was given at varied time intervals in the three studies, varying from 4 days prior to admission to the emergency room in hospital to within 3 hours of admission to hospital (within one week before admission [median 3 days] in Kaplan et al. *(8)*); within 3 days before admission in Roznovský et al. *(9)*; and less than 3 hours after admission to hospital in Auburtin et al. *(10)*).

[c] Downgraded by one level for serious imprecision as number of events did not reach optimal information size.

[d] Downgraded by two levels for very serious risk of bias as the study Kaplan et al. *(8)* is an NRSI and had a serious risk of bias in one domain and moderate risk of bias in one domain.

[e] Downgraded by two levels for very serious imprecision as the CIs were very wide, number of events did not reach optimal information size and upper and lower limits show mild to very significant harm.

[f] Downgraded by two levels for very serious imprecision as the CIs were very wide, number of events did not reach optimal information size and upper limit shows mild benefit and lower limit shows very significant harm.

[g] Downgraded by two levels for very serious risk of bias as the study Auburtin et al. *(10)* is an NRSI and had a serious risk of bias in one domain and no information in three domains.

[h] Downgraded by one level for serious imprecision as the point estimate crosses the line of no difference, though it is a narrow CI, suggesting there may be truly no difference.

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Appendix 1. Search strategy used to identify primary studies

Table WA5.A1.1 Database: MEDLINE (OVID), 1946 to November Week 5 2023, searched on 2 January 2023

No.	Searches	Results
1	Meningitis, Bacterial/ or ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome or Neisseria-meningitidis or meningococc* or N-meningitidis or Escherichia-coli or E-coli or GBS or streptococc* or S-agalactiae or H-influenza* or Haemophilus-influenza* or Hemophilus or Haemophilus or Leptospir* or L-monocytogenes or Listeria-monocytogenes or listerial or Borrelia-burgdorferi or B-burgdorferi or Borrelia or Lyme or Streptococcus-pneumoniae or S-pneumoniae or pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) adj3 meningit*).ti,ab. OR (Meningococc* adj5 (infection* OR disease*)).ti,ab.	29 292
2	Anti-Bacterial Agents/ or (anti-biotic* or antibiotic* or anti-bacteri* or antibacteri* or antimicrobial* or anti-microbial*).ti,ab.	693 742
3	Rifamycins/ or Vancomycin/ or Penicillins/ or Cephalosporins/	77 182
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axepim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR	523 552

	Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*).ti,ab.	
5	2 or 3 or 4	1 039 341
6	1 and 5	8 867
7	animals/ not (animals/ and humans/)	5 145 692
8	(letter or historical article or comment or editorial or news or case reports).pt.	4 464 549
9	6 not (7 or 8)	5 704

Table WA5.A1.2 Database: Embase (Elsevier) (www.embase.com), searched: 2 January 2023

No.	Searches	Results
1	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N.-meningitidis OR Escherichia-coli OR E.-coli OR GBS OR streptococc* OR S.-agalactiae OR H.-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L.-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B.-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S.-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S.Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab,kw,de OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,de,kw	51 027
2	antibiotic agent'/mj OR (anti-biotic* OR antibiotic* OR anti-bacteri* OR antibacteri* OR antimicrobial* OR anti-microbial*):ti,ab	899 463
3	rifamycin'/mj OR 'vancomycin'/mj OR 'penicillin derivative'/mj OR 'cephalosporin'/mj	51 489
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR BMY-28142 OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR Biseptol-480 OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR SQ-26776 OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR BAY-12-8039 OR BAY-128039 OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime Pentahydrate OR LY-139381 OR LY139381 OR Tazidime OR Ceftazidime OR GR-20263 OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR Ro13-9904 OR Ro13-9904 OR Ro139904 OR Ro-13-9904 OR Ro-13-9904	1 360 937

	OR Ro-13-9904 OR Ro-139904 OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR HR-756 OR HR756 OR Ru-24756 OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR BRL-2333 OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR Or-pen OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* or fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw,de	
5	#2 OR #3 OR #4	1 907 847
6	#1 AND #5	18 289
7	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 442 093
8	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR case-report*:ti OR case-series:ti OR genomic*:ti OR 'in vitro':ti	9 735 110
9	#6 NOT (#7 OR #8)	13 657

Table WA5.A1.3 Database: CENTRAL (www.cochranelibrary.com/advanced-search/search-manager), searched: 2 January 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis, Bacterial] explode all trees	489
2	((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N-meningitidis OR Escherichia-coli OR E-coli OR GBS OR streptococc* OR S-agalactiae OR H-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,kw	1 404
3	#1 OR #2	1 632
4	MeSH descriptor: [Anti-Bacterial Agents] this term only	15 349
5	MeSH descriptor: [Rifamycins] explode all trees	1 846
6	MeSH descriptor: [Vancomycin] explode all trees	982
7	MeSH descriptor: [Penicillins] explode all trees	6 320
8	MeSH descriptor: [Cephalosporins] explode all trees	4 785
9	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR	55 820

	"Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	63 714
11	#3 AND #10	372
12	Trials	361

Table WA5.A1.4 Database: ClinicalTrials.gov (https://classic.clinicaltrials.gov/) searched on 2 January 2024

No.	Searches	Results
#1 (Condition)	((bacterial OR Neisseria OR meningococus OR Escherichia-coli OR streptococcus OR influenza OR Hemophilus OR Leptospira OR Listeria-monocytogenes OR listerial OR Borrelia OR Lyme OR Streptococcus OR pneumococcus OR disease) AND (meningitis))	
#2 (Other terms)	anti-biotic OR antibiotic OR anti-bacterial OR antibacterial OR antimicrobial OR anti-microbial OR cephalosporin OR penicillin OR vancomycin OR rifampicin OR chloramphenicol OR ceftriaxone OR cefotaxime OR ciprofloxacin OR Ampicillin OR Amoxicillin	
3	#1 AND #2	122

6. Empiric antimicrobial treatment regimen (Part 1)

Authors

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Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organization

1. Background

Acute bacterial meningitis is a potentially life-threatening condition requiring immediate diagnosis and treatment. Despite the development of more effective antibiotics, bacterial meningitis continues to cause high mortality *(1)*.

Empiric antimicrobial selection is directed at the most likely bacteria and primarily determined by the age of the patient, the presence of specific risk factors, and the local prevalence of drug-resistant pathogens (e.g. reduced susceptibility to penicillin and third-generation cephalosporins of *Streptococcus pneumoniae*). The treatment of bacterial meningitis has been revolutionized by the availability of the third-generation cephalosporins *(2)*.

Third-generation cephalosporins, especially ceftriaxone and cefotaxime, have become the drugs of choice for empiric therapy, owing to their good meningeal penetration and distribution *(3)*. Cefotaxime was the first of the third-generation cephalosporins used in Europe for the treatment of meningitis, while ceftriaxone became established as an initial treatment for the three major meningeal pathogens of meningitis *(2)*.

According to several national and international guidelines for treating suspected or proven meningitis in settings with a high risk of decreased beta-lactam susceptibility of *S. pneumoniae*, a combination of vancomycin or rifampicin and either ceftriaxone or cefotaxime is recommended for children and adults. Moreover, in the presence of risk factors for an infection with *Listeria monocytogenes* (e.g. advanced age, immunocompromised state), empiric antibiotic treatment should include amoxicillin or ampicillin *(4)*.

Hence, this evidence focuses on the efficacy of empiric treatment for suspected or probable bacterial meningitis with parenteral ceftriaxone or cefotaxime monotherapy, or with a combination of these antibiotics and additional antimicrobials (i.e. ampicillin, amoxicillin, rifampicin or vancomycin). This work will inform the development of the *WHO guidelines for meningitis diagnosis, treatment and care*.

2. Methodology

2.1 Research question and study design

Among cases with suspected or probable acute bacterial meningitis, what is the effectiveness and safety of empiric treatment with parenteral ceftriaxone or cefotaxime combined with additional antimicrobials, compared to monotherapy?

Population: Suspected or probable cases of acute bacterial meningitis.

Subgroups: age groups (children; adults; elderly > 60 years); pregnant women; those with immunocompromised status; populations in areas where there is prevalence of pneumococcal resistance to beta-lactams.

Intervention: Parenteral ceftriaxone or cefotaxime combined with additional antimicrobials (i.e. ampicillin, amoxicillin, rifampicin and vancomycin).

Comparator: Monotherapy with ceftriaxone or cefotaxime.

Outcome

Critical outcomes:

- mortality;
- time to resolution of symptoms;
- disease complications (sepsis; disseminated intravascular coagulation; neurological complications, including neurological sequelae).

Important outcomes:

- adverse effects.

Study designs: A systematic review process was embarked upon and a search conducted to find primary studies relevant to the research question. The search was conducted for randomized controlled trials and prospective cohort studies that included a comparator arm pertaining to the research question.

2.2 Eligible studies

Published language: All relevant studies were searched for, regardless of language. Evidence from studies in English was evaluated immediately by the team. For studies in languages other than English, the translated version was obtained from online software.

Exclusion criteria:

- All non-randomized studies without a comparator arm were excluded (i.e. case reports, case series, and non-randomized studies without a comparator arm).
- Any ongoing trials or studies with outcome data that could not be evaluated were also excluded.

2.3 Search strategy

A search for primary studies relevant to the research question was conducted. The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (https://ClinicalTrials.gov/). All the databases were searched for studies published from 1946 to November 2023.

2.4 Selection of studies

A preliminary search for systematic reviews relevant to the research question was conducted. No systematic reviews specific to this topic were found. A search was then conducted for primary studies, either randomized controlled trials or prospective cohorts with comparators across the databases mentioned in section 2.3. This search covered research questions 5–10 (i.e. this report and five other reports in this web annex) on empiric antimicrobial treatment, the duration of antimicrobial treatment in both epidemic and non-epidemic settings, and post-exposure antimicrobial prophylaxis. The search yielded 15 158 studies. After filtering using the Rayyan tool *(5)*, 1194 duplicate articles were identified. Of these, 208 duplicates were manually removed by the review authors. Subsequently, the remaining 14 950 articles underwent independent screening by the review authors using Rayyan. After title and abstract screening, 14 880 studies were excluded since they were not relevant to our research question. Full-text screening was then conducted on 70 articles retrieved from the review authors' institutional libraries and the WHO libraries, resulting in the full text of 64 articles being obtained. However, the remaining six articles were excluded because four of them were clinical trials with unpublished data. Despite attempts to contact the authors, full-text versions of these studies could not be obtained. Additionally, full texts of the other two studies were also unavailable.

After thorough full-text screening of all 64 studies, no study relevant to this research question (i.e. this report) was found.

2.5 Deviations from the review protocol

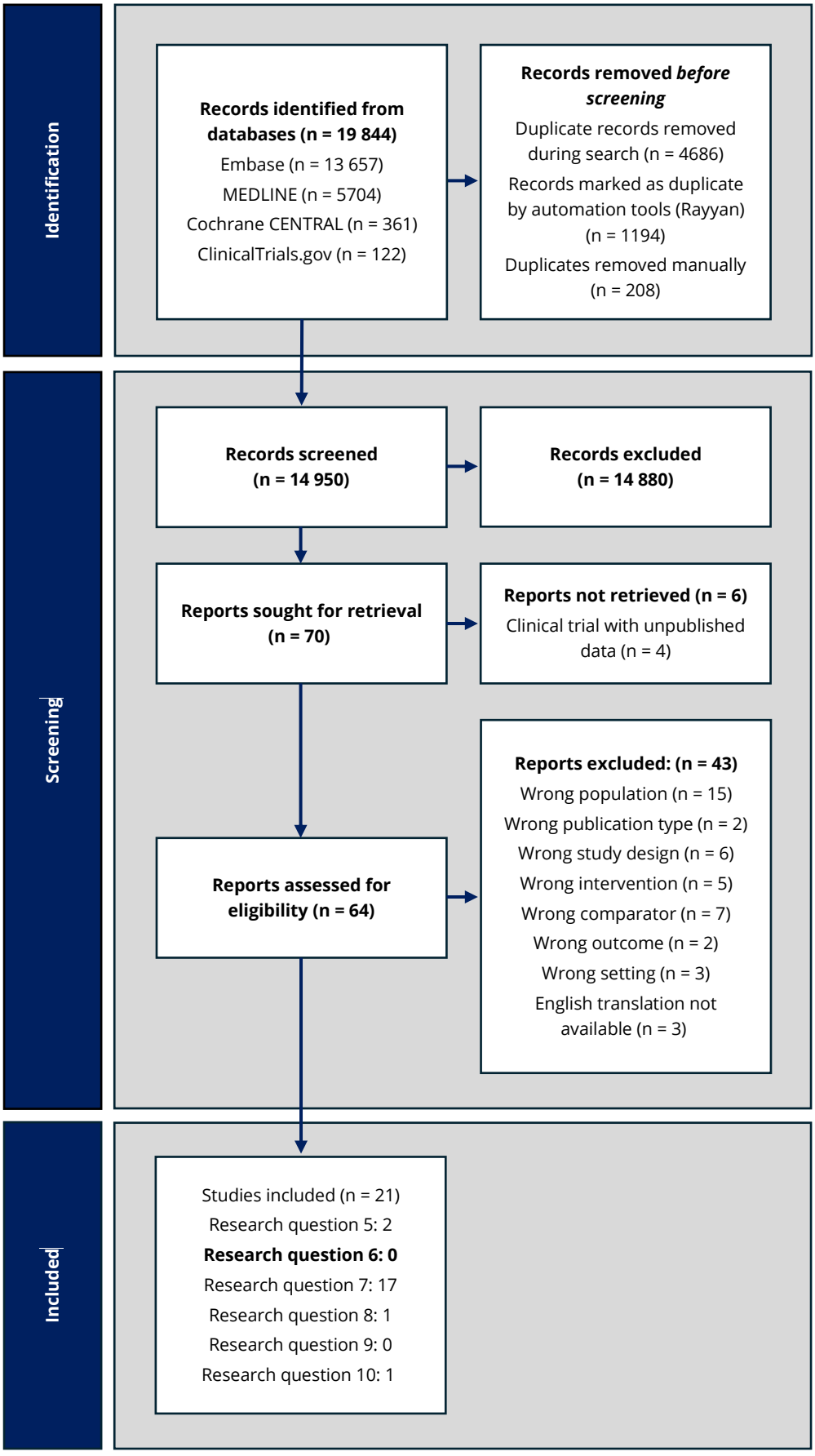
This was not applicable.

3. Results

3.1 Studies identified by the search process

Figure WA6.1 presents the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this systematic review.

Fig. WA6.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profile

No studies were found that could be included in the review.

3.1.2 Studies excluded from the review

Table WA6.1 presents the studies excluded from the review, along with the reasons for exclusion.

Table WA6.1 Studies excluded from the review, with reasons

Lead author (Year)	Reason for exclusion
Asensi (1990) *(6)*	This is a cross-over study in which cefotaxime was given as an empiric choice, and after a bacteriological test, randomization was carried out. One group was continued on cefotaxime, and in the other group cefotaxime was replaced with ampicillin. Thus, this study did not meet the criteria of this review's research question.
Tauzin (2019) *(7)*	This is a multi-centre observational study comparing the efficacy of third-generation cephalosporin with and without ciprofloxacin. This study was excluded because the comparator arm included ciprofloxacin and not third-generation cephalosporin monotherapy.
CTRI/2010/091/000174 *(8)*	Completed trial with no published data. The unpublished data were requested, but no reply was received.
CTRI/2008/091/000060 *(9)*	Completed trial with no published data. The unpublished data were requested, but no reply was received.

3.2 GRADE evidence profile

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach could not be applied here.

3.3 Description of intervention effects

No published trials meeting the inclusion criteria were identified.

3.4 Additional evidence not reported in GRADE evidence profile

It was not possible to find any retrospective studies which could be added to the evidence base here.

4. From evidence to recommendations

4.1 Summary of findings

A summary-of-findings table could not be created.

References[11]

1. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM. 2005;98(4):291–8 (https://doi.org/10.1093/qjmed/hci047).

2. Cherubin CE, Eng RHK, Norrby R, Modai J, Humbert G, Overturf G. Penetration of Newer Cephalosporins into Cerebrospinal Fluid. Clin Infect Dis. 1989;11(4):526–48 (https://doi.org/10.1093/clinids/11.4.526).

3. Prásil P, Buchta V, Paterová P, Hanovcová I. Průnik ceftriaxonu do likvoru a jeho v vztah k markerům zánetu v průbehu invazivní bakteriální infekce [Penetration of ceftriaxone into the cerebrospinal fluid and its relationship to inflammatory markers during bacterial meningitis]. Klin Mikrobiol Infekcni Lek. 2010;16(2):64–72 (in Czech).

4. Kaplan SL, Mason EO. Management of infections due to antibiotic-resistant *Streptococcus pneumoniae*. Clin Microbiol Rev. 1998;11(4):628–44 (https://doi.org/10.1128/CMR.11.4.628).

5. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5:210 (https://doi.org/10.1186/s13643-016-0384-4).

6. Modalités thérapeutiques des méningites purulentes de l'enfant. A propos de 101 observation [Therapeutic management of purulent meningitis in children. Report of 101 cases]. Arch Fr Pediatr. 1990;47(7):491–5 (in French).

7. Tauzin M, Ouldali N, Lévy C, Béchet S, Cohen R, Caeymaex L. Combination therapy with ciprofloxacin and third-generation cephalosporin versus third-generation cephalosporin monotherapy in *Escherichia coli* meningitis in infants: a multicentre propensity score–matched observational study. Clin Microbiol Infect. 2019;25(8):1006–12 (https://doi.org/10.1016/j.cmi.2018.12.026).

8. Clinical Trials Registry – India. A comparative clinical study to evaluate efficacy and safety of fixed dose combination of Ceftriaxone + Sulbactam (CSE 1034) vs Ceftriaxone in patients suffering from various bacterial infections. International Clinical Trials Registry Platform. 2010; (CTRI/2010/091/000174; https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2010/091/000174).

9. Clinical Trials Registry – India. A clinical trial to study the safety and efficacy of combination drug, vancomycin and ceftriaxone compared to vancomycin in mild to severe bacterial infections. International Clinical Trials Registry Platform. 2008; (CTRI/2008/091/000060;

[11] All references were accessed on 03 January 2025.

https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2008/091/000060).

Appendix 1. Search strategy used to identify primary studies

Table WA6.A1.1 Database: MEDLINE (OVID), 1946 to November Week 4 2023, searched on 2 January 2023

No.	Searches	Results
1	Meningitis, Bacterial/ or ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome or Neisseria-meningitidis or meningococc* or N-meningitidis or Escherichia-coli or E-coli or GBS or streptococc* or S-agalactiae or H-influenza* or Haemophilus-influenza* or Hemophilus or Haemophilus or Leptospir* or L-monocytogenes or Listeria-monocytogenes or listerial or Borrelia-burgdorferi or B-burgdorferi or Borrelia or Lyme or Streptococcus-pneumoniae or S-pneumoniae or pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) adj3 meningit*).ti,ab. OR (Meningococc* adj5 (infection* OR disease*)).ti,ab.	29 292
2	Anti-Bacterial Agents/ or (anti-biotic* or antibiotic* or anti-bacteri* or antibacteri* or antimicrobial* or anti-microbial*).ti,ab.	693 742
3	Rifamycins/ or Vancomycin/ or Penicillins/ or Cephalosporins/	77 182
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axepim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR	523 552

	Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*).ti,ab.	
5	2 or 3 or 4	1 039 341
6	1 and 5	8 867
7	animals/ not (animals/ and humans/)	5 145 692
8	(letter or historical article or comment or editorial or news or case reports).pt.	4 464 549
9	6 not (7 or 8)	5 704

Table WA6.A1.2 Database: Embase (Elsevier) (www.embase.com), searched on 2 January 2023

No.	Searches	Results
1	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N.-meningitidis OR Escherichia-coli OR E.-coli OR GBS OR streptococc* OR S.-agalactiae OR H.-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L.-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B.-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S.-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S.Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab,kw,de OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,de,kw	51 027
2	antibiotic agent'/mj OR (anti-biotic* OR antibiotic* OR anti-bacteri* OR antibacteri* OR antimicrobial* OR anti-microbial*):ti,ab	899 463
3	rifamycin'/mj OR 'vancomycin'/mj OR 'penicillin derivative'/mj OR 'cephalosporin'/mj	51 489
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR BMY-28142 OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR Biseptol-480 OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR SQ-26776 OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR BAY-12-8039 OR BAY-128039 OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime Pentahydrate OR LY-139381 OR LY139381 OR Tazidime OR Ceftazidime OR GR-20263 OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR Ro13-9904 OR Ro13-9904 OR Ro139904 OR Ro-13-	1 360 937

	9904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-139904 OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR HR-756 OR HR756 OR Ru-24756 OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR BRL-2333 OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR Or-pen OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* or fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw,de	
5	#2 OR #3 OR #4	1 907 847
6	#1 AND #5	18 289
7	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 442 093
8	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR case-report*:ti OR case-series:ti OR genomic*:ti OR 'in vitro':ti	9 735 110
9	#6 NOT (#7 OR #8)	13 657

Table WA6.A1.3 Database: CENTRAL (www.cochranelibrary.com/advanced-search/search-manager), searched on 2 January 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis, Bacterial] explode all trees	489
2	((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N-meningitidis OR Escherichia-coli OR E-coli OR GBS OR streptococc* OR S-agalactiae OR H-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,kw	1 404
3	#1 OR #2	1 632
4	MeSH descriptor: [Anti-Bacterial Agents] this term only	15 349
5	MeSH descriptor: [Rifamycins] explode all trees	1 846
6	MeSH descriptor: [Vancomycin] explode all trees	982
7	MeSH descriptor: [Penicillins] explode all trees	6 320
8	MeSH descriptor: [Cephalosporins] explode all trees	4 785
9	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR	55 820

	penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	63 714
11	#3 AND #10	372
12	Trials	361

Table WA6.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 2 January 2024

No.	Searches	Results
Condition	((bacterial OR Neisseria OR meningococus OR Escherichia-coli OR streptococcus OR influenza OR Hemophilus OR Leptospira OR Listeria-monocytogenes OR listerial OR Borrelia OR Lyme OR Streptococcus OR pneumococcus OR disease) AND (meningitis))	
Other terms	anti-biotic OR antibiotic OR anti-bacterial OR antibacterial OR antimicrobial OR anti-microbial OR cephalosporin OR penicillin OR vancomycin OR rifampicin OR chloramphenicol OR ceftriaxone OR cefotaxime OR ciprofloxacin OR Ampicillin OR Amoxicillin	
#3	#1 AND #2	122

7. Empiric antimicrobial treatment regimen (Part 2)

Authors

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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hib	*Haemophilus influenzae* type b
IDSA	Infectious Disease Society of America
MD	mean difference
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RR	risk ratio

1. Background

Acute bacterial meningitis is a potentially life-threatening condition requiring immediate diagnosis and treatment. Despite the development of more effective antibiotics, bacterial meningitis continues to have a high mortality rate *(1)*.

Third-generation cephalosporins, including ceftriaxone and cefotaxime, have now become the drugs of choice for the empiric treatment of acute bacterial meningitis globally, owing to their efficacy, excellent meningeal penetration and distribution and widespread availability *(2, 3)*. The main organisms causing acute bacterial meningitis in the lower-middle-income countries with the highest morbidity include *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib). Third-generation cephalosporins are recommended in patients with pneumococcal and meningococcal meningitis if the disease is caused by strains that are not susceptible to penicillin, or have reduced susceptibility to it *(4)*. In patients with Hib meningitis, the emergence of b-lactamase–producing strains and resistance to chloramphenicol has made third-generation cephalosporins the drugs of choice for empirical therapy *(5)*.

Third-generation cephalosporins have also acquired a primary role in the empiric treatment of acute bacterial meningitis in most settings, owing to the rising resistance to penicillin globally, especially in *S. pneumoniae (6-9)*. However, they may not be always available or accessible where resources are limited, leading to significant variations in clinical practice. Hence, this evidence synthesis focuses on the empiric treatment of suspected or probable bacterial meningitis with an alternative parenteral antimicrobial regimen (such as penicillin [i.e. benzylpenicillin, ampicillin, amoxicillin] or chloramphenicol alone or in combination) as compared with parenteral ceftriaxone or cefotaxime monotherapy.

This work has been carried out for the development of the *WHO guidelines for meningitis diagnosis, treatment and care*. The authors were Priscilla Rupali (PR), Anupa Thampy (AT), Jane Miracline (JM), Naveena Gracelin Princy (NGP), Hanna Alexander (HA) and Jisha Sara John (JSJ).

2. Methodology

2.1 Research question and study design

Among cases of suspected or probable acute bacterial meningitis, what is the effectiveness and safety of alternative parenteral antimicrobial regimens (penicillin [i.e. benzylpenicillin, ampicillin, amoxicillin] or chloramphenicol alone or in combination) compared to monotherapy with ceftriaxone or cefotaxime?

Population: Suspected or probable cases of acute bacterial meningitis. Subgroups: age groups (children; adults; elderly > 60 years); pregnant women; people with immunocompromised status; people living in locations with prevalence of pneumococcal resistance to beta-lactams.

Intervention: Alternative parenteral antimicrobial regimens (penicillin [i.e. benzylpenicillin, ampicillin, amoxicillin] or chloramphenicol alone or in combination).

Comparator: Monotherapy with ceftriaxone or cefotaxime.

Outcomes

Critical outcomes:

- Mortality;
- time to resolution of symptoms;
- disease complications (sepsis, disseminated intravascular coagulation, neurological complications, including neurological sequelae).

Important outcomes:

- adverse effects.

2.2 Eligibility and study selection

Study designs: A systematic review of the primary studies identified by our search strategy was performed. Randomized controlled trials (RCTs) with a comparator arm were included. Since there was an adequate number of RCTs, prospective cohort studies were not included.

Published language: All relevant studies were included, regardless of language. The studies in English were evaluated by the review team. The translated versions of studies in languages other than English were obtained using online software.

Exclusion criteria: The following were excluded:

- all non-randomized studies without a comparator arm (i.e. case reports, case series and other studies without a comparator);
- any ongoing trials and studies with outcome data that were not available or could not be evaluated; and

- prospective cohort studies.

2.3 Search strategy

The following databases were searched for primary studies: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (https://ClinicalTrials.gov). All the databases were searched for studies published from 1946 to November 2023.

2.4 Selection of studies

A search was conducted to identify recent systematic reviews that would be relevant to the research question. One systematic review relevant to this research question was found – a Cochrane review, by Prasad et al., comparing the effectiveness and safety of third-generation cephalosporins (ceftriaxone or cefotaxime) with conventional treatment using penicillin or ampicillin-chloramphenicol in patients with community-acquired acute bacterial meningitis *(10)*. According to the criteria used by AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews, revised version) *(11)*, the overall confidence for this systematic review is high. The review was not updated after 2011, so we were unable to use it.

Hence it was deemed appropriate to proceed to perform a new systematic review by focusing the search on the inclusion of primary studies i.e. RCTs and prospective cohort studies with a comparator, as specified in the review protocol, which has been published in PROSPERO *(12)*. A search was conducted across the databases mentioned in section 2.3 to identify primary studies relevant to research questions 5–10 (i.e. this report and five other reports in this web annex) on empiric antimicrobial treatment, the duration of antimicrobial treatment in both epidemic and non-epidemic settings, and post-exposure antimicrobial prophylaxis. The search yielded 15 158 studies. After filtering via the Rayyan tool *(13)*, 1194 duplicate articles were identified. Of these, 208 duplicates were manually removed by the review authors. Subsequently, the remaining 14 950 articles underwent independent screening by the review authors through Rayyan. After title and abstract screening, 14 880 studies were excluded since they were not relevant to the research questions. Full-text screening was then conducted on 70 articles retrieved from the review authors' institutional libraries and the WHO libraries, resulting in obtaining the full text of 64 articles. However, the remaining six articles were excluded because four of them were clinical trials with unpublished data. Despite attempts to contact the authors, full-text versions of these trials could not be obtained. Additionally, full texts for the other two studies were also unavailable. After thorough full-text screening, 43 trials were excluded.

Seventeen studies identified through the search were finally included. Three additional studies relevant to this research question (i.e. this report) and retrieved through external

sources were also included. The characteristics of the studies included are presented in Table WA7.1.

2.5 Data extraction and management

Four of the review authors (JM, NGP, HA, JSJ) used a piloted data extraction form to extract data on participant characteristics, disease severity, co-morbidity, antimicrobial treatment and administration, other treatments given, and outcome measures, as defined by the research question.

For dichotomous outcomes like mortality and neurological complications, the review authors recorded the number of participants who experienced the event and the number of participants in each treatment group. The number of participants analysed in each arm was recorded and the data available used to calculate the number of participants lost to follow-up.

2.6 Assessment of risk of bias in studies included in the review

Two of the four review authors mentioned above (JM, NGP, HA, JSJ) assessed the risk of bias for the primary and secondary outcomes using Version 2 of the Cochrane tool for assessing risk of bias tool in randomized trials (RoB 2) *(14)*. The risk of bias assessment was verified by the corresponding authors (PR, AT).

2.7 Data synthesis

Data were analysed using Review Manager software *(15)* by two of the review authors (JSJ, HA). When more than one study contributed to the evidence synthesis, data were pooled in meta-analyses using the random-effects model. Dichotomous data were compared using risk ratios (RR) and presented as such. All results are presented with the corresponding 95% confidence interval (CI).

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The GRADE framework was used to assess the certainty of the evidence *(16)*. GRADE (Grading of Recommendations Assessment, Development and Evaluation) is a transparent framework designed for the development and presentation of evidence summaries, offering a systematic approach to formulating clinical practice recommendations. The quality of the evidence is assessed for each outcome, and GRADE categorizes it into four levels of certainty: very low, low, moderate and high. Certainty in the evidence for each outcome is evaluated across five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. The GRADE levels of certainty are defined below.

Box WA7.1 The certainty of evidence used in GRADE	
High ⊕⊕⊕⊕	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The results of the analysis with effect estimates for the outcomes are provided in Table WA7.4.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No subgroup analysis was performed.

2.10 Sensitivity analysis

No sensitivity analysis was performed.

2.11 Deviations from the review protocol

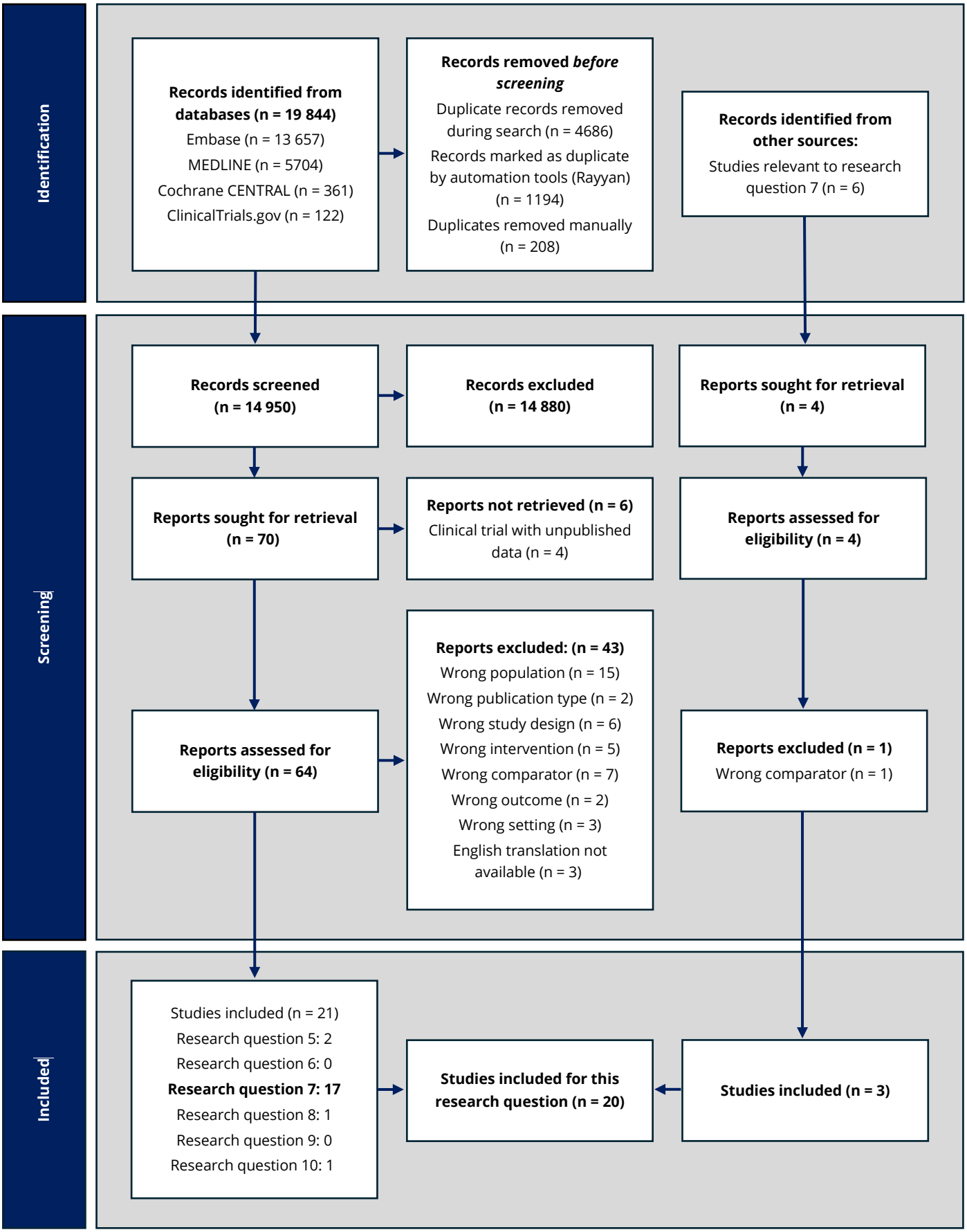
There was no deviation from the review protocol.

3. Results

3.1 Studies identified by the search process

Figure WA7.1 presents the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review.

Fig. WA7.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profile

Table WA7.1 presents the characteristics of the studies included in the GRADE evidence profile for this research question.

Table WA7.1 Characteristics of studies included in the GRADE evidence profile

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
Aronoff (1984), United States of America (USA) *(17)*	Prospective RCT	High	Ampicillin 200–300 mg/kg/day every 4 h and chloramphenicol succinate 100 mg/kg per day every 6 h	Infants and children aged 2 months to 18 years with suspected bacterial meningitis I: 8; C: 11	Ceftriaxone 50 mg/kg IV, as a 15-min infusion once every 12 h	Time to fever defervescence (mean days) Neurological sequelae	Daily physical examinations to evaluate clinical response (fever) Drug-related side-effects – information obtained from patients, parents and nursing staff	Neurological abnormalities noted at the end of therapy
Barson (1985), USA *(18)*	Prospective RCT	High	Ampicillin 200 mg/kg per day IV or chloramphenicol 100 mg/kg/day IV every 6 h	Children aged 1 month to 15 years with suspected or definite bacterial meningitis	Ceftriaxone 75 mg/kg per day followed by 50 mg/kg every 12 h	Time to fever defervescence (mean days) Neurological complications – deafness,	Time to defervescence defined as the beginning of the first 24-h period during which the maximum	Behavioural audiometry at the time of discharge

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
				I: 23; C: 27		seizures and cranial nerve palsy	rectal temp was 37.8 °C or less	
						Adverse events – diarrhoea	Behavioural audiometry for deafness	
							Diarrhoea – defined as four or more bowel movements in two or more days during hospitalization	
Bryan (1985), Brazil *(19)*	Prospective RCT	High	Ampicillin loading dose 75 mg/kg followed by 50 mg/kg every 4 h plus chloramphenicol loading dose 50 mg/kg followed by 25 mg/kg every 6 h	Patients with historical, clinical and laboratory findings consistent with acute bacterial meningitis were admitted to the study I: 18; C: 18	Ceftriaxone 100 mg/kg followed by 80 mg/kg	Mortality Time to fever defervescence (mean days) Neurological sequelae Adverse events	Fever response – daily monitoring in the ward Hearing loss – assessed by physical examination	Neurological complications – at time of discharge and follow-up, attempted 1–2 weeks post-discharge

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
Congeni (1984), USA *(20)*	RCT	High	Ampicillin 200–400 mg/kg per day Chloramphenicol 75 mg/kg per day	Children aged 1–15 years with bacterial meningitis I: 23; C: 22	Ceftriaxone 50 mg/kg	Duration of fever Neurological complications and sequelae	Seizure disorder – assessed by EEG Subdural effusion – asymmetry of trans-illumination or CT scan	Neurological complication – time of discharge
Del Rio (1983), USA *(21)*	Prospective RCT	High	Ampicillin 200 mg/kg per day Chloramphenicol 100 mg/kg per day	Patients with suspected or definite bacterial meningitis admitted to hospital were eligible for the study I: 39; C: 39	Ceftriaxone 75 mg/kg followed by 50 mg/kg every 12 h	Duration of fever Mortality Neurological sequelae Adverse events Hearing loss Diarrhoea	Fever – daily clinical examination Hearing loss – auditory brain-stem evoked response	Auditory brainstem response – time of discharge and follow-ups at 1–5 months
Girgis (1987), Egypt *(22)*	RCT	Some concerns	Ampicillin 160 mg/kg per day Chloramphenicol 100 mg/kg per day	30 patients aged 16–30 years with signs and symptoms of acute bacterial meningitis and with turbid CSF were enrolled	Ceftriaxone 100 mg/kg	Mortality Fever defervescence (mean days)	Response to therapy measured by mean days taken for patients to become afebrile	Not reported

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
				I: 15; C: 15				
Girgis (1988), Egypt *(23)*	RCT	Some concerns	Ampicillin 200 mg/kg per day Chloramphenicol 100 mg/kg per day	100 patients (70 children and 30 adults) I: 50; C: 50	Ceftriaxone 75 mg/kg followed by 50 mg/kg every 12 h	Mortality Fever defervescence Neurological sequelae Adverse effects	Hearing loss – audiometry (children > 5 years)	Audiometry – follow up monthly for 6 months. Examined neurologically and ophthalmologically during each visit
Haffejee (1988), South Africa *(24)*	Prospective, controlled, single-blind clinical trial	High	Benzyl penicillin 5–10 IU every 6 h Chloramphenicol 80–100 mg/kg per day	All infants and children admitted to the hospital with bacterial meningitis proven on Gram-stain of the CSF and/or CSF culture were enrolled into the study I: 15; C: 16	Cefotaxime 100–200 mg/kg per day	Fever defervescence Neurological complications Adverse effects	Not given	Sequelae – discharge and long term follow-up (range 6–52 months)
Jacobs (1985), USA *(25)*	Prospective RCT	High	Ampicillin 50–100 mg/kg per day Chloramphenicol 25 mg/kg per day	50 paediatric patients aged 1 week to 16 years I: 27; C: 23	Cefotaxime 25 mg/kg	Time to fever defervescence Neurological sequelae	Hearing loss – impedance audiometry (older than 6 months); auditory evoked	Prior to discharge or end of therapy and at 2 weeks and 2 months post-discharge

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
						Adverse effects	EEG (less than 6 months). All patients with seizure – neurological examination and EEG	
Marhoum Filali (1993), Morocco *(26)*	RCT	High	Penicillin G 300 000 IU/kg per day	Patients over 16 years of age hospitalized with suspected meningitis I: 20; C: 16	Ceftriaxone 2 g	Mortality Neurological complications Time to fever defervescence	Not given	Followed for 2 months
Narciso (1983), Italy *(27)*	RCT	High	Ampicillin 110 mg/kg	10 consecutive cases of purulent meningitis in adults	Ceftriaxone 100–80 mg/kg	Time to fever defervescence	Not given	Not reported
Nathan (2005), Niger *(28)*	Randomized, open-label, non-inferiority trial	Some concerns	Long-acting chloramphenicol 100 mg/kg	Individuals with suspected meningitis. The study was undertaken for 1 month during	Ceftriaxone 100 mg/kg	Mortality	Not given	Death or treatment failure at 72 h

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
				a meningitis epidemic. I: 256; C: 247				
Odio (1986), USA *(29)*	RCT	Some concerns	Ampicillin 50 mg/kg per dose Chloramphenicol 25 mg/kg per dose	Infants with suspected meningitis enrolled during 20-month study period I: 43; C: 42	Cefotaxime 50 mg/kg per dose	Fever defervescence (days) Neurological sequelae Adverse events	Neurological sequelae – neurological examination Denver developmental test	At end of the treatment, at 4–6 weeks, and at every follow-up visit at intervals of 3–6 months
Peltola (1989), Finland *(30)*	RCT	High	Ampicillin Chloramphenicol	220 consecutive cases of bacterial meningitis in children aged 3 months or older I: 53 + 46; C: 50 + 51	Ceftriaxone Cefotaxime	Mortality Fever defervescence Neurological sequelae (hearing loss, ataxia, hemiparesis)	Fever response – daily clinical examination Neurological sequelae – auditory brainstem response	Neurological sequelae – followed up after 6 months
Pichler (1985), Austria *(31)*	RCT	High	Piperacillin 6 g twice daily	All adult patients with clinical signs and symptoms of meningitis.	Ceftriaxone 2g once daily	Mortality Neurological complications	Not given	Time point for measurement of neurological sequelae – not reported

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
				I: 8; C: 7				
Sharma (1996), Nepal *(32)*	RCT	High	Benzylpenicillin 200 000 IU/kg per day Chloramphenicol 100 mg/kg per day	Children aged 5 months to 5 years admitted to the hospital for a period of 6 months (November 1993 to April 1994) with a diagnosis of pyogenic meningitis I: 12; C: 11	Ceftriaxone 50 mg/kg per day	Death Fever defervescence	Not given	Not reported
Steele (1983), USA *(33)*	Open comparative trial	High	Ampicillin 200–400 mg/kg/day Chloramphenicol 100 mg/kg per day	Thirty paediatric patients, aged 14 days to 14 years, with culture-positive bacterial meningitis. Four were aged 14–28 days, 22 were infants, and four were older than 2 years. I: 15, C: 15	Ceftriaxone 100 mg/kg/day	Death Neurological sequelae Time to fever defervescence Adverse reactions	Fever response and neurological function – daily clinical examination	Neurological examination after 3 months

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
Tuncer (1988), Türkiye *(34)*	RCT	High	Penicillin G 500 000 units/kg per day	Infants and children aged 1 month to 12 years. I: 20; C: 22. 12 of these patients had a poor prognosis, hence treated with anti-shock therapy.	Ceftriaxone 80–100 mg/kg per day	Mortality	Not given	Clinical status evaluation on every 6 h
Wells (1984), USA *(35)*	RCT	Some concerns	Ampicillin 50–100 mg/kg per day Chloramphenicol 25 mg/kg/day Genta 2.5 mg/kg per day substituted for Chloramphenicol in 2 patients	37 children, aged 1 week to 16 years, admitted to the hospital between May 1983 and February 1984 with suspected bacterial meningitis I: 18; C: 12	Cefotaxime 50mg/kg per day	Death, Neurological sequelae, Adverse effects	Neurological sequelae – auditory screening	Auditory screening at the end of the therapy
Zavala (1988), Mexico *(36)*	Open randomized study	High	Ampicillin 200–300 mg/kg per day	26 hospitalized adults who showed clinical evidence of acute bacterial	Ceftriaxone2–4 g/day	Adverse events	Not given	Not reported

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I); control (C)	Comparator	Outcome domains with available data (synthesis method/metric)	Measurement/ definition of outcomes	Time point at which outcome was measured
			Chloramphenicol 2–3 g/day	meningitis, confirmed by isolation of the pathogen from CSF. I: 13 (mean age 25.3 years); C: 13 (mean age 28.6 years)				

CSF: cerebrospinal fluid; CT: computed tomography; EEG: electroencephalogram; IU: international units; IV: intravenous; RCT: randomized controlled trial.

3.1.2 Studies excluded from the review

Table WA7.2 presents the studies excluded from this review, along with the reasons for excluding them,

Table WA7.2 Studies excluded from the review, with reasons for exclusion

Lead author (Year)	Reason for exclusion
Aronoff (1983) *(37)*	This study was conducted in patients with suspected bacterial infections other than meningitis. It was excluded because of wrong population.
Bernadino (1993) *(38)*	The translated full text of this study was not retrievable
Brink 2019 *(39)*	This study compared the effect of meropenem to cefotaxime plus ampicillin in treating meningitis. These were not the intervention and control drugs being assessed in this review; hence this study was excluded.
Cadoz (1982) *(40)*	The translated full text of this study was not retrievable.
Haffejee (1984) *(41)*	This study was conducted with patients with severe bacterial infections, and meningitis was not mentioned. This study was excluded because of wrong population.
Helwig (1990) *(42)*	In this study, among patients in the standard therapy group, 21 patients received penicillin/chloramphenicol and 17 patients received cefotaxime. The intervention arm received ceftriaxone. Disaggregated data about outcomes for the standard therapy group with just the non-cefotaxime were not available. Hence, this study was excluded.
Karvouniaris (2018) *(43)*	This was a systematic review comparing the efficacy of intravenous therapy combined with intraventricular therapy to that of standard IV antibiotic therapy.
Klugman (1995) *(44)*	This study was a comparative trial of meropenem versus cefotaxime. It was excluded because carbapenems are not included in the intervention arm for this research question.
Ngu (1987) *(45)*	The full text was not retrievable.
Steele (1984) *(46)*	This study was a secondary analysis of ceftriaxone dosing in bacterial meningitis and severe infections.
Rodriguez (1986) *(47)*	This study compared ceftazidime to ampicillin and chloramphenicol in treating bacterial meningitis. It was excluded because ceftazidime is not included in the intervention arm for

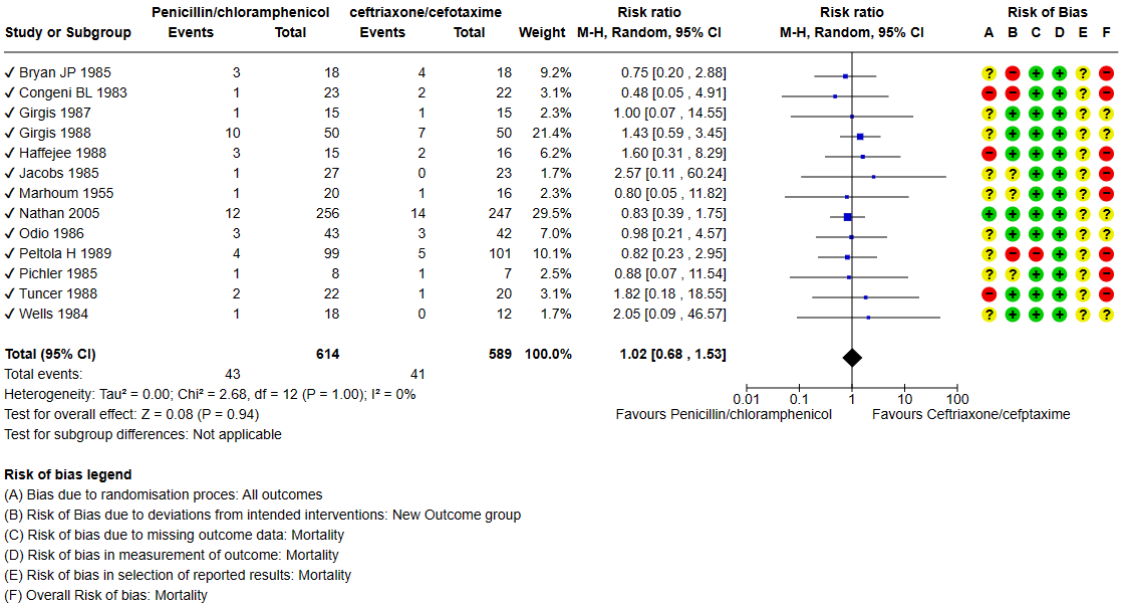
this research question. In addition, this drug cannot be used for treatment of *S. pneumoniae*, which is the commonest cause of acute bacterial meningitis.

3.2 Forest plots

The forest plots in Figs WA7.2 to WA7.5 illustrate the critical and important outcomes in detail.

3.2.1 Critical outcomes

Fig. WA7.2 Mortality



Risk of bias legend
(A) Bias due to randomisation proces: All outcomes
(B) Risk of Bias due to deviations from intended interventions: New Outcome group
(C) Risk of bias due to missing outcome data: Mortality
(D) Risk of bias in measurement of outcome: Mortality
(E) Risk of bias in selection of reported results: Mortality
(F) Overall Risk of bias: Mortality

Fig. WA7.3 Time to resolution of symptoms (fever – mean duration in days)

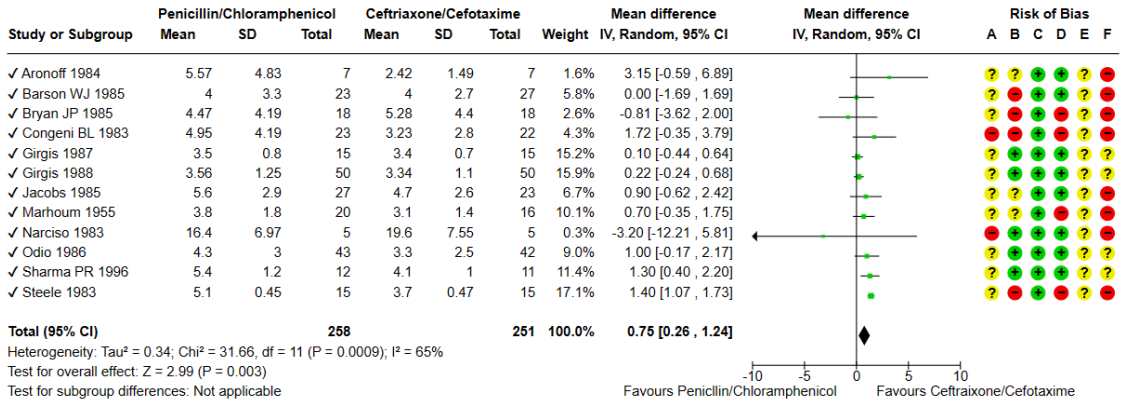
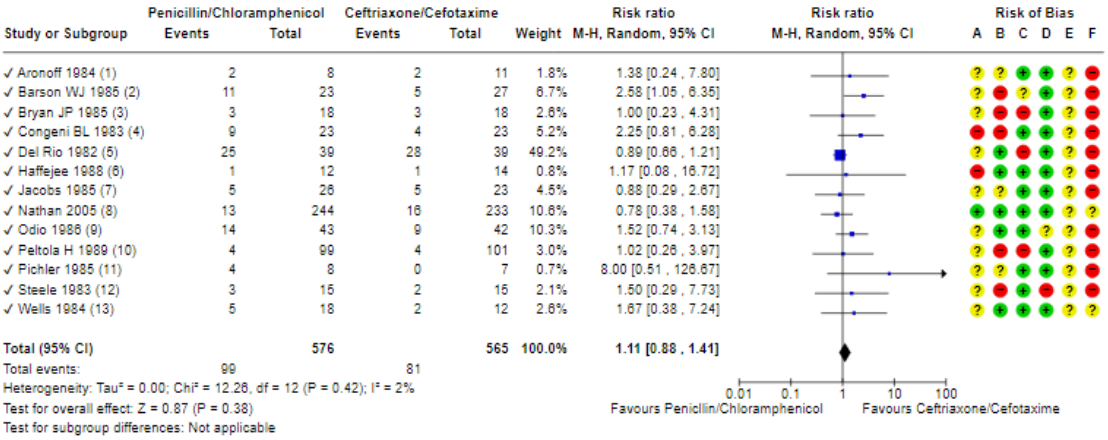
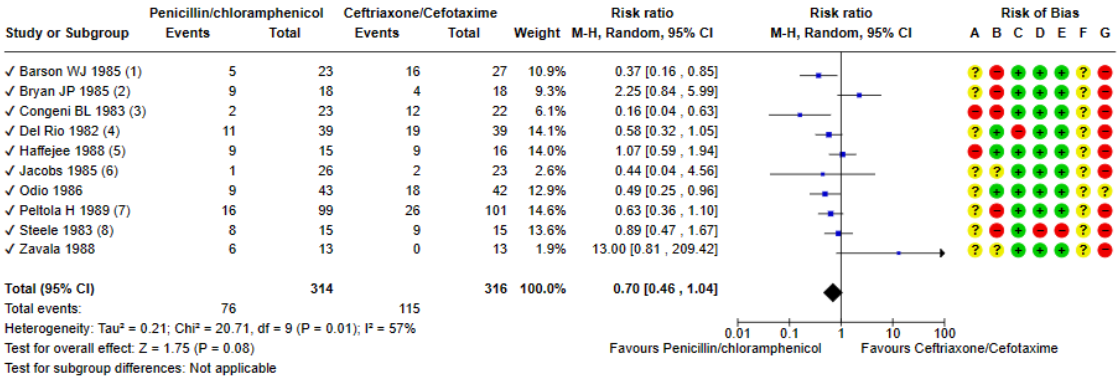


Fig. WA7.4 Neurological sequelae



3.2.2 Important outcomes

Fig. WA7.5 Adverse events



3.3 GRADE evidence profile

Table WA7.3 Alternative parenteral antimicrobial regimens (penicillin [i.e. benzylpenicillin, ampicillin, amoxicillin] or chloramphenicol alone or in combination) compared with monotherapy with ceftriaxone or cefotaxime for suspected or probable acute meningitis

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirectness	Imprecision	Other con-siderations	Other parenteral antibiotics	Ceftriaxone or cefotaxime	Relative (95% CI)	Absolute (95% CI)		
Mortality												
13	RCTs	Very serious[a]	Not serious	Not serious	Serious[b]	None	43/614 (7.0%)	41/589 (7.0%)	RR 1.02 (0.68 to 1.53)	1 more per 1000 (from 22 fewer to 37 more)	⨁◯◯◯ Very low	Critical
Time to resolution of symptoms – fever												
12	RCTs	Very serious[c]	Serious[d]	Not serious	Not serious	None	258 participants	251 participants	MD 0.75 days (0.26 to 1.24)		⨁◯◯◯ Very low	Critical
Disease complications, including neurological sequalae												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Other parenteral antibiotics	Ceftriaxone or cefotaxime	Relative (95% CI)	Absolute (95% CI)		
13	RCTs	Very serious[e]	Not serious	Not serious	Serious[f]	None	99/576 (17.2%)	81/565 (14.3%)	RR 1.11 (0.88 to 1.41)	16 more per 1000 (from 17 fewer to 59 more)	⨁◯◯◯ Very low	Critical
Adverse events												
10	RCTs	Very serious[g]	Serious[h]	Not serious	Serious[i]	None	76/314 (24.2%)	115/316 (36.4%)	RR 0.70 (0.46 to 1.04)	109 fewer per 1000 (from 197 fewer to 15 more)	⨁◯◯◯ Very low	Important

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

[a] Downgraded by two levels for very serious risk of bias as eight studies out of 13 had a high risk of bias in at least one domain and the rest had some concerns related to randomization.

[b] Downgraded by one level for serious imprecision as the confidence interval crosses the line of no difference, the upper limit shows significant harm and the lower limit shows significant benefit, which is clinically incompatible.

[c] Downgraded by two levels for very serious risk of bias as all studies included are either at high risk of bias or there are some concerns in at least one domain, and all studies had some concerns or a high risk of bias related to randomization.

[d] Downgraded by one level for serious inconsistency as moderate heterogeneity (I^2 = 65%) was identified.

[e] Downgraded by two levels for very serious risk of bias as 13 studies had a high risk of bias in at least one domain and the rest had some concerns related to randomization.

[f] Downgraded by one level for serious imprecision as the CI is wide, the upper limit shows significant harm and the lower limit shows benefit, which is clinically incompatible.

[g] Downgraded by two levels for very serious risk of bias as nine studies had a high risk of bias in at least one domain and the rest had some concerns related to randomization.

[h] Downgraded by one level for serious inconsistency as moderate heterogeneity (I^2 = 57%) was identified.

[i] Downgraded by one level for serious imprecision as the point estimate crosses the line of no difference, the upper limit shows harm and the lower limit shows significant benefit, which is clinically incompatible.

3.4 Description of intervention effects

The critical and important outcomes are described in the next two subsections.

3.4.1 Critical outcomes

All-cause mortality: Very low certainty evidence from 13 RCTs involving 1203 patients revealed that the effect of other parenteral antibiotics on mortality compared to ceftriaxone or cefotaxime was uncertain (RR 1.02; 95% CI 0.68 to 1.53) *(19, 20, 22-26, 28-31, 34, 35)*. All were small trials with a high risk of bias and the events were rare. The CI was wide, ranging from moderate benefit to significant harm.

Time to resolution of symptoms – fever (days): Very low certainty of evidence from 12 RCTs involving 509 patients revealed that the effect of other parenteral antibiotics on time to symptom resolution compared with ceftriaxone or cefotaxime was uncertain (mean difference [MD] 0.75 days; 95% CI 0.26 to 1.24 days) *(17-20, 22, 23, 25-27, 29, 32, 33)*. This suggests that resolution of fever (mean days) varied from reduction by 6 hours to more than 1 day and 6 hours in the intervention group as compared to the control group, crossing the line of no difference.

Neurological sequelae: Very low certainty of evidence from 13 RCTs involving 1141 patients revealed that the effect of other parenteral antibiotics on neurological sequelae compared to ceftriaxone or cefotaxime was uncertain (RR 1.11; 95% CI 0.88 to 1.41) *(17-21, 24, 25, 28-31, 33, 35)*. The CI was wide, ranging from minimal benefit to significant harm.

3.4.2 Important outcome

Adverse events: Very low certainty of evidence from 10 RCTs involving 630 patients revealed that the effect of other parenteral antibiotics on adverse events compared to ceftriaxone or cefotaxime was uncertain (RR 0.70; 95% CI 0.46 to 1.04) *(18-21, 24, 25, 29, 30, 33, 36)*. The CI was very wide, ranging from important benefit to possible harm.

3.5 Additional evidence not reported in GRADE evidence profiles

None,

3. From evidence to recommendations: summary of findings

Table WA7.4 presents the summary of findings for this review.

Table WA7.4 Summary of findings: Other parenteral antibiotics compared to ceftriaxone or cefotaxime for patients with suspected acute bacterial meningitis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ceftriaxone or cefotaxime	Risk with other parenteral antibiotics				
Mortality	70 per 1000	71 per 1000 (47 to 107)	RR 1.02 (0.68 to 1.53)	1203 (13 RCTs)	⊕◯◯◯ Very low[a,b]	The effect of other parenteral antibiotics on mortality is uncertain.
Time to resolution of symptoms – fever	0 per 1000	0 per 1000 (0 to 0)	MD 0.75 days (0.26 to 1.24)	509 (12 RCTs)	⊕◯◯◯ Very low[c,d]	The effect of other parenteral antibiotics on time to resolution of symptoms (fever) is uncertain
Disease complications, including neurological sequalae	143 per 1000	159 per 1000 (141 to 283)	RR 1.11 (0.88 to 1.41)	1141 (14 RCTs)	⊕◯◯◯ Very low[e,f]	The effect of other parenteral antibiotics on disease complications, including neurological sequalae, is uncertain.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ceftriaxone or cefotaxime	Risk with other parenteral antibiotics				
Adverse events	364 per 1000	255 per 1000 (167 to 378)	RR 0.70 (0.46 to 1.04)	630 (10 RCTs)	⊕◯◯◯ Very low[g,h,l,]	The effect of other parenteral antibiotics on adverse events is uncertain.

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: mean difference; RR: risk ratio.

[a] Downgraded by two levels for very serious risk of bias as 8 out of 13 studies had a high risk of bias in at least one domain and rest had some concerns related to randomization.

[b] Downgraded by one level for serious imprecision as the confidence interval crosses the line of no difference, the upper limit shows significant harm and the lower limit shows significant benefit, which is clinically incompatible.

[c] Downgraded by two levels for very serious risk of bias as all studies included are either at high risk of bias or have some concerns in at least one domain, and all studies had some concerns or a high risk of bias related to randomization.

[d] Downgraded by one level for serious inconsistency as moderate heterogeneity (I^2 = 65%) was identified.

[e] Downgraded by two levels for very serious risk of bias as 13 studies had a high risk of bias in at least one domain and rest had some concerns related to randomization.

[f] Downgraded by one level for serious imprecision as the CI is wide, the upper limit shows significant harm and lower limit shows no benefit.

[g] Downgraded by two levels for very serious risk of bias as nine studies had a high risk of bias in at least one domain and rest had some concerns related to randomization.

[h] Downgraded by one level for serious inconsistency as moderate heterogeneity (I^2 = 57%) was identified.

[l] Downgraded by one level for serious imprecision as the point estimate crosses the line of no difference, the upper limit shows harm and the lower limit shows significant benefit, which is clinically incompatible.

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Appendix 1. Search strategy used to identify primary studies

Table WA7.A1.1 Database: MEDLINE (OVID), 1946 to November Week 4 2023, searched on 2 January 2023

No.	Searches	Results
1	Meningitis, Bacterial/ or ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome or Neisseria-meningitidis or meningococc* or N-meningitidis or Escherichia-coli or E-coli or GBS or streptococc* or S-agalactiae or H-influenza* or Haemophilus-influenza* or Hemophilus or Haemophilus or Leptospir* or L-monocytogenes or Listeria-monocytogenes or listerial or Borrelia-burgdorferi or B-burgdorferi or Borrelia or Lyme or Streptococcus-pneumoniae or S-pneumoniae or pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) adj3 meningit*).ti,ab. OR (Meningococc* adj5 (infection* OR disease*)).ti,ab.	29 292
2	Anti-Bacterial Agents/ or (anti-biotic* or antibiotic* or anti-bacteri* or antibacteri* or antimicrobial* or anti-microbial*).ti,ab.	693 742
3	Rifamycins/ or Vancomycin/ or Penicillins/ or Cephalosporins/	77 182
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR Gmyticin OR Cefepim OR Maxipime OR Axepim OR Quadrocef OR “BMY 28142” OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR “Biseptol 480” OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR “SQ 26776” OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR “BAY 12 8039” OR “BAY 128039” OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR “CP 62993” OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR “LY 139381” OR LY139381 OR Tazidime OR Ceftazidime OR “GR 20263” OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR 295eningococc* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR “Ro13 9904” OR “Ro13 9904” OR Ro139904 OR “Ro 13 9904” OR “Ro 13 9904” OR “Ro 13 9904” OR “Ro 139904” OR Rocephin OR Rocefalin OR Rocephine OR Rocefin	523 552

	OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR “HR 756” OR HR756 OR “Ru 24756” OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR “BRL 2333” OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR “Or pen” OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR 296eningococcu* OR sulfa* OR ciprofloxacin* OR 296eningococc* OR 296eningoco* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR 296eningococcu* OR 296eningococc* OR 296eningococc* OR 296eningoco*).ti,ab.	
5	2 or 3 or 4	1 039 341
6	1 and 5	8 867
7	animals/ not (animals/ and humans/)	5 145 692
8	(letter or historical article or comment or editorial or news or case reports).pt.	4 464 549
9	6 not (7 or 8)	5 704

Table WA7.A1.2 Database: Embase (Elsevier) (www.embase.com), searched on 2 January 2023

No.	Searches	Results
1	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N.-meningitidis OR Escherichia-coli OR E.-coli OR GBS OR streptococc* OR S.-agalactiae OR H.-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L.-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B.-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S.-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S.Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (297eningoco*)):ti,ab,kw,de OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,de,kw	51 027
2	antibiotic agent'/mj OR (anti-biotic* OR antibiotic* OR anti-bacteri* OR antibacteri* OR antimicrobial* OR anti-microbial*):ti,ab	899 463
3	rifamycin'/mj OR 'vancomycin'/mj OR 'penicillin derivative'/mj OR 'cephalosporin'/mj	51 489
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR Gmyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR BMY-28142 OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR Biseptol-480 OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR SQ-26776 OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR BAY-12-8039 OR BAY-128039 OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime Pentahydrate OR LY-139381 OR LY139381 OR Tazidime OR Ceftazidime OR GR-20263 OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR 297eningococc* OR cefotaxime OR ciprofloxacin	1 360 937

	OR Lendacin OR Longacef OR Longaceph OR Ro13-9904 OR Ro13-9904 OR Ro139904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-139904 OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR HR-756 OR HR756 OR Ru-24756 OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR BRL-2333 OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR Or-pen OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR 298eningococcu* OR sulfa* OR ciprofloxacin* OR 298eningococc* OR 298eningoco* OR quinol* or fluoroquinol* OR fluoro-quinolon* OR rifampi* OR 298eningococcu* OR 298eningococc* OR 298eningococc* OR 298eningoco*):ti,ab,kw,de	
5	#2 OR #3 OR #4	1 907 847
6	#1 AND #5	18 289
7	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 442 093
8	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR case-report*:ti OR case-series:ti OR genomic*:ti OR 'in vitro':ti	9 735 110
9	#6 NOT (#7 OR #8)	13 657

Table WA7.A1.3 Database: CENTRAL (www.cochranelibrary.com/advanced-search/search-manager), searched on 2 January 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis, Bacterial] explode all trees	489
2	((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N-meningitidis OR Escherichia-coli OR E-coli OR GBS OR streptococc* OR S-agalactiae OR H-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (299eningoco*)):ti,ab OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,kw	1 404
3	#1 OR #2	1 632
4	MeSH descriptor: [Anti-Bacterial Agents] this term only	15 349
5	MeSH descriptor: [Rifamycins] explode all trees	1 846
6	MeSH descriptor: [Vancomycin] explode all trees	982
7	MeSH descriptor: [Penicillins] explode all trees	6 320
8	MeSH descriptor: [Cephalosporins] explode all trees	4 785
9	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR Gmyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR	55 820

	Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR 300eningococc* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR “Ro13 9904” OR “Ro13 9904” OR Ro139904 OR “Ro 13 9904” OR “Ro 13 9904” OR “Ro 13 9904” OR “Ro 139904” OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR “HR 756” OR HR756 OR “Ru 24756” OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR “BRL 2333” OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR “Or pen” OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR 300eningococcu* OR sulfa* OR ciprofloxacin* OR 300eningococc* OR 300eningoco* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR 300eningococcu* OR 300eningococc* OR 300eningococc* OR 300eningoco*):ti,ab,kw	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	63 714
11	#3 AND #10	372
12	Trials	361

Table WA7.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 2 January 2024

No.	Searches	Results
#1 (Condition)	((bacterial OR Neisseria OR 301eningococcus OR Escherichia-coli OR streptococcus OR influenza OR Hemophilus OR Leptospira OR Listeria-monocytogenes OR listerial OR Borrelia OR Lyme OR Streptococcus OR pneumococcus OR disease) AND (meningitis))	
#2 (Other terms)	anti-biotic OR antibiotic OR anti-bacterial OR antibacterial OR antimicrobial OR anti-microbial OR cephalosporin OR penicillin OR vancomycin OR rifampicin OR chloramphenicol OR ceftriaxone OR cefotaxime OR ciprofloxacin OR Ampicillin OR Amoxicillin	
#3	#1 AND #2	122

8. Duration of empiric antimicrobial treatment in non-epidemic settings

Authors

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Abbreviations

CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IV	intravenously
OIS	optimal information size
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
robvis	Risk-Of-Bias VISualization (a tool available as an R package and web app)
RR	risk ratio

1. Background

Acute bacterial meningitis is a life-threatening condition that requires prompt initiation of empiric antimicrobial treatment. This disease can lead to severe complications and has a significant risk of causing permanent neurological damage. The standard treatment for acute bacterial meningitis usually involves taking antibiotics for 10–14 days, but there are no clear guidelines on the ideal duration of treatment. In other organ system infections, whether it is pneumonia *(1, 2)*, intra-abdominal infections *(3)* or urinary tract infections *(4)*, shorter courses of antibiotics are increasingly being used, with comparable outcomes. A shorter course of antibiotics may be as effective as a longer course. This is especially beneficial in countries with limited resources, where it can reduce the length of hospital stay, and prevent some of the unwanted adverse effects produced by antibiotics, including antimicrobial resistance or drug-related side effects *(5)*.

In 2004, the Infectious Diseases Society of America recommended that the length of the treatment should depend on the pathogen and the clinical response. For the three most common pathogens causing bacterial meningitis in healthy adults and children, *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis,* these guidelines suggest 10 to 14 days, 7 to 10 days, and 5 to 10 days respectively *(6)*. Hence the duration of the antibiotic course varies from short to long depending on the infecting organism or the development of complications. In most cases of acute bacterial meningitis, however, patients often improve dramatically, suggesting there may be a role for a shorter duration of therapy, while treatment may be prolonged in patients with neurological complications like brain abscess or subdural empyema *(7)*.

While there may be data about the optimal duration of therapy when the infecting pathogen is known, the situation is often more complicated if the pathogen causing acute bacterial meningitis is unknown, as the duration of the disease may be dependent purely on clinical response or resolution of cellularity in the analysis of cerebrospinal fluid (CSF).

This review attempts to generate evidence on the duration of empiric antimicrobial treatment for a suspected or probable case of acute bacterial meningitis in the absence of pathogen identification.

This work has been carried out for the development of the *WHO guidelines for meningitis diagnosis, treatment and care*.

2. Methodology

2.1 Research question and study design

In non-epidemic settings, among cases of suspected or probable acute bacterial meningitis, in the absence of pathogen identification, does empiric antimicrobial treatment for 10 days reduce morbidity and mortality outcomes compared to a shorter or longer treatment course?

Population: Suspected or probable cases of acute bacterial meningitis in non-epidemic settings. Subgroups: age groups (children, adults, the elderly > 60 years); pregnant women; patients with immunocompromised status; patients in areas where there is a prevalence of pneumococcal resistance to beta-lactams.

Intervention: Empiric antimicrobial therapy for a duration of 10 days.

Comparator: Empiric antimicrobial therapy for a duration of less than 10 days (5–7) or more than 10 days (14–21).

Outcomes

Critical outcomes:

- mortality;
- disease relapse;
- disease complications (sepsis, disseminated intravascular coagulation, neurological complications, including neurological sequelae).

Important outcomes:

- adverse effects.

Study designs: A systematic review was performed using the primary studies identified by our search strategy. Randomized controlled trials (RCTs) and prospective cohort studies with a comparator arm were included. The available data from retrospective cohorts were summarized as additional evidence if applicable to the research question.

2.2 Eligible studies

Published language: All relevant studies were included, regardless of language. The studies in English were evaluated by the review team. For studies in languages other than English, translated versions were obtained from online software.

Exclusion criteria:

- All retrospective studies and prospective non-randomized cohort studies without a comparator were excluded.
- Case reports, case series and any ongoing trials and studies with outcome data that could not be evaluated were also excluded.

2.3 Search strategy

Searches for primary studies were conducted in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the US National Library of Medicine (ClinicalTrials.gov). All databases were searched for studies published from 1946 to November 2023.

2.4 Selection of studies

A preliminary search was conducted for systematic reviews relevant to the research question. Two systematic reviews *(8, 9)* were found through the search, and one review (meta-analysis) *(10)* was provided by WHO. The methodological quality of the systematic reviews was evaluated using AMSTAR (A MeaSurement Tool to Assess systematic Reviews) and they were both found to be of low quality.

The systematic review carried out by Van Hentenryck et al. *(8)* was a meta-analysis of one RCT, 25 cohort studies and six case series. The RCT included in this meta-analysis compares 10 days to 14 days of antibiotic therapy with patients randomized after pathogen identification *(11)*. We excluded this RCT as it did not provide disaggregated data for patients in whose cases no pathogen was identified.

The second systematic review, by Karageorgopoulos et al. *(9)*, analysed RCTs comparing short and long antibiotic durations for bacterial meningitis, but all five RCTs *(12-16)* reviewed were ineligible because they randomized the cases after identifying the pathogen, while our research question focuses on empirical treatment without pathogen identification. Similarly, the review provided by WHO, a meta-analysis by Sudo et al. (10), included six RCTs, with four *(12-14, 16)* not eligible because the cases had been randomized after the pathogen had been identified. However, the remaining two *(17, 18)* were eligible as they included patients with negative cultures, and randomization was not based on the pathogen.

A search was then conducted across the databases mentioned in section 2.3 to identify primary studies relevant to research questions 5–10 (i.e. this report and five other reports in this web annex) on empiric antimicrobial treatment, the duration of antimicrobial treatment in both epidemic and non-epidemic settings, and post-exposure antimicrobial prophylaxis. The search yielded 15 158 studies. After filtering using the Rayyan tool *(19)*, 1194 duplicate articles were identified. Of these, 208 duplicates were removed manually by the authors. Subsequently, the remaining 14 950 articles underwent independent screening by the authors through Rayyan. After title and abstract screening, 14 880 studies were excluded since they were not relevant to our research questions. Full-text screening was then conducted on 70 articles retrieved from the review authors' institutional libraries and WHO libraries, resulting in the full texts for 64 articles being obtained. However, the remaining six articles were excluded because four of them were clinical trials with unpublished data. Despite attempts to contact the authors, full-text

versions of these trials could not be obtained. Additionally, full texts of the other two studies were also unavailable.

After thorough full-text screening of all 64 studies, one study relevant to this research question (i.e. this report) was found, Molyneax et al. *(17)*. That study was also identified while screening systematic reviews, along with one other study, by Vasawani et al. *(18)*. As a result, both studies were included in the meta-analysis *(17, 18)*. The characteristics of the studies included are presented in Table WA8.1, and Fig. WA8.1 provides the Preferred Reporting Items for the Systematic reviews and Meta-Analyses (PRISMA) flow diagram for the search.

2.5 Data extraction and management

Two of three authors (JSJ, HA and JM) used a piloted data extraction form to extract data on the following: participant characteristics, disease severity, comorbidity, antimicrobial treatment and administration, other treatments given, and outcome measures as defined by the research question. For dichotomous outcomes like mortality and neurological complications, the authors recorded the number of participants who had experienced the event and the number of participants in each treatment group.

2.6 Assessment of risk of bias in studies included in the review

Two of the authors (JSJ and HA) assessed the risk of bias for the primary and secondary outcomes using the Cochrane risk of bias assessment tool *(20)*. The risk of bias assessment was verified by the corresponding authors (PR and AT) and the results were reported in a traffic light plot (Fig. WA8.2). The risk of bias summary was created using the robvis tool *(21)*.

2.7 Data synthesis

Data were analysed by two of the authors (JSJ, HA) using Review Manager software *(22)*. When more than one study contributed to the evidence synthesis, data were pooled in meta-analyses using a random-effects model. Dichotomous data are presented and compared using risk ratios (RR). All the results are presented with the corresponding 95% confidence interval (CI).

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework to assess the certainty of the evidence *(23)*. GRADE is a transparent framework designed for the development and presentation of evidence summaries, offering a systematic approach to formulating clinical practice recommendations. The quality of the evidence is assessed for each outcome, and GRADE categorizes it into four

levels of certainty: very low, low, moderate and high *(24)*. Certainty in the evidence for each outcome is evaluated across five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. The GRADE levels of certainty are defined below.

Box WA8.1 The certainty of evidence used in GRADE	
High ⊕⊕⊕⊕	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The results of the analysis are summarized in Table WA8.5, which also presents the summary effect estimates for the outcomes.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

No subgroup analysis was performed.

2.10 Sensitivity analysis

No sensitivity analysis was performed.

2.11 Deviations from the review protocol

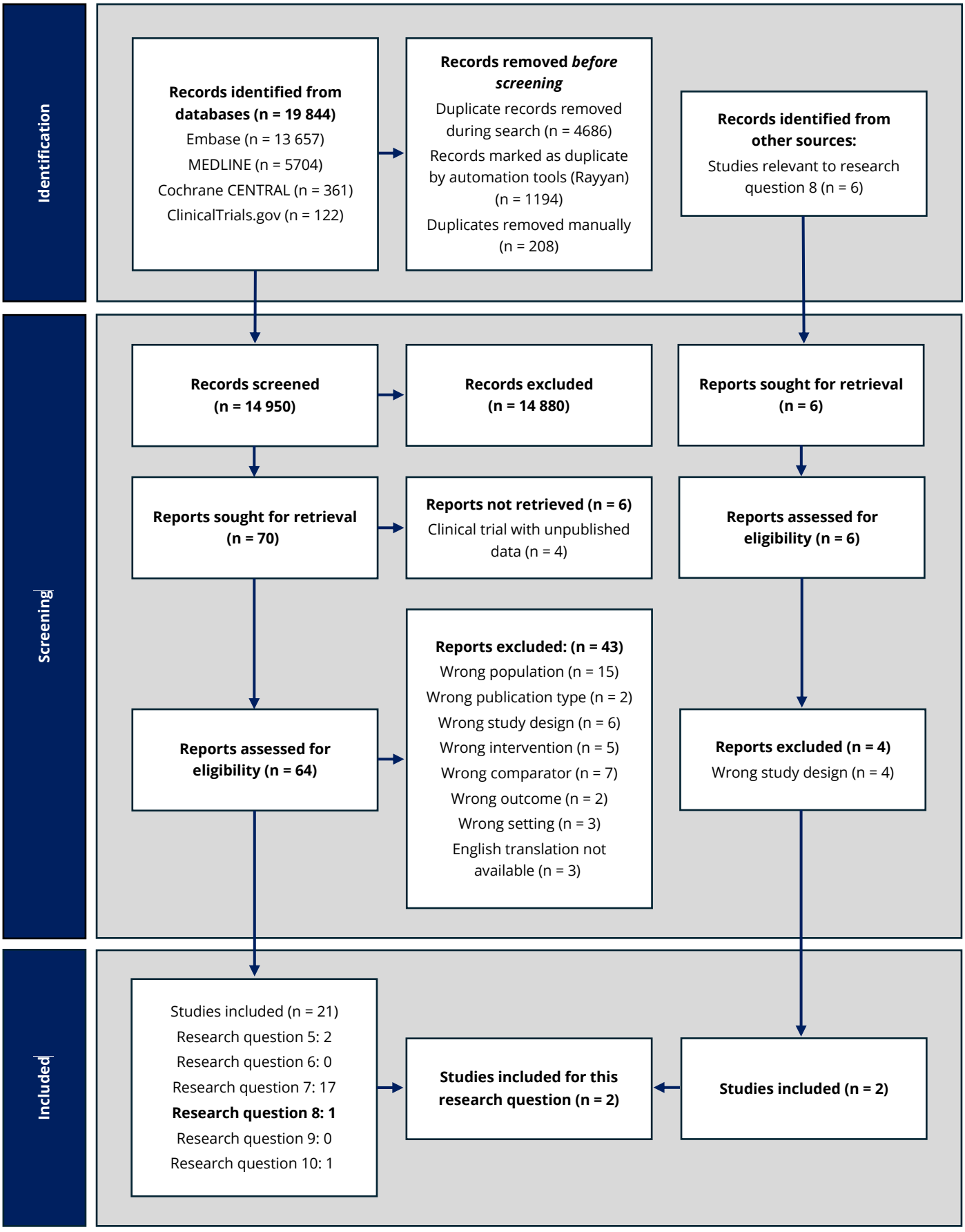
There was no deviation from the review protocol.

3. Results

3.1 Studies identified by the search process

Figure WA8.1 presents the PRISMA flow diagram for this review.

Fig. WA8.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profile

Table WA8.1 presents the characteristics of the studies included in the GRADE evidence profile.

Table WA8.1 Characteristics of studies included in the GRADE evidence profile

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population Sample size: intervention (I) / control (C)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time point of measurement
Molyneux (2011), Malawi *(17)*	Multi-country, double-blind, placebo-controlled, RCT	Low	On Day 5 patients were randomized to receive ceftriaxone (80–100 mg/kg) for 5 more days	Children aged 2 months to 12 years with purulent meningitis. I: 496 (no pathogen identified in 162) C: 508 (no pathogen identified in 168	On Day 5, patients were randomized to receive placebo for 5 more days	Mortality Disease complications	Hearing was assessed by trained staff with optoacoustic emissions tests and at some centres by brainstem auditory evoked response.	Mortality any time during the study Hearing assessment at Day 40 and Day 190
Vaswani (2020), India *(18)*	Prospective, open-label, non-blinded comparative RCT	Some concerns	Antibiotics given for 10 days Ceftriaxone (100 mg/kg per day in 2 divided	Patients with acute bacterial meningitis aged 3 months to 14 years	Antibiotic given for 7 days Ceftriaxone (100 mg/kg per day in 2 divided	Disease relapse Disease complications	Relapse of meningitis, defined as the recurrence of signs and symptoms of meningitis	Disease relapse was assessed during discharge (Day 10)

	doses administered every 12 h) and vancomycin (60 mg/kg per day in 4 divided doses administered every 6 h)	I: 48; C: 48	doses administered every 12 h) and vancomycin (60 mg/kg per day in 4 divided doses administered every 6 h)	within 2 weeks of discharge from hospital. Neuroimaging was done at discharge and neuro-developmental assessment was done using Denver Development Screening Test. Hearing assessment was done using Pure tone audiometry or brain stem auditory evoked responses. These tests were done during follow-ups.	Disease complication at Day 10 and during the follow-ups (Day 7, 15, 30 and 90)

RCT: randomized controlled trial.

3.1.2 Studies excluded from the review

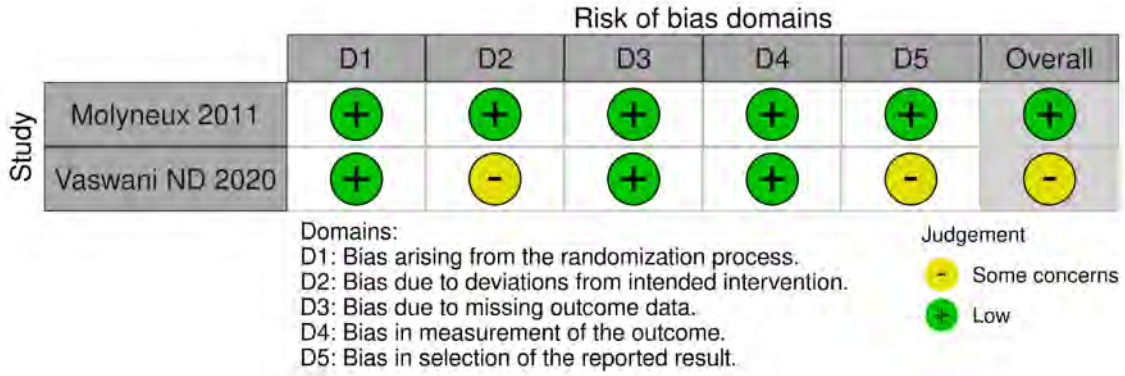
Table WA8.2 presents the studies that were excluded from the review, along with the reasons for their exclusion, and Fig. WA8.2 presents the results of the risk of bias summary.

Table WA8.2 Studies excluded from the review

Study	Reason for exclusion
Karageorgopoulos, 2009 *(9)*	This is a meta-analysis of RCTs comparing short and long duration of antibiotics for the treatment of bacterial meningitis. Upon analysis of each RCT in the review, all five RCTs were inconsistent with our research question because randomization had been done after pathogen identification but the research question clearly states empiric treatment in the absence of pathogen identification. Hence this study was excluded.
Mathur, 2015 *(11)*	This is an RCT conducted among neonates with meningitis. For 82.9% of the study population and 80% of the control the pathogen had not been identified. Disaggregated data for these patients was not obtainable for outcomes of mortality and sequelae. In addition, a population of neonates does not fit our criteria of community-acquired bacterial meningitis and is not generalizable.
Lin, 1985 *(12)*	This is a randomized trial involving infants from 1 month of age to children with suspected or proven bacterial meningitis. Randomization was done after pathogen identification; hence we excluded this study.
Martin, 1990 *(14)*	This is a prospective Swiss multicentre study in children with acute bacterial meningitis. For all the patients except seven, the organism was identified, and all of the seven received therapy of long duration. Hence, we excluded this study.
Roine, 2000 *(15)*	This is a randomized trial involving children with bacterial meningitis. We excluded this study because both the arms were of short duration, with no comparator arm of 10 days
No authors given, 2023 *(24)*	This is an unpublished completed clinical trial of longer-course intravenous antibiotics in neonates with uncomplicated meningitis. Data were not available, so it was excluded

RCT: randomized controlled trial.

Fig. WA8.2 Risk of bias summary (carried out using robvis tool)



3.2 Forest plots

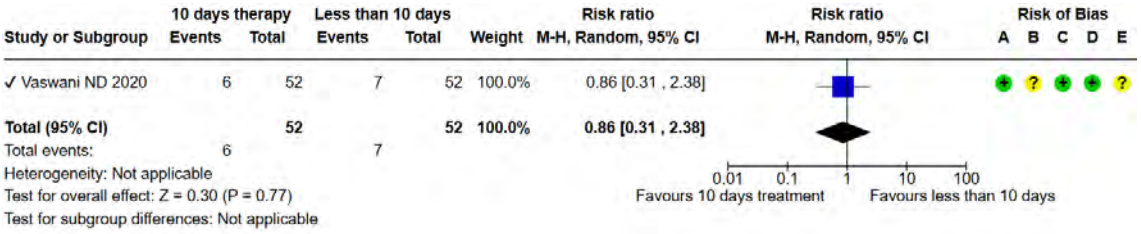
The forest plots in Figs WA8.3 to 5 illustrate the intervention outcomes in detail.

Fig. WA8.3 Mortality forest plot

Footnotes
(1) comparison between 10 days Vs 5 days. Mortality within 40 days were included in the data. (source prisma diagram)

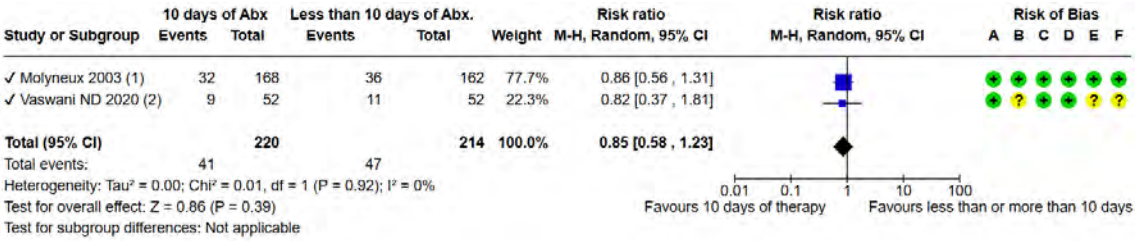
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in Selection of the Reported Result

Fig. WA8.4 Disease relapse forest plot



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in Selection of the Reported Result

Fig. WA8.5 Disease complications forest plot



Footnotes

(1) pathogen unidentified data from table 3

(2) nosocomial sepsis -2 in each group, hearing loss- 3 in each group,Neurological sequelae(motor deficit, nerve palsies)-6 in 7 day group,3 in 10 day group.Recurrent afeb

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in Selection of the Reported Result

(F) Overall risk of bias: New Outcome group

3.3 GRADE evidence profile

Table WA8.3 Empiric antimicrobial treatment for 10 days compared with a shorter or longer treatment course for suspected probably acute bacterial meningitis

Setting: Non-epidemic setting.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirectness**	**Imprecision**	**Other con-siderations**	**Empiric antimicrobial treatment for 10 days**	**Empiric antimicrobial treatment for < 10 days**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow-up: 30 days)												
1 *(17)*	RCT	Not serious	Not serious	Not serious	Very serious[a]	none	5/168 (3.0%)	5/162 (3.1%)	RR 0.96 (0.28 to 3.27)	1 fewer per 1000 (from 22 fewer to 70 more)	⨁⨁◯◯ Low	Critical
Disease relapse												
1 *(18)*	RCT	Not serious	Not serious	Not serious	Very serious[a]	None	6/52 (11.5%)	7/52 (13.5%)	RR 0.86 (0.31 to 2.38)	19 fewer per 1000 (from 93 fewer to 186 more)	⨁⨁◯◯ Low	Critical

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Empiric antimicrobial treatment for 10 days**	**Empiric antimicrobial treatment for < 10 days**	**Relative (95% CI)**	**Absolute (95% CI)**		
Disease complications, including neurological sequelae												
2 *(17, 18)*	RCT	Not serious	Not serious	Not serious	Very serious[a]	None	41/220 (18.6%)	47/214 (22.0%)	RR 0.85 (0.58 to 1.23)	33 fewer per 1000 (from 92 fewer to 51 more)	⨁⨁◯◯ Low	Critical

RCT: randomized controlled trial

[a] Downgraded by two levels for very serious imprecision as the point estimate crosses the line of no difference, number of events did not reach optimal information size (OIS) and upper limit shows significant benefit and lower limit shows significant harm which is clinically incompatible.

3.4 Description of intervention effects

All-cause mortality: Low certainty evidence from 1 RCT *(17)* in 330 patients revealed that the empiric antimicrobial treatment for 10 days might have little or no effect on all-cause mortality compared to empiric treatment for fewer than 10 days. The events were very rare and the confidence interval was very wide, ranging from important benefit to significant harm (RR 0.96, 95% CI 0.28 to 3.27).

Disease relapse: Low certainty evidence from 1 RCT *(18)* in 104 patients revealed that the empiric antimicrobial treatment for 10 days might have little or no effect on disease relapse compared to empiric antimicrobial treatment for fewer than 10 days. The events were very rare and did not meet the optimal information size (OIS) criteria. The confidence interval was wide, ranging from important benefit to appreciable harm (RR 0.86, 95% CI 0.31 to 2.38).

Disease complications: Low certainty evidence from 2 RCTs *(17, 18)* in 434 patients revealed that the empiric antimicrobial treatment for 10 days might have little to no effect on disease complications (neurological sequelae, hearing loss and hydrocephalus) compared to empiric antimicrobial treatment for less than 10 days. The confidence interval was wide, ranging from moderate benefit to harm (RR 0.85, 95% CI 0.58 to 1.23).

3.5 Additional evidence not reported in GRADE evidence profiles

No retrospective studies relevant to this research question were found.

3.6 Description of additional studies

Some additional studies are described in Table WA8.4 since they provide indirect evidence. While related to the question, these studies were excluded because the research question stipulates empiric antimicrobial treatment in the absence of pathogen identification, while in all of these studies, the pathogen was identified before randomization, and the duration of the treatment is based on the pathogen identified, which makes it a targeted therapy.

Table WA8.4 Characteristics of additional studies providing indirect evidence

Lead author (Year)	Study design	Population	Intervention	Comparator	Inclusion/Exclusion criteria	Reason for exclusion	Important results
Mathur (2015) *(11)*	RCT	Eligible neonates consecutively admitted with meningitis from May 2012 to January 2013	10 days of therapy	14 days of therapy	All cases of neonatal meningitis who by Day 7 of antibiotic treatment had clinical remission, normal CSF and no evidence of infection on cranial ultrasonography were enrolled in the study (on Day 7 of antibiotic therapy). Neonates with major congenital malformations were excluded.	82.9% of the study population and 80% of the control did not have pathogen identified. However, disaggregated data for these patients were not obtainable for outcomes of mortality and sequelae. In addition, population of neonates does not fit our criteria of community-acquired bacterial meningitis and would not be generalizable as the causes for neonatal meningitis are different.	Mortality at post-discharge follow-up was found to be 2.9% (1/35) in 10-day group and 5.7% (2/35) in 14-day group (*P*-value 1.00). Abnormal brainstem auditory evoked response was seen in 1 patient in 10-day group (*P* = 1.00). Occurrence of sepsis in 3 patients in 14-day group (*P*-value 0.24). This study revealed that 10 days of antibiotics in neonatal meningitis was as effective as 14 days of therapy and associated with lower mortality and adverse outcome.
Lin (1985) *(12)*	Randomized trial	All infants older than 1 month of age and children with suspected or proven bacterial meningitis admitted were enrolled into the study.	Duration of therapy was assigned after the etiologic agent was identified by the microbiology laboratory. Those with meningitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* or *Streptococcus agalactiae* (group B streptococcus) were assigned to receive either 7 or 10 days of therapy.		Intravascular coagulation, bacteraemia, and patients with meningitis due to *S. pneumoniae* who died within 3 days of ceftriaxone therapy were excluded from this evaluation.	115 infants enrolled, 80 had bacterial etiology whereas 35 had non-bacterial meningitis. Randomization was done after pathogen identification; hence this study was excluded.	No deaths and no neurological complications found in either arm. 8/27 (29%) in shorter arm and 8/25 (32%) in longer arm had hearing impairment at follow-up (RR 0.93; 95% CI 0.41, 2.09).

Lead author (Year)	Study design	Population	Intervention	Comparator	Inclusion/Exclusion criteria	Reason for exclusion	Important results
Kavaliotis (1989) *(13)*	Open prospective randomized comparative study	Cases of bacterial meningitis beyond the neonatal period, with a positive blood or CSF culture	All patients received ceftriaxone IV in an initial dose of 100 mg/kg (max. 4 g) **Group 1 (short arm) N = 26** / **Group 2 (long arm) N = 26** *N. meningitidis*: 4d = 11 / 8d = 16 *H. influenzae*: 6d = 12 / 12d = 9 *S. pneumoniae*: 7d = 3 / 14d = 1		Patients with known or suspected sensitivity to cephalosporin, with renal or hepatobiliary diseases and patients who received other antibiotics prior to admission were excluded.	Children aged 3 months to 12 years were enrolled in the study. They were randomized after the identification of the pathogen into short, i.e. 4, 6 and 7 days, vs long, i.e. 8, 12 and 14 days. For all patients the causative organisms were identified, hence we excluded this study.	No deaths in either group. All patients were cured and no relapses occurred. On discharge, 4 patients in long arm group had neurological deficits. Hearing loss (RR 0.14 95% CI 0.01, 2.63) *P* = 0.362; Ataxia (RR 0.33; 95% CI 0.01, 7.82) *P* = 1.5; 4/26 in short arm and 3/26 in long arm group had mild diarrhoea (RR 1.33; 95% CI 0.33, 5.38 (*P* = 0.615).
Martin (1990) *(14)*	Prospective Swiss multicentre study	119 children with acute bacterial meningitis	The exact length of ceftriaxone administration to the subjects in each group was predetermined by the bacteriological findings **Group 1 (short arm) N = 47** / **Group 2 (long arm) N = 45** *N. meningitidis*: 4d = 12 / 8d = 19 *H. influenzae*: 6d = 31 / 12d = 21 *S. pneumoniae*: 7d = 4 / 14d = 5		Patients with (i) no viable organisms in their CSF (culture-negative CSF), or with (ii) CSF pathogens too infrequent to randomize, i.e. *E. coli* or *S. agalactiae*, or with (iii) those in whom no repeat spinal tap within 15 h and 24 h was done were secondarily excluded from the randomized groups of the study	Children with acute bacterial meningitis enrolled into the study. They were randomized after the identification of the pathogen into short, i.e. 4, 6 and 7 days, vs long, i.e. 8, 12 and 14 days. For all patients organism was identified except for 7 patients and all the 7 patients only received long duration. Hence this study was excluded.	In the short course therapy arm, 4/47 (9%) improved and in the long course therapy arm, 5/45 (11%) improved (RR 0.77; 95% CI 0.22, 2.67). 5/47 (10%) in the shorter arm and 6/45 (13%) in the longer arm had neurological complication at discharge (RR 0.80; 95% CI 0.26, 2.43). No deaths and none of the patients required adjunctive antibiotics.

Lead author (Year)	Study design	Population	Intervention	Comparator	Inclusion/Exclusion criteria	Reason for exclusion	Important results
Singhi (2002) *(16)*	Prospective randomized study	73 consecutively admitted children between 3 months and 12 years with suspected bacterial meningitis	All children were started on ceftriaxone 100 mg/kg per day in two divided doses. Randomization to Group I (7 days of therapy) or Group II (10 days of therapy) was done on the 7th day.		Patients included with diagnosis of acute bacterial meningitis with clinical signs such as fever, headache, with any of the following: CSF blood culture for bacteria or positive latex or CSF Gram stain positive. Excluded from the study were children of less than 3 months, those who had received prior IV antibiotic treatment or those with recurrent meningitis	Patients randomized to short (7 days) vs long (10 days) on the Day 7 of treatment. 38% of cases did not have pathogen identified. However, disaggregated data were not available for this group with regard to mortality, disease relapse and complications. This study was excluded as 62% had pathogen identified and therapy was no longer considered empiric treatment.	Treatment failure 9/35 (25%) in shorter arm and 8/34 (23%) in longer arm (RR 1.09; 95% CI 0.48, 2.50) 7/33 (21%) in shorter arm and 8/34 (23%) in longer arm had hearing impairment (RR 0.90; 95% CI 0.37, 2.20)

Lead author (Year)	Study design	Population	Intervention	Comparator	Inclusion/Exclusion criteria	Reason for exclusion	Important results
Roine (2000) *(15)*	Randomized trial	All children with bacterial meningitis who were at least 3 months old were considered for enrolment.	7 days vs 4 days of ceftriaxone treatment		114 patients were excluded from the study by the following criteria: previous developmental abnormality; fatal outcome before Day 4; unknown etiology of meningitis; and not fulfilling the criteria for rapid initial recovery during the first 4 days of treatment	24% in 4-day group and 25% in 7-day group had no pathogen identified. But both the arms were short duration, with no 10-day comparator arm.	**Short-term outcomes (5–7 days)** / **Tx group – 4 days** / **Tx group – 7 days** Temperature > 37.4°C: 7 / 9 Irritable: 0 / 1 CRP rise > 30%: 2/37 / 1/39 **Long-term outcomes (1–3 months)** Convulsions: 0 / 1/40 Readmission: 3/47 / 0 Neurological sequelae: 0 / 2/39 Auditory sequelae: 1/38 / 3/32
Jadavji (1986) *(26)*	Prospective cohort No comparator arm	All infants and children admitted to hospital with microbiologically confirmed bacterial meningitis were recruited for this study.	7 days' treatment for bacterial meningitis without comparator		Review of all admission records was made. For this study, a patient was considered to have bacterial meningitis if the CSF culture was positive for *H. influenzae*, *S. pneumoniae* or *N. meningitidis*.	This was a prospective cohort of all infants with microbiologically confirmed meningitis treated for 7 days and followed for mortality or sequelae, without a comparator arm. Since pathogens were identified, which is inconsistent with our study, and there was no comparator arm,	No results attached

Lead author (Year)	Study design	Population	Intervention	Comparator	Inclusion/Exclusion criteria	Reason for exclusion	Important results
						this study was excluded.	

CRP: C-reactive protein; CSF: cerebrospinal fluid; IV: intravenously.

4. From evidence to recommendations: summary of findings

Table WA8.5 Summary of findings: Empiric antimicrobial treatment for 10 days compared with empiric treatment for less than 10 days (4–7 days) or more than 10 days (14–21 days) for suspected or probable cases of acute bacterial meningitis

Setting: Non-epidemic setting.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Comparator: Risk with empiric antimicrobial treatment for less than 10 days	Intervention: Risk with empiric antimicrobial treatment for 10 days				
Mortality follow-up: 30 days	31 per 1000	30 per 1000 (9 to 101)	RR 0.96 (0.28 to 3.27)	330 (1 RCT)	⊕⊕◯◯ Low[a]	Empiric antimicrobial treatment for 10 days in the culture negative meningitis, may result in little to no difference on mortality.
Disease relapse	135 per 1000	116 per 1000 (42 to 320)	RR 0.86 (0.31 to 2.38)	104 (1 RCT)	⊕⊕◯◯ Low[a]	Empiric antimicrobial treatment for 10 days may result in little to no difference on disease relapse.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Comparator: Risk with empiric antimicrobial treatment for less than 10 days	Intervention: Risk with empiric antimicrobial treatment for 10 days				
Disease complications including neurological sequelae	220 per 1000	187 per 1000 (127 to 270)	RR 0.85 (0.58 to 1.23)	434 (2 RCTs)	⨁⨁◯◯ Low[a]	Empiric antimicrobial treatment for 10 days may result in little to no difference on disease complications including neurological sequelae.

***** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

[a] Downgraded by two levels for very serious imprecision as the point estimate crosses the line of no difference, number of events did not reach optimal information size (OIS) and upper limit shows significant benefit and lower limit shows significant harm which is clinically incompatible.

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Appendix 1. Search strategy used to identify primary studies

Table WA8.A1.1 Database: MEDLINE (OVID), 1946 to November Week 5 2023, searched on 2 January 2023

No.	Searches	Results
1	Meningitis, Bacterial/ or ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome or Neisseria-meningitidis or meningococc* or N-meningitidis or Escherichia-coli or E-coli or GBS or streptococc* or S-agalactiae or H-influenza* or Haemophilus-influenza* or Hemophilus or Haemophilus or Leptospir* or L-monocytogenes or Listeria-monocytogenes or listerial or Borrelia-burgdorferi or B-burgdorferi or Borrelia or Lyme or Streptococcus-pneumoniae or S-pneumoniae or pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) adj3 meningit*).ti,ab. OR (Meningococc* adj5 (infection* OR disease*)).ti,ab.	29 292
2	Anti-Bacterial Agents/ or (anti-biotic* or antibiotic* or anti-bacteri* or antibacteri* or antimicrobial* or anti-microbial*).ti,ab.	693 742
3	Rifamycins/ or Vancomycin/ or Penicillins/ or Cephalosporins/	77 182
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axepim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro	523 552

	139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*).ti,ab.	
5	2 or 3 or 4	1 039 341
6	1 and 5	8 867
7	animals/ not (animals/ and humans/)	5 145 692
8	(letter or historical article or comment or editorial or news or case reports).pt.	4 464 549
9	6 not (7 or 8)	5 704

Table WA8.A1.2 Database: Embase (Elsevier) (www.embase.com), searched on 2 January 2023

No.	Searches	Results
1	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N.-meningitidis OR Escherichia-coli OR E.-coli OR GBS OR streptococc* OR S.-agalactiae OR H.-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L.-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B.-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S.-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S.Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab,kw,de OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,de,kw	51 027
2	antibiotic agent'/mj OR (anti-biotic* OR antibiotic* OR anti-bacteri* OR antibacteri* OR antimicrobial* OR anti-microbial*):ti,ab	899 463
3	rifamycin'/mj OR 'vancomycin'/mj OR 'penicillin derivative'/mj OR 'cephalosporin'/mj	51 489
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR BMY-28142 OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR Biseptol-480 OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR SQ-26776 OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR BAY-12-8039 OR BAY-128039 OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime Pentahydrate OR LY-139381 OR LY139381 OR Tazidime OR Ceftazidime OR GR-20263 OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR	1 360 937

	chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR Ro13-9904 OR Ro13-9904 OR Ro139904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-139904 OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR HR-756 OR HR756 OR Ru-24756 OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR BRL-2333 OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR Or-pen OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* or fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw,de	
5	#2 OR #3 OR #4	1 907 847
6	#1 AND #5	18 289
7	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 442 093
8	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR case-report*:ti OR case-series:ti OR genomic*:ti OR 'in vitro':ti	9 735 110
9	#6 NOT (#7 OR #8)	13 657

Table WA8.A1.3 Database: Cochrane Library (www.cochranelibrary.com/advanced-search/search-manager), searched on 2 January 2024

No.	Searches	Results
#1	MeSH descriptor: [Meningitis, Bacterial] explode all trees	489
#2	((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N-meningitidis OR Escherichia-coli OR E-coli OR GBS OR streptococc* OR S-agalactiae OR H-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,kw	1 404
#3	#1 OR #2	1 632
#4	MeSH descriptor: [Anti-Bacterial Agents] this term only	15 349
#5	MeSH descriptor: [Rifamycins] explode all trees	1 846
#6	MeSH descriptor: [Vancomycin] explode all trees	982
#7	MeSH descriptor: [Penicillins] explode all trees	6 320
#8	MeSH descriptor: [Cephalosporins] explode all trees	4 785
#9	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR	55 820

	Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw	
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	63 714
#11	#3 AND #10	372
#12	Trials	361

Table WA8.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 2 January 2024

No.	Searches	Results
#1 (Condition)	((bacterial OR Neisseria OR meningococus OR Escherichia-coli OR streptococcus OR influenza OR Hemophilus OR Leptospira OR Listeria-monocytogenes OR listerial OR Borrelia OR Lyme OR Streptococcus OR pneumococcus OR disease) AND (meningitis))	
#2 (Other terms)	anti-biotic OR antibiotic OR anti-bacterial OR antibacterial OR antimicrobial OR anti-microbial OR cephalosporin OR penicillin OR vancomycin OR rifampicin OR chloramphenicol OR ceftriaxone OR cefotaxime OR ciprofloxacin OR Ampicillin OR Amoxicillin	
#3	#1 AND #2	122

9. Duration of empiric antimicrobial treatment in epidemic settings

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Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CSF	cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organization

1. Background

Meningitis is a serious infection of the meninges – the membranes covering the brain and spinal cord. This disease remains a major public health challenge and is caused by many different pathogens, including bacteria, fungi and viruses. The form of the disease that causes the highest global burden is acute bacterial meningitis. The most frequent causative organisms are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*. *N. meningitidis* is the etiological agent of meningococcal meningitis that has the highest potential to produce large epidemics. Twelve serogroups of *N. meningitidis* have been identified, six of which (A, B, C, W, X and Y) can cause epidemics *(1)*.

The treatment of bacterial meningitis, including in epidemic settings, has been revolutionized by the availability of third-generation cephalosporins *(2)*. In 2005, a randomized non-inferiority trial conducted in Niger *(3)* showed that single-dose ceftriaxone provided a suitable alternative treatment for epidemic meningococcal meningitis compared to long-acting chloramphenicol (the risk difference for the treatment failure rate at 72 hours was 0.3%, 90% CI -3.8 to 4.5%), with its effectiveness and ease of administration favouring its use. However, in 2014 an evidence review was conducted as part of the process of developing the *WHO guidelines on meningitis outbreak response* and a total of 22 meningococcal meningitis epidemic events were analysed *(4)*. The review showed that in countries within the African meningitis belt, between 2002 and 2014, 11 serogroup W/X and 11 serogroup A epidemics occurred. It was estimated that 12.9% (95% CI 8.6–19.1%) of cases (n = 1874) during *N. meningitidis* serogroup A epidemics and 8.9% (95% CI 6.3–12.4%) of cases (n = 1880) during serogroup W or X outbreaks were due to *S. pneumoniae* or *H. influenzae (4)*. Thus, during meningococcal meningitis outbreaks, the use of single-dose ceftriaxone may lead to suboptimal treatment for a subset of patients, including those affected by pneumococcal or *Haemophilus* meningitis, which are generally associated with a higher risk of long-term neurological complications and mortality. Based on these findings, the guidelines recommended that adults, and children aged 2 months and older, with suspected bacterial meningitis living in an epidemic setting should receive a 5-day course of ceftriaxone *(4)*.

Over the past decade, the epidemiological landscape of epidemic-prone meningitis has changed, with non-serogroup A *N. meningitidis* and, less often, *S. pneumoniae* responsible for an increasing number of epidemics within and outside the African meningitis belt. Particularly when the causative pathogen remains unidentified, determining the optimal treatment duration may be challenging and often relies on clinical judgment and feasibility considerations.

Therefore, it is of critical importance to provide updated recommendations for meningococcal and pneumococcal epidemics, including antibiotic treatment duration among suspected and probable cases.

This evidence review therefore focuses on the efficacy and safety of empiric antimicrobial treatment with parenteral ceftriaxone for a duration of 5 days compared with a shorter or longer duration in an epidemic setting.

This work has been carried out for the development of the *WHO guidelines for meningitis diagnosis, treatment and care*.

2. Methodology

2.1 Research question and study design

In epidemic settings, among cases of suspected or probable acute bacterial meningitis, what are the effectiveness and safety of empiric treatment with parenteral ceftriaxone for 5 days compared with a different duration of treatment?

Population: Suspected or probable cases of acute bacterial meningitis in epidemic settings.

Subgroups: age groups (children, adults); causative pathogen (meningococcal outbreak, pneumococcal outbreak, mixed outbreak).

Intervention: Parenteral ceftriaxone for a total duration of 5 days.

Comparator: Parenteral ceftriaxone for a total duration less than 5 days (1–4 days) or more than 5 days (7–14 days).

Outcomes

Critical outcomes:

- case fatality ratio;
- disease relapse;
- time to resolution of symptoms;
- disease complications (sepsis; disseminated intravascular coagulation; neurological complications, including neurological sequelae).

Important outcomes:

- adverse effects.

2.2 Eligible studies

Study designs: The systematic review process began with a search conducted to find primary studies relevant to the research question above. A search was conducted for randomized controlled trials (RCTs) and prospective cohort studies that included a comparator arm pertaining to our research question.

Published language: All relevant studies were searched for, regardless of language. Evidence from studies in English was evaluated by the review team. For studies in languages other than English, the translated version was obtained from online software.

Exclusion criteria:

- All retrospective studies and prospective non-randomized cohort studies without a comparator arm were excluded.

- Case reports, case series, and any ongoing trials and studies with outcome data that could not be evaluated were also excluded.

2.3 Search strategy

A search was conducted for primary studies relevant to this research question. The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (ClinicalTrials.gov). All the databases were searched for studies published from 1946 to November 2023.

2.4 Selection of studies

A preliminary search for systematic reviews relevant to the research question was conducted. No systematic reviews relevant to this research question were found. Sudo et al. *(5)* conducted a meta-analysis comparing short versus long duration of treatment with ceftriaxone for patients with meningitis. However, this review was excluded because it involved studies in non-epidemic settings, whereas the current research question concerns empiric treatment in an epidemic setting. One more potentially relevant review was found, Karageorgeopoulos et al. *(6)*, which is a meta-analysis of randomized controlled trials (RCTs) involving children with bacterial meningitis. For similar reasons to the review by Sudo et al., this review was not considered pertinent to the research question addressed in this report.

A search was then conducted across the databases mentioned in section 2.3 to identify primary studies relevant to research questions 5–10 (i.e. this report and five other reports in this web annex) on empiric antimicrobial treatment, the duration of antimicrobial treatment in both epidemic and non-epidemic settings, and post-exposure antimicrobial prophylaxis. The search yielded 15 158 studies. After filtering using the Rayyan tool *(7)*, 1194 duplicate articles were identified. Of these, 208 duplicates were manually removed by the authors. Subsequently, the remaining 14 950 articles underwent independent screening by the authors through Rayyan. After title and abstract screening, 14 880 studies were excluded since they were not relevant to the research questions. Full-text screening was then conducted on 70 articles retrieved from the review authors' institutional libraries and WHO libraries, resulting in the full texts for 64 articles being obtained. However, the remaining six articles were excluded because four of them were clinical trials with unpublished data. Despite attempts to contact the authors, full-text versions could not be obtained. Additionally, full texts of the other two studies were also unavailable.

After thorough full-text screening, no study was found that was relevant to this research question (i.e. this report).

2.5 Deviations from the review protocol

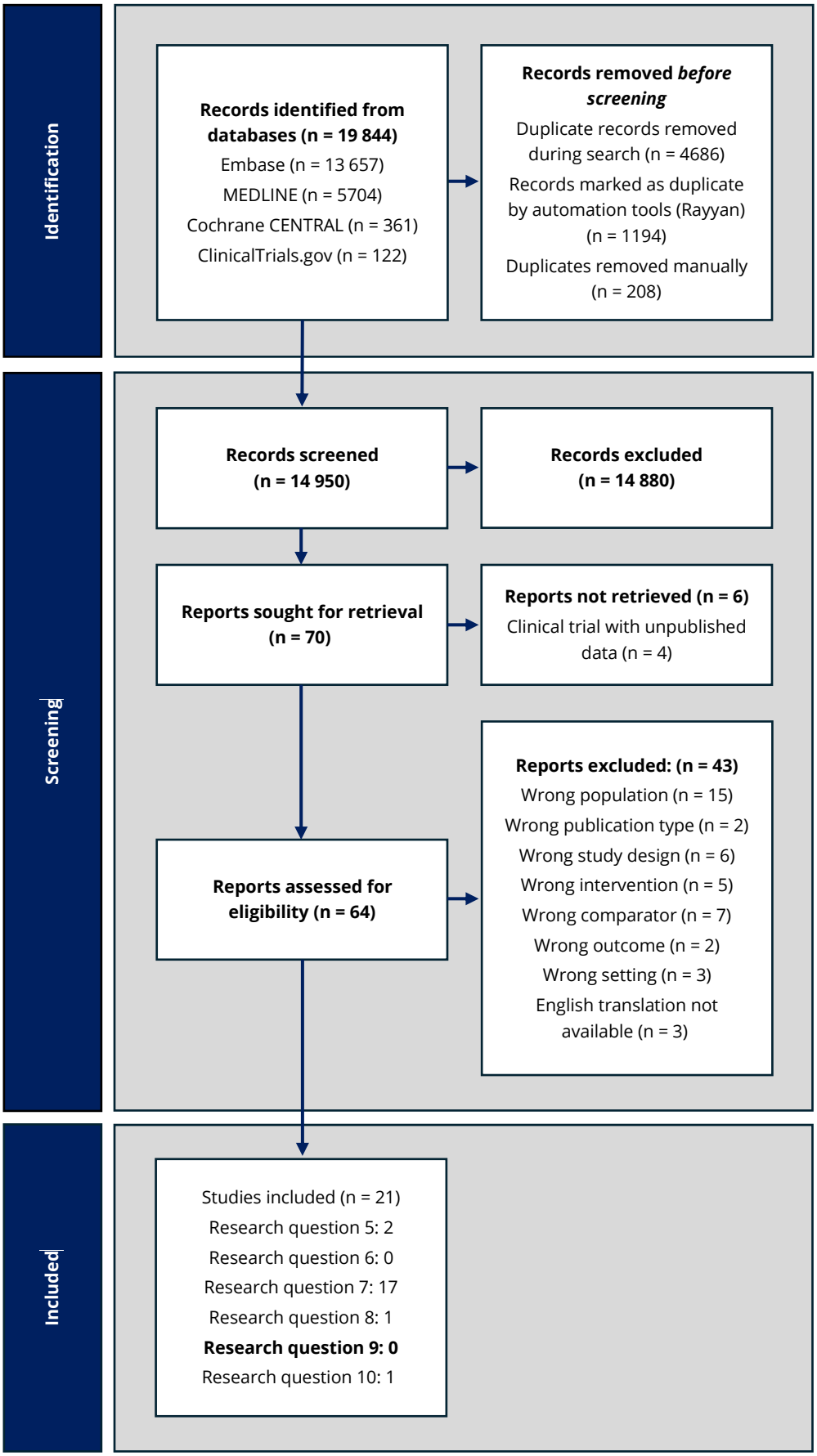
This was not applicable.

3. Results

3.1 Studies identified by the search process

Figure WA9.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this evidence synthesis.

Fig. WA9.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profiles

No study that was applicable to the research question could be included in the review.

3.1.2 Studies excluded from the review

Table WA9.1 shows the studies that were excluded from the review and gives the reasons why.

Table WA9.1 Studies excluded from the review, with reasons

Study	Reason for exclusion
Auvergnat et al. *(8)*	This was an observational study of 20 patients hospitalized with meningococcal meningitis. It analysed the effect of 5 days of ceftriaxone. There was no comparator arm, so this study was excluded.
Coldiron et al. *(9)*	This was a surveillance study done in Nigeria analysing the case-fatality ratio and sequelae resulting from an epidemic caused by *N. meningitidis*. Patients received 5 days of ceftriaxone. There was no comparator arm; hence this study was excluded.
Isaacs et al. *(10)*	This was a retrospective study which described the 12-year experience of meningococcal meningitis in one centre, though not in a specific epidemic or outbreak setting. It compared the effect of 5 days of ceftriaxone treatment versus longer than 5 days during this time frame. This study was excluded because the setting was not relevant to the current research question.
Kavaliotis et al. *(11)*	This was an open-label, randomized comparative trial that included all cases of bacterial meningitis beyond neonates in a single centre over a period of 2 years. All patients received ceftriaxone and were randomized to a shorter (4, 6, 7 days) or longer duration (8, 12, 14 days) arm. Since this study was conducted in a non-epidemic setting, it was excluded from this review.
Renevey et al. *(12)*	This was a non-comparative study involving patients aged from 3 weeks to 16 years with bacterial meningitis. All patients were treated with ceftriaxone for 7 days. The study analysed the safety and efficacy of 7 days of ceftriaxone without a comparator arm. The study was also carried out in a non-epidemic setting; hence it was excluded from this review.

3.3 GRADE evidence profile

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach could not be applied to this review.

3.4 Description of intervention effects

No published or ongoing trials meeting the inclusion criteria were identified.

3.5 Additional evidence not reported in the GRADE evidence profile

Kavaliotis et al. *(11)* was a prospective, randomized, comparative study of short-course (4–7 days) versus long-course (8–14 days) therapy with ceftriaxone. This study included patients of all ages suffering from bacterial meningitis, except newborns.

Table WA9.2 Additional evidence not reported in the GRADE evidence profile: details

Lead author, (Year)	Study design	Population	Intervention and Comparator			Inclusion/exclusion criteria	Reason for exclusion	Important results and inference
Kavaliotis, (1989) *(11)*	Open-label, prospective, randomized comparative study	Cases of bacterial meningitis beyond the neonatal period, with a positive blood or CSF culture	All patients received ceftriaxone IV in an initial dose of 100 mg/kg (max. 4 g)			Patients with known or suspected sensitivity to cephalosporin, with renal or hepatobiliary diseases, and patients who had received other antibiotics prior to admission were excluded.	This study was carried out in a non-epidemic setting.	No deaths in either group. All patients were cured and no relapses occurred. On discharge, 4 patients in the long-course group had neurological defects (3 patients had bilateral hearing loss and 1 had ataxia). The sample was extremely small and hence no clear conclusions can be drawn.
				Group 1 - short course (N = 26)	Group 2 - long course (N = 26)			
			N. meningitidis	4 d = 11	8 d = 16			
			H. influenzae	6 d = 12	12 d = 9			
			S. pneumoniae	7 d = 3	14 d = 1			

CSF: cerebrospinal fluid; IV: intravenously.

4. From evidence to recommendations

4.1 Summary of findings

No summary of findings table could be created.

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Appendix 1. Search strategy used to identify primary studies

Table WA9.A1.1 Database: MEDLINE (OVID), 1946 to November Week 4 2023, searched on 2 November 2023

No.	Searches	Results
1	Meningitis, Bacterial/ or ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome or Neisseria-meningitidis or meningococc* or N-meningitidis or Escherichia-coli or E-coli or GBS or streptococc* or S-agalactiae or H-influenza* or Haemophilus-influenza* or Hemophilus or Haemophilus or Leptospir* or L-monocytogenes or Listeria-monocytogenes or listerial or Borrelia-burgdorferi or B-burgdorferi or Borrelia or Lyme or Streptococcus-pneumoniae or S-pneumoniae or pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) adj3 meningit*).ti,ab. OR (Meningococc* adj5 (infection* OR disease*)).ti,ab.	29 292
2	Anti-Bacterial Agents/ or (anti-biotic* or antibiotic* or anti-bacteri* or antibacteri* or antimicrobial* or anti-microbial*).ti,ab.	693 742
3	Rifamycins/ or Vancomycin/ or Penicillins/ or Cephalosporins/	77 182
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axepim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13	523 552

	9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*).ti,ab.	
5	2 or 3 or 4	1 039 341
6	1 and 5	8 867
7	animals/ not (animals/ and humans/)	5 145 692
8	(letter or historical article or comment or editorial or news or case reports).pt.	4 464 549
9	6 not (7 or 8)	5 704

Table WA9.A1.2 Database: Embase (Elsevier) (www.embase.com), searched on 2 January 2023

No.	Searches	Results
1	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N.-meningitidis OR Escherichia-coli OR E.-coli OR GBS OR streptococc* OR S.-agalactiae OR H.-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L.-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B.-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S.-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S.Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab,kw,de OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,de,kw	51 027
2	antibiotic agent'/mj OR (anti-biotic* OR antibiotic* OR anti-bacteri* OR antibacteri* OR antimicrobial* OR anti-microbial*):ti,ab	899 463
3	rifamycin'/mj OR 'vancomycin'/mj OR 'penicillin derivative'/mj OR 'cephalosporin'/mj	51 489
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR BMY-28142 OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR Biseptol-480 OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR SQ-26776 OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR BAY-12-8039 OR BAY-128039 OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime Pentahydrate OR LY-139381 OR LY139381 OR Tazidime OR Ceftazidime OR GR-20263 OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin Polymyxin OR	1 360 937

	Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR Ro13-9904 OR Ro13-9904 OR Ro139904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-139904 OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR HR-756 OR HR756 OR Ru-24756 OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR BRL-2333 OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR Or-pen OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* or fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw,de	
5	#2 OR #3 OR #4	1 907 847
6	#1 AND #5	18 289
7	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 442 093
8	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR case-report*:ti OR case-series:ti OR genomic*:ti OR 'in vitro':ti	9 735 110
9	#6 NOT (#7 OR #8)	13 657

Table WA9.A1.3 Database: CENTRAL (www.cochranelibrary.com/advanced-search/search-manager), searched on 2 January 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis, Bacterial] explode all trees	489
2	((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N-meningitidis OR Escherichia-coli OR E-coli OR GBS OR streptococc* OR S-agalactiae OR H-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,kw	1 404
3	#1 OR #2	1 632
4	MeSH descriptor: [Anti-Bacterial Agents] this term only	15 349
5	MeSH descriptor: [Rifamycins] explode all trees	1 846
6	MeSH descriptor: [Vancomycin] explode all trees	982
7	MeSH descriptor: [Penicillins] explode all trees	6 320
8	MeSH descriptor: [Cephalosporins] explode all trees	4 785
9	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR	55 820

	20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw	
10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	63 714
11	#3 AND #10	372
12	Trials	361

Table WA9.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 2 January 2024

No.	Searches	Results
#1 (Condition)	((bacterial OR Neisseria OR meningococus OR Escherichia-coli OR streptococcus OR influenza OR Hemophilus OR Leptospira OR Listeria-monocytogenes OR listerial OR Borrelia OR Lyme OR Streptococcus OR pneumococcus OR disease) AND (meningitis))	
#2 (Other terms)	anti-biotic OR antibiotic OR anti-bacterial OR antibacterial OR antimicrobial OR anti-microbial OR cephalosporin OR penicillin OR vancomycin OR rifampicin OR chloramphenicol OR ceftriaxone OR cefotaxime OR ciprofloxacin OR Ampicillin OR Amoxicillin	
#3	#1 AND #2	122

10. Post-exposure antimicrobial prophylaxis

Authors

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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CI	confidence interval
GRADE	Grading of Recommendation, Assessment, Development and Evaluations
MDSG	Meningococcal Disease Surveillance Group
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
robvis	Risk-Of-Bias VISualization (a tool available as an R package and web app)
RR	risk ratio
WHO	World Health Organization

1. Background

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*, also known as meningococcus. Meningococcal disease remains a significant public health issue globally, accounting for recurrent epidemics, small-scale outbreaks and sporadic cases worldwide *(1, 2)*. Twelve serogroups of *N. meningitidis* have been identified, six of which (A, B, C, W, X and Y) can cause epidemics. Meningococcal meningitis can affect people of any age, but mainly affects babies, preschool children and young people *(1, 2)*.

Meningococcal disease manifests in a variety of ways, ranging from sporadic occurrences and small clusters to large epidemics in all parts of the world, and often exhibits seasonal fluctuations. Its geographical prevalence and epidemic potential vary depending on the serogroup involved. The most severe impact of meningococcal meningitis is observed within the "meningitis belt", an expanse across sub-Saharan Africa extending from Senegal to Ethiopia. Epidemics often occur in the dry season, causing substantial morbidity and mortality in the population, and putting further pressure on the already deficient health system in the region *(2, 3)*.

Meningococci are transmitted from person to person through droplets of respiratory or throat secretions from infected individuals. Close and prolonged contact – such as kissing, or sneezing or coughing on someone, or living in close proximity to an infected person – also facilitates the spread of the disease. The average incubation period is 4 days but can range between 2 and 10 days *(2)*. Meningococcal disease is associated with rapid progression and high fatality rates. Complications may include permanent sequelae like limb loss, hearing impairment and neurological complications.

Preventing *N. meningitidis* infection involves taking pre-exposure measures and post-exposure mitigation strategies. Pre-exposure measures include adherence to strict droplet precautions (e.g. using face masks and standing at a distance of 1 metre or more) and vaccination of individuals at increased risk (e.g. those with anatomical or functional asplenia, complement deficiencies or other forms of immune-compromise) as well as vaccination of travellers to endemic areas or those travelling in the midst of an epidemic, military recruits and certain high-risk populations, including college students living in dormitories or people attending mass gatherings, such as religious pilgrimages *(3, 4)*. Post-exposure antimicrobial prophylaxis is widely used to prevent secondary cases and/or decrease asymptomatic nasopharyngeal carriage. Antibiotics such as ciprofloxacin, rifampicin or ceftriaxone may be considered for this purpose *(5)*. However, the potential clinical benefits of prophylaxis have been recognized primarily as a result of studies that only investigate the eradication of nasopharyngeal carriage through antimicrobials. In addition, while antimicrobial prophylaxis is routinely used in high-income settings, there is no consensus on whether it should be implemented as part of the outbreak response within the African meningitis belt. This inconsistency in guidance has often led to differing recommendations across similar settings.

This evidence synthesis focuses mainly on antimicrobial prophylaxis for close contacts of the infected person, including household contacts and anyone directly exposed to oral secretions of cases of meningococcal disease.

This work has been carried out for the development of the *WHO guidelines for meningitis diagnosis, treatment and care*.

2. Methodology

2.1 Research question and study design

Should antimicrobial prophylaxis be provided to close contacts of cases of meningococcal meningitis to prevent additional cases and carriage?

Population: Close contacts, including household contacts of the infected person and anyone directly exposed to oral secretions of cases of meningococcal meningitis.

Subgroups: epidemic versus non-epidemic settings; geographical region (in the African meningitis belt versus outside the African meningitis belt).

Intervention: Antimicrobial prophylaxis (oral ciprofloxacin, parenteral ceftriaxone, oral rifampicin).

Comparator: No antimicrobial prophylaxis.

Outcomes

Critical outcomes: prevention of additional cases and meningococcal carriage.

Important outcomes: adverse effects.

Study design: A new systematic review was performed using the primary studies identified by the search strategy. Randomized controlled trials (RCTs) and prospective cohort studies with a comparator arm were included.

2.2 Eligible studies

Published language: All relevant studies were included, regardless of language. The studies in English were evaluated by the review team. The translated versions of studies in languages other than English were obtained using online software.

Exclusion criteria:

- All non-randomized studies without a comparator (e.g. case reports and case series and studies without a comparator arm) were excluded.
- Any ongoing trials and studies with outcome data that could not be evaluated were also excluded.

2.3 Search strategy

Searches for primary studies were conducted in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (ClinicalTrials.gov/). All the databases were searched for studies published from 1946 to November 2023.

2.4 Selection of studies

A preliminary search was conducted a for systematic reviews relevant to the research question. One Cochrane review by Zalmanovici et al. *(6)* was found that was relevant to our research question. AMSTAR-2 (the new AMSTAR – A MeaSurement Tool to Assess systematic Reviews) showed that the overall confidence in this study was high. However, it had not been updated since 2019. Another systematic review, Telsinghe et al. *(7)*, was found. However, according to AMSTAR-2, the overall confidence in that review was critically low because it did not contain any published protocol or methods. Therefore, a new systematic review was carried out, with the search focusing on primary studies, i.e. RCTs and prospective cohort studies with a comparator, as specified in the review protocol. Studies from the above-mentioned systematic review were retrieved if considered relevant to the research question, assessed for eligibility and included in this systematic review if they met the inclusion criteria.

A search was then conducted across the databases mentioned in section 2.3 to identify primary studies relevant to research questions 5–10 (i.e. this report and the five previous reports in this web annex) on empiric antimicrobial treatment, the duration of antimicrobial treatment in both epidemic and non-epidemic settings, and post-exposure antimicrobial prophylaxis. The search yielded 15 158 studies. After filtering using the Rayyan tool *(8)*, 1194 duplicate articles were identified. Of these, 208 duplicates were manually removed by the authors. Subsequently, the remaining 14 950 articles underwent independent screening by the authors through Rayyan. After title and abstract screening, 14 880 studies were excluded since they were not relevant to the research questions. Full-text screening was then conducted on 70 articles retrieved from the review authors' institutional libraries and WHO libraries, resulting in the full texts for 64 articles being obtained. However, the remaining six articles were excluded because four of them were clinical trials with unpublished data. Despite attempts to contact the authors, full-text versions of these trials could not be obtained. Additionally, full texts of the other two studies were also unavailable.

After thorough screening of the full texts, two studies were identified from the full-text screening process – Coldiron et al. 2018 *(9)* and Kaiser et al. 1974 *(10)* – that were relevant to this research question (i.e. this report), and one additional relevant study (Meningococcal Disease Surveillance Group [MDSG], 1976) *(11)* was retrieved from a

systematic review *(7).* However, Kaiser et al. was excluded from the meta-analysis as no outcomes relevant to research question were reported. The characteristics of the two studies included are presented in Table WA10.1, and Fig. WA10.2 provides the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram for the search.

2.5 Data extraction and management

Three of the authors (HA, JMJ and JSJ) used a piloted data extraction form to extract data on participant characteristics, antimicrobial treatment and administration, other treatments given, follow-up duration and outcome measures, as defined by the research question. For dichotomous outcomes, like secondary cases and adverse effects, the authors recorded the number of participants who had experienced the event and the number of participants in each treatment group. The number of cases analysed in each arm was recorded and the data available used to calculate the number of participants lost to follow-up.

2.6 Assessment of risk of bias in studies included in the review

Two of the authors (JSJ, HA) assessed the risk of bias for the primary and secondary outcomes using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool *(12)* for prospective cohort studies and the ROB-2 tool *(13)* for RCTs. The risk of bias assessment was verified by the corresponding authors (PR, AT). The results of the ROBINS-I test are reported in a traffic light plot (Fig. WA10.2) *(14)*.

2.7 Data synthesis

Data were analysed by two of the authors (JSJ, HA) using Review Manager software *(15)*. When more than one study had contributed to the evidence synthesis, data were pooled in meta-analyses using the random-effects model. Dichotomous data are presented and compared using risk ratios (RR). All results are presented with the corresponding 95% confidence interval (CI).

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the certainty of the evidence *(16)*. GRADE is a transparent framework designed for the development and presentation of evidence summaries, offering a systematic approach to the formulation of clinical practice recommendations. The quality of the evidence is assessed for each outcome, and GRADE categorizes it into four levels of certainty: very low, low, moderate and high. Certainty in the evidence for each outcome is evaluated across five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. The GRADE levels of certainty are defined in Box WA10.1.

Box WA10.1 The certainty of evidence used in GRADE	
High ⊕⊕⊕⊕	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The results of the analysis are summarized in Table WA10.2 (Summary of findings), where the summary effect estimates for the outcomes are also presented.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

A subgroup analysis of the studies carried out in the African meningitis belt was performed. The countries in the belt include Burkina Faso, Cameroon, Central African Republic, Chad, Eritrea, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Mali, Niger, Nigeria, Senegal, South Sudan, Sudan and Uganda.

2.10 Sensitivity analysis

A sensitivity analysis was performed by sequentially excluding studies that had a high (very serious) risk of bias and the results were compared with the effect estimate obtained when these studies were included.

2.11 Deviations from the review protocol

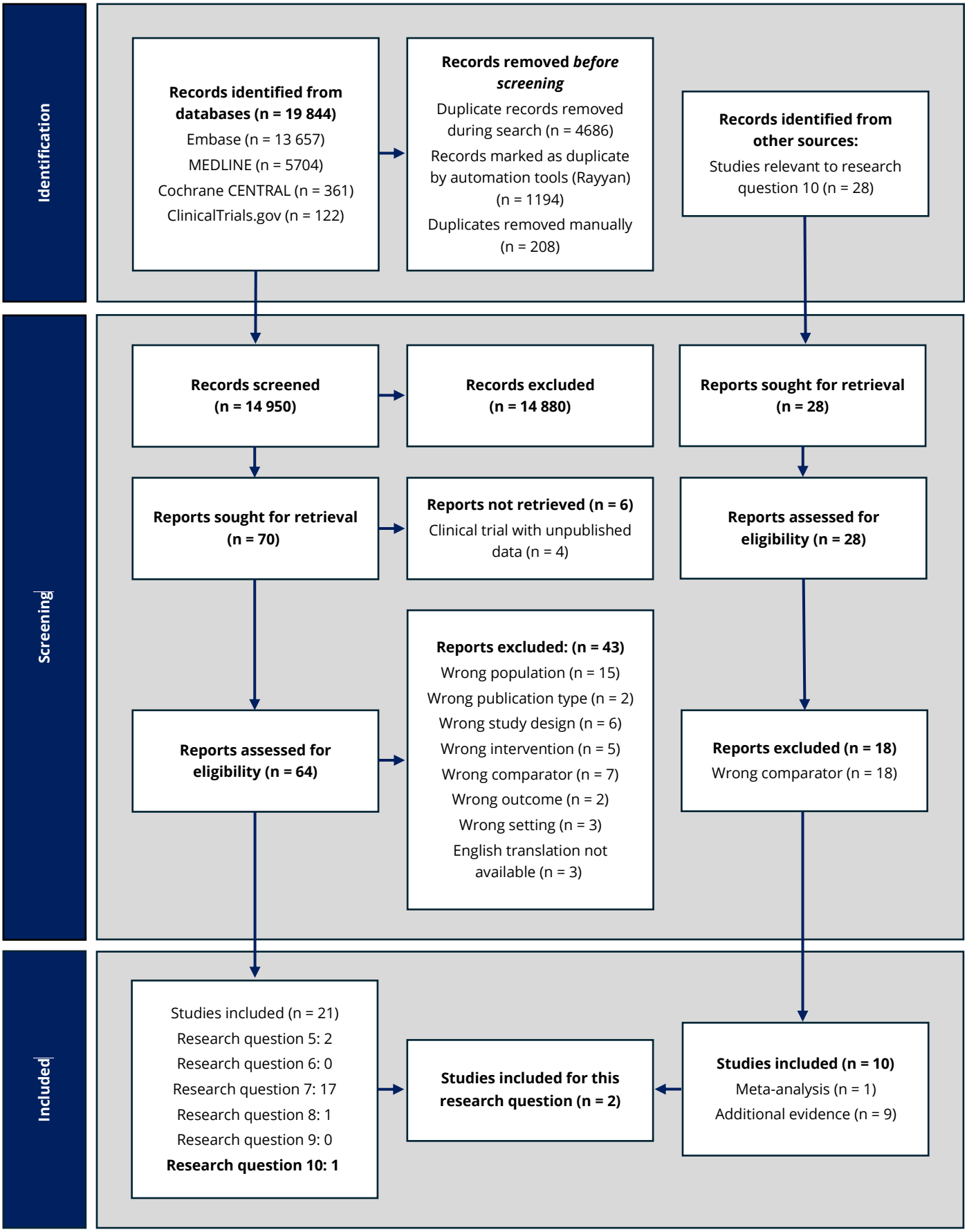
There was no deviation from the review protocol.

3. Results

3.1 Studies identified by the search process

Figure WA10.1 presents the PRISMA flow diagram for this systematic review.

Fig. WA10.1 PRISMA flow diagram for the systematic review



3.2 Studies included in the review and the GRADE evidence profiles

Table WA10.1 presents the characteristics of the studies included in the GRADE evidence profiles.

Table WA10.1 Characteristics of studies included in the GRADE evidence profiles

Lead author (year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data (synthesis method/metric)	Secondary outcome measures	Time point of measurement
Coldiron (2018), Niger *(9)*	RCT	Low	Dose of ciprofloxacin: > 12 years: 500 mg 5–12 years: 250 mg 1–4 years: 125 mg 3–11 months: 100 mg < 3 months: 75 mg	< 5 years of age I: 5765 C: 5984 5–14 years of age I: 5765 C: 5984 15–29 years of age I: 4981 C: 5570 > 30 years of age I: 5326 C: 5760	No antimicrobial prophylaxis	Meningitis attack rate	Proportion of participants with ciprofloxacin-resistant Enterobacteriaceae in their stools Proportion of patients who received ciprofloxacin as prophylaxis and still develop meningitis	From 22 April to 18 May 2017 was considered as the epidemic period and the observation was done during this period
MDSG (1976), the United States of	Prospective cohort study	Serious	Rifampicin, sulfonamide or minocycline	Group B, the most common serogroup,	No antibiotic prophylaxis, or drugs other	Attack rate per 1000 persons.	Serogroup-specific attack rates.	Within 30 days of the hospitalization

America (USA) *(11)*	accounted for 45% of the those in isolation. Total: 33 Intervention received = 693 persons or 177 households No antimicrobial prophylaxis given: 1179 persons or 297 households	than sulphonamides, minocycline, or rifampin	of the index case.

RCT: randomized controlled trial.

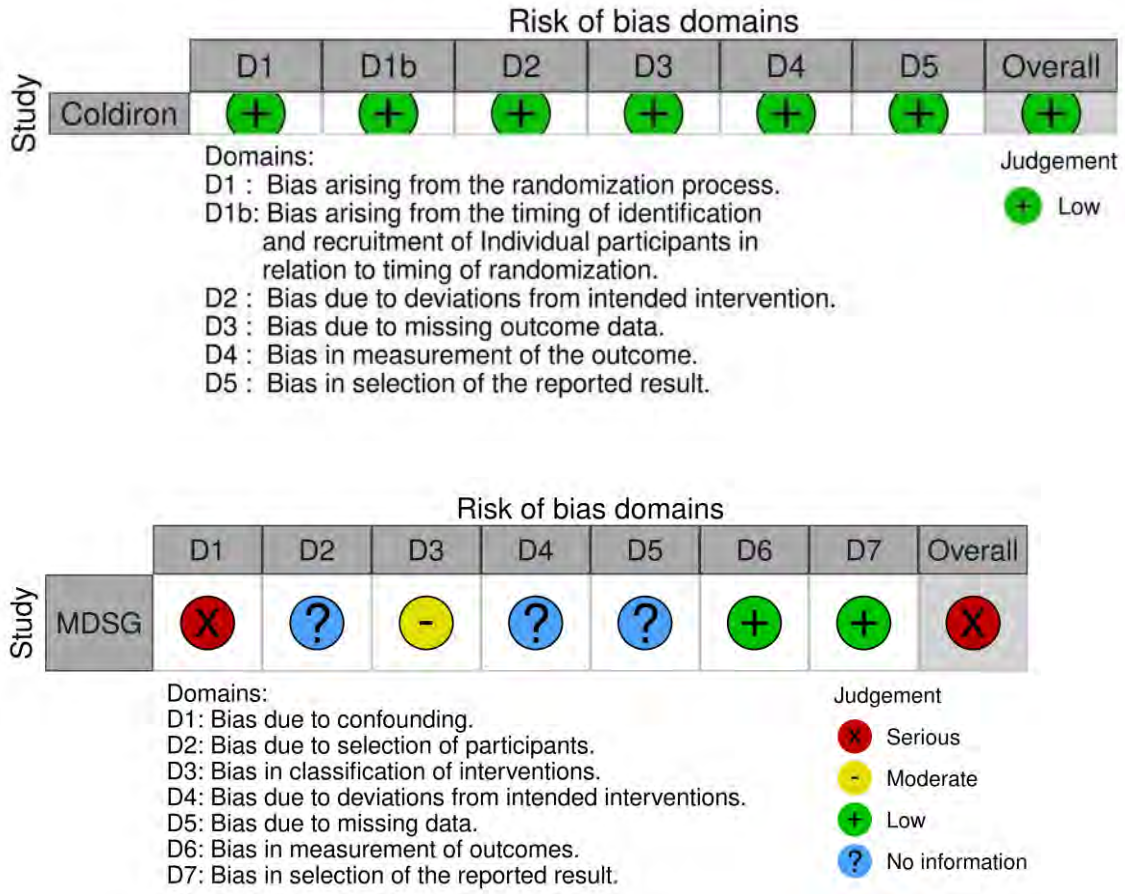
3.3 Studies excluded from the review and risk-of-bias summaries

The studies that were excluded from the review are presented in Table WA10.2, along with the reasons for exclusion. Figure WA10.2 presents the results of the risk-of-bias summary, carried out using the robvis tool.

Table WA10.2 Studies excluded from the review, with reasons

Lead author (Year)	Reason for exclusion
Blakebrough (1980) *(18)*	Comparator included an active intervention; trial had wrong population
Cuevas (1995) *(19)*	Comparator included an active intervention; trial had wrong population
Devine (1970) *(20)*	Study population was carriers (not contacts of meningococcal meningitis cases); intervention focused on eradication of carriage
Dowd (1966) *(21)*	Study population was carriers (not contacts of meningococcal meningitis cases); intervention focused on eradication of carriage
Edwards (1984) *(22)*	Study population was carriers (not contacts of meningococcal meningitis cases); intervention focuses on eradication of carriage
Girgis (1998) *(23)*	Study population was carriers (not contacts of meningococcal meningitis cases); intervention focuses on eradication of carriage
Judson (1984) *(24)*	Study population was carriers (not contacts of meningococcal meningitis cases); intervention focuses on eradication of carriage
Kaya (1997) *(25)*	Comparator included an active intervention; trial had wrong population
Munford (1974) *(26)*	Comparator included an active intervention; trial had wrong population
Pugsley (1984) *(27)*	Population focused on carriers not contacts
Schwartz (1988) *(28)*	Comparator included an active intervention; trial had wrong population
Simmons (2000) *(29)*	Comparator included an active intervention; trial had wrong population

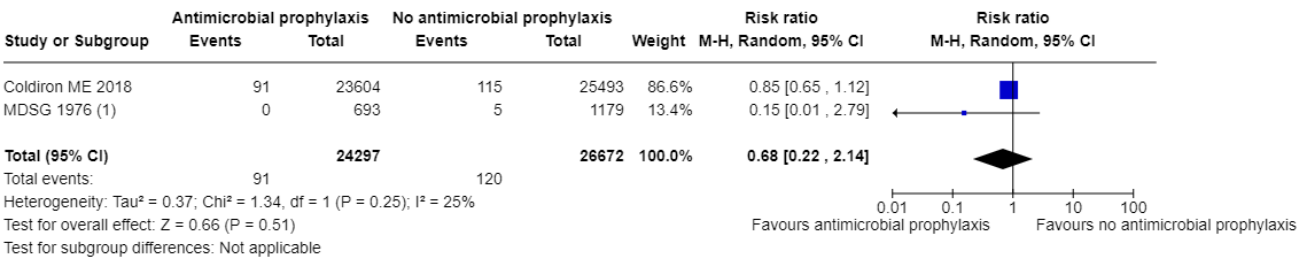
Fig. WA10.2 Risk of bias summaries (carried out using robvis tool)



3.4 Forest plots

Forest plots for each outcome are presented below (Figs WA10.3–WA10.6).

Fig. WA10.3 Prevention of additional cases

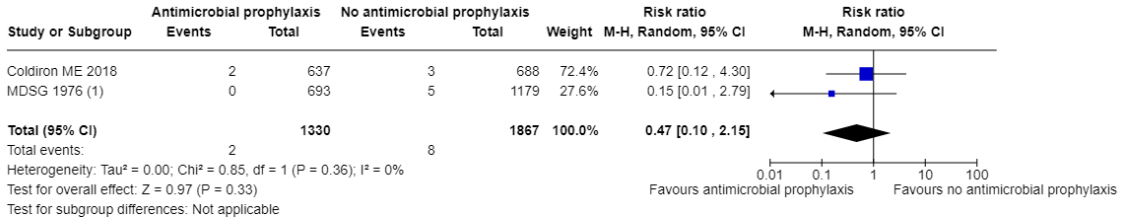


Footnotes

(1) The mean interval between theprimary and secondary cases was 15 days. Theoverall secondary attack rate in households inwhich one or more members were treated withrifampin,

The mean interval between the primary and secondary cases was 15 days. The overall secondary attack rate in households in which one or more members were treated with rifampin, minocycline, or sulpha (0 of 177 households) was considerably lower (*P* = 0.095) than that in households in which subjects were untreated or treated with agents recognized as unreliable (5 of 297 households or 1.7 per 100 households). Likewise, the attack rate in individual household contacts who were treated with sulpha, minocycline, or rifampin (0 of 693 persons) was less (*P* = 0.009) than the rate in untreated or inappropriately treated contacts (5 of 1179 persons or 4.24 per 1000 persons).

Fig. WA10.4 Accounting for design effects – using interclass correlation coefficient



Footnotes

(1) The mean interval between theprimary and secondary cases was 15 days. Theoverall secondary attack rate in households inwhich one or more members were treated withrifampin,

Fig. WA10.5 Sensitivity analysis

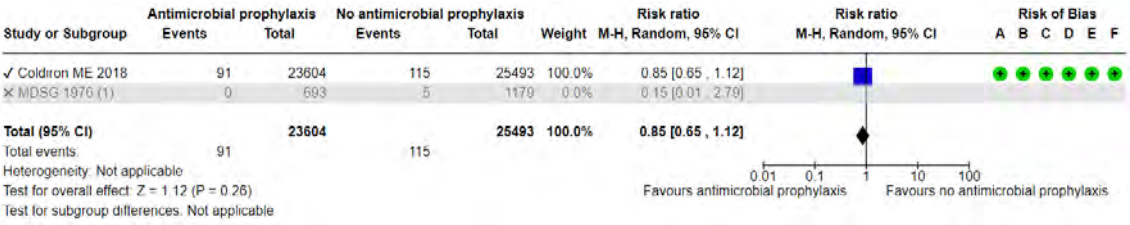
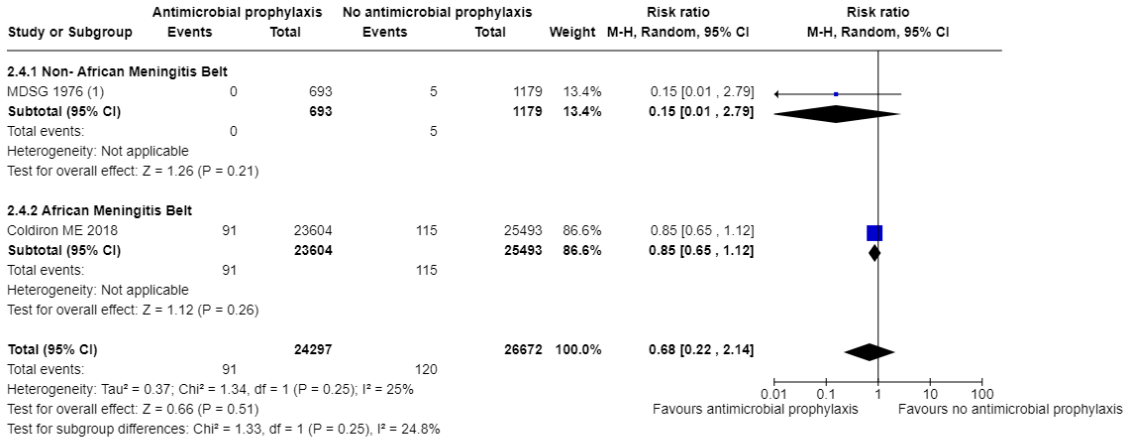


Fig. WA10.6 Subgroup analysis: African meningitis belt



Footnotes

(1) The mean interval between theprimary and secondary cases was 15 days. Theoverall secondary attack rate in households inwhich one or more members were treated withrifampin,

3.5 GRADE evidence profile

Table WA10.3 Antimicrobial prophylaxis for the prevention of additional cases of meningococcal disease

Certainty assessment							No. of patients		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic prophylaxis	No prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Prevention of additional cases												
2 *(9, 11)*	Randomized trials	Serious[a]	Not serious	Very serious[b]	Serious[c]	None	91/24 297 (0.4%)	120/26 672 (0.4%)	RR 0.47 (0.10 to 2.15)[d]	2 fewer per 1000 (from 4 fewer to 5 more)	⨁◯◯◯ Very low	Critical

CI: confidence interval; RR: risk ratio.

[a] Downgraded by one level for serious risk of bias as the study by MDSG *(11)* has a serious risk of bias in one domain, moderate risk in one domain and no information in three domains (ROBINS-I) (13.4% weightage)

[b] Downgraded by two levels for serious indirectness because in the Coldiron study *(9)*, only 4% of the population at risk received antibiotic chemoprophylaxis.

[c] Downgraded by one level for serious imprecision as the point estimate crosses the line of no difference with very wide CIs and upper limit shows significant harm and lower limit shows benefit.

[d] This RR is analysed sing interclass correlation coefficient and design effect for the Coldiron study as it was a cluster randomized trial.

3.6 Description of intervention effects

Prevention of additional cases: A very low certainty of evidence in two studies *(9, 11)* with 50 969 participants suggested that it was uncertain whether chemoprophylaxis had any effect on the prevention of secondary cases of meningococcal disease. The RR and CI used in the GRADE assessment were calculated using design effect for the Coldiron study (RR = 0.47; 95% CI 0.10 to 2.15). Incidence of a secondary meningitis after chemoprophylaxis was 0.374% (91/24 297), and 0.45% (120/26 672) had secondary meningitis without chemoprophylaxis, in an epidemic setting.

Prevention of meningococcal carriage as an outcome was not reported in either study.

No adverse events were reported in Coldiron et al. *(9)* and no information regarding adverse events was reported in the MDSG study *(11)*.

3.7 Sensitivity analysis

A sensitivity analysis was conducted in which the MDSG study *(11)* was excluded, owing to a serious risk of bias. After removing this study, the RR was 0.85, and the 95% CI was 0.65, 1.12. However, the GRADE assessment still revealed an overall very low certainty of evidence, as the evidence profile was downgraded by two levels for indirectness and one level for imprecision.

3.8 Subgroup analysis

A subgroup analysis of studies that were done in the African meningitis belt was performed. There was one study *(9)* with 49 097 participants. Very low certainty evidence from one three-arm cluster randomized trial conducted in the belt during a meningococcal meningitis outbreak showed that the effect of chemoprophylaxis with single-dose ciprofloxacin on secondary cases of meningococcal meningitis was uncertain (RR = 0.85, 95% CI = 0.65, 1.12). The study used ciprofloxacin as the intervention.

3.9 Additional evidence not reported in the GRADE evidence profiles

Table WA10.4 provides descriptions of additional studies, which focus on treatment options that eradicate meningococcal carriage. This information is not a primary or secondary outcome of the research question for this review but may provide some additional information.

Table WA10.4 Studies provided by the Guideline Development Group

Lead author (year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Inference
Kaiser (1974) *(10)*	RCT	Rifampicin 600 mg per day for 4 days	No chemoprophylaxis	Household contacts of meningococcal disease patients. Intervention = 35 control = 19	Close contacts over 5 years of age, excluding pregnant women, were considered eligible for participation in the drug trial	In the rifampin group, 12 out of 13 carriers tested negative on Day 6, resulting in an eradication rate of 92% ($P < 0.0005$). Importantly, no additional cases were reported in the rifampin group at the end of the trial
Borgono (1981) *(30)*	Double-blind RCT	Rifampicin 10 mg/kg for 2 days	Placebo	2132 children aged 1–18 years attending kindergarten and elementary school in Santiago, Chile, were asked to provide samples of pharyngeal secretion in order to identify their status as carriers of meningococcal infection.	12% diagnosed to be meningococcal carriers were randomized	108/118 (92%) of carriers on rifampicin vs 39/110 (35%) of carriers on placebo were negative on the 3rd day
Deal (1969) *(31)*	Double-blind RCT	Rifampin 600 mg for 4 days	Placebo	270 males, 21–28 years of age, cultured for meningococci were analysed. The serogroup B was prevalent in the population.	30 subjects with positive culture with heavy growth were randomized	In 11/15 (73%) on rifampin, culture became negative, whereas only 2/15 (13%) in placebo became negative during the study. One subject in the rifampin group had drowsiness but therapy was not stopped. One subject in placebo group had nausea and vomiting for a night.
Deviatkina (1978) *(32)*	Open-label RCT	Rifampin 300 mg	No prophylaxis	91 meningococcal carriers	Full text could not be retrieved	43/46 (93%) on rifampicin eradicated meningococcal

Lead author (year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Inference
						carriage vs 33/43 (76%) in the no prophylaxis group.
Devine (1970) *(33)*	Double-blind RCT	Rifampin 600 mg once daily for 4 days	Placebo	133 meningococcal carriers were included and were randomly divided into 2 treatment groups using a table of random numbers for a double-blind study.	69 men randomly assigned to the placebo group and 64 men assigned to the rifampin group. Cultures were done at 4 time points (1 prior to prophylaxis, 1 during, and 2 after treatment), and all serum and saliva specimens were obtained from 52 men in the placebo group and from 51 men in the rifampin-treated group, who were the subjects of this communication	After the fourth dose of rifampin, there was 46/51 (89%) reduction among meningococcal carriers
Devine (1970) *(34)*	Double-blind RCT	Minocycline 200 mg twice daily for 2 days	Placebo	Nasopharyngeal carriers of meningococci attending the Naval Service Training Command School at Great Lakes, Illinois, were identified and assigned by means of a table of random numbers to 2 groups: 29 received no prophylaxis and 53 received minocycline.	All the men in two companies of naval recruits in their 6th week of training were asked to volunteer to participate in this study. These individuals had received no antibiotics or sulfadiazine for at least 4 weeks	71% (37/53) eliminated their carrier state in treatment group vs 7% (2/29) in control group lost carrier status.
Dworzack (1988) *(35)*	Prospective placebo-controlled, randomized, double-blind study	Ciprofloxacin single 750 mg oral dose	Placebo	620 healthy volunteers were evaluated for persistent nasopharyngeal carriage of *N. meningitidis* by means of 2 cultures taken 1 week apart,	48 subjects whose cultures grew *N. meningitidis* on all 3 occasions were identified. These subjects provided a medical history and underwent a physical examination. 24	All 24 were culture negative on Day 7 and Day 21 in ciprofloxacin group (100%). Only four (17%) subjects in placebo group eradicated *N. meningitidis* when

Lead author (year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Inference
				followed by a 3rd culture taken 9 days later.	received ciprofloxacin and 24 received a placebo	culture was performed 1, 7 and 21 days later. 3/24 (12%) ciprofloxacin recipients and 2/24 (8%) placebo recipients noted gastrointestinal symptoms of abdominal cramps, nausea or diarrhoea. One subject who received ciprofloxacin noted headache and fatigue.
Guttler (1971) *(36)*	Open-label clustered RCT	Rifampin 600 mg per day OR Ampicillin 500 mg twice daily OR Minocycline 100 mg twice daily	Placebo	643 recruits from four basic combat training companies were analysed. 587 took their assigned drug	Five trainees who refused to participate were excluded	36/38 (95%) meningococcal carriers in minocycline group and 43/51 (84%) in rifampin group had initial eradication. No data about eradication in ampicillin group. No toxic adverse events encountered with rifampin or minocycline.
Pugsley (1987) *(37)*	Double-blind RCT	Ciprofloxacin 500 mg twice daily for 5 days	Placebo	46 of 651 healthy adult volunteers were persistent nasopharyngeal carriers of *N. meningitidis* on the basis of two cultures taken 1 week apart	42 carriers were included and 41 completed the study. 21 received the intervention and 21 received a placebo. One subject failed to return for the final nasopharyngeal culture.	21/21 (100%) carriers receiving ciprofloxacin had culture negatives after 1 day of therapy. Adverse reactions occurred with similar frequency among those in the placebo and ciprofloxacin groups and were not clinically important.
Renkonen (1987) *(38)*	Placebo-controlled double-blind group comparison trial	Ciprofloxacin 250 mg twice daily for 3–4 days	Placebo	552 voluntary healthy recruits who were not on any antimicrobial therapy were selected from 2 garrisons for	112 follow-up samples were obtained from the 120 treated recruits. The missing samples were equally divided between	54/56 (98%) meningococcal carrier reduction in the ciprofloxacin group and 7/53 (13%) reduction in placebo group.

Lead author (year)	Study design	Intervention	Comparator	Population	Inclusion criteria	Inference
				screening for meningococcal carriage. Two days later, 120 of the most heavily colonized recruits were selected for treatment with either ciprofloxacin or a placebo.	both treatment groups: 56 carriers in the ciprofloxacin group and 53 in the placebo group	Three people in each group complained of side-effects. All 6 complained of diarrhoea.

RCT: randomized controlled trial.

4. From evidence to recommendations: summary of findings

Table WA10.5 Summary of findings: Should antimicrobial prophylaxis be provided to close contacts of cases of meningococcal meningitis to prevent additional cases and carriage?

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prophylaxis	Risk with chemoprophylaxis				
Prevention of additional cases	4 per 1000	2 per 1000 (1 to 10)	RR 0.47 (0.10 to 2.15)[b]	50969 (2 RCTs)	⊕◯◯◯ Very low[c,d,e]	There is uncertainty as to whether chemoprophylaxis has any effect on the prevention of secondary cases of meningococcal disease.

CI: confidence interval; RR: risk ratio.

[a] The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] This RR is analysed using interclass correlation coefficient and design effect for the Coldiron study *(9)*.

[c] Downgraded by one level for serious risk of bias as the study by MDSG *(11)* has a serious risk of bias in one domain, moderate risk in one domain and no information in three domains (ROBINS-I) (13.4% weightage).

[d] Downgraded by two levels for serious indirectness because in the Coldiron study, only 4% of the population at risk received antibiotic chemoprophylaxis.

[e] Downgraded by one level for serious imprecision as the point estimate crosses the line of no difference with very wide CIs, while upper limit shows significant harm and lower limit shows benefit.

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Appendix 1. Search strategy used to identify primary studies

Table WA10.A1.1 Database: MEDLINE (OVID), 1946 to November Week 5 2023, searched on 2 January 2024

No.	Searches	Results
1	Meningitis, Bacterial/ or ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome or Neisseria-meningitidis or meningococc* or N-meningitidis or Escherichia-coli or E-coli or GBS or streptococc* or S-agalactiae or H-influenza* or Haemophilus-influenza* or Hemophilus or Haemophilus or Leptospir* or L-monocytogenes or Listeria-monocytogenes or listerial or Borrelia-burgdorferi or B-burgdorferi or Borrelia or Lyme or Streptococcus-pneumoniae or S-pneumoniae or pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) adj3 meningit*).ti,ab. OR (Meningococc* adj5 (infection* OR disease*)).ti,ab.	29 292
2	Anti-Bacterial Agents/ or (anti-biotic* or antibiotic* or anti-bacteri* or antibacteri* or antimicrobial* or anti-microbial*).ti,ab.	693 742
3	Rifamycins/ or Vancomycin/ or Penicillins/ or Cephalosporins/	77 182
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axepim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac	523 552

	OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*).ti,ab.	
5	2 or 3 or 4	1 039 341
6	1 and 5	8 867
7	animals/ not (animals/ and humans/)	5 145 692
8	(letter or historical article or comment or editorial or news or case reports).pt.	4 464 549
9	6 not (7 or 8)	5 704

Table WA10.A1.2 Database: Embase (Elsevier) (www.embase.com), searched on 2 January 2024

No.	Searches	Results
1	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR ((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N.-meningitidis OR Escherichia-coli OR E.-coli OR GBS OR streptococc* OR S.-agalactiae OR H.-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L.-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B.-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S.-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S.Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab,kw,de OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,de,kw	51 027
2	antibiotic agent'/mj OR (anti-biotic* OR antibiotic* OR anti-bacteri* OR antibacteri* OR antimicrobial* OR anti-microbial*):ti,ab	899 463
3	rifamycin'/mj OR 'vancomycin'/mj OR 'penicillin derivative'/mj OR 'cephalosporin'/mj	51 489
4	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR BMY-28142 OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR Biseptol-480 OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR SQ-26776 OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR BAY-12-8039 OR BAY-128039 OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime Pentahydrate OR LY-139381 OR LY139381 OR Tazidime OR Ceftazidime OR GR-20263 OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR Ro13-9904 OR Ro13-9904 OR Ro139904 OR Ro-13-	1 360 937

	9904 OR Ro-13-9904 OR Ro-13-9904 OR Ro-139904 OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR HR-756 OR HR756 OR Ru-24756 OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR BRL-2333 OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR Or-pen OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* or fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw,de	
5	#2 OR #3 OR #4	1 907 847
6	#1 AND #5	18 289
7	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 442 093
8	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR case-report*:ti OR case-series:ti OR genomic*:ti OR 'in vitro':ti	9 735 110
9	#6 NOT (#7 OR #8)	13 657

Table WA10.A1.3 Database: Cochrane Library (www.cochranelibrary.com/advanced-search/search-manager), searched on: 2 January 2024

No.	Searches	Results
#1	MeSH descriptor: [Meningitis, Bacterial] explode all trees	489
#2	((bacterial OR bacteraemia OR bacteremia OR Waterhouse-Friderichsen-syndrome OR Neisseria-meningitidis OR meningococc* OR N-meningitidis OR Escherichia-coli OR E-coli OR GBS OR streptococc* OR S-agalactiae OR H-influenza* OR Haemophilus-influenza* OR Hemophilus OR Haemophilus OR Leptospir* OR L-monocytogenes OR Listeria-monocytogenes OR listerial OR Borrelia-burgdorferi OR B-burgdorferi OR Borrelia OR Lyme OR Streptococcus-pneumoniae OR S-pneumoniae OR pneumococc* OR Streptococcus-oralis OR S-Oralis OR acute OR fulminat* OR fulminant* OR sudden-onset) NEAR/3 (meningit*)):ti,ab OR (Meningococc* NEAR/5 (infection* OR disease*)):ti,ab,kw	1 404
#3	#1 OR #2	1 632
#4	MeSH descriptor: [Anti-Bacterial Agents] this term only	15 349
#5	MeSH descriptor: [Rifamycins] explode all trees	1 846
#6	MeSH descriptor: [Vancomycin] explode all trees	982
#7	MeSH descriptor: [Penicillins] explode all trees	6 320
#8	MeSH descriptor: [Cephalosporins] explode all trees	4 785
#9	(gentamycin* OR gentamicin* OR garamycin OR Gentacycol* OR Gentavet OR Genticin OR G-Myticin OR GMyticin OR Cefepim OR Maxipime OR Axépim OR Quadrocef OR "BMY 28142" OR BMY28142 OR Meropenem* OR Merrem OR Ronem OR Penem OR SM-7338 OR SM7338 OR Trimethoprim OR Sulfamethoxazole OR Cotrimoxazole OR TMP-SMX OR Trimezole OR Trimoxazole OR Septrin OR Trimethoprimsulfa OR Bactifor OR Sumetrolim OR Bactrim OR Biseptol OR "Biseptol 480" OR Biseptol480 OR Eusaprim OR Kepinol OR Oriprim OR Septra OR Sulprim OR Trimosulfa OR Az-threonam OR Azthreonam OR "SQ 26776" OR SQ26776 OR Urobactam OR Azactam OR Octegra OR Proflox OR Moxifloxacin OR Avelox OR Avalox OR Actira OR "BAY 12 8039" OR "BAY 128039" OR BAY128039 OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Azythromycin OR Sumamed OR Toraseptol OR Vinzam OR "CP 62993" OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Zitromax OR Zentavion OR Fortaz OR Fortum OR Ceftazidime-Pentahydrate OR "LY 139381" OR LY139381 OR Tazidime OR Ceftazidime OR "GR 20263" OR GR20263 OR Nebramycin OR Tobramycin OR Obracin OR Tobracin OR Brulamycin OR Nebcin OR	55 820

	Nebicin OR Polymyxin OR Colimycin OR Colisticin OR Coly-Mycin OR Totazina OR Colistin-Polymyxin OR Aerosporin OR cephalosporin* OR penicillin* OR vancomycin* OR rifampicin OR chloramphenicol OR ceftriaxon* OR cefotaxime OR ciprofloxacin OR Lendacin OR Longacef OR Longaceph OR "Ro13 9904" OR "Ro13 9904" OR Ro139904 OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 13 9904" OR "Ro 139904" OR Rocephin OR Rocefalin OR Rocephine OR Rocefin OR Tacex OR Terbac OR Benaxona OR Cefaxona OR Cephotaxim* OR Cefotaxim* OR Cefradil OR Taporin OR Fotexina OR "HR 756" OR HR756 OR "Ru 24756" OR Ru24756 OR Benaxima OR Claforan OR Primafen OR Klaforan OR Aminobenzylpenicillin OR Ampicillin OR Pentrexyl OR Polycillin OR Ukapen OR Amcill OR Omnipen OR Amoxycillin* OR Amoxicillin* OR Hydroxyampicillin OR Actimoxi OR "BRL 2333" OR BRL2333 OR Clamoxyl OR Penamox OR Polymox OR Trimox OR Wymox OR Amoxil OR Benemycin OR Rifampicin OR Rimactan OR Tubocin OR Rifadin OR Rimactane OR Rifomycins OR Rifamycin OR Rifomycin OR Diatracin OR VANCO-cell OR Vanco-saar OR Vancocin* OR Vancomicina OR Vancomicin* OR Coliriocilina OR Crystapen OR "Or pen" OR Parcillin OR Pekamin OR Pengesod OR Penibiot OR Penicilina-G OR Penicillin-G OR Penilevel OR Peniroger OR Pfizerpen OR Sodiopen OR Sodipen OR Unicilina OR Ursopen OR Van-Pen-G OR Benpen OR Beta-lactam* OR Vanco-azupharma OR chloramphenicol OR Kloramfenikol OR Cloranfenicol OR Chlornitromycin OR Chlorocid OR Amphenicol OR Amphenicols OR Ophthochlor OR Syntomycin OR Levomycetin OR Chloromycetin OR Detreomycin OR Cefmenoxime OR Ceftazidime OR Cefodizime OR Moxalactam OR oxytetracyc* OR tetracyc* OR erythromyci* OR sulfa* OR ciprofloxacin* OR norfloxaci* OR ofloxaci* OR quinol* OR fluoroquinol* OR fluoro-quinolon* OR rifampi* OR azithromyci* OR coumermyci* OR minocyclin* OR macrolid*):ti,ab,kw	
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	63 714
#11	#3 AND #10	372
#12	Trials	361

Table WA10.A1.4 Database: ClinicalTrials.gov (https://classic.clinicaltrials.gov/), searched on 2 January 2024

No.	Searches	Results
#1 (Condition)	((bacterial OR Neisseria OR meningococus OR Escherichia-coli OR streptococcus OR influenza OR Hemophilus OR Leptospira OR Listeria-monocytogenes OR listerial OR Borrelia OR Lyme OR Streptococcus OR pneumococcus OR disease) AND (meningitis))	
#2 (Other terms)	anti-biotic OR antibiotic OR anti-bacterial OR antibacterial OR antimicrobial OR anti-microbial OR cephalosporin OR penicillin OR vancomycin OR rifampicin OR chloramphenicol OR ceftriaxone OR cefotaxime OR ciprofloxacin OR Ampicillin OR Amoxicillin	
#3	#1 AND #2	122

11. Adjunctive corticosteroids

Authors

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Abbreviations

CI	confidence interval
CSF	cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hib	*Haemophilus influenzae* type b
HICs	high-income countries
LMICs	low- and middle-income countries
NA	not applicable
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RoB 2	version 2 of the Cochrane risk-of-bias tool for randomized trials
ROBINS I	Risk Of Bias In Non-randomized Studies – of Interventions (tool)
RR	risk ratio

1. Background

Acute meningitis is a term used to denote infection of the meninges (protective membrane that lines the brain and spinal cord). It is associated with high morbidity and mortality, especially when there is a delay in diagnosis and treatment. *Defeating meningitis by 2030: a global road map* was approved by the Seventy-third session of the World Health Assembly in November 2020 *(1)*.

The road map sets out a comprehensive vision for 2030, "Towards a world free of meningitis", with three visionary goals:

1. Elimination of bacterial meningitis epidemics;

2. Reduction of cases of vaccine-preventable bacterial meningitis by 50% and deaths by 70%;

3. Reduction of disability and improvement of quality of life after meningitis due to any cause.

People with bacterial meningitis are usually treated by primary care and emergency medicine physicians at the time of initial presentation, sometimes in consultation with infectious disease specialists. In resource-limited settings, with insufficient laboratory support, a microbiological etiology confirmation is usually lacking. The objective of the new guidelines is to provide clinicians with recommendations for the treatment of bacterial meningitis which can be applied in all settings of medical practice.

People with acute meningitis are treated with appropriate antibiotics/antivirals and adjuvant therapy in the form of anti-seizure medication or corticosteroids. Intravenous adjunctive corticosteroids (i.e. dexamethasone, hydrocortisone, prednisone) are given before, with or after antibiotics, to reduce inflammation, decrease proinflammatory cytokines in the cerebrospinal fluid (CSF), diminish cerebral oedema, and reduce the risk of a poor outcome *(2-5)*.

For this systematic review a search was conducted to investigate the role of steroids as adjunctive therapy in the treatment of acute meningitis. This work precedes the development of guidelines for the defeating meningitis road map created by WHO.

The primary objective of this systematic review was to study the effects of adjunctive intravenous corticosteroids versus placebo on mortality and neurological sequelae in people with acute meningitis.

2. Methodology

2.1 Research question and study design

Among suspected, probable or confirmed cases of acute bacterial meningitis, do adjunctive corticosteroids (dexamethasone, hydrocortisone, prednisone) decrease morbidity and mortality outcomes?

Population: Suspected, probable or confirmed cases of acute bacterial meningitis. *Subgroup analysis:* Pathogen (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*, and Group B streptococcus); Age group (child, adult); World Bank income classification (high-income country, or low- or middle-income country; Disease severity (altered consciousness).

Intervention: Adjunctive corticosteroids (dexamethasone, hydrocortisone, prednisone).

Comparator: Standard treatment without adjunctive corticosteroids.

Outcomes

Critical outcomes:

- neurological sequelae[16]
- mortality.

Important outcomes:

- time to resolution of symptoms;
- adverse effects;
- disease complications (sepsis, disseminated intravascular coagulation, neurological complications, including neurological sequelae).

Study design: The study was designed as a systematic review with meta-analysis comprising only randomized controlled trials (RCTs) and was conducted in accordance with Cochrane guidelines for systematic reviews with meta-analysis. The aim of the study was to assess the impact of steroids on clinical outcomes. Where possible the RCTs identified by the searches were supplemented with relevant observational studies, including prospective cohort studies.

2.2 Eligible studies

Published language: All articles published in English were included.

Exclusion criteria

[16] Neurological sequelae are defined as: hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behavioural changes), hydrocephalus, motor deficits, vision impairment.

The following study types were excluded:

- Non-randomized studies without a comparator arm (e.g. case reports, editorials, case series, letters, editorials, abstracts, pathology-based studies and animal studies);
- Studies without adjunctive therapy with corticosteroids;
- Any ongoing trials and studies with no evaluable outcome data.

The following disease categories were excluded:

- Meningitis in newborns (0–28 days);
- Hospital-acquired, nosocomial and health-care-associated meningitis;
- Subacute and chronic meningitis, including tuberculous, cryptococcal and eosinophilic meningitis;
- Non-infectious meningitis (e.g. drugs, malignancy, autoimmune diseases).

2.3 Search strategy

The following databases were searched: PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Epistemonikos, Web of science, Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (https://clinicaltrials.gov/) using appropriate search terms. All the databases were searched for studies published from 1946 to 6 February 2024.

The reference lists of relevant publications were checked for any unidentified trials. In addition, clinical trial registries, including ClinicalTrials.gov, were searched for completed RCTs. National or regional databases or grey literature were also searched if it was deemed relevant.

2.4 Selection of studies

The data obtained from the search were uploaded to the Rayyan tool *(6)*. The search results were screened by the review authors independently using Rayyan software, and the full text of all the potentially relevant studies was retrieved. Each study was examined to ensure that there were no duplicates. Any disagreements were resolved through discussion. Studies excluded from the review and the reasons for exclusion are given in Table WA11.2.

Systematic reviews published before 6 February 2024 that would apply to the research question, were identified. These systematic reviews were used as seed articles along with prospective non-RCT studies on steroids in acute meningitis. Rayyan software was used to categorize articles according to the inclusion and exclusion criteria. The selection of studies was based on the following protocol:

- Two of the authors independently selected the studies from the bibliographical databases.

- The studies were screened on the basis of the title and abstract. Those eligible according to the parameters of the research question were subjected to full-text screening.
- Any disagreements between the two authors were resolved by discussion, and the third author was also involved in the final selection of eligible articles.
- The full text articles of the studies were then downloaded. The studies were divided into RCTs, systematic reviews and prospective cohort studies.
- The total number of citations that were retrieved from the databases, with the reasons for inclusion and exclusion, are presented in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (Fig. WA11.1).

2.5 Data extraction and management

The studies included were subjected to data extraction based on study characteristics, study setting and location, income status of the country concerned (i.e. high-income country or low- or middle-income country), demographic profile of participants, numbers in the study and comparator arms, details of the study drug or treatment, adverse effects and the intervention profile along with adjunctive treatment (see Appendix 2). The data collected on the corticosteroids include the following: type of corticosteroid, dosage, duration, administration in relation to the antibiotics, and outcome measures as defined by the research question (section 2.1). The follow-up data were extracted if they were available. When studies with multiple treatment groups were being analysed, the focus was solely on the treatment groups that received either corticosteroids or a placebo. Any disagreements were resolved through discussion.

For dichotomous outcomes, the number of participants who had experienced the event and the number of participants in each treatment group were recorded. The number of cases analysed in each arm was recorded and the discrepancy between the figures was used to calculate the number of participants lost to follow-up, which allowed the team to perform sensitivity analyses to investigate the effect of missing data if necessary. For continuous outcomes, attempts were made to extract means and standard deviations for the outcome in each group; medians were also recorded for narrative comparisons where means were unavailable. The review was performed and reported in accordance with the recommendations given in the *Cochrane handbook for systematic reviews of interventions*.

2.6 Assessment of risk of bias in studies included in the review

The methodological quality of the included studies was assessed using version 2 of the Cochrane risk-of-bias tool (RoB 2) *(7)* (Fig. WA11.2). Each of the included studies was assessed on the basis of a number of parameters, including the following: analysis of the randomization process to determine the risk of selection bias; detection of any deviation

from the protocol to determine the risk of performance bias; attrition bias; reporting bias; detection bias; and presence of any additional source of bias. The results of the RoB 2 analysis were used for the Grading of Recommendations Assessment, Development and Evaluation (GRADE) of these studies. For the non-RCTs that comprised prospective cohort studies with a comparator, the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool was used for the quality assessment. The treatment effect was measured using the risk ratio (RR), with a 95% confidence interval (CI). Visual inspection of funnel plots was used to detect the presence of publication bias.

2.7 Data synthesis

Review Manager Web software (version 5.4) was used to analyse the data *(8)*. Owing to the presence of substantial heterogeneity across the studies, which spanned a wide range of timeframes and geographical locations, and contained potential confounders, meta-analyses using a random-effects model based on an inverse variance method were performed. All outcome measures were dichotomous. RRs with 95% CIs were used as measures of the treatment effect. Where a meta-analysis was not appropriate, owing to important clinical or methodological heterogeneity, or if the study results differed to the extent that combining them in a pooled analysis would not make sense, the narrative data were summarized in tables.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The results of the analysis are summarized in Table WA11.4, and the summary effect estimates for the critical outcomes and other important outcomes are presented with illustrative comparative risks. The GRADE framework, as developed by the GRADE Working Group *(9)*, was used to evaluate the certainty of the evidence for each outcome. The GRADE levels of certainty are defined in Box WA11.1.

Box WA11.1 The certainty of evidence used in GRADE	
High ⊕⊕⊕⊕	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

The data extracted were divided into several subgroups, and heterogeneity assessment was done using I^2 statistics. The subgroups comprised the following:

- Age group: children (defined as under the age of 18 years) and adults;
- Causative pathogen: meningococcus, pneumococci and *Haemophilus influenzae*;
- Timing of therapy with adjunctive steroids in relation to the administration of antibiotics: steroids given prior to the administration of antibiotics;
- Presence or absence of neurological sequelae, and the nature of sequelae: short- and long-term (short-term sequelae were defined as the presence of at least one neurological deficit, except for hearing impairment, until six weeks after discharge; long-term sequelae were defined as presence of neurological deficit between six weeks and 12 months after discharge);
- Presence or absence of hearing impairment, and its severity;
- Adverse events associated with the therapy.

Mortality, hearing impairment and neurological sequelae were evaluated in relation to country income status. Studies were stratified on the basis of the World Bank income classification (high-income country, or low- or middle-income country).

Methodological quality of the included studies was assessed and these were classified into three categories – high, medium and low risk of bias – based on their scores using the RoB 2 tool (see Fig. WA11.2).

A heterogeneity assessment was performed by means of visual inspection of forest plots (see Fig. WA11.3 to WA11.24) to determine the closeness of point estimates to each other and the overlap of CIs. The Chi-square test was used, with a *P*-value of 0.10 to indicate statistical significance and the I^2 statistic to measure heterogeneity. The following ranges, outlined in the *Cochrane handbook for systematic reviews of interventions*, were used to interpret the I^2 statistic: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; 75–100%, considerable heterogeneity.

The magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. *P*-value from the Chi-square test) were also considered when determining the importance of the observed I^2 value.

2.10 Sensitivity analysis

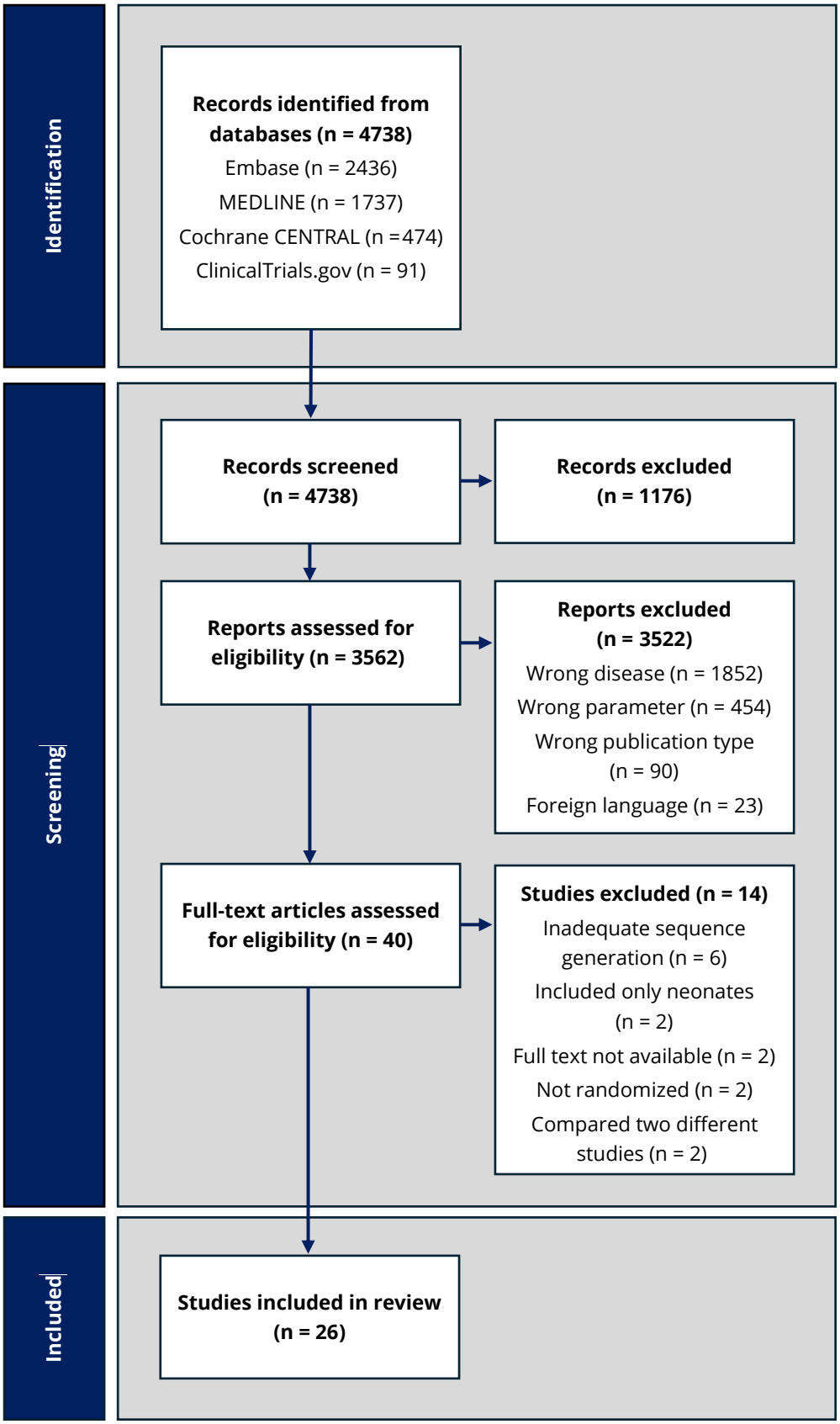
For trials with missing data, a worst-case scenario analysis was performed. Participants who had dropped out of the corticosteroid group were regarded as having had an unfavourable outcome, while those who had dropped out of the control group were deemed to have had a favourable outcome. Sensitivity analysis was conducted by imputing these missing data to assess the impact of these assumptions on the overall results.

3. Results

3.1 Studies identified by the search process

Figure WA11.1 presents the PRISMA flow diagram for this evidence synthesis.

Fig. WA11.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profiles

A total of 4738 studies were retrieved through various database searches. Around 1176 duplicates were removed, and 3562 studies were selected from the database. A total of 26 studies were identified for the final meta-analysis, and they included a total of 4458 people. This subsection presents the characteristics of the studies included in the GRADE evidence profiles (see Table WA11.1).

Table WA11.1 Characteristics of studies included in the GRADE evidence profiles

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
Bennett (1963), United States of America (USA) *(10)*	RCT	High	Hydrocortisone; after antibiotics	All ages Total sample size = 85 Intervention: 38 Control: 47	Placebo	Mortality – 45%	NA	NA Antibiotics not mentioned. Time points of steroids not mentioned
deLemos (1969), USA *(11)*	RCT	Some concerns	Methylprednisolone 120 mg per day, for 3 days after antibiotics	1 month to 17 years Total sample size: 117 Intervention: 54 Control: 63	Placebo	Mortality – 3%	NA	At baseline and at discharge
Belsey (1969), USA *(12)*	RCT	High	Dexamethasone 1.2 mg/m^2 per day for 4 days; timing not given	Up to 17 years of age Total sample size = 86 Intervention: 43 Control: 43	Placebo	Mortality	Adverse events, hearing loss, neurological sequelae	At admission and at 18 hours later; no other details of measurement available

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
Bademosi (1979), Nigeria *(13)*	Randomized, unblinded	High	Hydrocortisone, 100 mg; followed by oral prednisolone 60 mg per day for 14 days; before or with antibiotics; not clear	10–59 years of age Total sample size = 52 Intervention: 24 Control: 28	Placebo	Mortality – 44%	NA	At admission, discharge and at 1 year follow-up
Lebel (1988a), USA *(14)*	RCT	High	Dexamethasone 0.6 mg/g per day for 4 days; after antibiotics	Less than 16 years of age Total sample size: 100 Intervention: 51 Control: 49	Placebo	Mortality – 2%	Adverse events, hearing loss, neurological sequelae	2 and 5 days were assessed with MRI
Lebel (1988b), USA *(14)*	RCT	High	Dexamethasone 0.6 mg/kg per day for 4 days; after antibiotics	Less than 16 years of age Total sample size: 100 Intervention: 51 Control: 49	Placebo	Mortality – 2%	Adverse events, hearing loss, neurological sequelae	Baseline, discharge, 6 weeks and at 1 year
Girgis (1989); Egypt *(15)*	Randomized, unblinded	High	Dexamethasone 16–24 mg per day for 4 days; before or with antibiotics	Up to 70 years of age Total sample: 470	Placebo	Mortality – 15%	Hearing loss, neurological sequelae	Twice weekly during admission and then monthly

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
				Intervention: 225 Control: 245				once for 6 months
Lebel (1989), USA *(16)*	RCT	High	Dexamethasone 16–24 mg per day for 4 days; after antibiotics	Up to 16 years of age Total sample size: 61 Intervention: 30 Control: 31	Placebo	Mortality – 2%	Adverse events, hearing loss, neurological sequelae	NA
Odio (1991), USA *(17)*	RCT	Low	Dexamethasone 0.6 mg/kg per day for 4 days; before or with antibiotics	Up to 16 years of age Total sample size: 101 Intervention: 52 Control: 49	Placebo	Mortality – 2%	Adverse events, hearing loss, neurological sequelae	Followed up for 5–25 months
Schaad (1993), Switzerland *(18)*	RCT	High	Dexamethasone 0.8 mg/kg per day for 2 days; before or with antibiotics	Up to 16 years of age Total sample size: 115 Intervention: 60 Control: 55	Placebo	Mortality – nil	Adverse events, hearing loss, neurological sequelae	Admission, discharge, 3 and 9 months
King (1994), Canada *(19)*	RCT	Some concerns	Dexamethasone 0.6 mg/kg per day	Up to 13 years of age	Placebo	Mortality – 1%	Adverse events, hearing loss,	Baseline, discharge, 6

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
			for 4 days; after antibiotics	Total sample size: 101 Intervention: 50 Control: 51			neurological sequelae	weeks and at 1 year
Ciana (1995), Mozambique *(20)*	Randomized; unblinded	Some concerns	Dexamethasone 0.4 mg/kg per day for 3 days; timing NA	Up to 6 years of age Total sample size: 70 Intervention: 34 Control: 36	Placebo	Mortality – 28%	Adverse events, neurological sequelae	Baseline and at discharge
Kanra (1995), Türkiye *(21)*	RCT	Low	Dexamethasone 0.6 mg/kg per day for 4 days; before or with antibiotics	Up to 6 years of age Total sample size: 53 Intervention: 27 Control: 26	No dexamethasone	Mortality – 5%	Adverse events, hearing loss, neurological sequelae	Baseline, discharge, 6 weeks
Kilpi (1995), Finland *(22)*	Randomized, unblinded	Some concerns	Dexamethasone 1.5 mg/Kg per day for 3 days; before or with antibiotics	Up to 15 years Total sample size: 58 Intervention: 32 Control: 26	Placebo	Mortality – 2%	Adverse events, hearing loss, neurological sequelae	Baseline, discharge, 3 and 6 months

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
Wald (1995), USA *(23)*	RCT	High	Dexamethasone 0.6mg/kg per day for 4 days; after antibiotics	Up to 12 years Total sample size: 143 Intervention: 69 Control: 74	Placebo	Mortality – 1%	Adverse events, hearing loss, neurological sequelae	6 weekly for 3 months, 67% were followed for 1 year
Qazi (1996), Pakistan *(24)*	RCT	Low	Dexamethasone 0.6 mg/kg per day for 4 days; before or with antibiotics	Up to 12 years Total sample size: 89 Intervention: 48 Control: 41	Placebo	Mortality – 15%	Adverse events, hearing loss, neurological sequelae	Baseline, discharge, month and at 1 year
Shembesh (1997), Libya *(25)*	RCT	High	Dexamethasone 0.6 mg/kg per day for 4 days; NA	2–12 months of age Total sample size: 77 Intervention: 38 Control: 39	Placebo	Mortality – 10.5%	Adverse events, hearing loss, neurological sequelae	Baseline and after 4 days
Thomas (1999), France, Switzerland, *(26)*	RCT	Low	Dexamethasone 40 mg per day for 3 days; after antibiotics	Up to 99 years Total sample size: 60 Intervention: 31 Control: 29	Placebo	Mortality – 13%	Adverse events, hearing loss, neurological sequelae	Baseline and after 30 days of therapy

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
Gans (2002), Kingdom of the Netherlands, Belgium, Denmark, Austria, Germany *(27)*	RCT	Low	Dexamethasone 40 mg per day for 4 days; before or with antibiotics	Adults Total sample size: 301 Intervention:157 Control: 144	Placebo	Mortality – 11%	Adverse events, hearing loss, neurological sequelae	Baseline and at 8 weeks
Gijwani (2002), India *(28)*	RCT	Low	Dexamethasone 0.6 mg/kg per day for 4 days; prior to antibiotics	Adults Total sample size: 40 Intervention: 20 Control: 20	Placebo	Mortality	Adverse events, hearing loss, neurological sequelae	14, 45 and 90 days after discharge
Molyneux (2002), Malawi *(29)*	RCT	Low	Dexamethasone 0.8 mg/kg per day for 2 days; before or with antibiotics	Up to 13 years of age Total sample size: 598 Intervention: 307 Control: 295	Placebo	Mortality – 31%	Hearing loss, neurological sequelae	Baseline, 1 and 6 months after discharge
Weisfelt (2006), Europe multicentre *(30)*	RCT	Low	Dexamethasone 40 mg per day for 4 days; before or with antibiotics	Adults Total sample size: 87 Intervention: 46	Placebo	NA	Neuropsychological evaluation and hearing assessment	? 8 weeks, details NA

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
				Control: 41				
Sankar (2007), India *(31)*	RCT	Low	Dexamethasone 0.9 mg/kg per day for 2 days; timing with antibiotics NA	Up to 12 years of age Total sample size: 25 Intervention: 12 Control: 13	Placebo	Mortality – 4%	Adverse events, hearing loss, neurological sequelae	Discharge and at 1 month
Peltola (2007), Latin America *(32)*	RCT	Low	Dexamethasone 0.15 mg/kg administered every 6 h for 2 days; prior to antibiotics	Up to 16 years Total sample size: 654 Intervention:166 Control: 163	Glycerol and dexamethasone with glycerol were the other groups	Mortality – 13%	Adverse events, hearing loss, neurological sequelae	Discharge and at 1 and 2 months
Thi Hoang Mai (2007), Viet Nam *(33)*	RCT	Low	Dexamethasone 0.8 mg/kg /day for 4 days; before or with antibiotics	Adults Total sample size: 435 Intervention: 217 Control: 218	Placebo	Mortality – 11%	Adverse events, hearing loss, neurological sequelae	1 and 6 months
Khan (2016), Pakistan *(34)*	RCT	Some concerns	Dexamethasone 40 mg/day for 4 days; timing not clear	Adults Total sample size: 480	Placebo	Mortality – 5.4%	NA	NA

Lead author (Year), Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/ intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
				Intervention: 240 Control: 240				

MRI: magnetic resonance imaging; NA: not applicable; RCT: randomized controlled trial.

3.1.2 Studies excluded from the review

This subsection presents the details of the studies excluded from the review, along with the reasons for exclusion (see Table WA11.2).

Table WA11.2 Studies excluded from the review, with reasons

Lead author (year)	Study type	Population	Intervention	Comparator	Outcome	Reasons for exclusion
Ayaz (2008) *(35)*	Prospective randomized study	People with community-acquired bacterial meningitis	Ceftriaxone with dexamethasone	Ceftriaxone alone (no placebo)	Mortality	Inadequate randomization (odd and even numbers in groups); not placebo-controlled
Daoud (1999) *(36)*	Clinical trial	Newborns with meningitis	Dexamethasone given to alternate study participants	No dexamethasone	Mortality	Inadequate sequence generation; no placebo; only newborns included
Farina (1995) *(37)*	NA	NA	NA	NA	NA	Not enough data for inclusion (abstract only)
Gupta (1996) *(38)*	Randomized trial	People aged 12–70 years with acute bacterial meningitis	Dexamethasone given to alternate study participants	NA	Mortality; sequelae; rapidity of recovery	Inadequate sequence generation; not placebo-controlled
Jensen (2016) *(39)*	Non-controlled trial	People with meningitis	Dexamethasone given to alternate study participants	No placebo	Mortality	Inadequate sequence

						generation; no placebo
Lepper (1959) *(40)*	NA	NA	NA	NA	NA	Inadequate sequence generation
Marguet (1993) *(41)*	Comparative study	People aged 1 month to 14 years with meningitis	Dexamethasone	Antibiotic alone	Mortality	Not randomized; no placebo
Ozen (2006) *(42)*	Comparative study	People with bacterial meningitis	Dexamethasone	No dexamethasone	IQ and Gestalt test	Not randomized; no placebo; outcome measure not relevant
Passos (1979) *(43)*	Comparative study	People with purulent meningitis	Dexamethasone	No placebo	Mortality	Inadequate sequence generation
Syrogiannopoulos (1994) *(44)*	Prospective randomized study	Children aged 2.5 months to 15 years	Dexamethasone for 4 days	Dexamethasone for 2 days	Neurological and audiological sequelae	No placebo group; comparison of 2-day and 4-day regimens of dexamethasone
Tolaj (2010) *(45)*	RCT	People with invasive meningococcal disease	Dexamethasone	No dexamethasone	Mortality	Randomization not mentioned in methodology; no placebo
Mathur (2012) *(46)*	RCT	Newborns with meningitis	Dexamethasone	Placebo – normal saline	Mortality	Only newborns included in the study
Bhaumik (1998) *(47)*	Randomized trial	People aged more than 12 years with bacterial meningitis	Dexamethasone	No dexamethasone	Mortality	Full text not available; no placebo

Scarborough (2007) *(4)*	RCT	People with bacterial meningitis	Dexamethasone	Placebo	Mortality	90% of the study participants were HIV-positive

NA: not applicable; RCT: randomized controlled trial.

3.2 Intervention effects

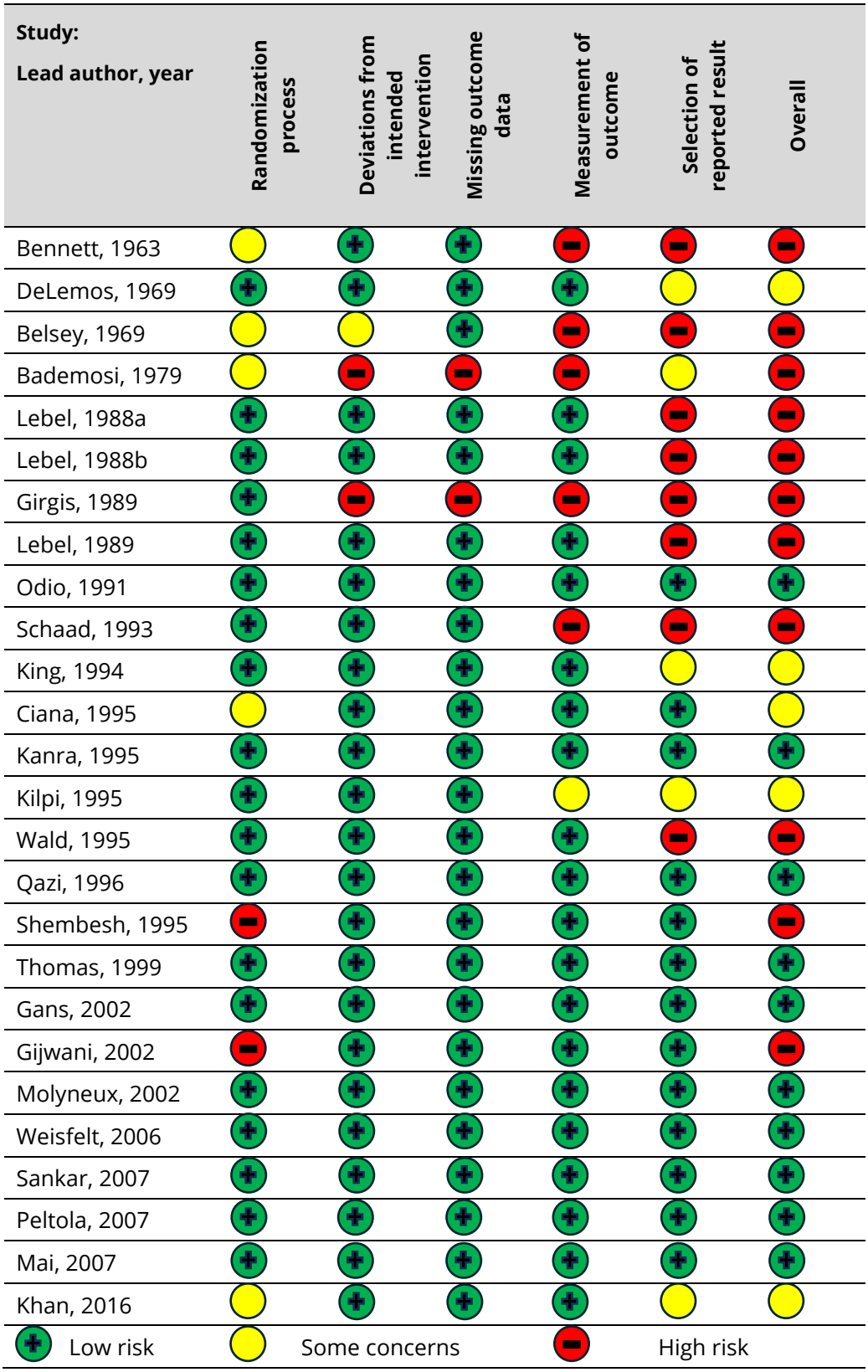
3.2.1 Description of study

Among the 26 studies identified for the final meta-analysis, nine studies were from low- and middle-income countries (LMICs), while the remaining 17 were from high-income countries (HICs). The age distribution was given in all 24 studies and in 17 of those it was predominantly in the paediatric age group. Adjunctive therapy in the form of corticosteroids was given as intravenous dexamethasone in all 24 studies, with a dosage ranging from 0.4–1.5 mg/kg/day over a duration of 2–4 days. In two studies *(10, 13)* hydrocortisone, oral prednisolone or a combination of both was administered. The details of the administration of corticosteroids in relation to antibiotics were available in 13 studies; corticosteroids were administered prior to antibiotics in eight studies, along with antibiotics in two studies and after the antibiotic in three studies.

3.2.2 Risk of bias

Ten of the 26 studies included had a low risk of bias. Bias due to improper standard randomization was observed in two studies *(13, 15)* while it was doubtful in five studies *(10, 12, 13, 20, 34)*. Deviation from the intended intervention and missing outcome data were observed in two studies *(13, 15)*. The other studies showed bias in measurement of outcomes, attrition or reporting of the results (see Fig. WA11.2).

Fig. WA11.2. Risk of bias in studies included in the review (assessed using RoB 2 tool



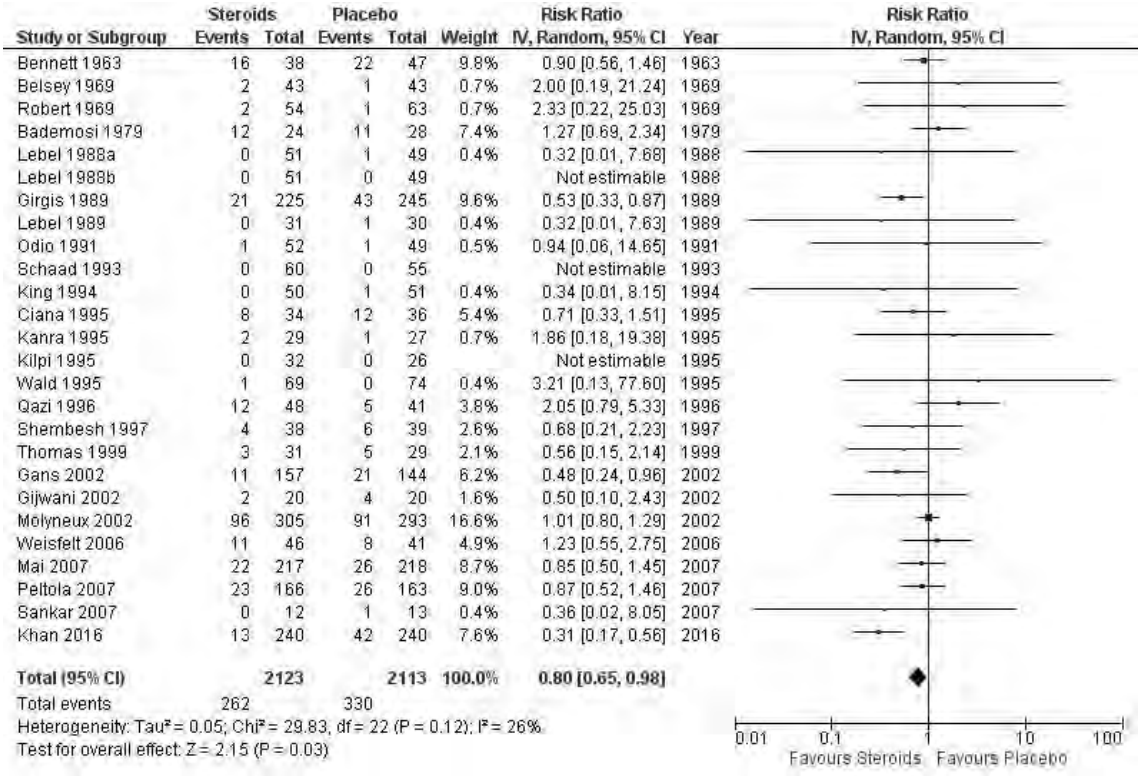
3.3 Forest plots

This section contains forest plots that depict the primary outcomes and subgroup analysis of the evidence synthesis in detail.

3.3.1 Primary outcomes

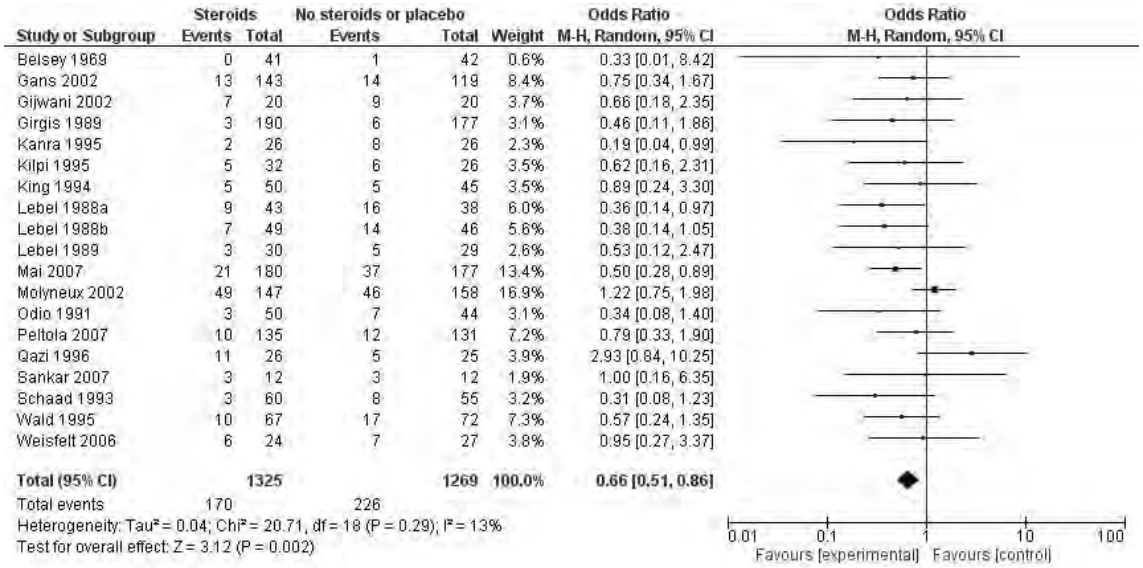
All-cause mortality: Moderate certainty evidence from 26 RCTs involving 4236 participants suggested that adjunctive corticosteroid therapy probably reduced mortality (compared to placebo) (RR 0.80, 95% CI 0.65–0.98, *P* = 0.03) *(10-34)*.

Fig. WA11.3 Impact of adjunctive corticosteroids on all-cause mortality



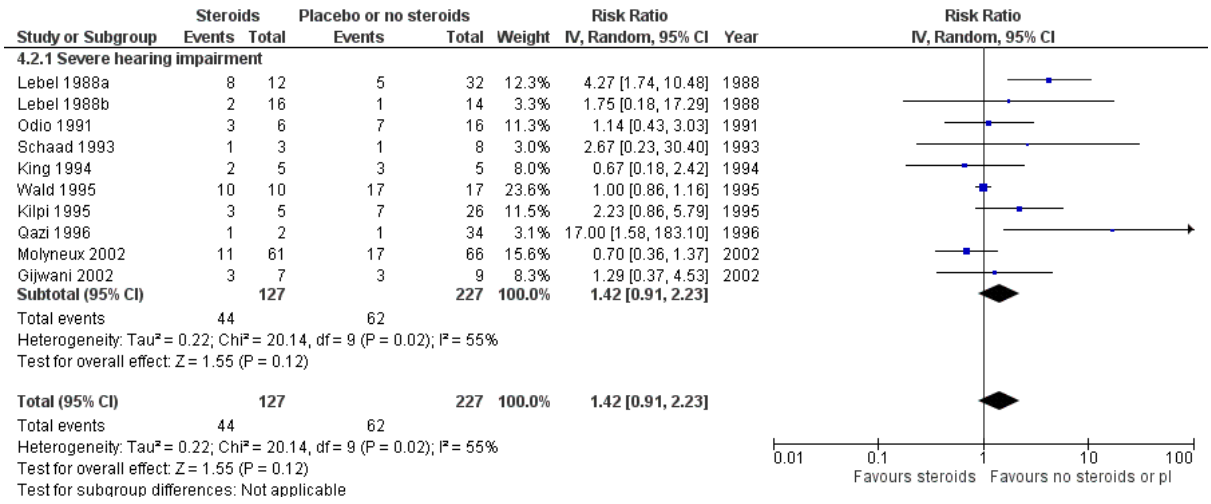
Any hearing loss: High certainty evidence from 19 RCTs involving 2594 participants showed that adjunctive corticosteroid therapy reduced the risk of hearing loss (compared to placebo) (RR 0.66, 95% CI 0.51 to 0.86, *P* = 0.002) *(12, 14-19, 21-24, 27-33)*.

Fig. WA11.4 Impact of adjunctive corticosteroids on the development of any hearing loss



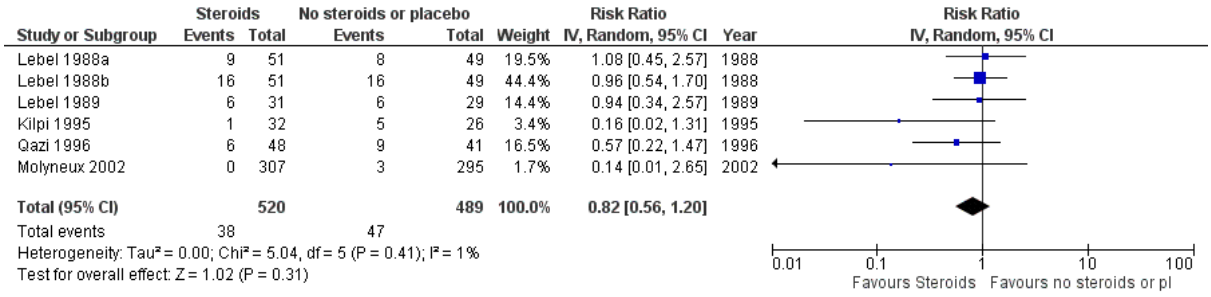
Severe hearing loss: Very low certainty evidence from 10 RCTs involving 354 participants showed that the effect of adjunctive corticosteroid therapy (compared to placebo) on severe hearing loss was uncertain (RR 1.42, 95% CI 0.91–2.23, *P* = 0.12) *(14, 17-19, 22-24, 28, 29)*.

Fig. WA11.5 Impact of adjunctive corticosteroids on the development of severe hearing loss



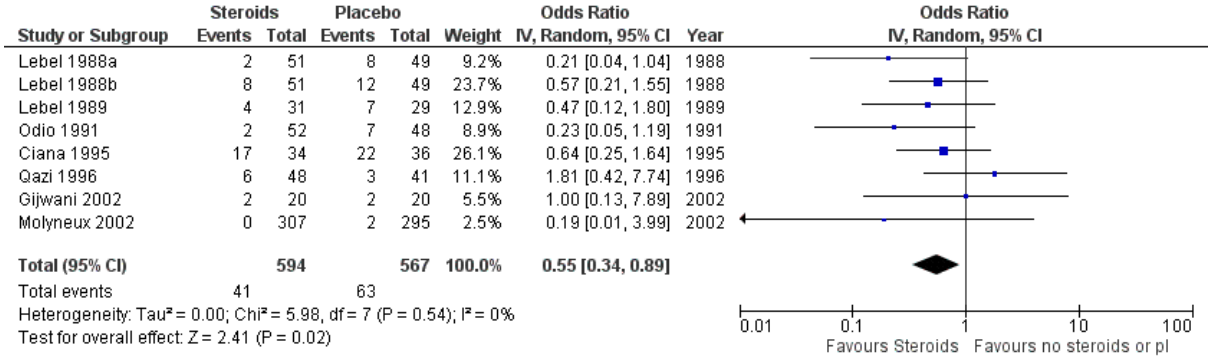
Ataxia: Very low certainty evidence from six RCTs involving 1009 participants showed that the effect of adjunctive corticosteroid therapy on ataxia compared to care without adjunctive corticosteroids was uncertain (RR 0.82, 95% CI 0.56–1.2, *P* = 0.41) *(14, 16, 22, 24, 29)*.

Fig. WA11.6 Impact of adjunctive corticosteroids on the development of ataxia



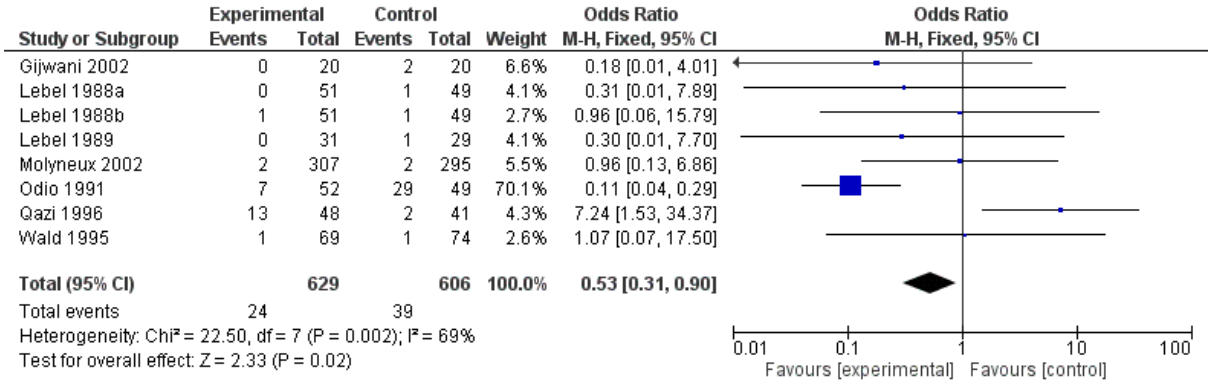
Post-meningitis epilepsy: Low certainty evidence from eight RCTs involving 1161 participants suggested that adjunctive corticosteroid therapy may have reduced post-meningitis epilepsy (compared to placebo) (RR 0.55, 95% CI 0.34–0.89, *P* = 0.02) *(14, 16, 17, 20, 24, 28, 29)*.

Fig. WA11.7 Impact of adjunctive corticosteroids on the development of post-meningitis epilepsy



Hydrocephalus: Very low certainty evidence from eight RCTs involving 1235 participants showed that the effect of adjunctive corticosteroid therapy on hydrocephalus (compared to placebo) was uncertain (RR 0.53, 95% CI 0.31–0.90, *P* = 0.02) *(14, 16, 17, 23, 24, 28, 29)*.

Fig. WA11.8 Impact of adjunctive corticosteroids on the development of hydrocephalus



Adverse events

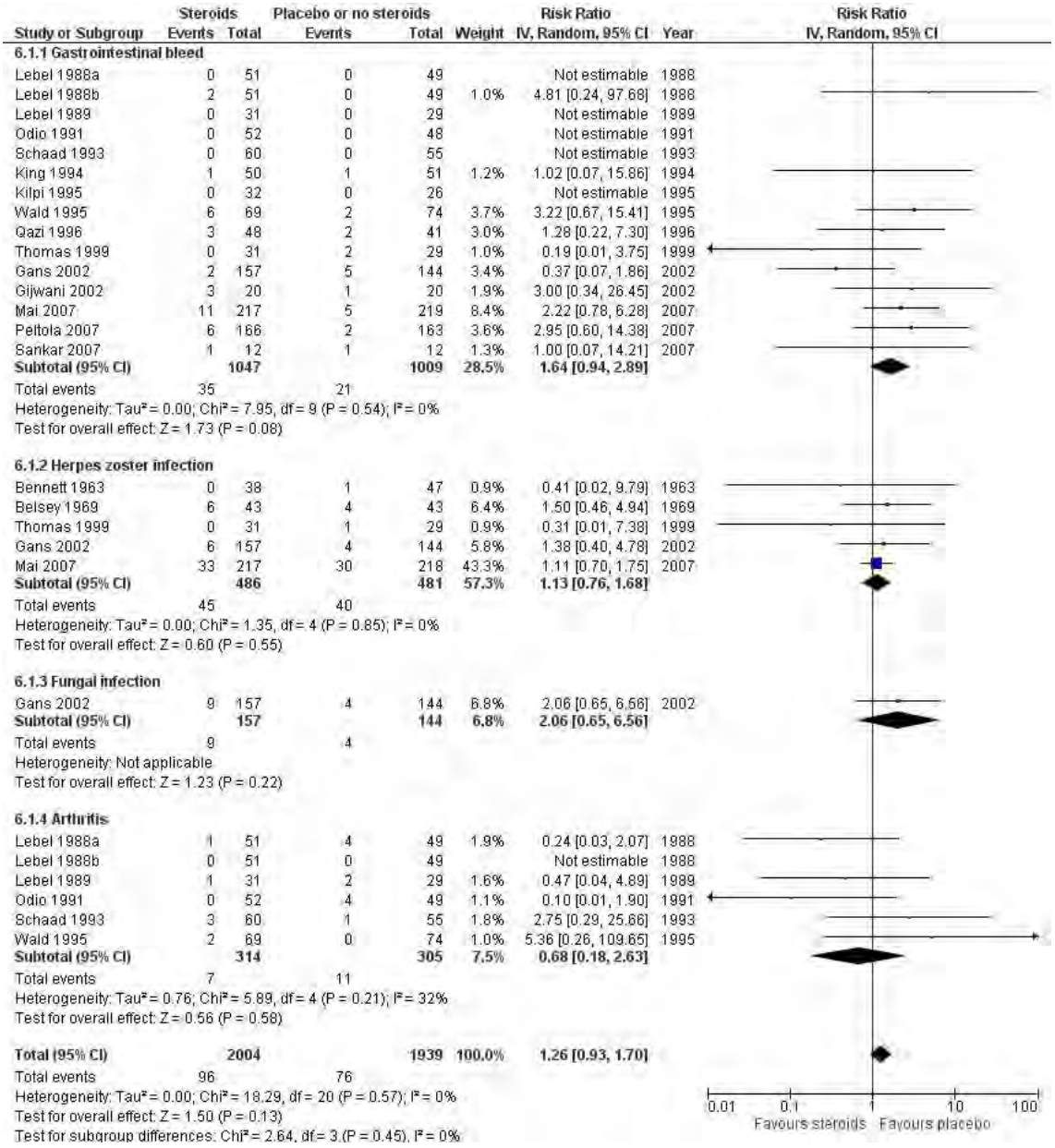
Total: Low certainty of evidence from 21 RCTs involving 3943 participants suggested that adjunctive corticosteroid therapy may have had little to no effect on adverse events (compared to placebo) (RR 1.26 with 95% CI of 0.93–1.70, P = 0.13).

Gastro-intestinal bleeding: Low certainty evidence from 15 RCTs involving 2056 participants suggested that adjunctive corticosteroid therapy may have had little to no effect on incidence of gastrointestinal bleeding (compared to placebo) (RR 1.64, 95% CI 0.94–2.89, P = 0.08) *(14, 16-19, 22-24, 26-28, 31-33)*.

Herpes zoster infection: Low certainty evidence from five RCTs involving 967 participants suggested that adjunctive corticosteroid therapy may have had little to no effect on the incidence of herpes zoster infection (compared to placebo) (RR 1.13, 95% CI 0.76–1.68, P = 0.55) *(10, 12, 26, 27, 33)*.

Arthritis: Low certainty evidence from 5 RCTs involving 619 participants suggested that adjunctive corticosteroid therapy did not result in increased arthritis (compared to placebo) (RR 0.68, 95% CI 0.18–2.63, P = 0.58) *(14, 16-18, 23)*.

Fig. WA11.9 Impact of adjunctive corticosteroids with respect to adverse events

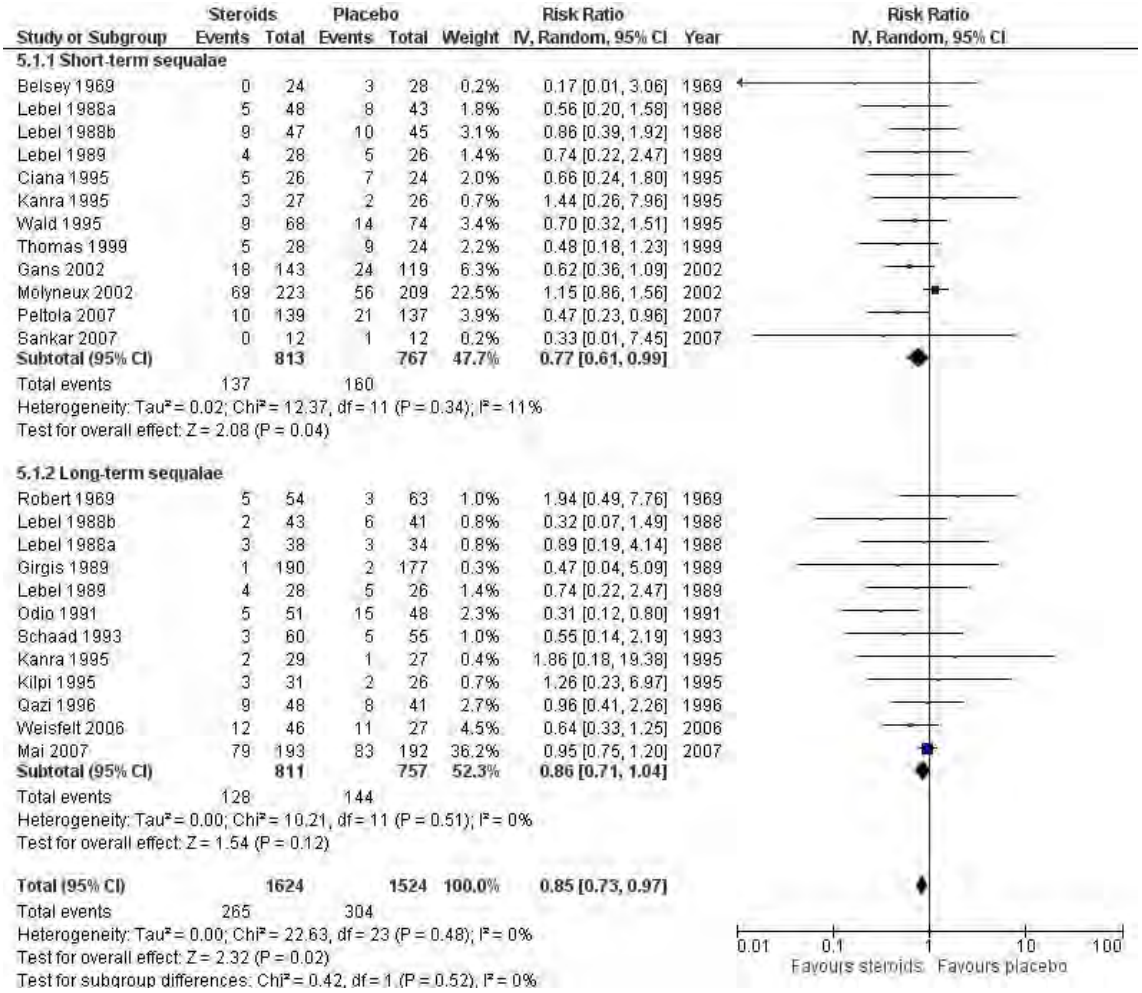


Neurological sequelae: A neurological sequela is considered short term when assessment is done at 6 weeks, and long term when the duration is beyond 6 weeks to 12 months or later.

- Low certainty evidence from 12 RCTs involving 1580 participants suggested that adjunctive corticosteroid therapy may have reduced the risk of short-term neurological sequelae compared to placebo (RR 0.77, 95% CI 0.61–0.99, *P* = 0.04) *(12, 14, 16, 20, 21, 23, 26, 27, 29, 31, 32)*.
- Very low certainty evidence from 12 RCTs involving 1580 participants suggested that the effect of adjunctive corticosteroid therapy on long-term neurological sequelae

compared with placebo was uncertain (RR 0.86, 95% CI 0.71–1.04, *P* = 0.12) *(11, 14-18, 21, 22, 24, 30, 33)*.

Fig. WA11.10 Impact of adjunctive corticosteroids on the development of short- and long-term neurological sequelae

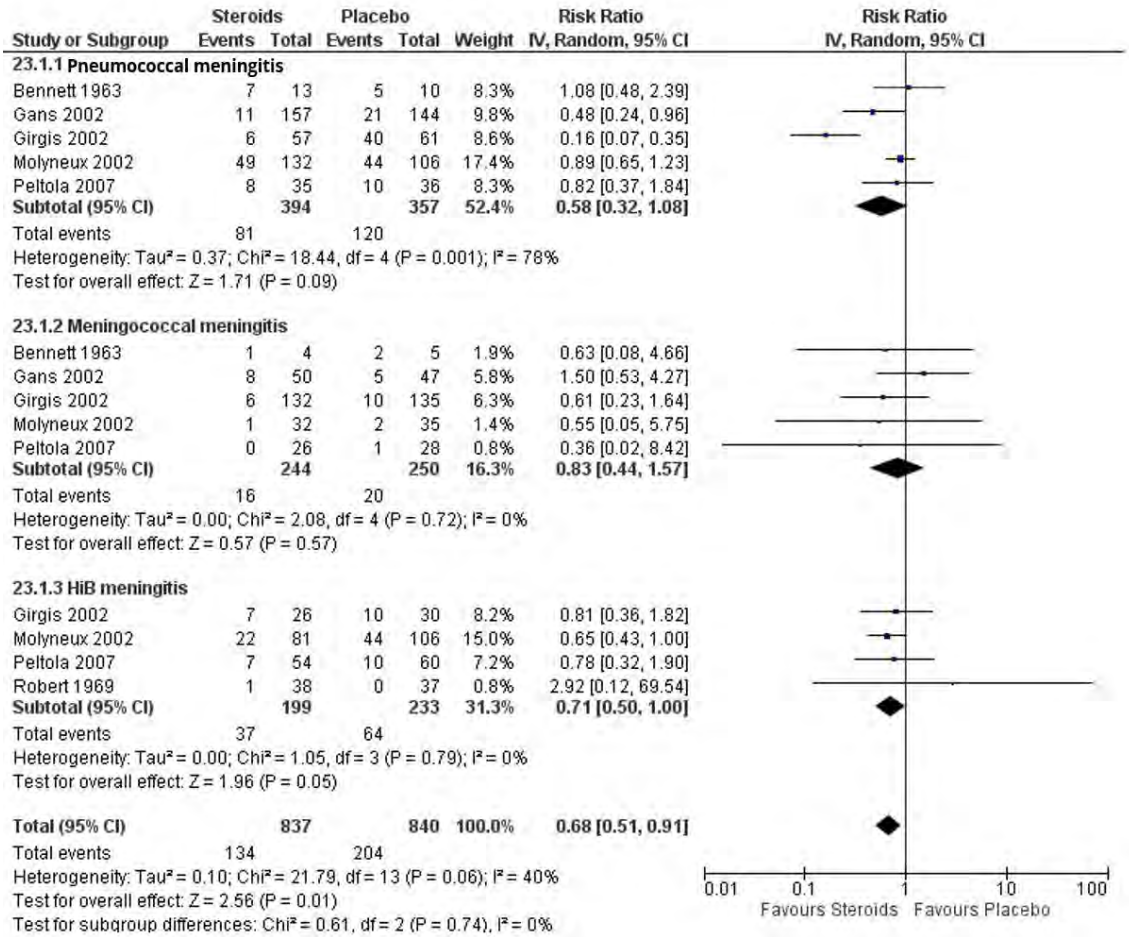


3.1.2 Subgroup analysis

All-cause mortality by etiological organism

- Low certainty evidence from five RCTs suggested that the effect of adjunctive corticosteroid therapy on mortality resulting from cases of pneumococcal meningitis may have had little to no effect when compared to placebo (RR 0.58, 95% CI 0.32–1.08, *P* = 0.09) *(10, 15, 27, 29, 32)*.
- Moderate certainty evidence from five RCTs suggested that corticosteroid therapy probably had little to no effect on mortality resulting from cases of meningococcal meningitis (RR 0.83, 95% CI 0.44–1.57, *P* = 0.02) *(10, 15, 27, 29, 32)*.
- High certainty evidence from four RCTs showed that corticosteroid therapy resulted in a mild reduction in mortality resulting from *H. influenzae* type b meningitis (RR 0.71, 95% CI 0.5–1, *P* = 0.05) *(11, 15, 29, 32)*.

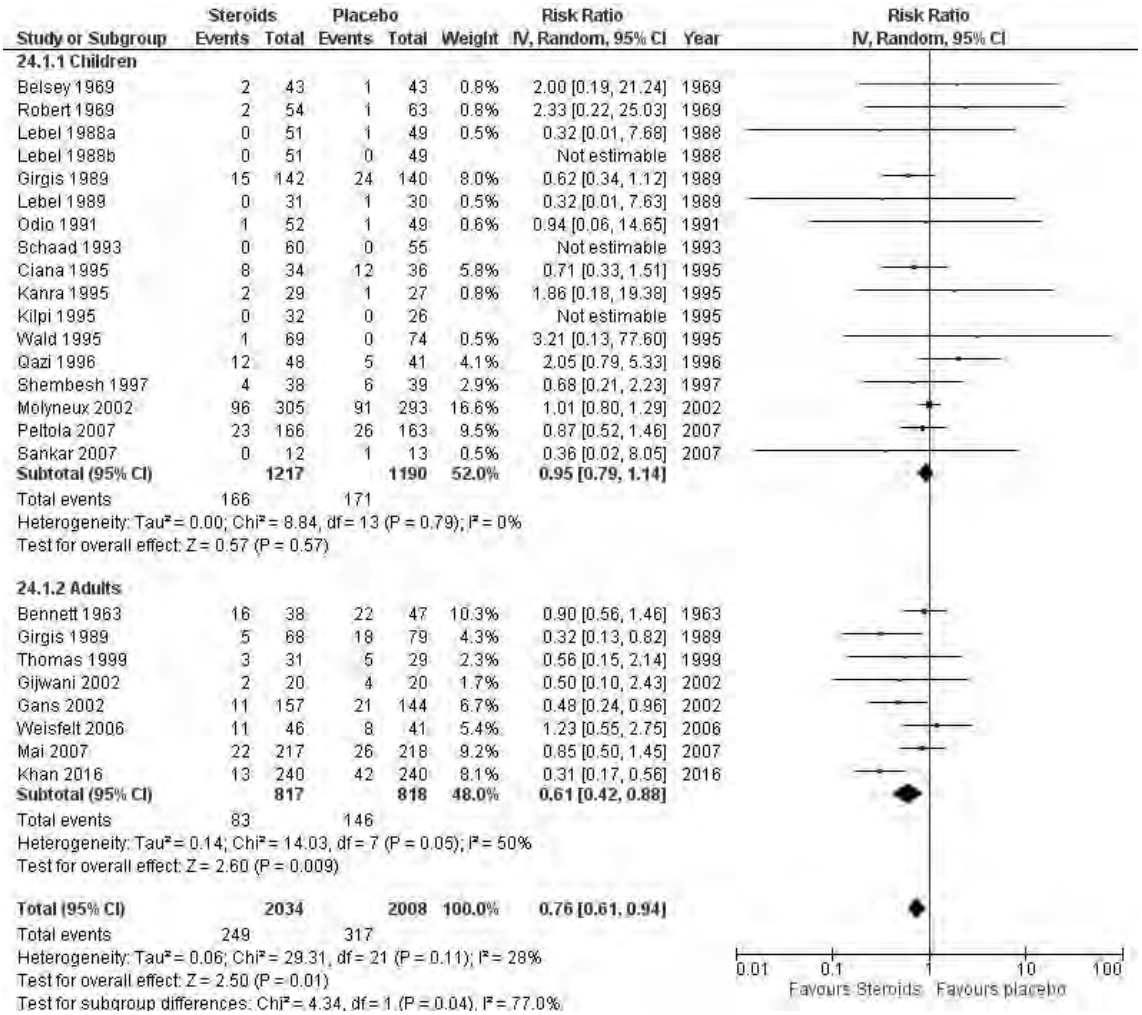
Fig. WA11.11 Risk ratios for all-cause mortality by etiological organism



All-cause mortality by age group

- Low certainty evidence from 14 RCTs suggested that corticosteroid therapy may have had little to no effect on mortality in children (RR 0.95, 95% CI 0.79–1.14, *P* = 0.57) *(11, 12, 14-18, 20-25, 29, 31, 32)*.
- Low certainty evidence from eight RCTs suggested that adjunctive corticosteroid therapy may have reduced mortality in adults (compared to placebo) (RR 0.61, 95% CI 0.42–0.88, *P* = 0.009) *(10, 15, 26-28, 30, 33, 34)*.

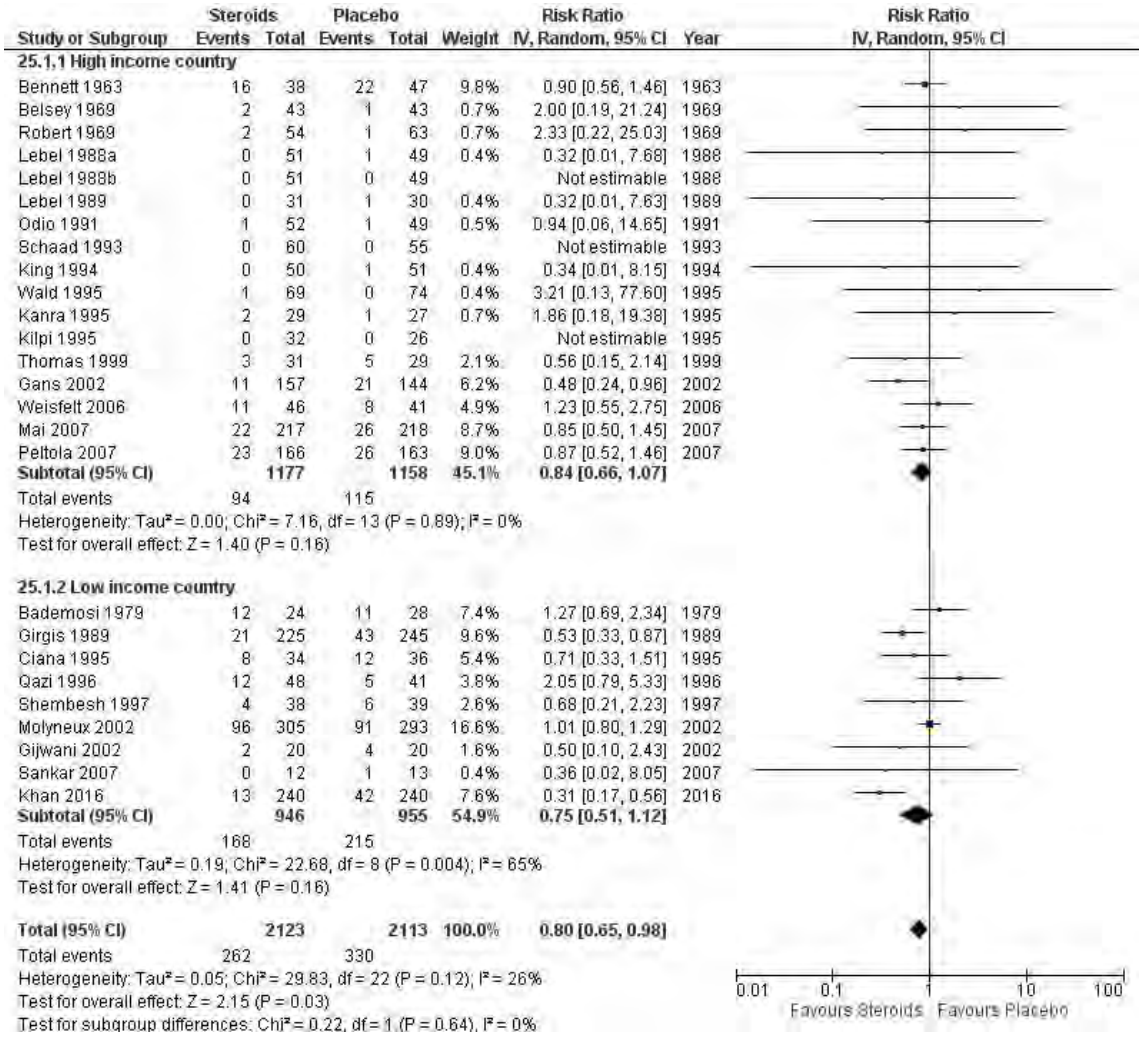
Fig. WA11.12 Risk ratios for all-cause mortality by age group



All-cause mortality by World Bank income classification

- Low certainty evidence from 14 RCTs suggested that adjunctive corticosteroid therapy may have had little to no effect on mortality in HICs when compared to placebo (RR 0.84, 95% CI 0.66–1.07, *P* = 0.16) *(10-12, 14, 16-19, 21-23, 26, 27, 30, 32, 33)*
- Very low certainty evidence from nine RCTs suggested that the effect of corticosteroid therapy on mortality in LMICs was uncertain (RR 0.75, 95% CI 0.51–1.12, *P* = 0.16) *(13, 15, 20, 24, 25, 28, 29, 31, 34)*.

Fig. WA11.13 Risk ratios for all-cause mortality by World Bank income classification

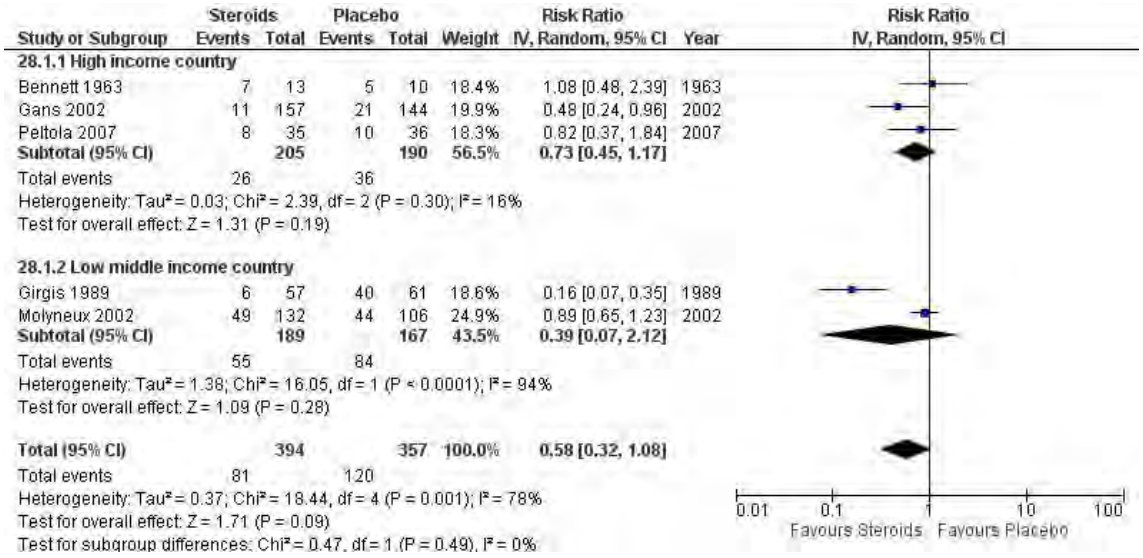


All-cause mortality resulting from pneumococcal meningitis

a. By World Bank income classification:

- In HICs there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 26 of 205 (12.68%) versus 36 of 190 (18.94%) (RR 0.73, 95% CI 0.45–1.17, *P* = 0.19) *(10, 27, 32)*.
- In LMICs, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 55 of 189 (29.10%) versus 84 of 167 (50.29%) (RR 0.39, 95% CI 0.07–2.12, *P* = 0.28) *(15, 29)*.

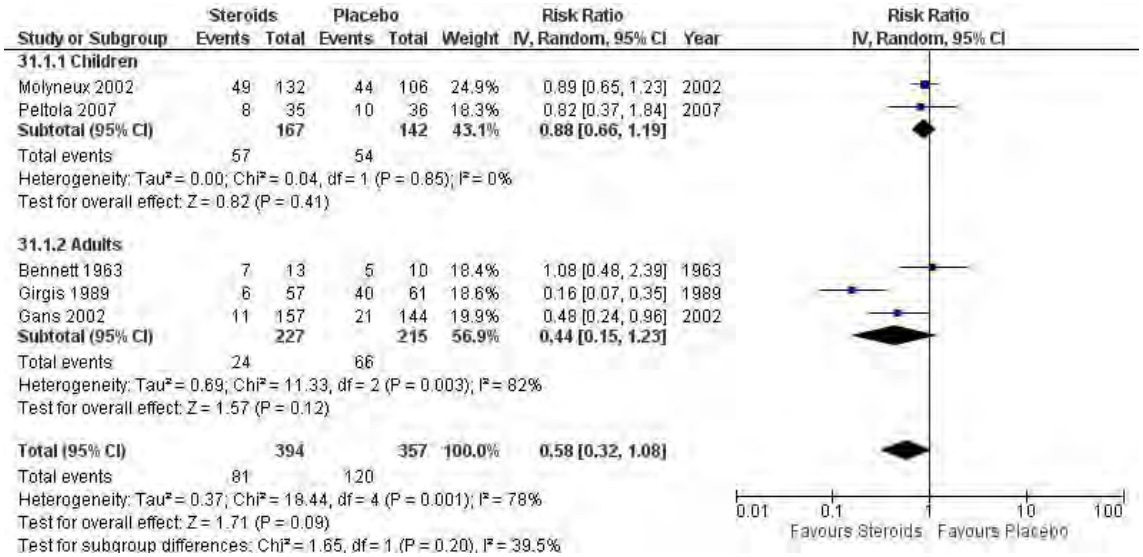
Fig. WA11.14 Risk ratios for all-cause mortality resulting from pneumococcal meningitis by World Bank income classification



b. By age group:

- In children, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 57 of 167 (34.13%) versus 54 of 142 (38.02%) (RR 0.88 with 95% CI 0.66–1.19, *P* = 0.41).
- In adults, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 24 of 227 (10.57%) versus 66 of 215 (30.69%) (RR 0.44 95% CI 0.15–1.23, *P* = 0.12) *(10, 15, 27)*.

Fig. WA11.15 Risk ratios for all-cause mortality resulting from pneumococcal meningitis by age group

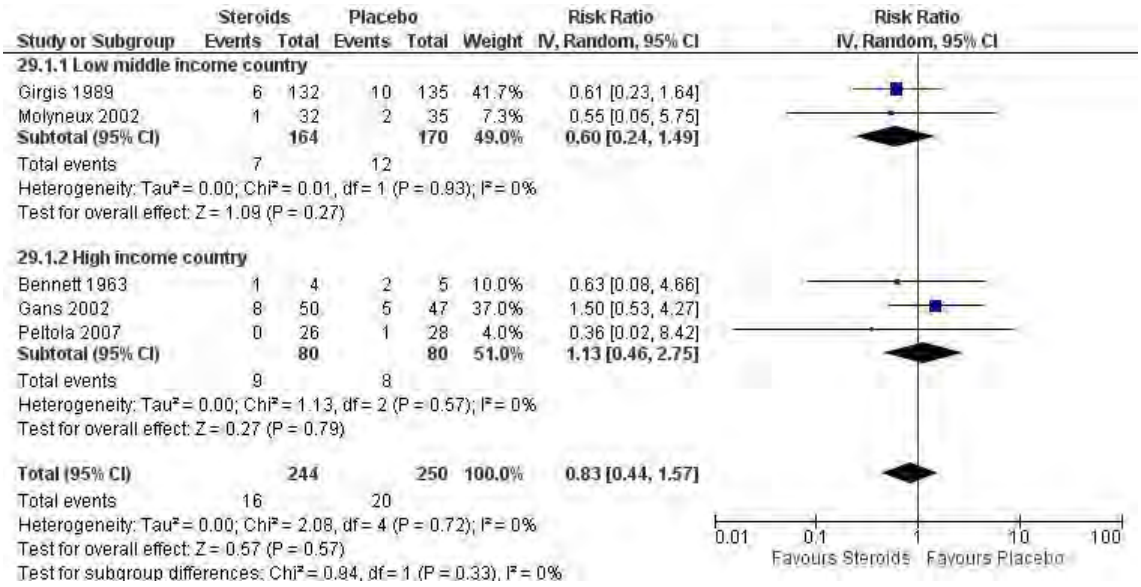


All-cause mortality resulting from meningococcal meningitis

a. By World Bank income classification:

- In HICs, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 9 of 80 (11.25%) versus 8 of 80 (10%) (RR 1.13 with 95% CI 0.46–2.75, *P* = 0.79) *(10, 27, 32)*.
- In LMICs, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 7 of 164 (4.26%) versus 12 of 170 (7.05%) (RR 0.60 95% CI 0.24–1.49, *P* = 0.27) *(15, 29)*.

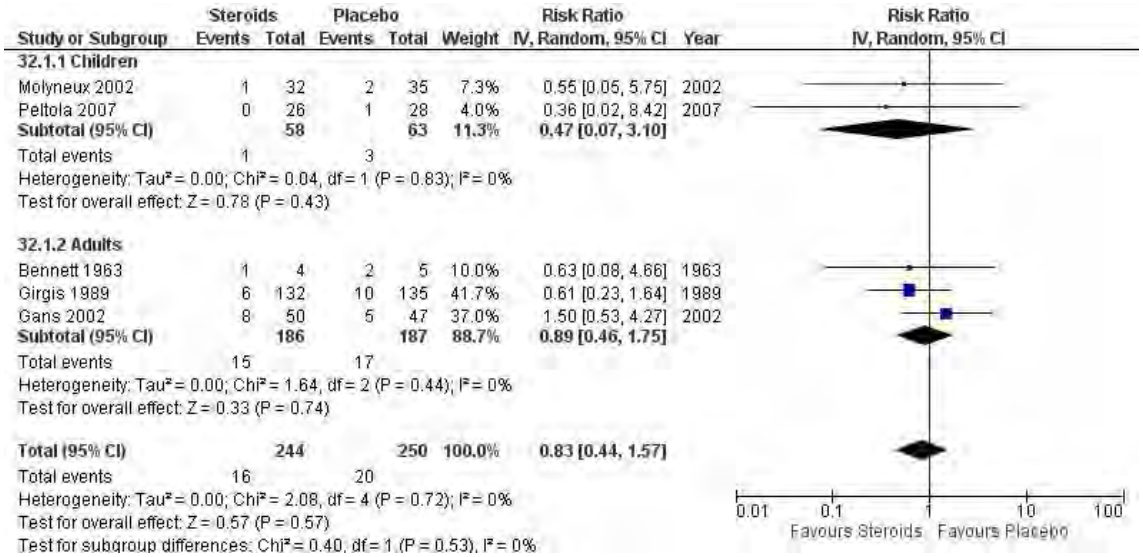
Fig. WA11.16 Risk ratios for all-cause mortality resulting from meningococcal meningitis by World Bank income classification



b. By age group:

- In children, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 1 of 58 (1.72%) versus 3 of 63 (4.76%) (RR 0.47 95% CI 0.07–3.10, P = 0.43) *(29, 32)*.
- In adults, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 15 of 186 (8.06%) versus 17 of 187 (9.09%), RR 0.89 95% CI 0.46–1.75, P = 0.74) *(10, 15, 27)*.

Fig. WA11.17 Risk ratios for all-cause mortality resulting from meningococcal meningitis by age group

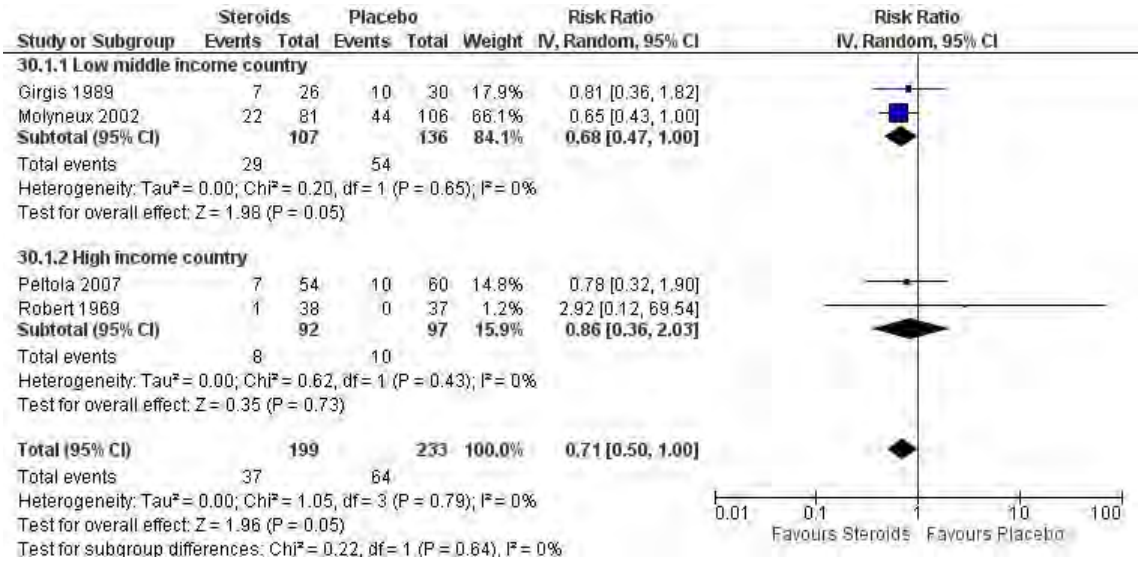


All-cause mortality resulting from *Haemophilus influenzae* type b (Hib) meningitis

a. By World Bank income classification:

- In HICs, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 8 of 92 (8.69%) versus 10 of 97 (10.30%), RR 0.86 95% CI 0.36–2.03, *P* = 0.73 *(11, 32)*.
- In LMICs, there was a statistically significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 29 of 107 (27.10%) versus 54 of 136 (39.70%) (RR 0.68 with 95% CI of 0.47–1.00, *P* = 0.05) *(15, 29)*.

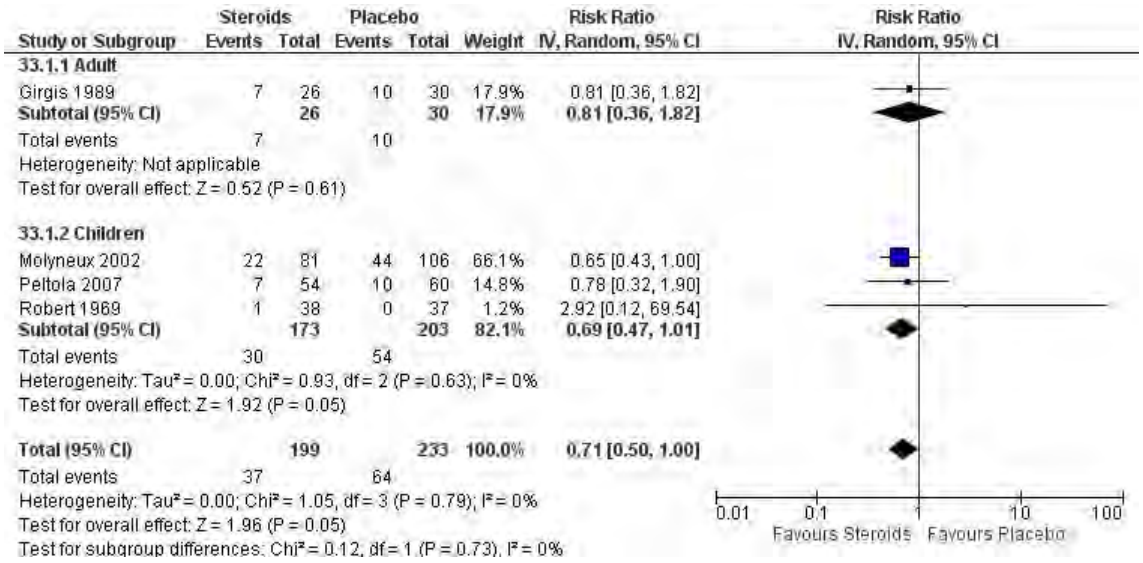
Fig. WA11.18 Risk ratios for all-cause mortality resulting from Hib meningitis by World Bank income classification



b. By age group:

- In adults, there was no significant difference in mortality in the group treated with corticosteroids compared to the placebo group. Mortality: 7 of 26 (26.92%) versus 10 of 30 (33.33%) (RR 0.81 with 95% CI of 0.36–1.82, P = 0.61) *(15).*
- In children, there was a statistically significant difference in mortality in the group treated with corticosteroids compared to placebo group. Mortality: 30 of 173 (17.34%) versus 54 of 203 (26.60%) (RR 0.69 95% CI 0.47–1.01, P = 0.05) *(11, 29, 32).*

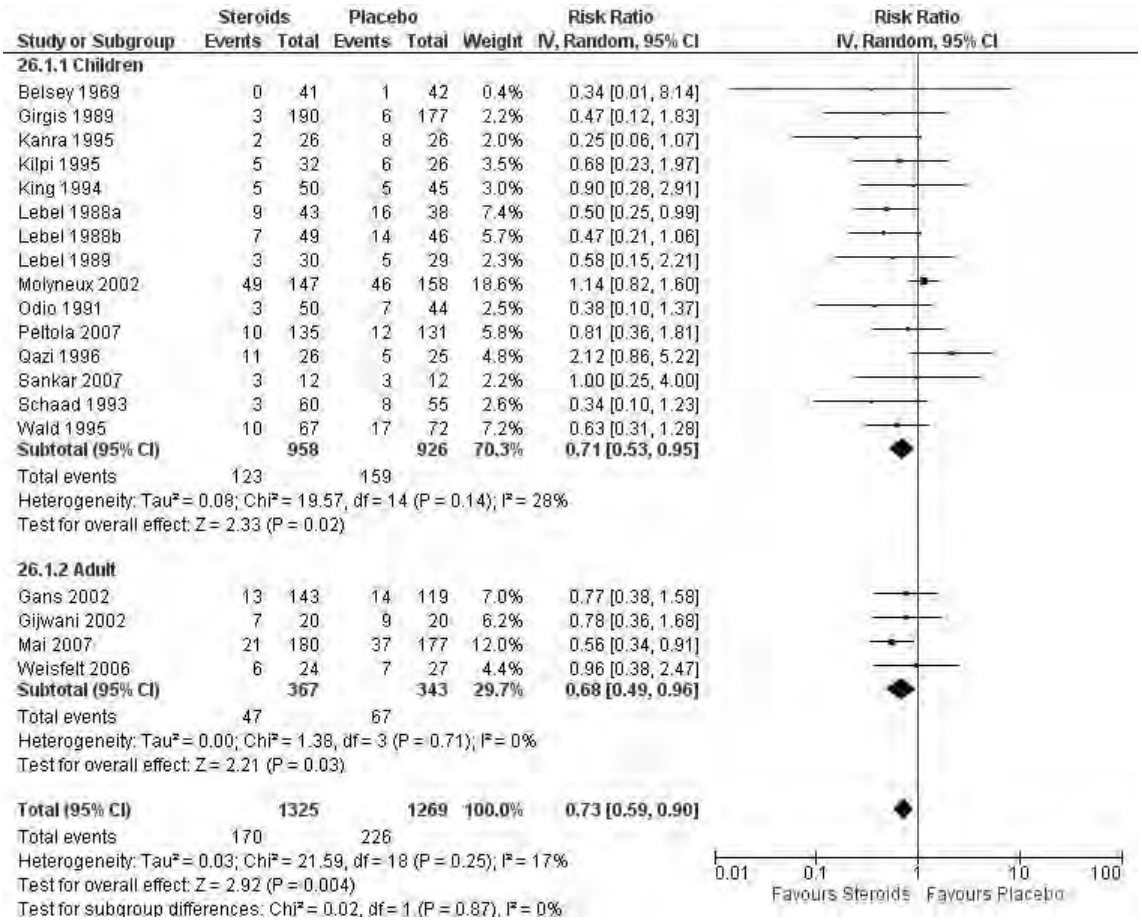
Fig. WA11.19 Risk ratios for all-cause mortality resulting from Hib meningitis by age group



Hearing loss in children and adults

- Moderate certainty evidence from 15 RCTs suggested that corticosteroid therapy probably reduced the risk of hearing loss in children (RR 0.71, 95% CI 0.53–0.95, *P* = 0.02) *(12, 14-19, 21-24, 29, 31, 32)*.
- Low certainty evidence from four RCTs suggested that adjunctive corticosteroid therapy may have reduced the risk of hearing loss in adults when compared to placebo (RR 0.68, 95% CI 0.49–0.96, *P* = 0.03) *(27, 28, 30, 33)*.

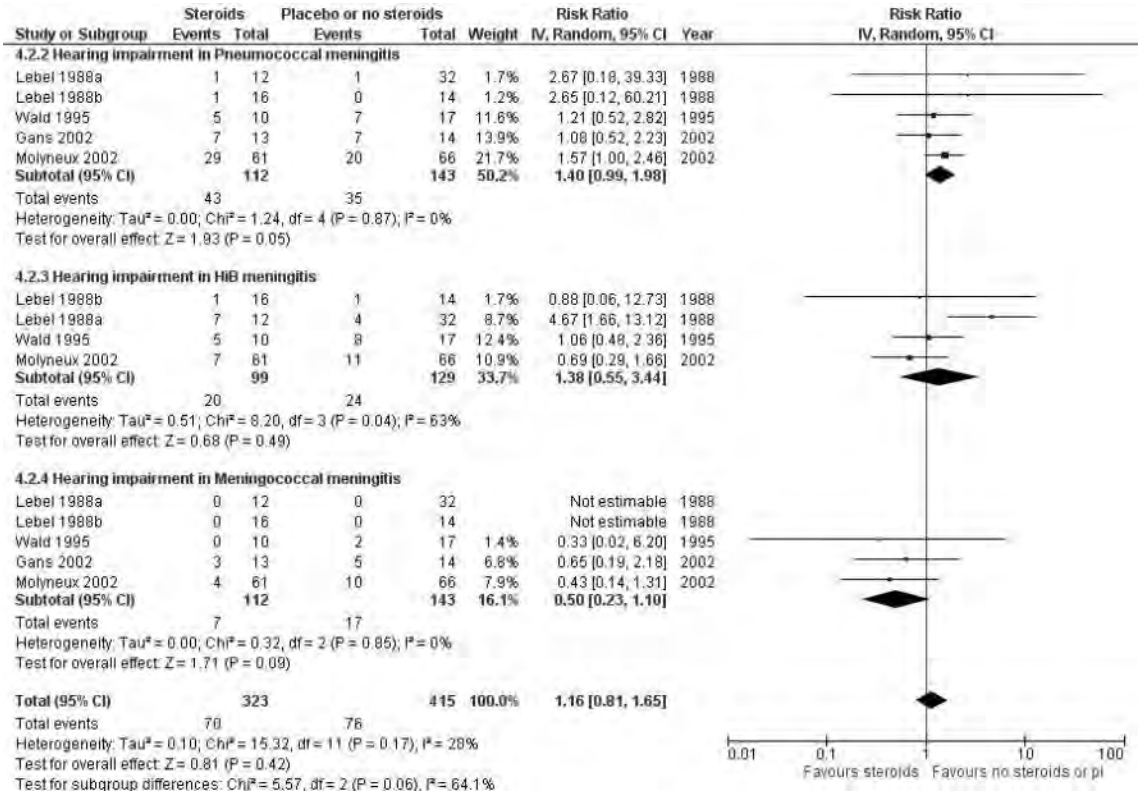
Fig. WA11.20 Risk ratios of developing hearing loss by age group



Hearing impairment by etiological organism

- Low certainty evidence from five RCTs suggested that adjunctive corticosteroid therapy may have increased the risk of hearing loss resulting from pneumococcal meningitis when compared to a placebo (RR 1.40, 95% CI 0.99–1.98, *P* = 0.05) *(14, 23, 27, 29)*.
- Low certainty evidence from five RCTs suggested that corticosteroid therapy may have had little to no effect on hearing loss resulting from meningococcal meningitis (RR 0.5, 95% CI 0.23–1.10, *P* = 0.09) *(14, 23, 27, 29)*.
- Very low certainty evidence from four RCTs suggested that the effect of corticosteroid therapy on hearing loss resulting from Hib meningitis was uncertain (RR 1.38, 95% CI 0.55–3.44, *P* = 0.49) *(14, 23, 29)*.

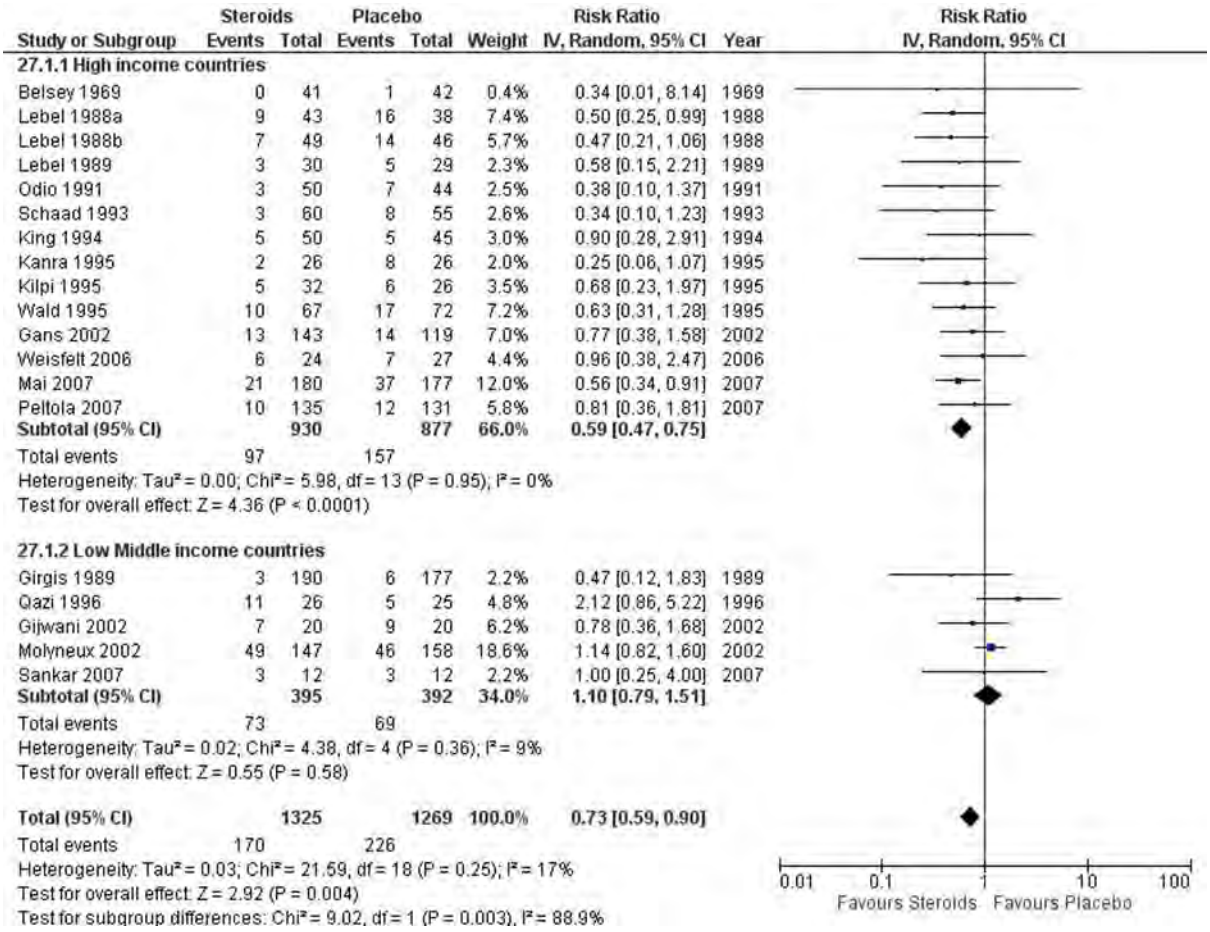
Fig. WA11.21 Risk ratios of developing hearing loss by etiological organism



Hearing impairment by World Bank income classification

- Moderate certainty evidence from 14 RCTs suggested that adjunctive corticosteroid therapy likely reduced the risk of hearing loss in HICs when compared to placebo (RR 0.59, 95% CI 0.47–0.75, *P* < 0.0001) *(12, 14, 16-19, 21-23, 27, 30, 32, 33)*.
- Low certainty evidence from five RCTs suggested that corticosteroid therapy may have had little to no effect on hearing loss in LMICs (RR 1.10, 95%, CI 0.79–1.51, *P* = 0.58) *(15, 24, 28, 29, 31)*.

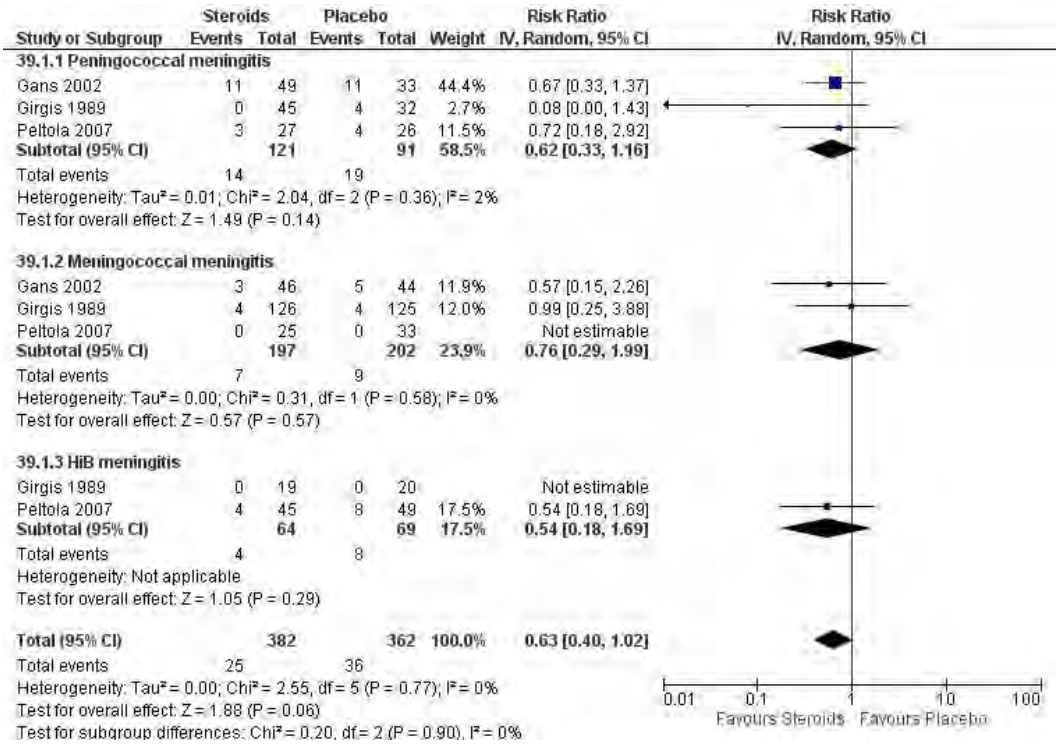
Fig. WA11.22 Risk ratios of developing hearing loss by World Bank income classification



Neurological sequelae by etiological organism

- Low certainty evidence from three RCTs suggested that corticosteroid treatment at admission may have had little to no effect on the development of neurological sequelae resulting from pneumococcal meningitis compared with a placebo (RR 0.62 and 95% CI of 0.33–1.16, *P* = 0.14) *(15, 27, 32)*.
- Low certainty evidence from three RCTs suggested that corticosteroid treatment at admission may have had little to no effect on the development of neurological sequelae resulting from meningococcal meningitis compared with a placebo (RR 0.76, 95% CI 0.29–1.99, *P* = 0.57) *(15, 27, 32)*.
- Very low certainty evidence from two RCTs suggested that the effect of corticosteroid treatment on the development of neurological sequelae resulting from Hib meningitis at admission compared with placebo was uncertain (RR 0.54, 95% CI 0.18–1.69, *P* = 0.29) *(15, 32)*.

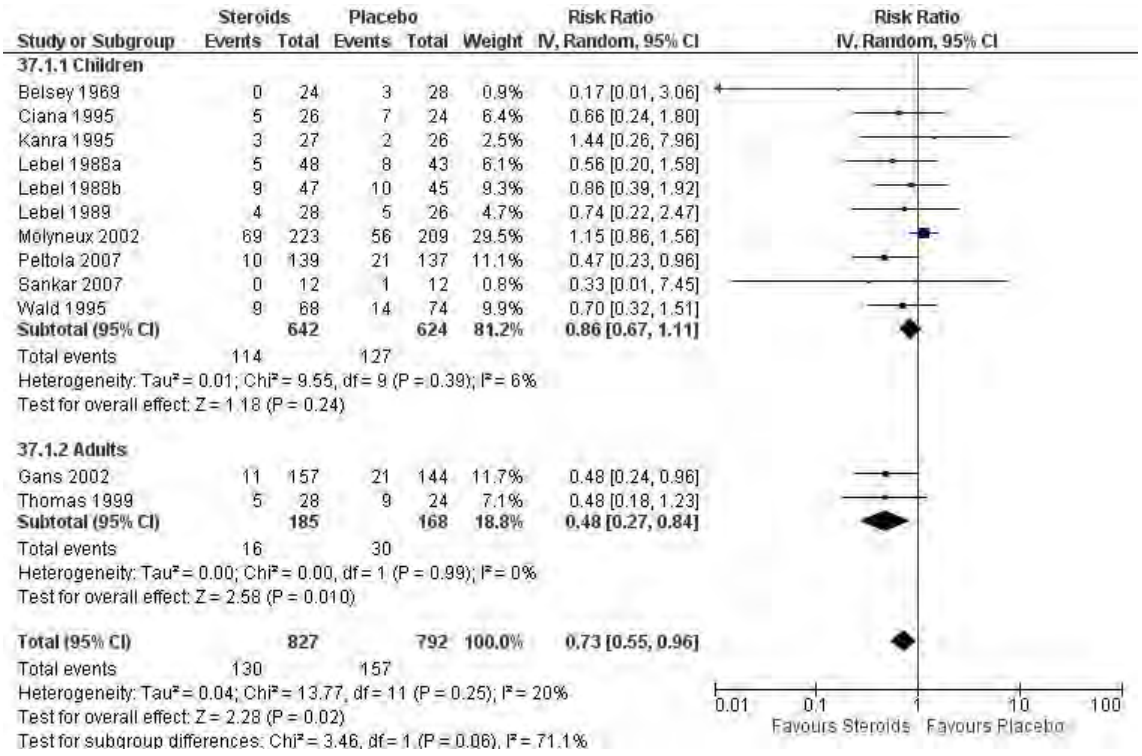
Fig. WA11.23 Risk ratios of developing neurological sequelae by etiological organism



Short-term neurological sequelae by age group

- Low certainty evidence from two RCTs suggested that adjunctive corticosteroid therapy may have reduced the risk of short-term neurological sequelae in adults (compared to placebo) (RR 0.48, 95% CI of 0.27–0.84, *P* = 0.01) *(26, 27)*.
- Low certainty evidence from 10 RCTs suggested that corticosteroid therapy may have had little to no effect on short-term neurological sequelae in children (RR 0.86,95% CI 0.67–1.11, *P* = 0.24) *(12, 14, 16, 20, 21, 23, 29, 31, 32)*.

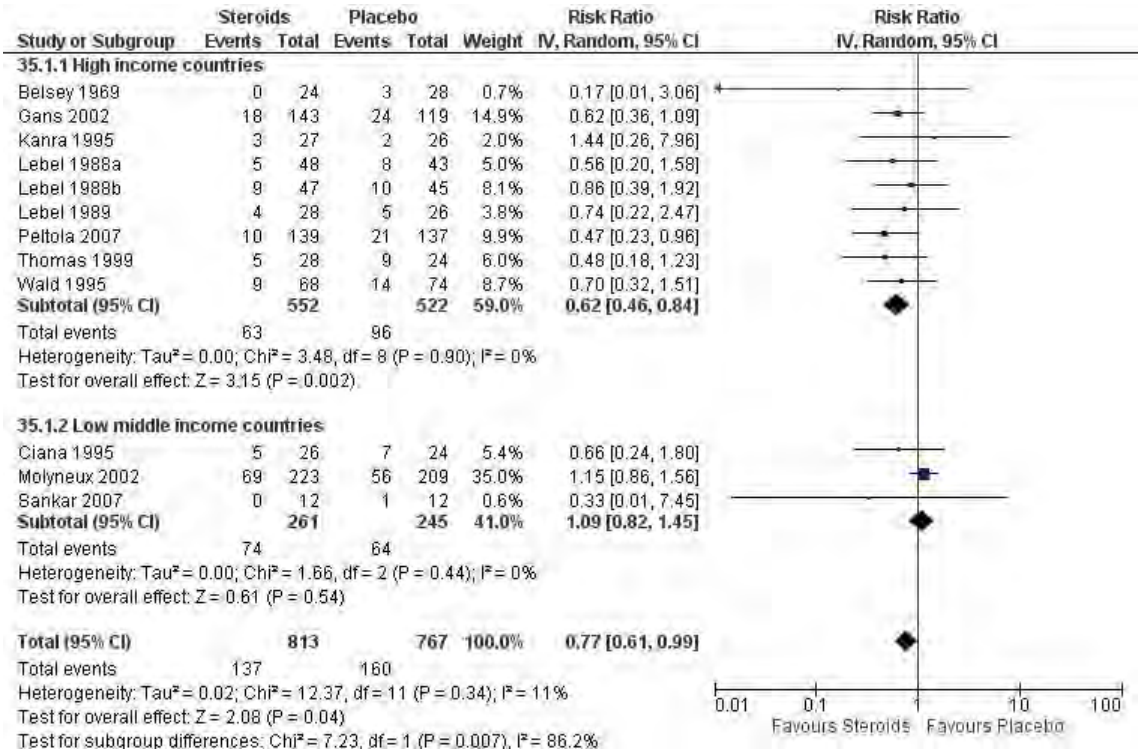
Fig. WA11.24 Risk ratios of developing short-term neurological sequelae by age group



Short-term neurological sequelae by World Bank income classification

- Moderate certainty evidence from nine RCTs suggested that adjunctive corticosteroid therapy likely reduced the risk of short-term neurological sequelae in HICs (compared to placebo) (RR 0.62, 95% CI 0.46–0.84, *P* = 0.002) *(12, 14, 16, 21, 23, 26, 27, 32)*.
- Moderate certainty evidence from five RCTs suggested that corticosteroid therapy likely had little to no effect on short-term neurological sequelae in LMICs (RR 1.09, 95% CI 0.82–1.45, *P* = 0.54) *(20, 29, 31)*.

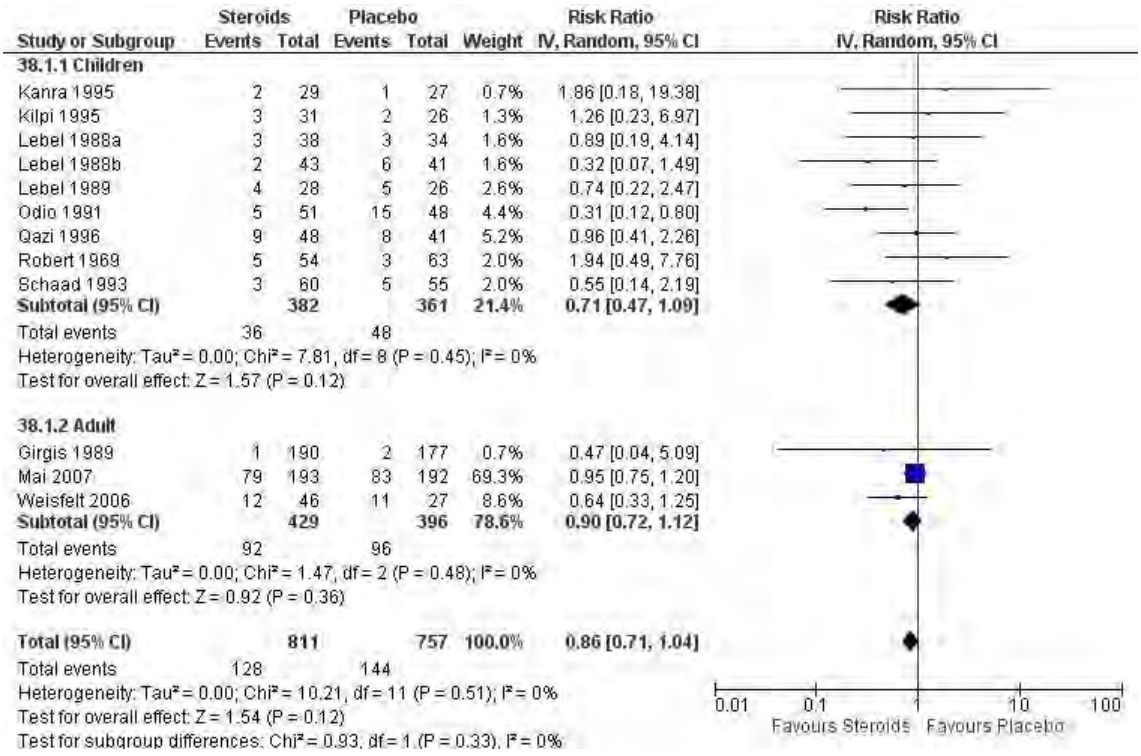
Fig. WA11.25 Risk ratios of developing short-term neurological sequelae by World Bank income classification



Long-term neurological sequelae by age group

- Low certainty evidence from nine RCTs suggested that corticosteroid therapy may have had little to no effect on long-term neurological sequelae in children (RR 0.71, 95% CI 0.47–1.09, *P* = 0.12) *(11, 14, 16-18, 21, 22, 24)*.
- Low certainty evidence from three RCTs suggested that adjunctive corticosteroid therapy may have had little to no effect on long-term neurological sequelae in adults when compared to placebo (RR 0.90, 95% CI 0.72–1.12, *P* = 0.36) *(15, 30, 33)*.

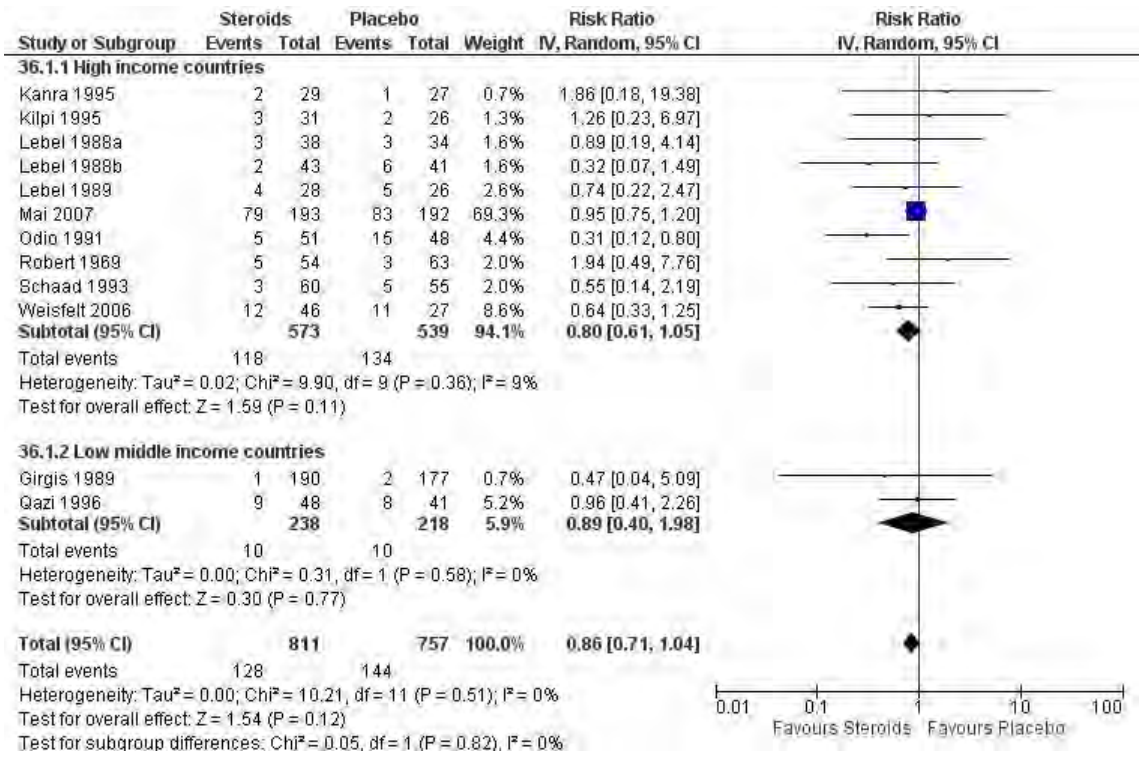
Fig. WA11.26 Risk ratios of developing long-term neurological sequelae by age group



Long-term neurological sequelae by World Bank income classification

- Low certainty evidence from 10 RCTs suggested that adjunctive corticosteroid therapy may have had little to no effect on long-term neurological sequelae in HICs when compared to placebo (RR 0.80, 95% CI 0.61–1.05, P = 0.11) *(14, 16, 21, 22, 33)*.
- Low certainty evidence from two RCTs suggested that corticosteroid therapy may have had little to no effect on long-term neurological sequelae in LMICs (RR 0.89, 95% CI 0.40–1.98, P = 0.77) *(15, 24)*.

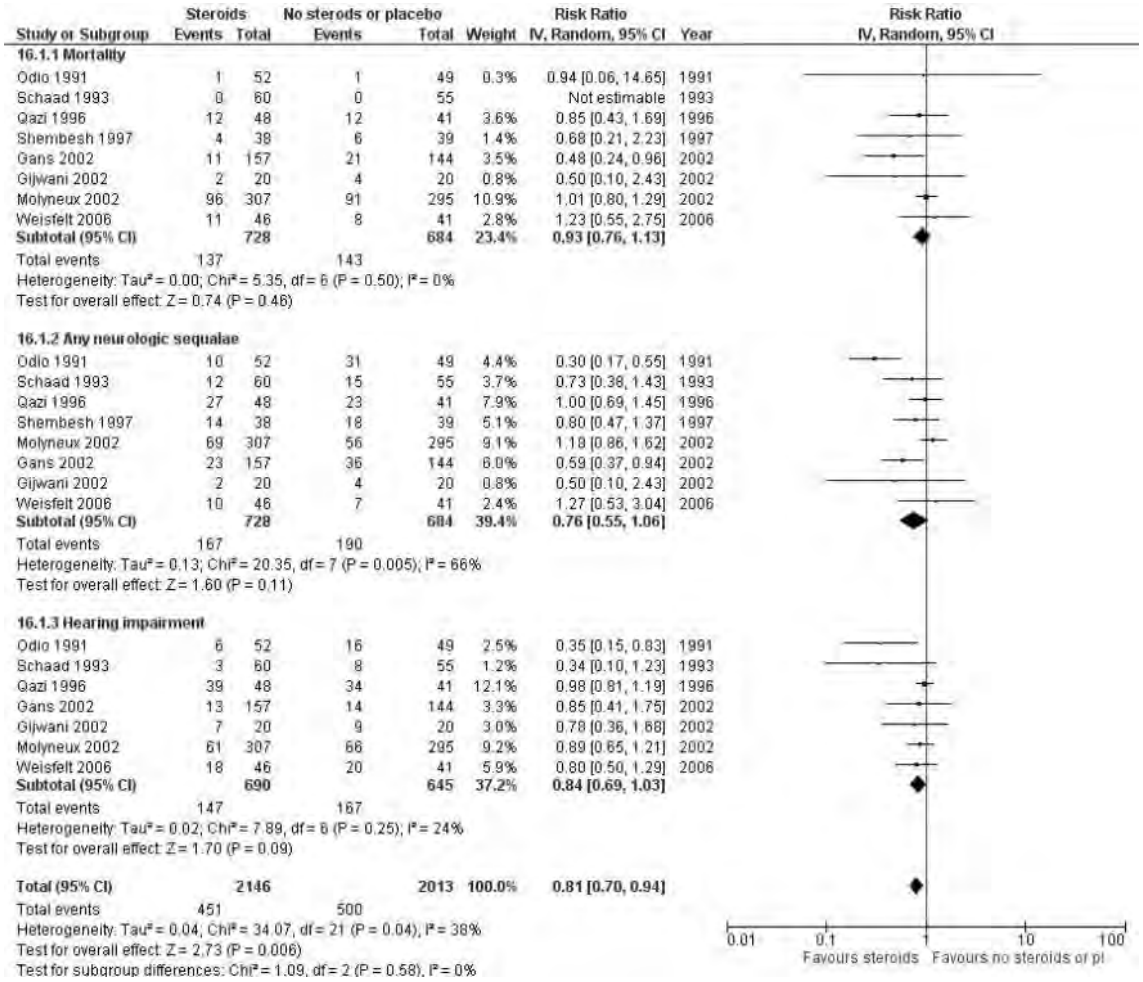
Fig. WA11.27 Risk ratios of developing long-term neurological sequelae by World Bank income classification



Outcomes when corticosteroids were given prior to antibiotics

- Low certainty evidence from seven RCTs suggested that corticosteroid treatment may have had little to no effect on mortality when corticosteroids were given prior to antibiotics, compared with placebo (RR 0.93, 95% CI 0.76–1.13, *P* = 0.46) *(17, 18, 24, 25, 27, 28, 30)*.
- Very low certainty evidence from eight RCTs suggested that the effect of corticosteroid treatment on outcomes of neurological sequelae when corticosteroids were given prior to antibiotics, compared with placebo, was uncertain (RR 0.76, 95% CI 0.55–1.06, *P* = 0.11) *(17, 18, 24, 25, 27-30)*.
- Low certainty evidence from eight RCTs suggested that corticosteroid treatment may have had little to no effect on hearing loss when corticosteroids were given prior to antibiotics, compared with placebo (RR 0.84, 95% CI 0.69–1.03, *P* = 0.09) *(17, 18, 24, 27-30)*.

Fig. WA11.28 Risk ratios of mortality, any neurological sequelae and hearing impairment when corticosteroids were given prior to antibiotics



3.4 GRADE evidence profile

This section presents the GRADE evidence profiles of the studies included in this review (see Table WA11.3).

Table WA11.3 GRADE evidence profiles

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
26	RCT	Not serious	Not serious	Not serious	Very serious	Undetected	204	203	0.80 (0.65 to 0.98)	125 per 1000 (102 to 153)	Moderate	Critical
Any hearing loss												
19	RCT	Not serious	Not serious	Not serious	Not serious	NA	1325	1269	0.66 (0.51 to 0.86)	118 per 1000 (91 to 153)	High	Critical
Severe hearing loss												
10	RCT	Serious	Serious	Not serious	Serious	Publication bias suspected	127	227	1.42 (0.91 to 2.23)	388 per 1000 (249 to 609)	Very low	Critical

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
Short-term neurological sequelae (i.e. within 6 weeks of discharge)												
12	RCT	Serious	Not serious	Not serious	Serious	NA	813	767	0.77 (0.61 to 0.99)	161 per 1000 (127 to 207)	Low	Critical
Long-term neurological sequelae (i.e. after 6 weeks to 12 months of discharge)												
12	RCT	Serious	Serious	Not serious	Serious	NA	811	757	0.86 (0.71 to 1.04)	164 per 1000 (135 to 198)	Very low	Critical
Post-meningitis epilepsy												
8	RCT	Very serious	Not serious	Not serious	Not serious	NA	594	567	0.55 (0.34 to 0.89)	61 per 1000 (38 to 99)	Low	Critical
Ataxia												
6	RCT	Very serious	Not serious	Not serious	Serious	NA	520	489	0.82 (0.56 to 1.20)	79 per 1000 (54 to 115)	Very low	Critical
Hydrocephalus												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
8	RCT	Very serious	Very serious	Not serious	Not serious	NA	629	606	0.53 (0.31 to 0.90)	34 per 1000 (20 to 58)	Very low	Critical
Mortality resulting from pneumococcal meningitis												
5	RCT	Not serious	Serious	Not serious	Serious	NA	394	357	0.58 (0.32 to 1.08)	195 per 1000 (108 to 363)	Low	Critical
Mortality resulting from meningococcal meningitis												
5	RCT	Not serious	Not serious	Not serious	Serious	NA	244	248	0.83 (0.44 to 1.57)	66 per 1000 (35 to 126)	Moderate	Critical
Mortality resulting from Haemophilus influenzae meningitis												
4	RCT	Not serious	Not serious	Not serious	Not serious	NA	199	233	0.71 (0.50 to 1.00)	195 per 1000 (137 to 275)	High	Critical
Mortality outcomes when steroids were administered prior to antibiotics												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
7	RCT	Serious	Not serious	Not serious	Serious	NA	728	684	0.93 (0.76 to 1.13)	217 per 1000 (159 to 236)	Low	Critical
Hearing loss when steroids were administered prior to antibiotics												
8	RCT	Serious	Not serious	Not serious	Serious	NA	690	645	0.84 (0.69 to 1.03)	217 per 1000 (169 to 234)	Low	Critical
Neurological sequelae when steroids were administered prior to antibiotics												
8	RCT	Serious	Serious	Not serious	Serious	NA	728	684	0.76 (0.55 to 1.06)	211 per 1000 (153 to 294)	Very low	Critical
Hearing loss resulting from pneumococcal meningitis												
5	RCT	Serious	Not serious	Not serious	Serious	NA	112	143	1.40 (0.99 to 1.98)	343 per 1000 (242 to 485)	Low	Critical
Hearing loss resulting from Hib meningitis												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
4	RCT	Serious	Very serious	Not serious	Very serious	NA	99	129	1.38 (0.55 to 3.44)	257 per 1000 (102 to 640)	Very low	Critical
Hearing loss resulting from meningococcal meningitis												
5	RCT	Serious	Not serious	Not serious	Serious	NA	112	143	0.50 (0.23 to 1.10)	59 per 1000 (27 to 131)	Low	Critical
Neurological sequelae resulting from pneumococcal meningitis												
3	RCT	Serious	Not serious	Not serious	Serious	NA	121	91	0.62 (0.3 to 1.16)	129 per 1000 (69 to 242)	Low	Critical
Neurological sequelae resulting from Hib meningitis												
2	RCT	Serious	Very serious	Not serious	Serious	NA	64	69	0.54 (0.18 to 1.69)	63 per 1000 (21 to 196)	Very low	Critical
Neurological sequelae resulting from meningococcal meningitis												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
3	RCT	Serious	Not serious	Not serious	Serious	NA	197	202	0.76 (0.29 to 1.99)	34 per 1000 (13 to 89)	Low	Critical
Mortality outcomes in children												
17	RCT	Serious	Not serious	Not serious	Serious	NA	1217	1190	0.95 (0.79 to 1.14)	137 per 1000 (114 to 164)	Low	Critical
Mortality outcomes in adults												
8	RCT	Serious	Serious	Not serious	Not serious	NA	817	818	0.61 (0.42 to 0.88)	109 per 1000 (75 to 157)	Low	Critical
Hearing loss in children												
15	RCT	Serious	Not serious	Not serious	Not serious	NA	958	926	0.71 (0.53 to 0.95)	122 per 1000 (91 to 163)	Moderate	Critical
Hearing loss in adults												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
4	RCT	Serious	Not serious	Not serious	Serious	NA	367	343	0.73 (0.59 to 0.90)	143 per 1000 (115 to 176)	Low	Critical
Short-term neurological sequelae in children												
10	RCT	Serious	Not serious	Not serious	Serious	NA	642	624	0.89 (0.67 to 1.11)	181 per 1000 (136 to 226)	Low	Critical
Short-term neurological sequelae in adults												
2	RCT	Not serious	Not serious	Not serious	Very serious	NA	185	168	0.48 (0.27 to 0.84)	86 per 1000 (48 to 150)	Low	Critical
Long-term neurological sequelae in children												
9	RCT	Serious	Not serious	Not serious	Serious	NA	382	361	0.71 (0.47 to 1.09)	94 per 1000 (62 to 145)	Low	Critical
Long-term neurological sequelae in adults												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
3	RCT	Serious	Not serious	Not serious	Serious	NA	429	396	0.90 (0.72 to 1.12)	218 per 1000 (175 to 276)	Low	Critical
Mortality outcomes in HICs												
17	RCT	Serious	Not serious	Not serious	Serious	NA	1177	1158	0.84 (0.66 to 1.07)	83 per 1000 (66 to 106)	Low	Critical
Mortality outcomes in LMICs												
9	RCT	Serious	Serious	Not serious	Serious	NA	946	955	0.75 (0.51 to 1.12)	169 per 1000 (115 to 252)	Very low	Critical
Hearing loss in HICs												
14	RCT	Serious	Not serious	Not serious	Not serious	NA	395	392	0.59 (0.47 to 0.75)	106 per 1000 (86 to 134)	Moderate	Critical
Hearing loss in LMICs												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
5	RCT	Serious	Not serious	Not serious	Serious	NA	946	955	1.10 (0.79 to 1.51)	194 per 1000 (139 to 266)	Low	Critical
Short-term neurological sequelae in HICs												
9	RCT	Serious	Not serious	Not serious	Not serious	NA	552	522	0.62 (0.46 to 0.84)	114 per 1000 (85 to 154)	Moderate	Critical
Short-term neurological sequelae in LMICs												
5	RCT	Not serious	Not serious	Not serious	Serious	NA	261	245	1.09 (0.82 to 1.45)	285 per 1000 (214 to 379)	Moderate	Critical
Long-term neurological sequelae in HICs												
10	RCT	Serious	Not serious	Not serious	Serious	NA	573	539	0.80 (0.61 to 1.05)	199 per 1000 (152 to 261)	Low	Critical
Long-term neurological sequelae in LMICs												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
2	RCT	Serious	Not serious	Not serious	Serious	NA	238	218	0.89 (0.40 to 1.98)	41 per 1000 (18 to 91)	Low	Critical
Mortality outcomes when steroids were administered prior to antibiotics												
7	RCT	Serious	Not serious	Not serious	Serious	-	728	684	0.93 (0.76 to 1.13)	217 per 1000 (159 to 236)	Low	Critical
Hearing loss when steroids were administered prior to antibiotics												
8	RCT	Serious	Not serious	Not serious	Serious	NA	690	645	0.84 (0.69 to 1.03)	217 per 1000 (169 to 234)	Low	Critical
Neurological sequelae when steroids were administered prior to antibiotics												
8	RCT	Serious	Serious	Not serious	Serious	NA	728	684	0.76 (0.55 to 1.06)	211 per 1000 (153 to 294)	Very low	Critical
Adverse events												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
21	RCT	Serious	Not serious	Not serious	Serious	NA	728	684	1.26 (0.93 to 1.70)	49 per 1000 (36 to 67)	Very low	Critical
Gastrointestinal bleeding												
15	RCT	Serious	Not serious	Not serious	Serious	NA	1047	1009	1.64 (0.94 to 2.89)	34 per 1000 (20 to 60)	Low	Critical
Herpes zoster infection												
5	RCT	Serious	Not serious	Not serious	Serious	NA	486	481	1.13 (0.76 to 1.68)	94 per 1000 (63 to 140)	Low	Critical
Arthritis												
6	RCT	Serious	Not serious	Not serious	Serious	NA	314	305	0.68 (0.18 to 2.63)	25 per 1000 (6 to 95)	Low	Critical

4. From evidence to recommendations

4.1 Summary of findings

Table WA11.4 summarizes the findings of this evidence synthesis.

Table WA11.4 Summary of findings: steroids compared to placebo in the treatment of meningitis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Mortality	156 per 1000	125 per 1000 (102 to 153)	**RR 0.80** (0.65 to 0.98)	4236 (26 RCTs)	⊕⊕⊕◯ Moderate[a]	Steroids probably reduced mortality slightly.
Any hearing impairment	178 per 1000	118 per 1000 (91 to 153)	**RR 0.66** (0.51 to 0.86)	2594 (19 RCTs)	⊕⊕⊕⊕ High[a,b]	Steroids likely resulted in a slight reduction in any hearing impairment.
Severe hearing impairment	273 per 1000	388 per 1000 (249 to 609)	**RR 1.42** (0.91 to 2.23)	354 (10 RCTs)	⊕◯◯◯ Very low[a,c,d,e]	Steroids may have increased/had little to no effect on severe hearing loss but the evidence was very uncertain.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Short-term neurological sequelae	209 per 1000	161 per 1000 (127 to 207)	**RR 0.77** (0.61 to 0.99)	1580 (12 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have resulted in a slight reduction in short-term neurological sequelae.
Long-term neurological sequelae	190 per 1000	164 per 1000 (135 to 198)	**RR 0.86** (0.71 to 1.04)	1568 (12 RCTs)	⊕◯◯◯ Very low[c,d]	The evidence was very uncertain about the effect of steroids on long-term neurological sequelae.
Post-meningitis epilepsy	111 per 1000	61 per 1000 (38 to 99)	**RR 0.55** (0.34 to 0.89)	1161 (8 RCTs)	⊕⊕◯◯ Low[c]	The evidence suggested that steroids reduced post-meningitis epilepsy.
Ataxia	96 per 1000	79 per 1000 (54 to 115)	**RR 0.82** (0.56 to 1.20)	1009 (6 RCTs)	⊕◯◯◯ Very low[a,f]	The evidence about the effect of steroids on ataxia was very uncertain.
Hydrocephalus	64 per 1000	34 per 1000 (20 to 58)	**RR 0.53** (0.31 to 0.90)	1235 (8 RCTs)	⊕◯◯◯ Very low[b,c]	Steroids may have reduced/had little to no effect on hydrocephalus but the evidence was very uncertain.
Mortality resulting from pneumococcal meningitis	336 per 1000	195 per 1000 (108 to 363)	**RR 0.58** (0.32 to 1.08)	751 (5 RCTs)	⊕⊕◯◯ Low[a,b]	The evidence suggested that steroids did not reduce mortality resulting from pneumococcal meningitis.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Mortality resulting from meningococcal meningitis	80 per 1000	66 per 1000 (35 to 126)	**RR 0.83** (0.44 to 1.57)	494 (5 RCTs)	⊕⊕⊕◯ Moderate[d]	Steroids probably had little to no effect on mortality resulting from meningococcal meningitis.
Mortality resulting from *Haemophilus influenzae* meningitis	275 per 1000	195 per 1000 (137 to 275)	**RR 0.71** (0.50 to 1.00)	432 (4 RCTs)	⊕⊕⊕⊕ High	Steroids had little to no effect on mortality resulting from *Haemophilus influenzae* meningitis.
Hearing loss resulting from pneumococcal meningitis	245 per 1000	343 per 1000 (242 to 485)	**RR 1.40** (0.99 to 1.98)	255 (5 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids did not decrease hearing loss resulting from pneumococcal meningitis.
Hearing loss resulting from meningococcal meningitis	119 per 1000	59 per 1000 (27 to 131)	**RR 0.50** (0.23 to 1.10)	255 (5 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on hearing loss resulting from meningococcal meningitis.
Hearing loss resulting from Hib meningitis	186 per 1000	257 per 1000 (102 to 640)	**RR 1.38** (0.55 to 3.44)	228 (4 RCTs)	⊕◯◯◯ Very low[a,c,d]	The evidence was very uncertain about the effect of steroids on hearing loss resulting from Hib meningitis.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Neurological sequelae resulting from pneumococcal meningitis	209 per 1000	129 per 1000 (69 to 242)	**RR 0.62** (0.33 to 1.16)	212 (3 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on neurological sequelae resulting from pneumococcal meningitis.
Neurological sequelae resulting from meningococcal meningitis	45 per 1000	34 per 1000 (13 to 89)	**RR 0.76** (0.29 to 1.99)	399 (3 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on neurological sequelae resulting from meningococcal meningitis.
Neurological sequelae resulting from Hib meningitis	116 per 1000	63 per 1000 (21 to 196)	**RR 0.54** (0.18 to 1.69)	133 (2 RCTs)	⊕◯◯◯ Very low[a,c,d]	The evidence about the effect of steroids on neurologic sequelae resulting from Hib meningitis was very uncertain.
Mortality outcomes when steroids were administered before antibiotics	209 per 1000	194 per 1000 (159 to 236)	**RR 0.93** (0.76 to 1.13)	1412 (7 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids had little to no effect on mortality outcomes when steroids were administered before antibiotics.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Neurological sequelae when steroids were administered before antibiotics	278 per 1000	211 per 1000 (153 to 294)	**RR 0.76** (0.55 to 1.06)	1412 (8 RCTs)	⊕◯◯◯ Very low[a,c,d]	Steroids may have reduced or had little to no effect on neurological sequelae when steroids were administered before antibiotics but the evidence was very uncertain.
Hearing loss sequelae when steroids were administered before antibiotics	259 per 1000	217 per 1000 (179 to 267)	**RR 0.84** (0.69 to 1.03)	1335 (8 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have resulted in little to no difference in hearing loss sequelae when steroids were administered before antibiotics.
Mortality outcomes in children	144 per 1000	137 per 1000 (114 to 164)	**RR 0.95** (0.79 to 1.14)	2407 (17 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids did not reduce mortality outcomes in children.
Mortality outcomes in adults	178 per 1000	109 per 1000 (75 to 157)	**RR 0.61** (0.42 to 0.88)	1635 (8 RCTs)	⊕⊕◯◯ Low[a,c]	Steroids may have reduced mortality outcomes in adults.
Hearing loss in children	172 per 1000	122 per 1000 (91 to 163)	**RR 0.71** (0.53 to 0.95)	1884 (15 RCTs)	⊕⊕⊕◯ Moderate[c]	Steroids likely reduced hearing loss in children slightly.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Hearing loss in adults	195 per 1000	143 per 1000 (115 to 176)	**RR 0.73** (0.59 to 0.90)	710 (4 RCTs)	⊕⊕◯◯ Low[c,g]	The evidence suggested that steroids resulted in a slight reduction in hearing loss in adults.
Short-term neurological sequelae in children	204 per 1000	181 per 1000 (136 to 226)	**RR 0.89** (0.67 to 1.11)	1266 (10 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on short-term neurological sequelae in children.
Short-term neurological sequelae in adults	179 per 1000	86 per 1000 (48 to 150)	**RR 0.48** (0.27 to 0.84)	353 (2 RCTs)	⊕⊕◯◯ Low[g]	Steroids may have reduced short-term neurological sequelae in adults.
Long-term neurological sequelae in children	133 per 1000	94 per 1000 (62 to 145)	**RR 0.71** (0.47 to 1.09)	743 (9 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on long-term neurological sequelae in children.
Long-term neurological sequelae in adults	242 per 1000	218 per 1000 (175 to 272)	**RR 0.90** (0.72 to 1.12)	825 (3 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on long-term neurological sequelae in adults.
Hearing loss in HICs	179 per 1000	106 per 1000 (84 to 134)	**RR 0.59** (0.47 to 0.75)	1807 (14 RCTs)	⊕⊕⊕◯ Moderate[c]	Steroids likely reduced hearing loss in HICs.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Hearing loss in LMICs	176 per 1000	194 per 1000 (139 to 266)	**RR 1.10** (0.79 to 1.51)	787 (5 RCTs)	⊕⊕◯◯ Low[c,d]	Steroids may have had little to no effect on hearing loss in LMICs.
Short-term neurological sequelae in HICs	184 per 1000	114 per 1000 (85 to 154)	**RR 0.62** (0.46 to 0.84)	1074 (9 RCTs)	⊕⊕⊕◯ Moderate[c]	The evidence suggested that steroids likely reduced short-term neurological sequelae in HICs.
Short-term neurological sequelae in LMICs	261 per 1000	285 per 1000 (214 to 379)	**RR 1.09** (0.82 to 1.45)	506 (3 RCTs)	⊕⊕⊕◯ Moderate[d]	The evidence suggested that steroids may have had little to no effect on short-term neurological sequelae in LMICs.
Long-term neurological sequelae in HICs	249 per 1000	199 per 1000 (152 to 261)	**RR 0.80** (0.61 to 1.05)	1112 (10 RCTs)	⊕⊕◯◯ Low[b,c]	The evidence suggested that steroids had little to no effect on long-term neurological sequelae in HICs.
Long-term neurological sequelae in LMICs	46 per 1000	41 per 1000 (18 to 91)	**RR 0.89** (0.40 to 1.98)	456 (2 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids did not reduce long-term neurological sequelae in LMICs.
Mortality in HICs	99 per 1000	83 per 1000 (66 to 106)	**RR 0.84** (0.66 to 1.07)	2335 (14 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids had little to no effect on mortality in HICs.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with steroids				
Mortality in LMICs	225 per 1000	169 per 1000 (115 to 252)	**RR 0.75** (0.51 to 1.12)	1901 (9 RCTs)	⊕◯◯◯ Very low[a,c,d]	The evidence was very uncertain about the effect of steroids on mortality in LMICs.
Adverse events	39 per 1000	49 per 1000 (36 to 67)	**RR 1.26** (0.93 to 1.70)	3943 (21 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids did not increase adverse events.
Gastrointestinal bleeding	21 per 1000	34 per 1000 (20 to 60)	**RR 1.64** (0.94 to 2.89)	2056 (15 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids did not increase gastrointestinal bleeding.
Herpes zoster infection	83 per 1000	94 per 1000 (63 to 140)	**RR 1.13** (0.76 to 1.68)	967 (5 RCTs)	⊕⊕◯◯ Low[c,d]	The evidence suggested that steroids did not increase the occurrence of herpes zoster infection.
Arthritis	36 per 1000	25 per 1000 (6 to 95)	**RR 0.68** (0.18 to 2.63)	619 (6 RCTs)	⊕⊕◯◯ Low[b,c]	The evidence suggested that steroids had little to no effect on the occurrence of arthritis.

***** The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; Hib: *Haemophilus influenzae* type b; HICs: high-income countries; LMICs: low- and middle-income countries; RR: risk ratio.
[a] Heterogeneity noted across the studies as a result of visual inspection and I^2 tests.
[b] Wide CIs probably due to heterogeneity.
[c] Serious risk of bias noted across the studies included.

[d] Wide CIs.
[e] Publication bias was detected.
[f] Very serious risk of bias detected.
[g.] Optimal information size criteria not met; hence evidence downgraded.

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Appendix 1. Search strategy used to identify primary studies

A group search of primary studies was conducted for the research questions related to adjunctive corticosteroid therapy. The databases searched included Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (ClinicalTrials.gov).

Table WA11.A1.1 Database: Embase (Elsevier) (https://www.embase.com/#advancedSearch/), searched on 6 February 2024

No.	Searches	Results
1	('meningitis'/exp OR (meningiti* OR (Meningococc* NEAR/3 (infection* OR diseases))):ti,ab)	150 372
2	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR 'fungal meningitis'/exp OR 'HIV-associated meningitis'/exp OR 'parasitic meningitis'/exp OR 'virus meningitis'/exp OR 'aseptic meningitis'/exp OR 'Staphylococcus aureus'/exp OR 'Staphylococcus'/exp OR 'Enterobacteriaceae'/exp OR 'Streptococcus agalactiae'/exp OR 'Streptococcus pyogenes'/exp OR 'Enterovirus'/exp OR 'Herpesviridae'/exp OR 'herpes virus infection'/exp OR 'Simplexvirus'/exp OR 'Flavivirus'/exp OR 'West Nile virus'/exp OR 'Togaviridae'/exp OR 'Mumps'/exp OR 'Mumps virus'/exp OR 'Orthomyxoviridae'/exp OR 'HIV'/exp OR 'Adenoviridae'/exp OR 'Rubella'/exp OR 'Lymphocytic Choriomeningitis'/exp OR 'Rickettsiales'/exp OR 'Spirochaetales'/exp OR 'Leptospira'/exp OR 'Brucella'/exp OR 'Treponema pallidum'/exp OR 'Coxiella'/exp OR 'Mycoplasma'/exp OR 'Naegleria'/exp OR 'Angiostrongylus'/exp OR 'Coccidioides'/exp OR 'Candida'/exp OR 'Histoplasma'/exp OR 'Blastomyces'/exp OR 'Aspergillus'/exp OR 'Syphilis'/exp OR 'Lyme Disease'/exp OR 'Scrub Typhus'/exp OR ((Bacterial OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired) NEAR/5 (meningiti*)):ti,ab,kw,de OR (infectious-meningiti* OR Acute OR fulminat* OR Fulminant OR Sudden-onset OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal*	5 034 758

	OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi):ti,ab,kw,de	
3	(osmotic* OR osmotic-therap* OR glycerol OR mannitol OR hypertonic-saline OR hypertonic-agent* OR sodium-lactate OR osmotic-pressure OR osmotic-diuretic OR sorbitol OR propanetriol OR sodium-chloride OR Osmolality OR Osmol*):ti,ab,kw	218 401
4	(intravenous-fluid* OR oral-fluid* OR fluid-restriction* OR fluid-management OR maintenance-fluid* OR isotonic-solution* OR fluid-therap* OR fluid-balance OR electrolyte-balance OR supportive-therap* OR restricted-fluid* OR plasma-arginine OR restricting-fluids OR rehydration OR hydrat* OR hyponatremia OR water-deprivation OR water-restriction OR dehydration OR dehydrat* OR electrolyt* OR sodium-chloride OR saline OR plasma-substitute OR hypertonic-solution OR ors OR parenteral-nutrition-solution OR albumin OR dextran OR starch OR hemaccel OR gelofusine):ti,ab,kw	1 001 602
5	(steroid* OR corticosteroid* OR glucocorticoids OR dexameth* OR prednisolone OR predniso* OR hydrocortisone OR adrenal-cortex-hormone*):ti,ab,kw	778 336
6	((Adjunct* OR adjuvant*) NEAR/5 (treatment* OR therap*)):ti,ab,kw	169 578
7	#1 AND #2	102 468
8	#3 OR #4 OR #5 OR #6	3 339 245
9	#7 AND #8	8 809
10	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR 'case report'/de	11 277 185
11	#9 NOT #10	6 084
12	[animals]/lim NOT ([animals]/lim AND [humans]/lim)	6 459 077

13	#11 NOT #12	5 485
14	auto inflamm*':ti OR autoimmun*:ti OR 'auto immun*':ti OR rheumatoid:ti OR parkison*:ti OR dementia:ti OR tubercul*:ti OR vaccin*:ti OR cryptococc*:ti OR sarcoid*:ti OR lupus:ti OR infant:ti OR infants:ti OR 'neo natal':ti OR neonatal:ti OR newborn*:ti	1 295 593
15	#13 NOT #14	3 137
16	#17 AND [1998-2024]/py	2 436

Table WA11.A1.2 Database: PubMed (https://pubmed.ncbi.nlm.nih.gov/), searched on 6 February 2024

No.	Searches	Results
1	("Meningitis"[Mesh] OR meningit*[tiab]) OR "Meningococcus disease"[tiab:~3] OR "Meningococcal disease"[tiab:~3] OR "Meningococcal infection"[tiab:~3] OR "Meningococcal infections"[tiab:~3]	92 731
2	Acute[tiab] OR "fulminat*"[tiab] OR "Fulminant"[tiab] OR "Sudden-onset"[tiab] OR "Infectious meningitis"[tiab] OR "Meningitis, bacterial"[Mesh] OR"Bacterial meningitis"[tiab:~5] OR "Meningitis, Aseptic"[Mesh] OR "Aseptic meningitis"[tiab:~3] OR "Meningitis, Viral"[Mesh] OR "Viral meningitis"[tiab:~5] OR "Meningitis, Fungal"[Mesh] OR "Fungal meningitis"[tiab:~5] OR "Parasitic meningitis"[tiab:~5] OR "community acquired meningitis"[tiab:~3] OR "Meningitis, Meningococcal"[Mesh] OR "Meningitis, Pneumococcal"[Mesh] OR "Meningitis, Haemophilus"[Mesh] OR "Meningitis, Listeria"[Mesh] OR "Staphylococcus aureus"[Mesh] OR "Enterobacteriaceae"[Mesh] OR "Enterobacter"[Mesh] OR "Escherichia coli"[Mesh] OR "Streptococcus agalactiae"[Mesh] OR "Streptococcus pyogenes"[Mesh] OR "Enterovirus"[Mesh] OR "Herpesviridae"[Mesh] OR "Herpesviridae Infections"[Mesh] OR "Simplexvirus"[Mesh] OR "Flavivirus"[Mesh] OR "West Nile virus"[Mesh] OR "Togaviridae"[Mesh] OR "Mumps"[Mesh] OR "Mumps virus"[Mesh] OR "Orthomyxoviridae"[Mesh] OR "HIV"[Mesh] OR "Adenoviridae"[Mesh] OR "Rubella"[Mesh] OR "Lymphocytic Choriomeningitis"[Mesh] OR "Rickettsiales"[Mesh] OR "Spirochaetales"[Mesh] OR "Leptospira"[Mesh] OR "Brucella"[Mesh] OR "Treponema pallidum"[Mesh] OR "Coxiella"[Mesh] OR "Mycoplasma"[Mesh] OR "Naegleria"[Mesh] OR "Angiostrongylus"[Mesh] OR "Coccidioides"[Mesh] OR "Candida"[Mesh] OR "Histoplasma"[Mesh] OR "Blastomyces"[Mesh] OR "Aspergillus"[Mesh] OR "Syphilis"[Mesh] OR "Lyme Disease"[Mesh] OR "Scrub Typhus"[Mesh] OR "Meningococc*"[tiab] OR "Neisseria meningitidis"[tiab] OR "N. Meningitidis"[tiab] OR "Pneumococc*"[tiab] OR "S-pneumoniae*"[tiab] OR "Haemophilus influenzae"[tiab] OR "Listeri*"[tiab] OR L-monocytogenes[tiab] OR "Staphylococc*"[tiab] OR "Staph aureus"[tiab] OR "Enterobacter*"[tiab] OR "Enterococc*"[tiab] OR "Escherichia coli"[tiab] OR "E-coli"[tiab] OR "Streptococcus agalactiae"[tiab] OR "S agalactiae*"[tiab] OR "S pyogenes"[tiab] OR "Enterovir*"[tiab] OR "Coxsackieviruses"[tiab] OR "Herpesviridae"[tiab] OR "Herpesvirus*"[tiab] OR "herpes virus*"[tiab] OR "Varicella zoster"[tiab] OR flavi-virus*[tiab] OR Japanese-encephal*[tiab] OR Tick-borne-encephal*[tiab] OR Powassan-virus*[tiab] OR "West Nile virus"[tiab] OR "Togaviridae"[tiab] OR Toga-virus*[tiab] OR Togavir*[tiab] OR equine-encephal* OR Bunyavirus*[tiab] OR crosse-encephal*[tiab] OR Toscana-virus*[tiab] OR Reovirus*[tiab]	3 364 413

	OR tick-fever*[tiab] OR paramyxovir*[tiab] OR "Mumps"[tiab] OR morbillivirus*[tiab] OR parainfluenza*[tiab] OR "Orthomyxovir*"[tiab] OR "Influenza"[tiab] OR "HIV"[tiab] OR "human-immuno-deficienc*"[tiab] OR "Adenoviridae"[tiab] OR adenovirus*[tiab] OR Arenavir*[tiab] OR "Choriomeningit*"[tiab] OR "LCMV"[tiab] OR "Rickettsi*"[tiab] OR Orientia-spp[tiab] OR Ehrlichia-spp[tiab] OR "spirochet*"[tiab] OR Borrelia-spp[tiab] OR B-burgdorferi[tiab] OR "leptospir*"[tiab] OR "Treponema pallidum"[tiab] OR "Brucell*"[tiab] OR "Coxiella"[tiab] OR "Mycoplasma"[tiab] OR spirillum*[tiab] OR "Naegleria"[tiab] OR "angiostrongyl*"[tiab] OR Trichinella-spiralis*[tiab] OR "Candida"[tiab] OR "Coccidioid*"[tiab] OR "Histoplasm*"[tiab] OR "Blastomyc*"[tiab] OR Sporothrix*[tiab] OR "Aspergill*" [tiab] OR "Lyme"[tiab] OR "Syphili*"[tiab] OR "Scrub Typhus"[tiab] OR tsutsugamushi[tiab]	
3	#1 AND #2	68 069
4	osmotic*[tiab] OR osmotic-therap*[tiab] OR glycerol[tiab] OR mannitol[tiab] OR hypertonic-saline[tiab] OR hypertonic-agent*[tiab] OR sodium-lactate[tiab] OR osmotic-pressure[tiab] OR osmotic-diuretic[tiab] OR sorbitol[tiab] OR propanetriol[tiab] OR sodium-chloride[tiab] OR Osmolality[tiab] OR Osmol*[tiab]	186 146
5	#3 AND #4	257
6	(intravenous-fluid*[tiab] OR oral-fluid*[tiab] OR fluid-restriction*[tiab] OR fluid-management[tiab] OR maintenance-fluid*[tiab] OR isotonic-solution*[tiab] OR fluid-therap*[tiab] OR fluid-balance[tiab] OR electrolyte-balance[tiab] OR supportive-therap*[tiab] OR restricted-fluid*[tiab] OR plasma-arginine[tiab] OR restricting-fluids[tiab] OR rehydration[tiab] OR hydrat*[tiab] OR hyponatremia[tiab] OR water-deprivation[tiab] OR water-restriction[tiab] OR dehydration[tiab] OR dehydrat*[tiab] OR electrolyt*[tiab] OR sodium-chloride[tiab] OR saline[tiab] OR plasma-substitute[tiab] OR hypertonic-solution[tiab] OR ors[tiab] OR parenteral-nutrition-solution[tiab] OR albumin[tiab] OR dextran[tiab] OR starch[tiab] OR hemaccel[tiab] OR gelofusine[tiab])	778 552
7	#3 AND #6	1 120
8	Steroids[Mesh] OR steroid*[tiab] OR corticosteroid*[tiab] OR glucocorticoids[tiab] OR dexameth*[tiab] OR prednisolone[tiab] OR predniso*[tiab] OR hydrocortisone[tiab] OR adrenal-cortex-hormone*[tiab]	1 231 280
9	#3 AND #8	3 694

10	("adjunctive treatment"[tiab:~5] OR "adjunctive treatments"[tiab:~5] OR "Adjunctive therapy"[tiab:~5] OR "Adjunctive therapies"[tiab:~5] OR "adjuvant therapy"[tiab:~5] OR "adjuvant therapies"[tiab:~5] OR "adjunctive treatments"[tiab:~5] OR "adjunctive treatment"[tiab:~5] OR "adjunct therapy"[tiab:~5] OR "adjunct therapies"[tiab:~5] OR "adjunct treatments"[tiab:~5] OR "adjunct treatment"[tiab:~5])	86 083
11	#3 AND #10	507
12	#11 OR #9 OR #7 OR #5	4 995
13	"Letter"[Publication Type] OR "Editorial"[Publication Type] OR "comment"[Publication Type] OR "case reports"[publication type]	4 374 866
14	#12 NOT #13	3 204
15	("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	5 191 262
16	#14 NOT #15	2 766
17	#16 Filters: from 1998 - 2024	1 737

Table WA11.A1.3 Database: CENTRAL (https://www.cochranelibrary.com/advanced-search/search-manager?search=7376359), searched on 2 May 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis] explode all trees	856
2	meningit*:ti,ab OR (Meningococc* NEAR/3 (disease* OR infection*)):ti,ab,kw	2 547
3	(osmotic* OR osmotic-therap* OR glycerol OR mannitol OR hypertonic-saline OR hypertonic-agent* OR sodium-lactate OR osmotic-pressure OR osmotic-diuretic OR sorbitol OR propanetriol OR sodium-chloride OR Osmolality OR Osmol*):ti,ab,kw	18 452
4	(intravenous-fluid* OR oral-fluid* OR fluid-restriction* OR fluid-management OR maintenance-fluid* OR isotonic-solution* OR fluid-therap* OR fluid-balance OR electrolyte-balance OR supportive-therap* OR restricted-fluid* OR plasma-arginine OR restricting-fluids OR rehydration OR hydrat* OR hyponatremia OR water-deprivation OR water-restriction OR dehydration OR dehydrat* OR electrolyt* OR sodium-chloride OR saline OR plasma-substitute OR hypertonic-solution* OR hyptertonic-agent* OR ors OR parenteral-nutrition-solution OR albumin OR dextran OR starch OR hemaccel OR gelofusine):ti,ab,kw	94 256
5	MeSH descriptor: [Steroids] explode all trees	75 652
6	(steroid* OR corticosteroid* OR glucocorticoids OR dexameth* OR prednisolone OR predniso* OR hydrocortisone OR adrenal-cortex-hormone*):ti,ab,kw	93 271
7	((Adjunct* OR adjuvant*) NEAR/5 (treatment* OR therap*)):ti,ab,kw	34 213
8	#1 OR #2	2 718
9	#3 OR #4 OR #5 OR #6 OR #7	259 766
10	#9 AND #8	482
11	Limits Jan 1998 to Dec 2024	474

Table WA11.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 7 February 2024

No.	Searches	Field	Results
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	(osmotic OR glycerol OR mannitol OR "hypertonic saline" OR "sodium lactate" OR sorbitol OR propanetriol OR "sodium chloride" OR Osmolality) NOT vaccine	Intervention	
3	1 and 2		15
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	("isotonic solution" OR plasma OR rehydration OR hydrate OR hydration OR hyponatremia OR dehydration OR dehydrate OR electrolyte OR saline OR hypertonic OR "parenteral nutrition" OR albumin OR dextran) NOT Vaccine	Intervention	
3	1 and 2		50
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	hemaccel OR gelofusine OR starch	Intervention	
3	1 and 2		0
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	

2	(Steroids OR steroid OR corticosteroid OR glucocorticoids OR dexamethasone OR prednisolone OR prednisone OR hydrocortisone OR “adrenal cortex hormone”)	Intervention	
3	1 and 2		47
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	"adjunctive treatment" OR "adjunctive treatments" OR "Adjunctive therapy" OR "Adjunctive therapies" OR "adjuvant therapy" OR "adjuvant therapies" OR "adjunctive treatments" OR "adjunctive treatment" OR "adjunct therapy"	Intervention	
3	1 and 2		7
Total			119
Duplicates			28
To screen			91

Appendix 2. Categories in the data extraction form

Study name		
Publication details	Type of study	
	Duration	
	Location	
	Type of country: LMIC/HIC	
	Date of trial	
	Date of publication	
	Sponsor and funding	
	Protocol publication (for RCTs)	
		Intervention **Comparator**
Study details	Number of participants	
	Patients who completed study	
	Reason for discontinuation	
	Missing outcomes	
	Deviation from protocol	
	Inclusion criteria	
	Exclusion criteria	
Patient demographic data	Age	
	Gender	
	Vaccination status (pneumococcal vaccine)	
	Immunocompromised	
	Source of Infection: RTA/sinus/abscess/ any other risk factor	
	Duration of illness	

Clinical features		**Intervention**	**Comparator**
	Seizures		
	Altered sensorium		
	Hemiparesis		
	Papilloedema		
	Cranial nerve palsy		
Disease details	Causative organism		
	Culture and sensitivity details		
	Severity		
	Risk assessment scale		
Comorbidity/ Confounding factors	Diabetes		
	Hypertension		
	Stroke		
	Seizure		
Corticosteroid details	Name		
	Type of corticosteroid, start of therapy from date of admission or symptoms		
	Dose		
	Frequency		
	Route		
	duration		
Other therapeutic intervention	Antimicrobial therapy		
	Other adjunctive therapies		
	Immunosuppressants		
Antimicrobial therapy		**Intervention**	**Comparator**
	Type of antibiotic		

	Dosage			
	Duration of therapy			
CSF analysis			**Intervention**	**Comparator**
	Cell count and type – at admission			
	Cell count and type – at discharge /2nd analysis			
	Protein – at admission			
	Protein – at discharge /2nd analysis			
	Glucose – at admission			
	Glucose – at discharge/2nd analysis			
	Change between the 1st and 2nd LP			
	P value			
Outcomes	Outcomes assessed in the study, with number of participants assessed for each outcome			
	Approach to primary analysis (e.g. per protocol, intention to treat)			
	Were any imputations made for missing data?			
Critical outcomes	Mortality – total study 28 to 30 days in hospital	No. of patients		
	Mortality with respect to each of the etiological organisms			
	Time to resolution of symptoms	No. of days Median (range)		
		Length of hospital stay		
	Disease complications	Sepsis		
		DIC		

		Neurological complications
		Cognitive impairment
		Seizures
		Hearing sequelae
		GI bleeding
		Infection/Fever
		Arthritis
		Behavioural changes
		Hyperglycaemia
Important outcomes	Adverse effects – antimicrobe-related adverse events like *C. difficile* infection and candidemia infection	No. of patients
		No. of events
		Drug-related adverse events
	CSF culture positivity rate	No. of patients with positive culture
		Proposition of positive culture
	Blood culture positivity rate	No. of patients
		Positivity rate
Follow-up	What was planned, way participants were followed up	
	Results, length of follow-up	
	Lost to follow-up: number and characteristics	

CSF: cerebrospinal fluid; DIC: disseminated intravascular coagulation; GI: gastrointestinal; HIC: high-income country; LMICs: low- and middle-income countries; LP: lumbar puncture; RCT: randomized controlled trial.

12. Osmotic agents

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Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CSF	cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hib	*Haemophilus influenzae* type b
HIC	high-income country
LMICs	low- and middle-income countries
RCT	randomized controlled trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROB-2	Cochrane risk of bias tool 2

1. Background

Acute meningitis denotes infection of the meninges, the protective membrane that lines the brain and spinal cord. Acute bacterial meningitis is among the world's most severe infectious diseases and is associated with high morbidity and mortality, especially when there is a delay in diagnosis and treatment. *(1)*. According to the Global Burden of Disease study for 2019, there were approximately 2.51 million new cases of meningitis reported worldwide, leading to an estimated 236 000 deaths *(2)*. Notably, *Neisseria meningitidis* was responsible for 17.3% of these cases, followed by *Streptococcus pneumoniae* at 13.0%. Across all age groups, the pathogen causing the most meningitis-related fatalities was *Streptococcus pneumoniae,* accounting for 18.1% of all meningitis-related deaths. *Neisseria meningitidis* followed closely, contributing to 13.6% of these fatalities *(2)*. Beyond the risk of mortality, survivors of meningitis often experience long-lasting and debilitating neurological consequences, including cognitive impairment, hearing loss, motor weakness or paralysis, lack of coordination and new onset of epilepsy.

People with acute bacterial meningitis are usually treated by primary care and emergency medicine physicians at the time of initial presentation, sometimes in consultation with infectious disease specialists. In resource-limited settings, with insufficient laboratory support, a microbiological confirmation is often lacking. The objective of these practice guidelines is to provide clinicians with recommendations for the treatment of bacterial meningitis which can be applied in all settings of medical practice.

Acute bacterial meningitis is often associated with elevation of intracranial pressure, which in turn leads to a reduction in cerebral perfusion and to cerebral oedema, predisposing to brainstem herniation. Osmotic therapy represents an adjunctive therapeutic modality that involves the administration of pharmacologically inert substances to elevate the osmotic pressure of plasma, thereby promoting the translocation of water from the interstitial space to the vascular compartment *(3)*. These osmotic agents include mannitol, sorbitol, glycerol and hypertonic saline. While the primary objective of these agents is to mitigate intracranial pressure by creating an osmotic gradient, they may also confer advantageous ancillary effects. For instance, mannitol has been demonstrated to scavenge reactive oxygen species and ameliorate blood viscosity, thus enhancing circulatory dynamics and inducing vasoconstriction, resulting in a reduction of cerebral blood volume *(4, 5)*. Hypertonic saline serves as an efficacious volume expander, leading to enhancements in systemic haemodynamics. The most commonly studied osmotic agent in bacterial meningitis is glycerol. While theoretically its utility was justified, a Cochrane review by Wall et al. published in 2018 that included five randomized controlled trials (RCTs) showed no definite reduction in mortality resulting from osmotic therapies *(6)*.

The primary objective of this review is to study the effects of adjuvant osmotic therapy versus placebo on mortality, and neurological and audiological parameters in people with acute bacterial meningitis.

2. Methodology

21. Research question and study design

Among suspected, probable or confirmed cases of acute bacterial meningitis, should osmotic agents be used to decrease morbidity and mortality outcomes?

Population: Suspected, probable or confirmed cases of acute bacterial meningitis.

Subgroup analysis: Pathogens (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and Group B Streptococcus); age group (child, adult); World Bank income classification (high-income country [HIC], low- or middle-income country [LMIC]); disease severity (altered consciousness).

Intervention: Adjunctive osmotic agent (glycerol, mannitol, sorbitol, hypertonic saline, sodium lactate).

Comparator: Standard care without adjunctive osmotic agent; head-to-head comparison.

Outcomes

Critical outcomes:

- Neurological complications (neurological sequelae,[18] hearing loss)
- Mortality
- Adverse effects.

Important outcomes: Impact on disease course (time to resolution of symptoms, persistent fever).

Study design: The study was designed as a systematic review with meta-analysis comprising only RCTs. It was planned in accordance with the Cochrane guidelines for systematic reviews with meta-analysis. The objective was to identify all relevant RCTs of osmotic agents being used to treat acute meningitis. The RCTs were supplemented with relevant prospective or retrospective observation studies that had a comparator arm.

2.2 Eligible studies

Published language: All relevant studies were identified, regardless of language. Studies in English were assessed by the review team.

Exclusion criteria

The following study types were excluded:

[18] Neurological sequelae are defined as hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behavioural changes), hydrocephalus, motor deficits and/or vision impairment.

- Non-randomized studies without a comparator; i.e. case reports, case series, letters, editorials, abstracts, etc.;
- Studies without adjunctive osmotic therapy;
- Any on-going trials and studies, with no evaluable outcome data.

The following disease categories were excluded:

- Meningitis in newborns (0–28 days);
- Hospital-acquired, nosocomial and health-care-associated meningitis;
- Subacute and chronic meningitis, including tuberculous, cryptococcal and eosinophilic meningitis;
- Non-infectious meningitis (e.g. drugs, malignancy, autoimmune diseases).

2.3 Search strategy

The following databases were searched: PubMed, the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Epistemonikos, Web of science, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Clinical trial registry maintained by the United States National Library of Medicine (ClinicalTrials.gov). All the databases were searched for studies published from 1946 to 6 February 2024.

The reference lists of relevant publications were checked for any unidentified trials. In addition, clinical trial registries, including ClinicalTrials.gov, were searched for completed RCTs. National or regional databases were searched, as was grey literature if deemed relevant.

2.4 Selection of studies

The data obtained from the search were uploaded to the Rayyan too and screened by the review authors independently using Rayyan software. The full text of all potentially relevant studies was retrieved. Each study report was examined to ensure that there were no duplicates. Any disagreements were resolved through discussion.

Systematic reviews published before 6 February 2024 that would apply to the research question were identified, including one Cochrane review by Wall et al. *(6)*, and were used as seed articles. Rayyan software was used to categorize articles according to the inclusion and exclusion criteria. The process was as follows:

- The studies were selected from the bibliographic databases by two of the authors independently on the basis of the title and abstract.
- Those that fitted the inclusion and exclusion criteria were selected.
- Conflicts between the two authors were then resolved through discussion, and the third author was also involved in the final selection of studies.

- The full text of the studies was then downloaded. The studies were divided into RCTs, systematic reviews and prospective cohort studies.
- The total number of citations that were retrieved from the databases, with the reasons for inclusion and exclusion, are presented in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) format (see Fig. WA12.1).

2.5 Data extraction and management

The review authors used a piloted data extraction form (Appendix 2) to record data on study characteristics, study setting, participant characteristics, disease severity, comorbidity, adjunctive osmotic treatment and administration, other treatments given, and outcome measures, as defined by the research question. When there were studies with multiple treatment groups, only studies with groups receiving osmotic agents and a placebo were considered. Any disagreements were resolved through discussion.

The extracted data included study characteristics, income status, demographic profile, study characteristics, location, number of participants in the study and comparator arm, details of the study drug or treatment, adverse effects, and the investigation profile along with treatment details.

For dichotomous outcomes, the number of participants who had experienced the event and the number of participants in each treatment group were recorded. The number of participants analysed in each arm was recorded and the discrepancy between the figures was used to calculate the number of participants lost to follow-up. Sensitivity analyses were performed to investigate the effect of missing data if necessary. For continuous outcomes, the aim was to extract means and standard deviation for the outcome in each group; medians were also recorded for narrative comparisons where means were unavailable. The review was performed and reported in accordance with the recommendations stated in the *Cochrane handbook for systematic reviews of interventions*.

2.6 Assessment of risk of bias in studies included in the review

The methodological quality of the included studies was assessed using Version 2 of the Cochrane risk-of-bias tool (RoB 2) (see Figs. WA12.2 and 3). Each of the included studies was assessed on the basis of a number of pre-defined parameters, including the following: analysis of the randomization process to assess the risk of selection bias; detection of any deviation from the protocol to assess the risk of performance bias; attrition bias; reporting bias; detection bias; and presence of any additional source of bias. The results of the RoB 2 analysis were used in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) of the outcomes. The treatment effect was measured using the risk ratio (RR), with 95% confidence interval (CI). Visual inspection of funnel plots was used to detect the presence of publication bias.

2.7 Data synthesis

The data were analysed using Review Manager Web software (version 5.4) *(7)*. Owing to the presence of substantial heterogeneity across the studies, which spanned a wide range of timeframes and geographical locations and contained potential confounders, the meta-analyses were performed using a random-effects model based on the inverse variance method. All outcome measures were dichotomous.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

The results of the analysis are summarized in Table WA12.4 (Summary of findings), and the summary effect estimates for the critical outcomes and other important outcomes are presented with illustrative comparative risks. The GRADE framework was used to evaluate the certainty of the evidence for each outcome, as developed by the GRADE Working Group *(8)*. The GRADE levels of certainty are defined in Box WA12.1.

Box WA12.1 The certainty of evidence used in GRADE	
High ⊕⊕⊕⊕	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

A subgroup analysis was performed to assess heterogeneity on the basis of the following.

- Causative pathogens: *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and Group B streptococcus;
- Presence or absence of neurological sequelae in study participants receiving osmotic therapy alone and those who received adjunctive corticosteroids;
- Presence or absence of hearing loss in patients receiving osmotic therapy alone and those who received adjunct corticosteroids.

Heterogeneity assessment was performed by means of visual inspection of forest plots (see section 3.3) to determine the closeness of point estimates to each other and the overlap of CIs. The Chi-square test, with a *P*-value of 0.10, was used to indicate statistical significance. and the I^2 statistic to measure heterogeneity. The following ranges, outlined

in the *Cochrane handbook for systematic reviews of interventions*, were used to interpret the I^2 statistic – 0–40%: might not be important; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; 75%–100%: considerable heterogeneity.

The magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. *P*-value from the Chi-square test) were considered when determining the importance of the observed I^2 value.

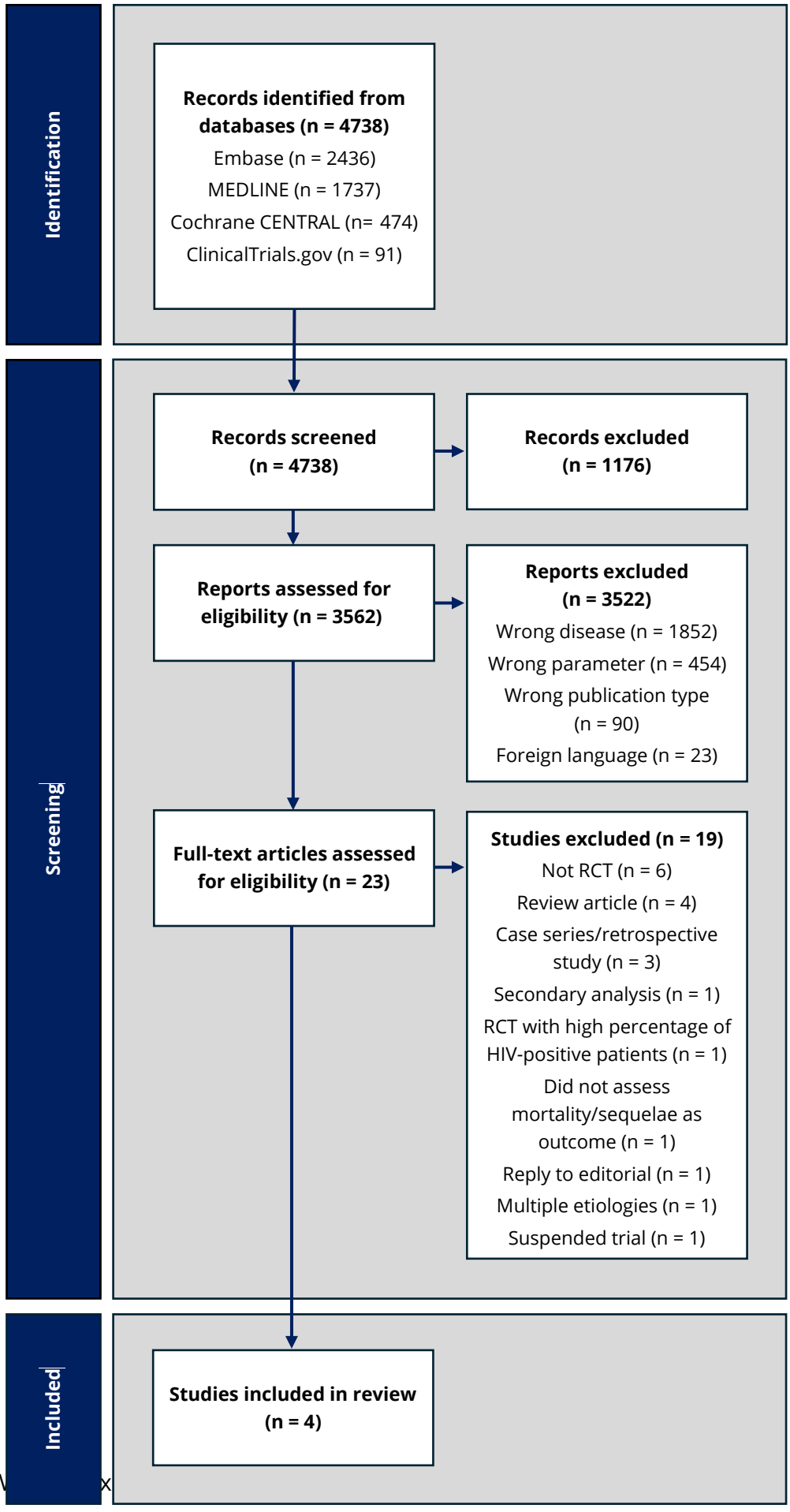
3. Results

3.1 Studies identified by the search process

Figure WA12.1 presents the PRISMA flow diagram for this review.

A total of 4738 records were screened, of which 1176 duplicates were removed. Of the remaining 3562 articles, 1852 involved the wrong disease, 477 assessed parameters that were not relevant to the scope of this review, 90 lacked real-world patient data (e.g. case reports, case series, pathogenicity studies, animal studies, editorials or correspondence), and 1097 were excluded for other reasons. Of the 23 remaining studies, four were eligible for inclusion in the review.

Fig. WA12.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profiles

Our search yielded a total of 4738 studies from various database searches. Among these, 1176 were duplicates. After the duplicates had been removed, 3562 articles underwent thorough screening in accordance with the pre-specified inclusion and exclusion criteria. Subsequently, a total of four studies were identified for inclusion in the final meta-analysis. All the studies included had four arms: (i) glycerol alone, (ii) glycerol with dexamethasone, (iii) dexamethasone, and (iv) placebo. Table WA12.1 presents the characteristics of the studies included in the GRADE evidence profiles.

Table WA12.1 Characteristics of studies included in the GRADE evidence profiles

Lead author (Year), Country of conduct	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
Kilpi (1995), Finland *(4)*	RCT	High	Intervention arms: 1. Glycerol 2. Glycerol + dexamethasone 3. Dexamethasone Drug dosage and duration: Glycerol 4.5 g/kg (maximum 180 g/day) divided into 3 doses/day. Increased by 50% for dose 1 and decreased by 50% for last 3 doses. Treatment given for 3 days Dexamethasone 1.5 mg/kg once daily IV divided into 3 doses/24 hours; 50% dose adjustments as per	Children aged from 3 months to 15 years Total sample size: 122 Intervention: 1. Glycerol: 30 2. Glycerol + dexamethasone: 34 3. Dexamethasone: 32 Control: 26	Only placebo group: Neither glycerol nor dexamethasone; no other details given on placebo	Mortality	Neurological deficits, epilepsy, hearing loss	Baseline, 2, 3 and 6 months

Lead author (Year), Country of conduct	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
			glycerol. Given for 3 days. All patients were treated with ceftriaxone (100mg/kg) once daily for 7 days.					
Peltola (2007), Argentina, Brazil, Dominican Republic, Ecuador, Paraguay *(9)*	Double-blind RCT	Unclear	Intervention arms: 1. Glycerol + IV placebo 2. Glycerol + dexamethasone 3. Dexamethasone Drug dosage and duration: • Glycerol 1.5 g/kg in an 85% oral solution divided into 4 doses/day given for 2 days • Dexamethasone 0.15 mg/kg once daily IV divided into 4 doses/day.	Children 2 months to16 years of age Total sample size: 654 Intervention: 1. Glycerol + IV placebo166 2. Glycerol + dexamethasone159 3. Dexamethasone + oral placebo166 Control: 163	IV placebo + oral placebo: Saline and carboxymethylcellulose for dexamethasone and glycerol, respectively	Mortality	Neurological deficits, epilepsy, hearing loss	Baseline, discharge, 1–2 months after discharge

Lead author (Year), Country of conduct	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
			Treatment given for 2 days All patients were treated with ceftriaxone (80–100 mg/kg) once daily for 7–10 days.					
Sankar (2007), India *(10)*	Double-blind RCT	Low	Intervention arms: 1. Glycerol + placebo (normal saline) (IV) 2. Dexamethasone IV + oral placebo; 3. Glycerol + dexamethasone IV Drug dosage and duration: • Glycerol 1.5 g/kg every 6 h • Dexamethasone 0.15 mg/kg every 6 h	Children 2 months to 12 years of age Total sample size: 58 Intervention: 1. Glycerol + IV placebo 13 2. Dexamethasone + oral placebo 12 3. Glycerol + dexamethasone 20 Control: 13	Placebo: Saline and carboxymethylcellulose for dexamethasone and glycerol, respectively	Mortality	Neurological deficits, epilepsy, hearing loss	Baseline, discharge, at 1 month follow-up

Lead author (Year), Country of conduct	Study design	Overall risk of bias (study level)	Intervention	Population (sample size/intervention/ control)	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
			Ceftriaxone 100 mg/kg/day intravenously was administered to all patients once a day for a minimum of 7 days.					
Molyneux (2014), Malawi, *(11)*	Double-blind RCT	Unclear	Intervention arms: 1. Oral glycerol + rectal placebo; 2. Rectal paracetamol + oral placebo 3. Oral glycerol plus rectal paracetamol All children received intravenous ceftriaxone 100 mg/kg/d for 5 days.	Children aged under 2 months Total sample size: 360 Intervention: 1. Oral glycerol + rectal placebo 90 2. Rectal paracetamol + oral placebo 87 3. Oral glycerol plus rectal paracetamol 92 Control: 91	Placebo only (rectal placebo plus oral placebo) Oral placebo: Carboxymethyl-cellulose Rectal placebo: A cocoa butter base	Mortality	Neurological deficits, epilepsy	Baseline, 6 months

RCT: randomized controlled trial.

3.1.2 Studies excluded from the review

Table WA12.2 gives details of the studies that were excluded from this review. The study by Peltola et al. (2010) *(3)*, which was a detailed analysis of hearing impairment following meningitis, represented a re-analysis of a previous RCT (Peltola et al., 2007) *(9)*. Hence, that study was excluded.

Table WA12.2. Studies excluded from the review, with reasons

Lead author (Year)	Study type	Population	Intervention	Comparator	Outcome	Reasons for exclusion
Singhi (2008) *(12)*	RCT	Children aged 2 months to 12 years with bacterial meningitis	85% glycerol 6 g/kg per day (6 ml/kg per day) divided into four doses, with the maximum of 25 ml per dose orally (n = 9)	Placebo (n = 9)	Changes in plasma osmolality and in urine output	Outcome measures did not include details of mortality or neurological sequelae
Peltola (2010) *(3)*	Secondary analysis of Peltola (2007)	Children of age 2 months to 15 years with bacterial meningitis	85% glycerol (1 ml contains 1 g of glycerol) at 6 g (6 ml) per kg per day orally divided into four doses – up to 25 ml per dose for 48 h	Placebo	Deafness	This was a secondary analysis of the previous study (Peltola et al., 2007)
Ajdukiewicz (2011) *(13)*	RCT	Patients with bacterial meningitis from Malawi	Oral glycerol 75 mg in 135 ml oral glucose 50% solution 135 ml (n = 137)	Placebo (n = 128)	Death or disability by Day 40; hearing loss	85% of patients were HIV-positive
Wall (2013) *(14)*	Analysis of previous trials and observational studies	Patients over 13 years of age with either CSF-proven microbiological evidence of ABM, or a high clinical index of suspicion of ABM plus a CSF white blood cell count that was > 50%	Patients treated with glycerol (n = 123)	Patients not treated with glycerol (n = 111)	Mortality	The study is not an RCT; it is an analysis of previous studies; high prevalence of HIV (87%)

Lead author (Year)	Study type	Population	Intervention	Comparator	Outcome	Reasons for exclusion
		neutrophils and > 100 cells/mm^3 in HIV-negative or 5 cells/mm^3 in HIV-positive				
Wall (2017) *(15)*		Clinical data from the Malawi Meningitis Database, and patient data from a recent clinical trial – age > 14 years with proven CSF infection on culture, PCR or Gram stain of bacteria known to cause meningitis (proven meningitis), or appropriate clinical history < 5 days with a CSF WBC count > 50 cells/µl and > 50% neutrophils (probable meningitis)	Glycerol (n = 592)	Placebo (n = 549)	Mortality	Not an RCT; analysis of previous studies; high prevalence of HIV (87%)
Wall (2014) *(16)*	Retrospective review of data	Patients of all age groups with ABM	NA	NA	NA	The study focused on influence of *Haemophilus influenzae* type b vaccination and antiretroviral therapy on acute bacterial meningitis
Almirante (1995) *(17)*	Case series	Patients over age of 10 years with	NA	NA	Mortality	Case series of mannitol used for

Lead author (Year)	Study type	Population	Intervention	Comparator	Outcome	Reasons for exclusion
		pneumococcal meningitis diagnosed by isolation in CSF				bacterial meningitis; no randomization or placebo use documented
CTRI/2015/04/005668 *(18)*	RCT	Newborns with bacterial meningitis	Oral glycerol	Standard treatment	NA	Trial was suspended
Glimaker (2014) *(19)*	Prospectively designed intervention–control comparison study	Patients aged 16–75 years with bacterial meningitis	Multiple interventions – CSF drainage, hypertonic saline, hyperventilation, external cooling	Controls retrospectively identified	Mortality	Multiple interventions, not an RCT, retrospectively identified controls
Herson (1977) *(20)*	Retrospective	Patients with *Hemophilus influenzae* meningitis	NA	NA	NA	Retrospective study
Kumar (2014) *(21)*	RCT	Children with raised intracranial pressure due to acute CNS infections, including meningitis	Cerebral perfusion pressure-targeted therapy (maintaining cerebral perfusion pressure ≥ 60 mmHg, using normal saline bolus and vasoactive therapy with dopamine, and if needed noradrenaline)	Intracranial pressure-targeted therapy (n = 55) (maintaining intracranial pressure < 20 mm Hg using osmotherapy while ensuring normal blood pressure)	Mortality	Multiple diagnoses, including aseptic meningitis, fungal meningitis and viral encephalitis
Molyneux (2015) *(22)*	Review article	NA	NA	NA	NA	Review article
Pavesio (1991) *(23)*	Review of literature	NA	NA	NA	NA	Literature review and documented personal

Lead author (Year)	Study type	Population	Intervention	Comparator	Outcome	Reasons for exclusion
						experience of the use of mannitol in meningitis
Pelegrin (2012) *(24)*	Retrospective cohort study	Patients with bacterial meningitis 1987 to 2009	Dexamethasone, mannitol and phenytoin	NA	NA	Retrospective study; no data were collected prospectively and participants were not randomized to receive any of the interventions
Peltola (2013) *(5)*	Review article	NA	NA	NA	NA	Review article
Singhi (2004) *(25)*	Review article	NA	NA	NA	NA	Review article.; not an RCT
Singhi (2008) *(26)*	Letter in response to the journal editorial summary of Peltola 2007 *(9)*	NA	NA	NA	NA	Letter in response to the journal editorial summary of Peltola 2007 *(9)*
Urciouli (1963) *(27)*	Not an RCT	Patients with neurosurgical infections	Mannitol	NA	NA	Not an RCT; mannitol tested for neurosurgical infections and not ABM
Vaziri (2016) *(28)*	Systematic review	ABM	NA	NA	NA	Not an RCT

ABM: acute bacterial meningitis; CNS: central nervous system; CSF: cerebrospinal fluid; NA: not applicable; PCR: polymerase chain reaction; RCT: randomized controlled trial; WBC: white blood cell.

3.2 Intervention effects

3.2.1 Risk of bias

The four studies included were subjected to risk-of-bias analysis using the RoB 2 tool. Overall, the risk of bias was low. The risk of selection bias, measured in terms of random sequence generation and allocation concealment, was low in three of the studies (Kilpi et al., 1995; Molyneux et al., 2014; and Sankar et al., 2007) *(4, 10, 11)*. In the domain of bias attributed to blinding of outcome assessments, a high risk was identified in the study by Kilpi et al. (1995) *(4)* (see Figs. WA12.2 and 3). That study did not specify which type of concealment was carried out *(6)*. We assessed Peltola et al. (2007) *(9)* as having a low risk of reporting bias because all the data seemed to be clearly and fully presented *(9)*. The study by Kilpi et al. exhibited attrition of cases, hence was considered to have an unclear risk of selection bias *(4)*. Sankar et al., (2007) was deemed to have an unclear risk of reporting bias since adverse effects and treatment cessation times were not provided *(10)*. In the other bias domain, Kilpi et al. (1995) and Peltola et al. (2007) were considered to have an unclear risk of bias, owing to receipt of partial funding *(4, 9)*.

Fig. WA12.2 Risk of bias in studies included in the review (assessed using RoB 2 tool)

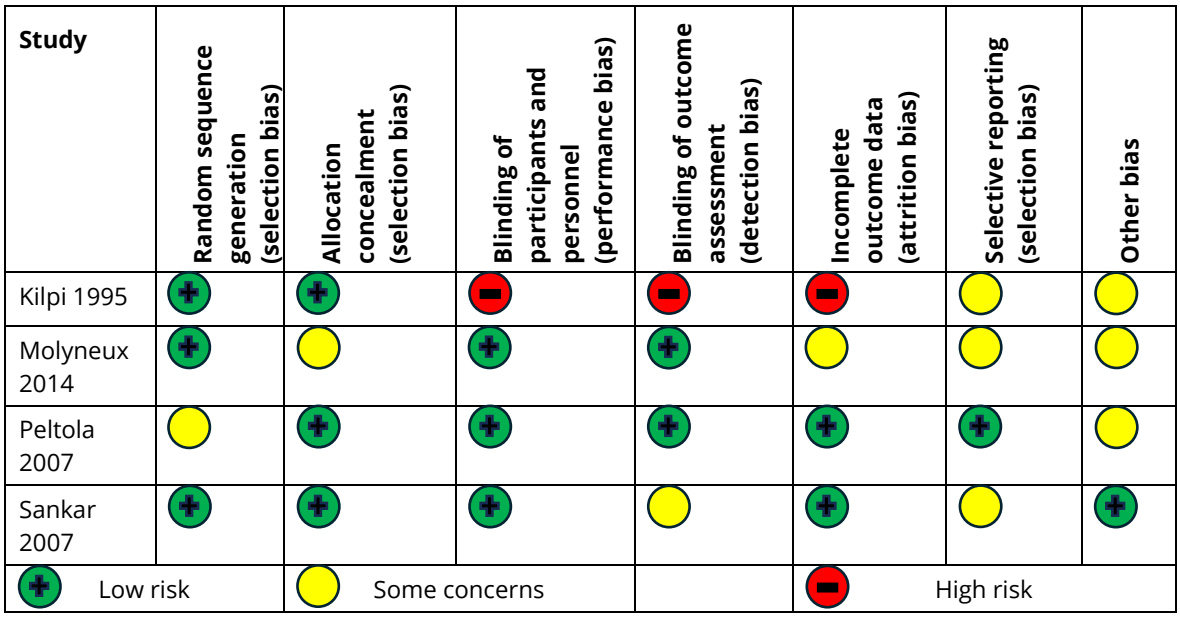
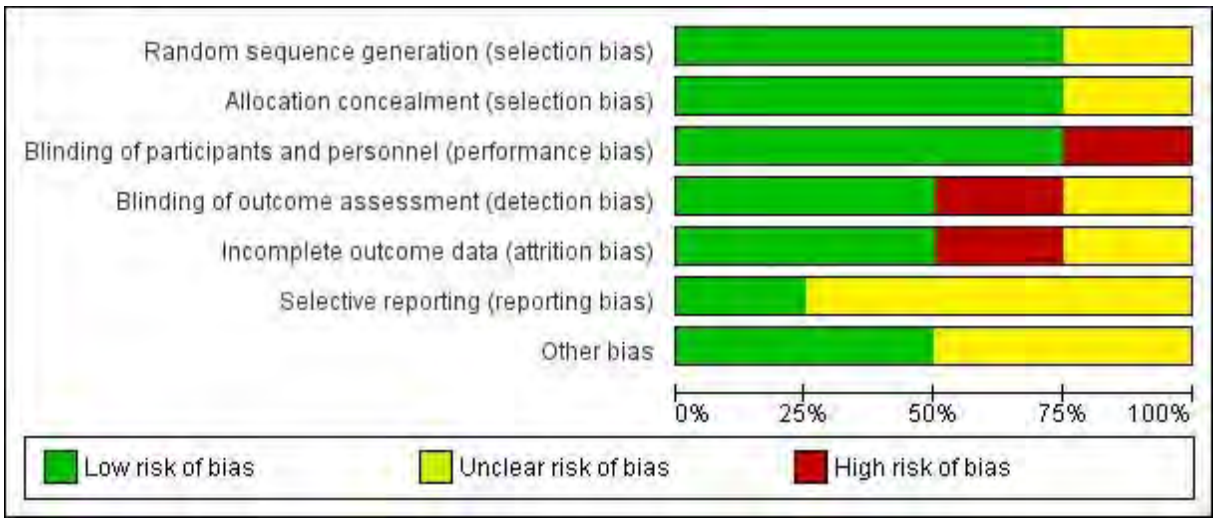


Fig. WA12.3 Review authors' judgements of individual risk-of-bias items presented as percentages across all included studies



3.3 Forest plots

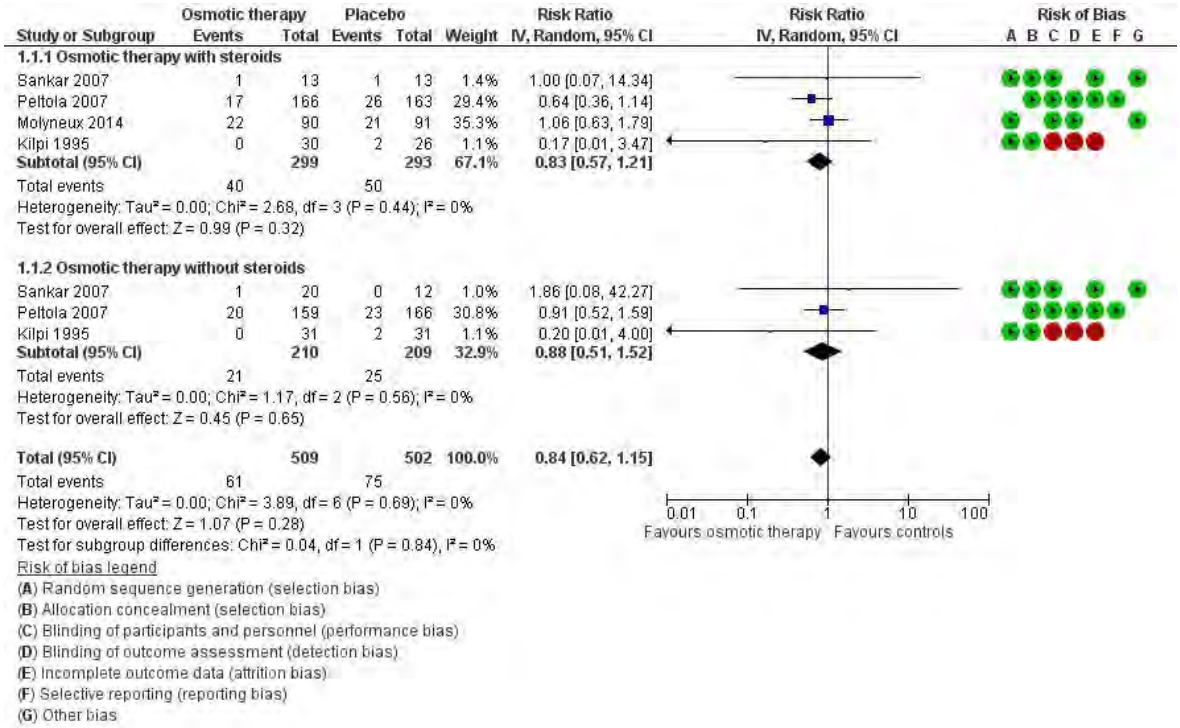
This subsection gives details of the primary outcomes of the evidence synthesis, illustrating them with forest plots.

All-cause mortality: Low certainty evidence from four RCTs involving 1011 children at 1 month follow-up suggests that osmotic therapy may have had little to no effect on mortality resulting from meningitis (RR 0.84, CI 0.62–1.15, *P* = 0.28).

Among the patients who did not receive adjunctive steroids, there was no statistically significant difference in mortality noted in the osmotic therapy group compared to the placebo group (21 of 210 [10%] versus 25 out of 209 [11.9%]) (RR 0.88, 95%, CI 0.51–1.52, *P* = 0.65) *(4, 9, 10)*. Among the patients who received steroids, no statistically significant difference in mortality was noted in the osmotic therapy group compared to the placebo group (40 of 299 [13.37%] versus 50 out of 293 [17.06%]) (RR 0.83, 95% CI 0.57–1.21, *P* = 0.32) *(4, 9-11)*.

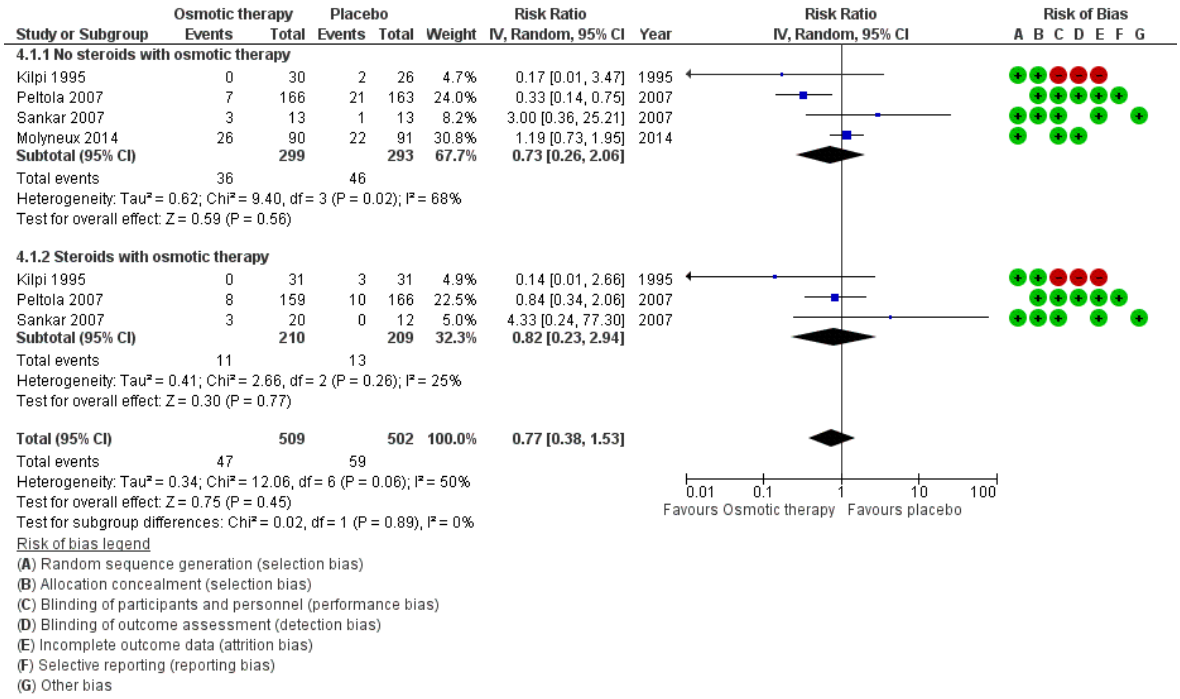
Overall, no statistically significant difference in mortality was noted in the osmotic therapy group compared to the placebo group (61 of 509 [11.9%] versus 75 out of 502 [14.9%]) (RR 0.84, 95% CI 0.62–1.15, *P* = 0.28) *(4, 9-11)*.

Fig. WA12.4 Mortality of people with meningitis receiving osmotic therapy with and without steroids



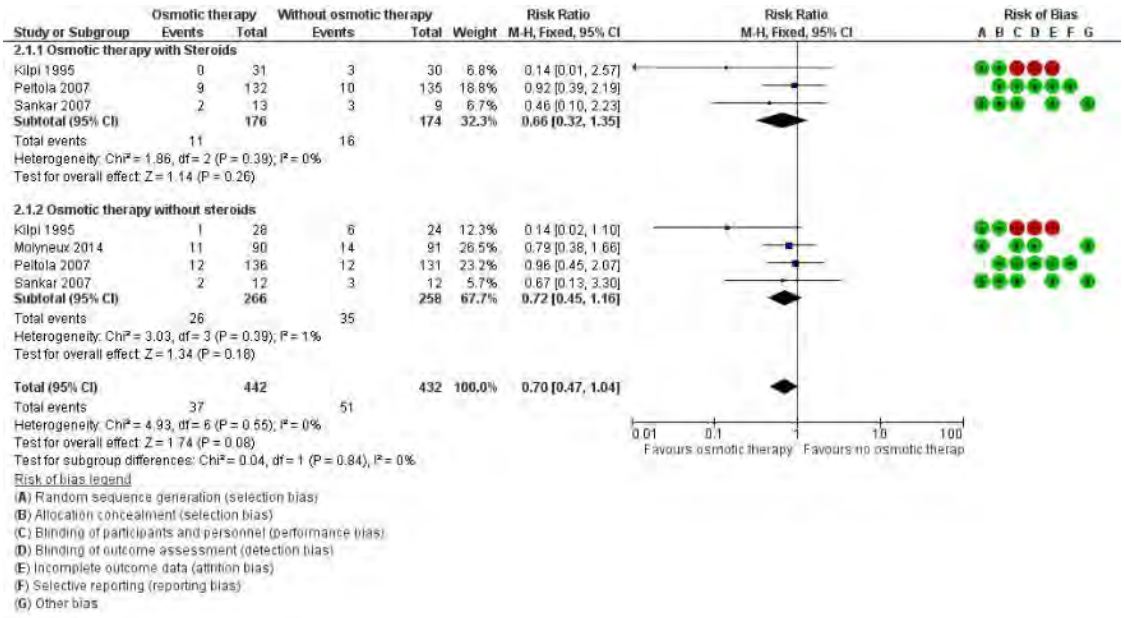
Neurological sequelae: Low certainty evidence from four RCTs involving 1011 children, at 2 months follow-up suggested that osmotic therapy may have had little to no effect on neurological sequelae resulting from meningitis compared with care without osmotic agents (RR- 0.77, CI 0.38–1.53), *P* = 0.45) *(4, 9-11)*.

Fig. WA12.5 Neurological sequelae of people with meningitis receiving osmotic therapy with and without steroids



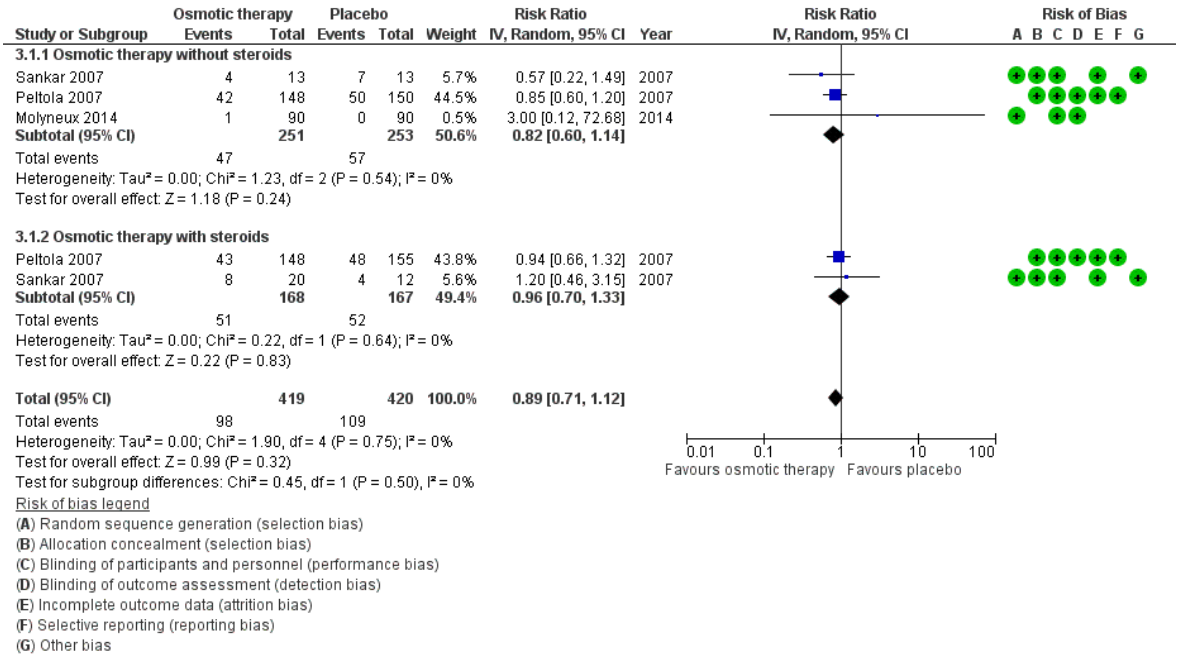
Hearing loss: Low certainty evidence from four RCTs involving 874 children, at 1.5 months, suggested that osmotic therapy may have had little to no effect on hearing loss resulting from meningitis compared with treatment without osmotic agents (RR 0.70, CI 0.47–1.04), *P* = 0.08) *(4, 9-11)*.

Fig. WA12.6 Effect of osmotic therapy with and without steroids on hearing loss in people with acute bacterial meningitis



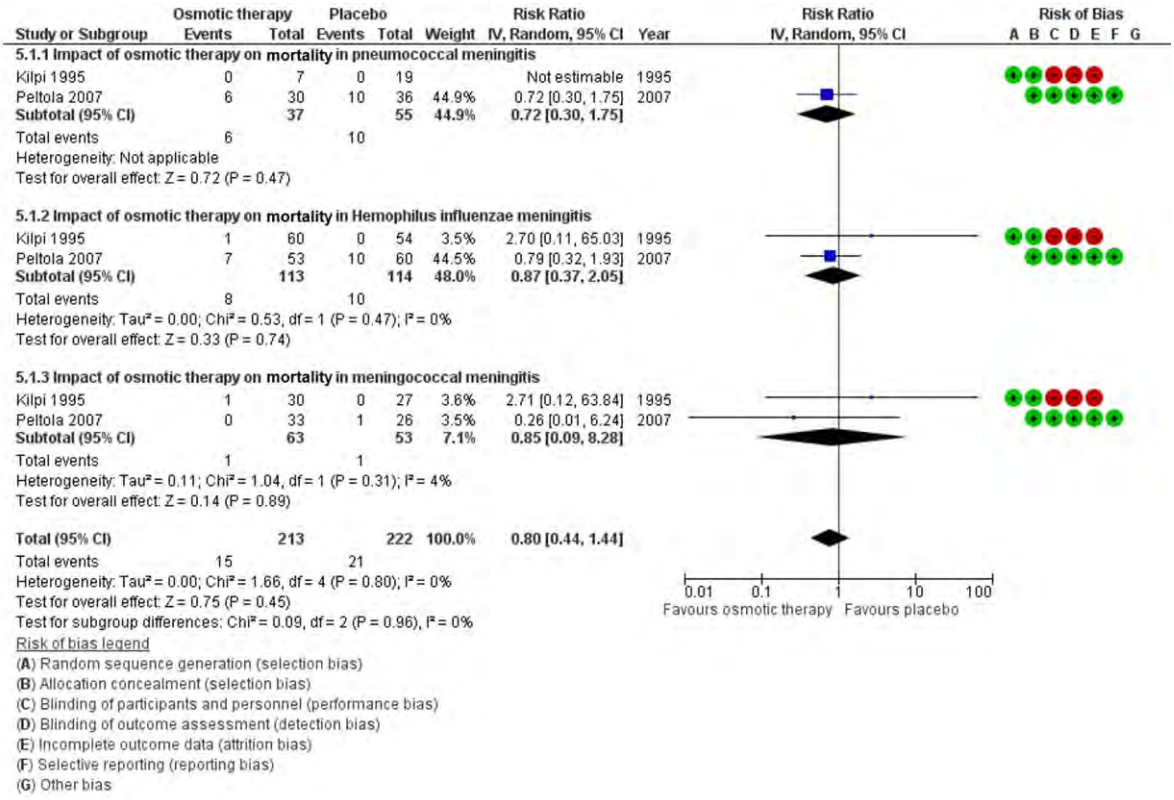
Post-meningitis epilepsy or symptomatic seizures: Low certainty evidence from three RCTs, involving 839 children, at 1 month follow-up, suggested that osmotic therapy may have had little to no effect on seizures resulting from meningitis compared to care without osmotic agents (RR 0.89, CI 0.71–1.12, *P* = 0.32) *(4, 9, 10)*.

Fig. WA12.7 Risk of developing post-meningitis symptomatic seizures or epilepsy for people with meningitis treated with osmotic therapy with and without steroids



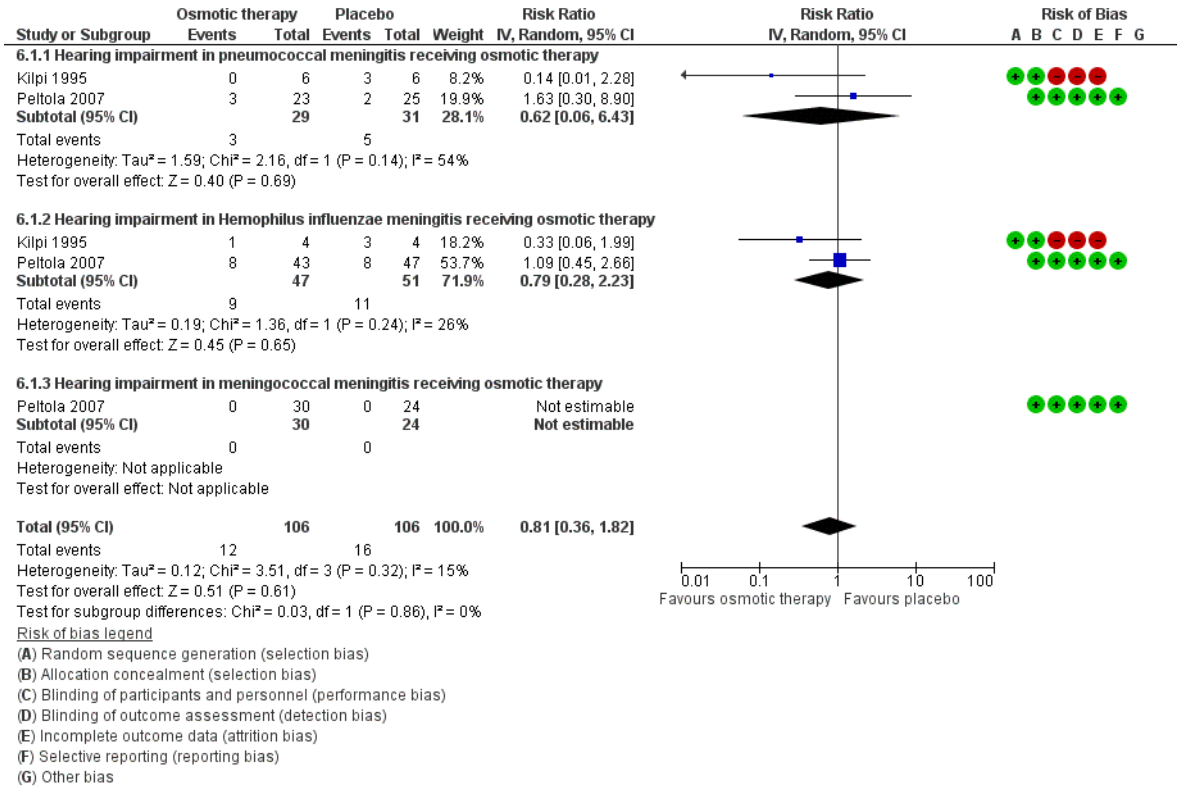
Pathogen-specific mortality: No statistically significant difference in mortality was noted in the osmotic therapy group compared to the placebo group as regards pneumococcal meningitis (6 of 37 [16.2%] versus 10 out of 55 [18.18%]) (RR 0.72, 95% CI 0.3–1.75, *P* = 0.47) *(4, 9)*. Likewise, there was no statistically significant difference in mortality in the osmotic therapy group compared to the placebo group as regards *Hemophilus influenzae* type b (Hib) meningitis (8 of 113 [7.07%] versus 10 out of 114 [8.77%], (RR 0.87, 95% CI 0.37–2.05, *P* = 0.74) *(4, 9)*. With regard to meningococcal meningitis, there was no significant difference in mortality outcomes between the osmotic therapy group and the placebo group (1 of 63 [1.58%] versus 1 out of 53 [1.88%]), (RR 0.85, 95% CI 0.09–8.28, *P* = 0.89) *(4, 9)*.

Fig. WA12.8 Mortality of people with meningitis treated with and without osmotic therapy, disaggregated by causative pathogen



Hearing loss by causative pathogen: No statistically significant difference in hearing loss was observed in the osmotic therapy group compared with the placebo group as regards pneumococcal meningitis (3 of 29 [10.3%] versus 5 out of 31 [16.12%]), (RR 0.62, 95% CI 0.06–6.43, *P* = 0.69) *(4, 9)*. Similarly, there was no statistically significant difference noted in the osmotic therapy group compared with the placebo group as regards Hib meningitis (9 of 47 [19.1%] versus 11 out of 51 [21.56%]), (RR 0.79, 95% CI 0.28–2.23, *P* = 0.65) *(4, 9)*.

Fig. WA12.9 Hearing loss among people with meningitis treated with and without osmotic therapy, disaggregated by causative pathogen



3.3 GRADE evidence profile

Table WA12.3 GRADE evidence profile

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	RCT	Not serious	Not serious	Not serious	Very serious	Undetected	757	740	RR 0.84 (0.65–1.15)	133 per 1000 (172–246)	Low	Critical
Neurological sequelae												
4	RCT	Not serious	Not serious	Not serious	Very serious	644	626	Placebo	RR 0.77 (0.38–1.53)	90 per 1000 (45–147)	Low	Critical
Post-meningitis seizures												
3	RCT	Not serious	Not serious	Not serious	Very serious	Undetected	548	541	RR 0.89 (0.71–1.12)	231 per 1000 (205–394)	Low	Critical
Hearing loss												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
4	RCT	Not serious	Not serious	Not serious	Very serious	Undetected	637	637	RR 0.70 (0.47–1.04)	83 per 1000 (108–178)	Low	Critical

RCT: randomized controlled trial; RR: risk ratio.

[a] There are four categories of certainty of evidence in the GRADE framework: high, moderate, low and very low. See section 2.8 for further details.

4. From evidence to recommendations

4.1 Summary of findings

Table WA12.4 summarizes the findings of this evidence synthesis.

Table WA12.4 Summary of findings: osmotic therapy versus placebo in people with meningitis

Outcome	Anticipated absolute effect (95% CI)		No. of participants and studies	Effects	Certainty of evidence	Plain language summary
	Risk with placebo	Risk with osmotic therapy				
Mortality	149 per 1000	125 per 1000	1011 (4 RCTs)	**RR 0.84** (0.62–1.15)	Low	Osmotic therapy may have had little to no effect on mortality
Neurological sequelae	118 per 1000	90 per 1000	1011 (4 RCTs)	**RR 0.77** (0.38–1.53)	Low	Osmotic therapy may have had little to no effect on neurological sequelae
Post-meningitis seizures	260 per 1000	231 per 1000	839 (3 RCTs)	**RR 0.89** (0.71–1.12)	Low	Osmotic therapy may have had little to no effect on post-meningitis seizures
Hearing loss	118 per 1000	83 per 1000	874 (4 RCTs)	**RR 0.70** (0.47–1.04)	Low	Osmotic therapy may have had little to no effect on hearing loss

RCT: randomized controlled trial; RR: risk ratio.

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Appendix 1. Search strategy for identifying primary studies

A group search of primary studies was conducted for the research questions related to adjunctive osmotic agents therapy. The databases searched included Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL) and clinical trial registry maintained by the United States National Library of Medicine (https://clinicaltrials.gov/).

Table WA12.A1.1 Database: Embase (Elsevier) (https://www.embase.com/#advancedSearch/), searched on 6 February 2024

No.	Searches	Results
1	('meningitis'/exp OR (meningiti* OR (Meningococc* NEAR/3 (infection* OR diseases))):ti,ab)	150 372
2	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR 'fungal meningitis'/exp OR 'HIV-associated meningitis'/exp OR 'parasitic meningitis'/exp OR 'virus meningitis'/exp OR 'aseptic meningitis'/exp OR 'Staphylococcus aureus'/exp OR 'Staphylococcus'/exp OR 'Enterobacteriaceae'/exp OR 'Streptococcus agalactiae'/exp OR 'Streptococcus pyogenes'/exp OR 'Enterovirus'/exp OR 'Herpesviridae'/exp OR 'herpes virus infection'/exp OR 'Simplexvirus'/exp OR 'Flavivirus'/exp OR 'West Nile virus'/exp OR 'Togaviridae'/exp OR 'Mumps'/exp OR 'Mumps virus'/exp OR 'Orthomyxoviridae'/exp OR 'HIV'/exp OR 'Adenoviridae'/exp OR 'Rubella'/exp OR 'Lymphocytic Choriomeningitis'/exp OR 'Rickettsiales'/exp OR 'Spirochaetales'/exp OR 'Leptospira'/exp OR 'Brucella'/exp OR 'Treponema pallidum'/exp OR 'Coxiella'/exp OR 'Mycoplasma'/exp OR 'Naegleria'/exp OR 'Angiostrongylus'/exp OR 'Coccidioides'/exp OR 'Candida'/exp OR 'Histoplasma'/exp OR 'Blastomyces'/exp OR 'Aspergillus'/exp OR 'Syphilis'/exp OR 'Lyme Disease'/exp OR 'Scrub Typhus'/exp OR ((Bacterial OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired) NEAR/5 (meningiti*)):ti,ab,kw,de OR (infectious-meningiti* OR Acute OR fulminat* OR Fulminant OR Sudden-onset OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal*	5 034 758

	OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi):ti,ab,kw,de	
3	(osmotic* OR osmotic-therap* OR glycerol OR mannitol OR hypertonic-saline OR hypertonic-agent* OR sodium-lactate OR osmotic-pressure OR osmotic-diuretic OR sorbitol OR propanetriol OR sodium-chloride OR Osmolality OR Osmol*):ti,ab,kw	218 401
4	(intravenous-fluid* OR oral-fluid* OR fluid-restriction* OR fluid-management OR maintenance-fluid* OR isotonic-solution* OR fluid-therap* OR fluid-balance OR electrolyte-balance OR supportive-therap* OR restricted-fluid* OR plasma-arginine OR restricting-fluids OR rehydration OR hydrat* OR hyponatremia OR water-deprivation OR water-restriction OR dehydration OR dehydrat* OR electrolyt* OR sodium-chloride OR saline OR plasma-substitute OR hypertonic-solution OR ors OR parenteral-nutrition-solution OR albumin OR dextran OR starch OR hemaccel OR gelofusine):ti,ab,kw	1 001 602
5	(steroid* OR corticosteroid* OR glucocorticoids OR dexameth* OR prednisolone OR predniso* OR hydrocortisone OR adrenal-cortex-hormone*):ti,ab,kw	778 336
6	((Adjunct* OR adjuvant*) NEAR/5 (treatment* OR therap*)):ti,ab,kw	169 578
7	#1 AND #2	102 468
8	#3 OR #4 OR #5 OR #6	3 339 245
9	#7 AND #8	8 809
10	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR 'case report'/de	11 277 185
11	#9 NOT #10	6 084
12	[animals]/lim NOT ([animals]/lim AND [humans]/lim)	6 459 077

13	#11 NOT #12	5 485
14	auto inflamm*':ti OR autoimmun*:ti OR 'auto immun*':ti OR rheumatoid:ti OR parkison*:ti OR dementia:ti OR tubercul*:ti OR vaccin*:ti OR cryptococc*:ti OR sarcoid*:ti OR lupus:ti OR infant:ti OR infants:ti OR 'neo natal':ti OR neonatal:ti OR newborn*:ti	1 295 593
15	#13 NOT #14	3 137
16	#17 AND [1998-2024]/py	2 436

Table WA12.A1.2 Database: PubMed (https://pubmed.ncbi.nlm.nih.gov/), searched on 6 February 2024

No.	Searches	Results
1	("Meningitis"[Mesh] OR meningit*[tiab]) OR "Meningococcus disease"[tiab:~3] OR "Meningococcal disease"[tiab:~3] OR "Meningococcal infection"[tiab:~3] OR "Meningococcal infections"[tiab:~3]	92 731
2	Acute[tiab] OR "fulminat*"[tiab] OR "Fulminant"[tiab] OR "Sudden-onset"[tiab] OR "Infectious meningitis"[tiab] OR "Meningitis, bacterial"[Mesh] OR"Bacterial meningitis"[tiab:~5] OR "Meningitis, Aseptic"[Mesh] OR "Aseptic meningitis"[tiab:~3] OR "Meningitis, Viral"[Mesh] OR "Viral meningitis"[tiab:~5] OR "Meningitis, Fungal"[Mesh] OR "Fungal meningitis"[tiab:~5] OR "Parasitic meningitis"[tiab:~5] OR "community acquired meningitis"[tiab:~3] OR "Meningitis, Meningococcal"[Mesh] OR "Meningitis, Pneumococcal"[Mesh] OR "Meningitis, Haemophilus"[Mesh] OR "Meningitis, Listeria"[Mesh] OR "Staphylococcus aureus"[Mesh] OR "Enterobacteriaceae"[Mesh] OR "Enterobacter"[Mesh] OR "Escherichia coli"[Mesh] OR "Streptococcus agalactiae"[Mesh] OR "Streptococcus pyogenes"[Mesh] OR "Enterovirus"[Mesh] OR "Herpesviridae"[Mesh] OR "Herpesviridae Infections"[Mesh] OR "Simplexvirus"[Mesh] OR "Flavivirus"[Mesh] OR "West Nile virus"[Mesh] OR "Togaviridae"[Mesh] OR "Mumps"[Mesh] OR "Mumps virus"[Mesh] OR "Orthomyxoviridae"[Mesh] OR "HIV"[Mesh] OR "Adenoviridae"[Mesh] OR "Rubella"[Mesh] OR "Lymphocytic Choriomeningitis"[Mesh] OR "Rickettsiales"[Mesh] OR "Spirochaetales"[Mesh] OR "Leptospira"[Mesh] OR "Brucella"[Mesh] OR "Treponema pallidum"[Mesh] OR "Coxiella"[Mesh] OR "Mycoplasma"[Mesh] OR "Naegleria"[Mesh] OR "Angiostrongylus"[Mesh] OR "Coccidioides"[Mesh] OR "Candida"[Mesh] OR "Histoplasma"[Mesh] OR "Blastomyces"[Mesh] OR "Aspergillus"[Mesh] OR "Syphilis"[Mesh] OR "Lyme Disease"[Mesh] OR "Scrub Typhus"[Mesh] OR "Meningococc*"[tiab] OR "Neisseria meningitidis"[tiab] OR "N. Meningitidis"[tiab] OR "Pneumococc*"[tiab] OR "S-pneumoniae*"[tiab] OR "Haemophilus influenzae"[tiab] OR "Listeri*"[tiab] OR L-monocytogenes[tiab] OR "Staphylococc*"[tiab] OR "Staph aureus"[tiab] OR "Enterobacter*"[tiab] OR "Enterococc*"[tiab] OR "Escherichia coli"[tiab] OR "E-coli"[tiab] OR "Streptococcus agalactiae"[tiab] OR "S agalactiae*"[tiab] OR "S pyogenes"[tiab] OR "Enterovir*"[tiab] OR "Coxsackieviruses"[tiab] OR "Herpesviridae"[tiab] OR "Herpesvirus*"[tiab] OR "herpes virus*"[tiab] OR "Varicella zoster"[tiab] OR flavi-virus*[tiab] OR Japanese-encephal*[tiab] OR Tick-borne-encephal*[tiab] OR Powassan-virus*[tiab] OR "West Nile virus"[tiab] OR "Togaviridae"[tiab] OR Toga-virus*[tiab] OR Togavir*[tiab] OR equine-encephal* OR Bunyavirus*[tiab] OR crosse-encephal*[tiab] OR Toscana-virus*[tiab] OR Reovirus*[tiab]	3 364 413

	OR tick-fever*[tiab] OR paramyxovir*[tiab] OR "Mumps"[tiab] OR morbillivirus*[tiab] OR parainfluenza*[tiab] OR "Orthomyxovir*"[tiab] OR "Influenza"[tiab] OR "HIV"[tiab] OR "human-immuno-deficienc*"[tiab] OR "Adenoviridae"[tiab] OR adenovirus*[tiab] OR Arenavir*[tiab] OR "Choriomeningit*"[tiab] OR "LCMV"[tiab] OR "Rickettsi*"[tiab] OR Orientia-spp[tiab] OR Ehrlichia-spp[tiab] OR "spirochet*"[tiab] OR Borrelia-spp[tiab] OR B-burgdorferi[tiab] OR "leptospir*"[tiab] OR "Treponema pallidum"[tiab] OR "Brucell*"[tiab] OR "Coxiella"[tiab] OR "Mycoplasma"[tiab] OR spirillum*[tiab] OR "Naegleria"[tiab] OR "angiostrongyl*"[tiab] OR Trichinella-spiralis*[tiab] OR "Candida"[tiab] OR "Coccidioid*"[tiab] OR "Histoplasm*"[tiab] OR "Blastomyc*"[tiab] OR Sporothrix*[tiab] OR "Aspergill*" [tiab] OR "Lyme"[tiab] OR "Syphili*"[tiab] OR "Scrub Typhus"[tiab] OR tsutsugamushi[tiab]	
3	#1 AND #2	68 069
4	osmotic*[tiab] OR osmotic-therap*[tiab] OR glycerol[tiab] OR mannitol[tiab] OR hypertonic-saline[tiab] OR hypertonic-agent*[tiab] OR sodium-lactate[tiab] OR osmotic-pressure[tiab] OR osmotic-diuretic[tiab] OR sorbitol[tiab] OR propanetriol[tiab] OR sodium-chloride[tiab] OR Osmolality[tiab] OR Osmol*[tiab]	186 146
5	#3 AND #4	257
6	(intravenous-fluid*[tiab] OR oral-fluid*[tiab] OR fluid-restriction*[tiab] OR fluid-management[tiab] OR maintenance-fluid*[tiab] OR isotonic-solution*[tiab] OR fluid-therap*[tiab] OR fluid-balance[tiab] OR electrolyte-balance[tiab] OR supportive-therap*[tiab] OR restricted-fluid*[tiab] OR plasma-arginine[tiab] OR restricting-fluids[tiab] OR rehydration[tiab] OR hydrat*[tiab] OR hyponatremia[tiab] OR water-deprivation[tiab] OR water-restriction[tiab] OR dehydration[tiab] OR dehydrat*[tiab] OR electrolyt*[tiab] OR sodium-chloride[tiab] OR saline[tiab] OR plasma-substitute[tiab] OR hypertonic-solution[tiab] OR ors[tiab] OR parenteral-nutrition-solution[tiab] OR albumin[tiab] OR dextran[tiab] OR starch[tiab] OR hemaccel[tiab] OR gelofusine[tiab])	778 552
7	#3 AND #6	1 120
8	Steroids[Mesh] OR steroid*[tiab] OR corticosteroid*[tiab] OR glucocorticoids[tiab] OR dexameth*[tiab] OR prednisolone[tiab] OR predniso*[tiab] OR hydrocortisone[tiab] OR adrenal-cortex-hormone*[tiab]	1 231 280
9	#3 AND #8	3 694

10	("adjunctive treatment"[tiab:~5] OR "adjunctive treatments"[tiab:~5] OR "Adjunctive therapy"[tiab:~5] OR "Adjunctive therapies"[tiab:~5] OR "adjuvant therapy"[tiab:~5] OR "adjuvant therapies"[tiab:~5] OR "adjunctive treatments"[tiab:~5] OR "adjunctive treatment"[tiab:~5] OR "adjunct therapy"[tiab:~5] OR "adjunct therapies"[tiab:~5] OR "adjunct treatments"[tiab:~5] OR "adjunct treatment"[tiab:~5])	86 083
11	#3 AND #10	507
12	#11 OR #9 OR #7 OR #5	4 995
13	"Letter"[Publication Type] OR "Editorial"[Publication Type] OR "comment"[Publication Type] OR "case reports"[publication type]	4 374 866
14	#12 NOT #13	3 204
15	("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	5 191 262
16	#14 NOT #15	2 766
17	#16 Filters: from 1998 - 2024	1 737

Table WA12.A1.3 Database: CENTRAL (https://www.cochranelibrary.com/advanced-search/search-manager?search=7376359), searched on 2 May 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis] explode all trees	856
2	meningit*:ti,ab OR (Meningococc* NEAR/3 (disease* OR infection*)):ti,ab,kw	2 547
3	(osmotic* OR osmotic-therap* OR glycerol OR mannitol OR hypertonic-saline OR hypertonic-agent* OR sodium-lactate OR osmotic-pressure OR osmotic-diuretic OR sorbitol OR propanetriol OR sodium-chloride OR Osmolality OR Osmol*):ti,ab,kw	18 452
4	(intravenous-fluid* OR oral-fluid* OR fluid-restriction* OR fluid-management OR maintenance-fluid* OR isotonic-solution* OR fluid-therap* OR fluid-balance OR electrolyte-balance OR supportive-therap* OR restricted-fluid* OR plasma-arginine OR restricting-fluids OR rehydration OR hydrat* OR hyponatremia OR water-deprivation OR water-restriction OR dehydration OR dehydrat* OR electrolyt* OR sodium-chloride OR saline OR plasma-substitute OR hypertonic-solution* OR hyptertonic-agent* OR ors OR parenteral-nutrition-solution OR albumin OR dextran OR starch OR hemaccel OR gelofusine):ti,ab,kw	94 256
5	MeSH descriptor: [Steroids] explode all trees	75 652
6	(steroid* OR corticosteroid* OR glucocorticoids OR dexameth* OR prednisolone OR predniso* OR hydrocortisone OR adrenal-cortex-hormone*):ti,ab,kw	93 271
7	((Adjunct* OR adjuvant*) NEAR/5 (treatment* OR therap*)):ti,ab,kw	34 213
8	#1 OR #2	2 718
9	#3 OR #4 OR #5 OR #6 OR #7	259 766
10	#9 AND #8	482
11	Limits Jan 1998 to Dec 2024	474

Table WA12.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 7 February 2024

No.	Searches	Field	Results
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	(osmotic OR glycerol OR mannitol OR "hypertonic saline" OR "sodium lactate" OR sorbitol OR propanetriol OR "sodium chloride" OR Osmolality) NOT vaccine	Intervention	
3	1 and 2		15
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	("isotonic solution" OR plasma OR rehydration OR hydrate OR hydration OR hyponatremia OR dehydration OR dehydrate OR electrolyte OR saline OR hypertonic OR "parenteral nutrition" OR albumin OR dextran) NOT Vaccine	Intervention	
3	1 and 2		50
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	hemaccel OR gelofusine OR starch	Intervention	
3	1 and 2		0
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	

2	(Steroids OR steroid OR corticosteroid OR glucocorticoids OR dexamethasone OR prednisolone OR prednisone OR hydrocortisone OR “adrenal cortex hormone”)	Intervention	
3	1 and 2		47
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	"adjunctive treatment" OR "adjunctive treatments" OR "Adjunctive therapy" OR "Adjunctive therapies" OR "adjuvant therapy" OR "adjuvant therapies" OR "adjunctive treatments" OR "adjunctive treatment" OR "adjunct therapy"	Intervention	
3	1 and 2		7
Total			119
Duplicates			28
To screen			91

Appendix 2. Categories in the data extraction form

Study name		
Publication details	Type of study	
	Duration	
	Location	
	Type of country: LMIC/HIC	
	Date of trial	
	Date of publication	
	Sponsor and funding	
	Protocol publication (for RCTs)	
		Intervention **Comparator**
Study details	Number of participants	
	Patients who completed study	
	Reason for discontinuation	
	Missing outcomes	
	Deviation from protocol	
	Inclusion criteria	
	Exclusion criteria	
Patient demographic data	Age	
	Gender	
	Vaccination status (pneumococcal vaccine)	
	Immunocompromised	
	Source of Infection: RTA/sinus/abscess/ any other risk factor	
	Duration of illness	

Clinical features		**Intervention**	**Comparator**
	Seizures		
	Altered sensorium		
	Hemiparesis		
	Papilloedema		
	Cranial nerve palsy		
Disease details	Causative organism		
	Culture and sensitivity details		
	Severity		
	Risk assessment scale		
Comorbidity/ Confounding factors	Diabetes		
	Hypertension		
	Stroke		
	Seizure		
Corticosteroid details	Name		
	Type of corticosteroid, start of therapy from date of admission or symptoms		
	Dose		
	Frequency		
	Route		
	duration		
Other therapeutic intervention	Antimicrobial therapy		
	Other adjunctive therapies		
	Immunosuppressants		
Antimicrobial therapy		**Intervention**	**Comparator**
	Type of antibiotic		

	Dosage			
	Duration of therapy			
CSF analysis			**Intervention**	**Comparator**
	Cell count and type – at admission			
	Cell count and type – at discharge /2nd analysis			
	Protein – at admission			
	Protein – at discharge /2nd analysis			
	Glucose – at admission			
	Glucose – at discharge/2nd analysis			
	Change between the 1st and 2nd LP			
	P value			
Outcomes	Outcomes assessed in the study, with number of participants assessed for each outcome			
	Approach to primary analysis (e.g. per protocol, intention to treat)			
	Were any imputations made for missing data?			
Critical outcomes	Mortality – total study 28 to 30 days in hospital	No. of patients		
	Mortality with respect to each of the etiological organisms			
	Time to resolution of symptoms	No. of days Median (range)		
		Length of hospital stay		
	Disease complications	Sepsis		
		DIC		

		Neurological complications
		Cognitive impairment
		Seizures
		Hearing sequelae
		GI bleeding
		Infection/Fever
		Arthritis
		Behavioural changes
		Hyperglycaemia
Important outcomes	Adverse effects – antimicrobe-related adverse events like *C. difficile* infection and candidemia infection	No. of patients
		No. of events
		Drug-related adverse events
	CSF culture positivity rate	No. of patients with positive culture
		Proposition of positive culture
	Blood culture positivity rate	No. of patients
		Positivity rate
Follow-up	What was planned, way participants were followed up	
	Results, length of follow-up	
	Lost to follow-up: number and characteristics	

CSF: cerebrospinal fluid; DIC: disseminated intravascular coagulation; GI: gastrointestinal; HIC: high-income country; LMICs: low- and middle-income countries; LP: lumbar puncture; RCT: randomized controlled trial.

13. Fluid management

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Abbreviations

CI	confidence interval
CSF	cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RoB 2	Version 2 of the Cochrane risk-of-bias tool for randomized trials
RR	risk ratio

1. Background

Acute meningitis is a term used to denote infection of the meninges (protective membrane that lines the brain and spinal cord). It is associated with high morbidity and mortality, especially when there is a delay in diagnosis and treatment.

Acute bacterial meningitis continues to be a disease marked by high mortality and morbidity rates. The prognosis of individuals suffering from bacterial meningitis is influenced by various factors, including age, the time elapsing before effective antibiotic treatment, the type of microorganism responsible, the quantity of bacteria or active bacterial products in the cerebrospinal fluid (CSF) at the time of diagnosis, the host's inflammatory response, and the time taken to sterilize CSF cultures *(1)*.

The highest mortality and morbidity rates are observed in newborns and elderly people. Nearly one in five individuals contracting bacterial meningitis does not survive, and many survivors experience long-term neurological deficits *(1)*. A significant proportion of children with meningitis face permanent, severe or moderately severe disabilities, along with more subtle deficits *(2, 3)*.

Prompt and appropriate antimicrobial and supportive treatment substantially improve the chances of survival, particularly in infants and children, where case fatality rates for bacterial meningitis have fallen to below 10% and to less than 5% for meningococcal meningitis *(4)*.

Management of fluid and electrolyte balance plays a crucial role in the treatment of meningitis. Both over-hydration and under-hydration have been associated with adverse outcomes. Initial fluid restriction in the management of meningitis in children has been advocated *(5, 6)*. The rationale behind fluid restriction is based on reports of hyponatraemia, which is attributed to increased levels of circulating antidiuretic hormone. Associations have been observed between the degree of hyponatraemia, the presence of seizures, the severity of the acute disease, and adverse neurodevelopmental outcomes *(7)*. These findings have been linked with a high incidence of cerebral oedema among individuals with acute bacterial meningitis *(5, 8, 9)*. Consequently, some researchers have proposed that fluid restriction could mitigate exacerbations of cerebral oedema and improve neurological outcomes *(10)*.

The primary objective of this review was to study the effects of adjuvant fluid restriction on mortality, and neurological and audiological parameters in people with acute bacterial meningitis.

2. Methodology

2.1 Research question and study design

Among suspected, probable or confirmed cases of acute bacterial meningitis, should fluid restriction be recommended as a way of decreasing morbidity and mortality outcomes?

Population: Suspected, probable or confirmed cases of acute bacterial meningitis.

Subgroup analysis: Pathogen (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*, and Group B streptococcus); Age group (child, adult); World Bank income classification (high-income country, low- or middle-income country).

Intervention: Fluid restriction.

Comparator: Standard care without fluid restriction.

Outcomes

Critical outcomes:

- neurological complications (neurological sequelae,[20] hearing loss)
- mortality
- adverse effects.

Important outcomes: impact on disease course (time to resolution of symptoms, persistent fever).

Study design: The study was designed as a systematic review with meta-analysis including only randomized control trials (RCTs). It was planned in accordance with the Cochrane guidelines for systematic reviews with meta-analysis. The objective was to identify all relevant RCTs on fluid restriction in acute meningitis. Where possible, the RCTs were supplemented with relevant prospective or retrospective observation studies having a comparator arm.

2.2. Eligible studies

Published language: All relevant studies were searched for, regardless of language. Articles written in English were considered by the research team.

Exclusion criteria

The following study types were excluded:

[20] Neurological sequelae are defined as follows: hearing loss, speech and/or language impairment, seizures, neurocognitive impairment, psychological after-effects (stress, depression, behavioural changes), hydrocephalus, motor deficits, vision impairment.

- Non-randomized studies without a comparator arm (e.g. case reports, case series, letters, editorials, abstracts, etc.);
- Studies lacking data on fluid restriction;
- Any ongoing trials and studies, or studies with no evaluable outcome data.

The following disease categories were excluded:

- Meningitis in newborns (0–28 days);
- Hospital-acquired, nosocomial and health-care-associated meningitis;
- Subacute and chronic meningitis, including tuberculous, cryptococcal and eosinophilic meningitis;
- Non-infectious meningitis (e.g. drugs, malignancy, autoimmune diseases).

2.3 Search strategy

The following databases were searched: PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Epistemonikos, Web of science, Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (ClinicalTrials.gov). All the databases were searched for studies published from 1946 to 6 February 2024.

The reference lists of relevant publications were checked for any unidentified trials. In addition, clinical trial registries were searched, including ClinicalTrials.gov, for completed RCTs. National or regional databases or grey literature were also searched if it was deemed relevant.

2.4 Selection of studies

The data obtained from the search were uploaded to the Rayyan tool *(11)* and screened by the authors independently using Rayyan software. The full text of all potentially relevant studies was retrieved. Each study report was examined to ensure that no duplicates were included. Any disagreements were resolved through discussion. The reasons for excluding studies are given in Table WA13.2.

Relevant systematic reviews, including one Cochrane review by Maconochie et al. *(12)*, were identified up to 6 February 2024 and used as a seed articles. Rayyan software was used to categorize articles according to the inclusion and exclusion criteria. The selection of studies was carried out as follows.

- Studies were selected from the bibliographic database by two authors independently on the basis of the title and abstract.
- Those that addressed the research question and met the inclusion and exclusion criteria were selected.
- Any conflicts between the two authors were resolved by discussion, and the third author was also involved in the final selection of the studies.

- The full text of the studies was then downloaded. The studies were divided into RCTs, systematic reviews and prospective cohort studies.
- The total number of citations retrieved from the databases, with reasons for inclusion and exclusion, are presented in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) format (see Fig. WA13.1).

2.5 Data extraction and management

A piloted data extraction form was used to record data on study characteristics, study setting, participant characteristics, disease severity, comorbidity, adjunctive corticosteroids treatment and administration, other treatments given, and outcome measures as defined by the research question (see Appendix 2). When there were studies with multiple treatment groups, only the studies that included groups receiving corticosteroids and groups receiving a placebo were considered in the review. Any disagreements were resolved through discussion.

Other data extracted included World Bank country income classification (i.e. high-income country, low- or middle-income country), demographic profile of the study participants, study characteristics, location, number of study participants in the intervention and comparator arms, details of the study drug or treatment, adverse effects and the investigation profile, along with treatment details. The details of the corticosteroids that were collected include type of corticosteroid, dosage, duration and administration in relation to the antibiotics.

For dichotomous outcomes, the number of participants who had experienced the event and the number of participants in each treatment group were recorded. The number of participants analysed in each arm was also recorded, and the discrepancy between the figures was used to calculate the number of participants lost to follow-up, which allowed the team to perform sensitivity analyses to investigate the effect of missing data if necessary. For continuous outcomes, means and standard deviations for the outcomes in each group were extracted; medians were recorded for narrative comparisons where means were unavailable. The review was performed and recorded in accordance with the recommendations given in the *Cochrane handbook for systematic reviews of interventions*.

2.6 Assessment of risk of bias in studies included in the review

The methodological quality of the included studies was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB 2) *(13)* (see Figs WA13.2a and 2b). Each of the included studies was assessed on the basis of a number of pre-defined parameters, including the following: analysis of the randomization process to assess the risk of selection bias; detection of any deviation from the protocol to assess the risk of performance bias; attrition bias; reporting bias; detection bias; and presence of any additional source of bias. The results of the RoB 2 analysis were used in the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) of the outcomes. The treatment effect was measured using the risk ratio (RR), with 95% confidence interval (CI). Visual inspection of funnel plots was used to detect the presence of publication bias.

2.7 Data synthesis

The data were analysed using Review Manager Web software (Version 5.4) *(14)*. Owing to the presence of substantial heterogeneity across the studies, which spanned a wide range of timeframes and geographical locations, and contained potential confounders, the meta-analyses were performed using a random-effect model based on the inverse variance method. All outcome measures were dichotomous.

2.8 Assessment of the certainty of the evidence (GRADE evidence profiles)

The results of the analysis are summarized in Table WA13.4, which also presents the estimates of the summary effects for the critical outcomes and other important outcomes, with illustrative comparative risks. The GRADE framework, as developed by the GRADE Working Group *(15)*, was used to evaluate the certainty of the evidence for each outcome. GRADE levels of certainty are defined in Box WA13.1.

Box WA13.1 The certainty of evidence used in GRADE	
High ⊕⊕⊕⊕	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

2.9 Analysis of primary outcome

Primary outcome measures comprised:

- Mortality among people with meningitis undergoing fluid restriction,
- Neurological sequelae.

2.10 Analysis of subgroups or subsets and investigation of heterogeneity

Heterogeneity was assessed by performing subgroup analysis of study participants on the basis of the following.

- Causative pathogens: *Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae* and Group B streptococcus.
- Presence or absence of neurological sequelae in people with meningitis undergoing fluid restriction with and without hyponatraemia.

A heterogeneity assessment was performed by means of visual inspection of the forest plots in order to determine the closeness of point estimates to each other and the overlap of CIs. We used the Chi-square test with a *P*-value of 0.10 to indicate statistical significance and the I^2 statistic to measure heterogeneity. The following ranges. outlined in the *Cochrane handbook for systematic reviews of interventions*, were used to interpret the I^2 statistic – 0–40%: might not be important; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; 75–100%: considerable heterogeneity *(16)*.

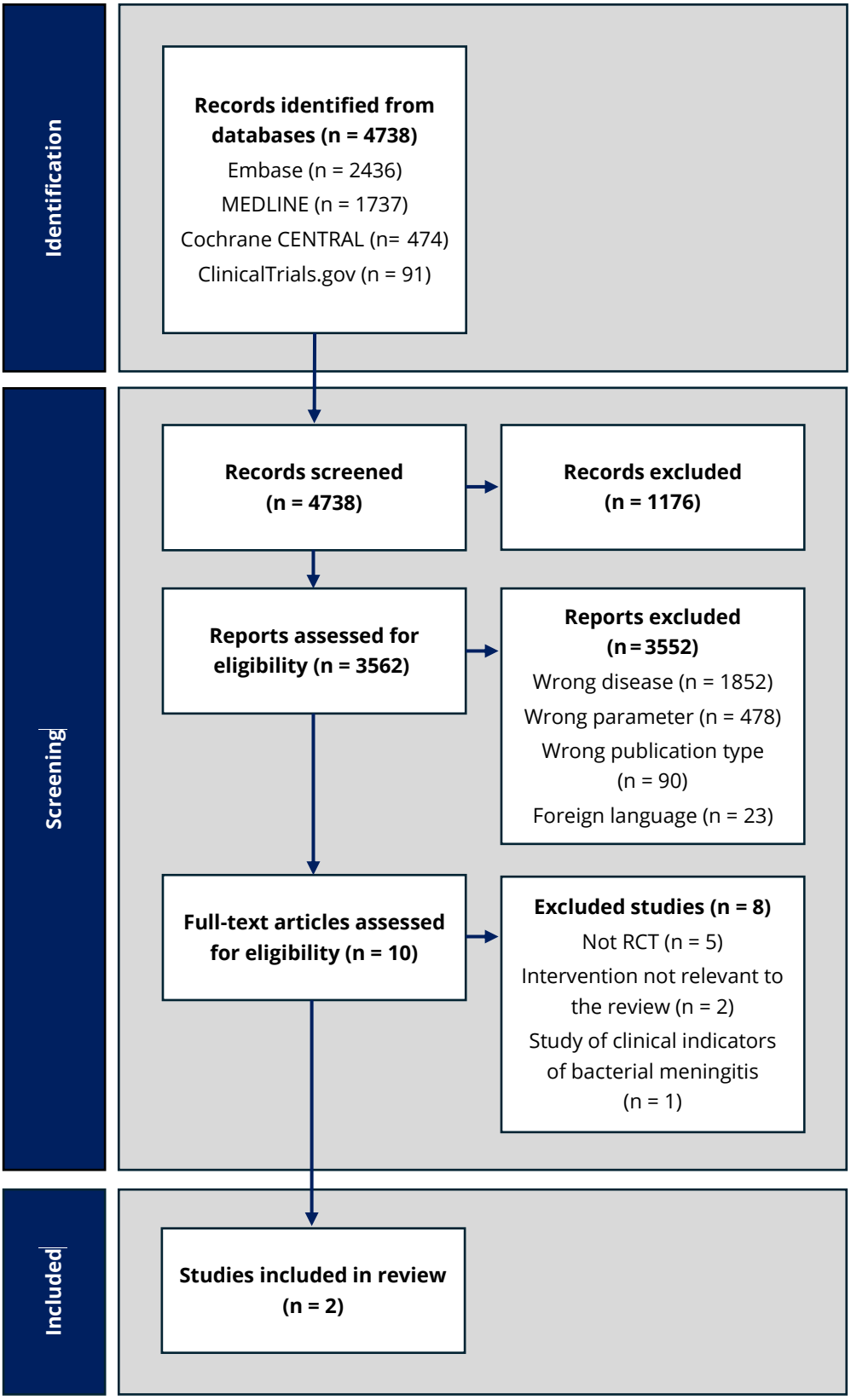
The magnitude and direction of effects were considered, as were the strength of the evidence for heterogeneity (e.g. *P* value from the Chi-square test when determining the importance of the observed I^2 value).

3. Results

3.1 Studies identified by the search process

Figure WA13.1 presents the PRISMA flow diagram for this review.

Fig. WA13.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review and the GRADE evidence profiles

A total of 4738 records were screened, of which 1176 duplicates were removed. Of the remaining 3562 articles, 3552 were excluded for the following reasons: 1852 articles involved the wrong disease, 478 assessed parameters that were not relevant to the scope of this review, 90 were based on unsuitable articles lacking data on real-world cases (e.g. case reports, case series, pathogenicity studies, animal studies, editorials and correspondence), and 1109 were excluded for other reasons. Of the 10 remaining studies, two were eligible for meta-analysis. Details of these are given in Table WA13.1.

Table WA13.1 Characteristics of the studies included in the GRADE evidence profiles

Lead author (Year), Country of conduct	Study design	Overall risk of bias (study level)	Population	Intervention	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
Duke (2002), Papua New Guinea *(17)*	RCT	Low	Children up to 12 years of age	Breast milk by nasogastric tube at 60% of normal maintenance volumes (n = 172)	Intravenous half-normal saline and 5% dextrose at 100% of normal maintenance volumes (n = 174) for the first 48 h of treatment	Mortality	Neurological sequelae (seizures, motor weakness), visual impairment, hydrocephalus, hearing impairment hypoglycaemia, hyponatraemia, pulmonary oedema	Baseline, 14 days, 3 months
Singhi (1995), India *(18)*	RCT	High	Children up to 7 years of age	65% calculated maintenance fluid requirement, given as intravenous 1/5th normal saline in 5% dextrose for 24 hours, followed by a gradual liberalisation at a rate of 10 ml/kg per 8 h after 24 hours of hospital stay if serum	Maintenance fluid requirements (110 ml/kg for first 10 kg, 50 ml/kg for next 10 kg and 25 ml/kg for subsequent weight) given intravenously and comprising 1/5th normal saline in 5% dextrose as long as	Mortality	Hypoglycaemia, change in osmolality	N at baseline and after 48 hours

Lead author (Year), Country of conduct	Study design	Overall risk of bias (study level)	Population	Intervention	Comparator	Outcome domains with available data (synthesis method/ metric)	Specific outcome measure	Time points of measurement
				sodium and plasma osmolality had returned to normal and if there were no clinical signs of dehydration (n = 28)	they required intravenous fluids (n = 22)			

RCT: randomized controlled trial.

3.1.2 Studies excluded from the review

This subsection presents details of the studies excluded from the review and reasons for exclusion (see Table WA13.2).

Table WA13.2. Studies excluded from the review, with reasons

Lead author (Year)	Study type	Population	Intervention	Comparator	Outcome	Reasons for exclusion
Brown (1994) *(10)*	Review article	NA	NA	NA	NA	Not an RCT
Duke (1998) *(19)*	Review article	NA	NA	NA	NA	Not an RCT
Floret (1999) *(20)*	Review article	NA	NA	NA	NA	Not an RCT
Berkley (2004) *(21)*	Retrospective	People with bacterial meningitis	NA	NA	NA	Study of indicators of bacterial meningitis; not an RCT
Pelkonen (2011) *(22)*	RCT	Children 2 months to 13 years of age with acute bacterial meningitis	Cefotaxime infusion/bolus with paracetamol	Cefotaxime infusion/bolus with placebo	Mortality	Intervention is not relevant to this review
Maitland (2013) *(23)*	RCT	Children, aged 60 days to 12 years, with severe febrile illness	Albumin bolus/saline bolus	No bolus	Mortality	Intervention not relevant to the review; study included children with severe infections (not limited to acute bacterial meningitis)

Roine (2014) *(24)*	Post hoc analysis of Pelkonen et al.	Children 2 months to 13 years of age with acute bacterial meningitis	NA	NA	NA	Not an RCT
van Paridon (2015) *(25)*	Retrospective study	People with sepsis	NA	NA	NA	Not an RCT

NA: not applicable; RCT: randomized controlled trial.

3.2 Intervention effects

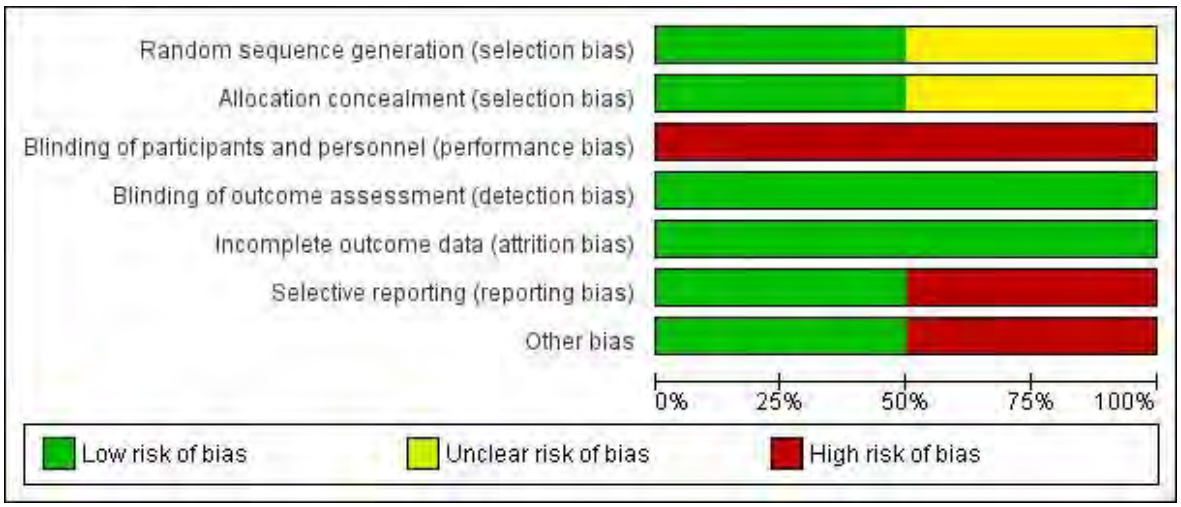
3.2.1 Risk of bias

Overall, one of the included studies (Singhi et al., 1995) had a high risk of bias, while the other had a low risk (Duke et al., 2002) *(17, 18)*. The study by Duke et al. used opaque sealed, envelopes that were numbered using a computer-generated sequence, thereby ensuring random allocation. The other study used a random numbers table but the allocation concealment process was not described. There was no blinding done in the study by Duke et al., and it was unclear whether or not blinding was done in the study by Singhi et al. Figs. WA13.2a and 2b present the results of the risk-of-bias assessment.

Fig. WA13.2a. Risk of bias in studies included in the review (assessed using the RoB 2 tool)

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (selection bias)	Other bias
Duke 2002	+	+	−	+	+	+	+
Singhi 1995	?	?	−	+	+	−	−
+ Low risk		? Some concerns			− High risk		

Fig. WA13.2b. Review authors' judgements of individual risk-of-bias items presented as percentages across all included studies



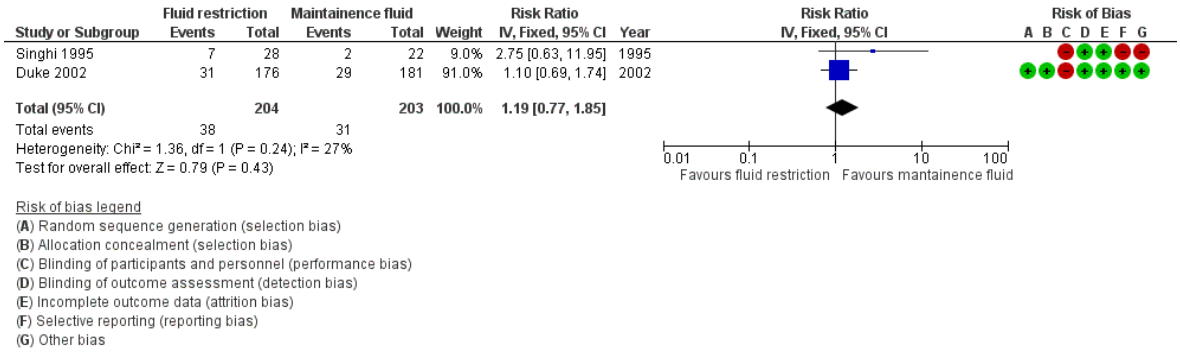
3.3 Forest plots

This section outlines the primary outcomes and subgroup analysis of the evidence synthesis in detail, giving forest plots for the primary outcomes.

3.3.1 Primary outcomes

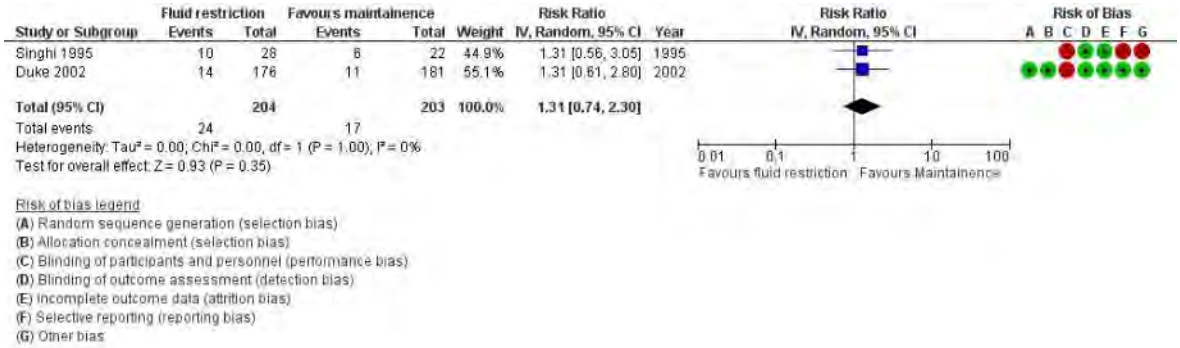
Mortality: Very low certainty evidence from two RCTs involving 407 children suggested that the effect of fluid restriction on mortality at admission compared with normal fluid maintenance was uncertain (RR 1.19, 95% CI 0.77–1.85) (20, 21) *(16, 17)*.

Fig. WA13.3 Effect of fluid restriction vs fluid maintenance on mortality



Neurological sequelae: Very low certainty evidence from two RCTs involving 407 children suggested that the effect of fluid restriction on sequelae at admission compared with normal fluid maintenance was uncertain (RR 1.31, 95% CI 0.74–2.30) *(17, 18)*.

Fig. WA13.4 Effect of fluid restriction vs fluid maintenance on neurological sequelae



3.3.2 Subgroup analysis

Mortality: A single study (Singhi et al., 1995 *[18]*) reported on mortality according to hyponatraemia status. Evidence showed no difference in mortality among those with or without hyponatraemia between the fluid-restricted group and standard maintenance groups. Mortality: 4 out of 15 (26.67%) versus 0 out of 11 (0%) in the hyponatraemia group and 3 out of 13 (23%) versus 2 out of 11 (18%) in the no hyponatraemia group; *P* = 0.48.

Neurological sequelae: A single study (Singhi et al., 1995 *[18]*) reported on sequelae according to hyponatraemia status. Evidence showed no difference in sequelae among those with or without hyponatraemia between the fluid-restricted group and the standard maintenance groups. Sequelae: 6 out of 15 (40%) versus 4 out of 11 (36.36%) in the hyponatraemia group and 4 out of 13 (23%) versus 2 out of 11 (18%) in the no hyponatraemia group; *P* = 0.48.

3.4 GRADE evidence profile

This section presents the GRADE evidence profiles of the studies included in this review (see Table WA13.3).

Table WA13.3 GRADE evidence profile: fluid restriction in cases of meningitis

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other con-siderations	Interven-tions	Control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	RCT	Serious	Not serious	Not serious	Very serious	Undetected	204	203	RR 1.19 (0.77–1.85)	176 per 1000	Very low	Fluid restriction probably does not reduce mortality
Neurological sequelae												

Certainty assessment							Sample size		Effect		Certainty[a]	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions	Control	Relative (95% CI)	Absolute (95% CI)		
2	RCT	Serious	Not serious	Not serious	Very serious	Undetected	204	203	RR 1.31 (0.7–2.30)	110 per 1000	Very low	The evidence suggests that fluid restriction does not increase neurological sequelae overall

[a] There are four categories of certainty of evidence in the GRADE framework: high, moderate, low and very low. See section 2.8 for further details.

4. From evidence to recommendations

4.1 Summary of findings

Table WA13.4 summarizes the findings of this evidence synthesis.

Table WA13.4 Summary of findings: fluid restriction compared with fluid maintenance for people with meningitis

Outcome	Anticipated absolute effect (95% CI)		No. of participants and studies	Effects	Certainty of evidence	Plain language summary
	Risk with maintenance fluid	Risk with fluid restriction				
Mortality	148 per 1000	176 per 1000 (114 to 273)	407 (3 RCTs)	RR 1.19 (0.77–1.85)	Very low	The effect of fluid restriction on mortality at admission compared with normal fluid maintenance was uncertain
Neurological sequelae	84 per 1000	90 per 1000 (62 to 193)	407 (2 RCTs)	RR 1.31 (0.74–2.30)	Very low	The effect of fluid restriction on neurological sequelae compared with normal fluid maintenance was uncertain

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Appendix 1. Search strategy for identifying primary studies

A group search of primary studies was conducted for the research questions concerning adjunctive fluid restriction therapy. The databases searched included Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Cochrane Central Register of Controlled Trials (CENTRAL) and the clinical trial registry maintained by the United States National Library of Medicine (https://ClinicalTrials.gov).

Table WA13.A1.1 Database: Embase (Elsevier) (https://www.embase.com/#advancedSearch/), searched on 6 February 2024

No.	Searches	Results
1	('meningitis'/exp OR (meningiti* OR (Meningococc* NEAR/3 (infection* OR diseases))):ti,ab)	150 372
2	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR 'fungal meningitis'/exp OR 'HIV-associated meningitis'/exp OR 'parasitic meningitis'/exp OR 'virus meningitis'/exp OR 'aseptic meningitis'/exp OR 'Staphylococcus aureus'/exp OR 'Staphylococcus'/exp OR 'Enterobacteriaceae'/exp OR 'Streptococcus agalactiae'/exp OR 'Streptococcus pyogenes'/exp OR 'Enterovirus'/exp OR 'Herpesviridae'/exp OR 'herpes virus infection'/exp OR 'Simplexvirus'/exp OR 'Flavivirus'/exp OR 'West Nile virus'/exp OR 'Togaviridae'/exp OR 'Mumps'/exp OR 'Mumps virus'/exp OR 'Orthomyxoviridae'/exp OR 'HIV'/exp OR 'Adenoviridae'/exp OR 'Rubella'/exp OR 'Lymphocytic Choriomeningitis'/exp OR 'Rickettsiales'/exp OR 'Spirochaetales'/exp OR 'Leptospira'/exp OR 'Brucella'/exp OR 'Treponema pallidum'/exp OR 'Coxiella'/exp OR 'Mycoplasma'/exp OR 'Naegleria'/exp OR 'Angiostrongylus'/exp OR 'Coccidioides'/exp OR 'Candida'/exp OR 'Histoplasma'/exp OR 'Blastomyces'/exp OR 'Aspergillus'/exp OR 'Syphilis'/exp OR 'Lyme Disease'/exp OR 'Scrub Typhus'/exp OR ((Bacterial OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired) NEAR/5 (meningiti*)):ti,ab,kw,de OR (infectious-meningiti* OR Acute OR fulminat* OR Fulminant OR Sudden-onset OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR	5 034 758

	Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi):ti,ab,kw,de	
3	(osmotic* OR osmotic-therap* OR glycerol OR mannitol OR hypertonic-saline OR hypertonic-agent* OR sodium-lactate OR osmotic-pressure OR osmotic-diuretic OR sorbitol OR propanetriol OR sodium-chloride OR Osmolality OR Osmol*):ti,ab,kw	218 401
4	(intravenous-fluid* OR oral-fluid* OR fluid-restriction* OR fluid-management OR maintenance-fluid* OR isotonic-solution* OR fluid-therap* OR fluid-balance OR electrolyte-balance OR supportive-therap* OR restricted-fluid* OR plasma-arginine OR restricting-fluids OR rehydration OR hydrat* OR hyponatremia OR water-deprivation OR water-restriction OR dehydration OR dehydrat* OR electrolyt* OR sodium-chloride OR saline OR plasma-substitute OR hypertonic-solution OR ors OR parenteral-nutrition-solution OR albumin OR dextran OR starch OR hemaccel OR gelofusine):ti,ab,kw	1 001 602
5	(steroid* OR corticosteroid* OR glucocorticoids OR dexameth* OR prednisolone OR predniso* OR hydrocortisone OR adrenal-cortex-hormone*):ti,ab,kw	778 336
6	((Adjunct* OR adjuvant*) NEAR/5 (treatment* OR therap*)):ti,ab,kw	169 578
7	#1 AND #2	102 468
8	#3 OR #4 OR #5 OR #6	3 339 245
9	#7 AND #8	8 809

10	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR 'case report'/de	11 277 185
11	#9 NOT #10	6 084
12	[animals]/lim NOT ([animals]/lim AND [humans]/lim)	6 459 077
13	#11 NOT #12	5 485
14	auto inflamm*':ti OR autoimmun*:ti OR 'auto immun*':ti OR rheumatoid:ti OR parkison*:ti OR dementia:ti OR tubercul*:ti OR vaccin*:ti OR cryptococc*:ti OR sarcoid*:ti OR lupus:ti OR infant:ti OR infants:ti OR 'neo natal':ti OR neonatal:ti OR newborn*:ti	1 295 593
15	#13 NOT #14	3 137
16	#17 AND [1998-2024]/py	2 436

Table WA13.A1.2 Database: PubMed (https://pubmed.ncbi.nlm.nih.gov/), searched on 6 February 2024

No.	Searches	Results
1	("Meningitis"[Mesh] OR meningit*[tiab]) OR "Meningococcus disease"[tiab:~3] OR "Meningococcal disease"[tiab:~3] OR "Meningococcal infection"[tiab:~3] OR "Meningococcal infections"[tiab:~3]	92 731
2	Acute[tiab] OR "fulminat*"[tiab] OR "Fulminant"[tiab] OR "Sudden-onset"[tiab] OR "Infectious meningitis"[tiab] OR "Meningitis, bacterial"[Mesh] OR"Bacterial meningitis"[tiab:~5] OR "Meningitis, Aseptic"[Mesh] OR "Aseptic meningitis"[tiab:~3] OR "Meningitis, Viral"[Mesh] OR "Viral meningitis"[tiab:~5] OR "Meningitis, Fungal"[Mesh] OR "Fungal meningitis"[tiab:~5] OR "Parasitic meningitis"[tiab:~5] OR "community acquired meningitis"[tiab:~3] OR "Meningitis, Meningococcal"[Mesh] OR "Meningitis, Pneumococcal"[Mesh] OR "Meningitis, Haemophilus"[Mesh] OR "Meningitis, Listeria"[Mesh] OR "Staphylococcus aureus"[Mesh] OR "Enterobacteriaceae"[Mesh] OR "Enterobacter"[Mesh] OR "Escherichia coli"[Mesh] OR "Streptococcus agalactiae"[Mesh] OR "Streptococcus pyogenes"[Mesh] OR "Enterovirus"[Mesh] OR "Herpesviridae"[Mesh] OR "Herpesviridae Infections"[Mesh] OR "Simplexvirus"[Mesh] OR "Flavivirus"[Mesh] OR "West Nile virus"[Mesh] OR "Togaviridae"[Mesh] OR "Mumps"[Mesh] OR "Mumps virus"[Mesh] OR "Orthomyxoviridae"[Mesh] OR "HIV"[Mesh] OR "Adenoviridae"[Mesh] OR "Rubella"[Mesh] OR "Lymphocytic Choriomeningitis"[Mesh] OR "Rickettsiales"[Mesh] OR "Spirochaetales"[Mesh] OR "Leptospira"[Mesh] OR "Brucella"[Mesh] OR "Treponema pallidum"[Mesh] OR "Coxiella"[Mesh] OR "Mycoplasma"[Mesh] OR "Naegleria"[Mesh] OR "Angiostrongylus"[Mesh] OR "Coccidioides"[Mesh] OR "Candida"[Mesh] OR "Histoplasma"[Mesh] OR "Blastomyces"[Mesh] OR "Aspergillus"[Mesh] OR "Syphilis"[Mesh] OR "Lyme Disease"[Mesh] OR "Scrub Typhus"[Mesh] OR "Meningococc*"[tiab] OR "Neisseria meningitidis"[tiab] OR "N. Meningitidis"[tiab] OR "Pneumococc*"[tiab] OR "S-pneumoniae*"[tiab] OR "Haemophilus influenzae"[tiab] OR "Listeri*"[tiab] OR L-monocytogenes[tiab] OR "Staphylococc*"[tiab] OR "Staph aureus"[tiab] OR "Enterobacter*"[tiab] OR "Enterococc*"[tiab] OR "Escherichia coli"[tiab] OR "E-coli"[tiab] OR "Streptococcus agalactiae"[tiab] OR "S agalactiae*"[tiab] OR "S pyogenes"[tiab] OR "Enterovir*"[tiab] OR "Coxsackieviruses"[tiab] OR "Herpesviridae"[tiab] OR "Herpesvirus*"[tiab] OR "herpes virus*"[tiab] OR "Varicella zoster"[tiab] OR flavi-virus*[tiab] OR Japanese-encephal*[tiab] OR Tick-borne-encephal*[tiab] OR Powassan-virus*[tiab] OR "West Nile virus"[tiab] OR "Togaviridae"[tiab] OR Toga-virus*[tiab] OR Togavir*[tiab] OR equine-encephal* OR Bunyavirus*[tiab] OR crosse-encephal*[tiab] OR Toscana-virus*[tiab] OR Reovirus*[tiab]	3 364 413

	OR tick-fever*[tiab] OR paramyxovir*[tiab] OR "Mumps"[tiab] OR morbillivirus*[tiab] OR parainfluenza*[tiab] OR "Orthomyxovir*"[tiab] OR "Influenza"[tiab] OR "HIV"[tiab] OR "human-immuno-deficienc*"[tiab] OR "Adenoviridae"[tiab] OR adenovirus*[tiab] OR Arenavir*[tiab] OR "Choriomeningit*"[tiab] OR "LCMV"[tiab] OR "Rickettsi*"[tiab] OR Orientia-spp[tiab] OR Ehrlichia-spp[tiab] OR "spirochet*"[tiab] OR Borrelia-spp[tiab] OR B-burgdorferi[tiab] OR "leptospir*"[tiab] OR "Treponema pallidum"[tiab] OR "Brucell*"[tiab] OR "Coxiella"[tiab] OR "Mycoplasma"[tiab] OR spirillum*[tiab] OR "Naegleria"[tiab] OR "angiostrongyl*"[tiab] OR Trichinella-spiralis*[tiab] OR "Candida"[tiab] OR "Coccidioid*"[tiab] OR "Histoplasm*"[tiab] OR "Blastomyc*"[tiab] OR Sporothrix*[tiab] OR "Aspergill*" [tiab] OR "Lyme"[tiab] OR "Syphili*"[tiab] OR "Scrub Typhus"[tiab] OR tsutsugamushi[tiab]	
3	#1 AND #2	68 069
4	osmotic*[tiab] OR osmotic-therap*[tiab] OR glycerol[tiab] OR mannitol[tiab] OR hypertonic-saline[tiab] OR hypertonic-agent*[tiab] OR sodium-lactate[tiab] OR osmotic-pressure[tiab] OR osmotic-diuretic[tiab] OR sorbitol[tiab] OR propanetriol[tiab] OR sodium-chloride[tiab] OR Osmolality[tiab] OR Osmol*[tiab]	186 146
5	#3 AND #4	257
6	(intravenous-fluid*[tiab] OR oral-fluid*[tiab] OR fluid-restriction*[tiab] OR fluid-management[tiab] OR maintenance-fluid*[tiab] OR isotonic-solution*[tiab] OR fluid-therap*[tiab] OR fluid-balance[tiab] OR electrolyte-balance[tiab] OR supportive-therap*[tiab] OR restricted-fluid*[tiab] OR plasma-arginine[tiab] OR restricting-fluids[tiab] OR rehydration[tiab] OR hydrat*[tiab] OR hyponatremia[tiab] OR water-deprivation[tiab] OR water-restriction[tiab] OR dehydration[tiab] OR dehydrat*[tiab] OR electrolyt*[tiab] OR sodium-chloride[tiab] OR saline[tiab] OR plasma-substitute[tiab] OR hypertonic-solution[tiab] OR ors[tiab] OR parenteral-nutrition-solution[tiab] OR albumin[tiab] OR dextran[tiab] OR starch[tiab] OR hemaccel[tiab] OR gelofusine[tiab])	778 552
7	#3 AND #6	1 120
8	Steroids[Mesh] OR steroid*[tiab] OR corticosteroid*[tiab] OR glucocorticoids[tiab] OR dexameth*[tiab] OR prednisolone[tiab] OR predniso*[tiab] OR hydrocortisone[tiab] OR adrenal-cortex-hormone*[tiab]	1 231 280
9	#3 AND #8	3 694

10	("adjunctive treatment"[tiab:~5] OR "adjunctive treatments"[tiab:~5] OR "Adjunctive therapy"[tiab:~5] OR "Adjunctive therapies"[tiab:~5] OR "adjuvant therapy"[tiab:~5] OR "adjuvant therapies"[tiab:~5] OR "adjunctive treatments"[tiab:~5] OR "adjunctive treatment"[tiab:~5] OR "adjunct therapy"[tiab:~5] OR "adjunct therapies"[tiab:~5] OR "adjunct treatments"[tiab:~5] OR "adjunct treatment"[tiab:~5])	86 083
11	#3 AND #10	507
12	#11 OR #9 OR #7 OR #5	4 995
13	"Letter"[Publication Type] OR "Editorial"[Publication Type] OR "comment"[Publication Type] OR "case reports"[publication type]	4 374 866
14	#12 NOT #13	3 204
15	("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	5 191 262
16	#14 NOT #15	2 766
17	#16 Filters: from 1998 - 2024	1 737

Table WA13.A1.3 Database: CENTRAL (https://www.cochranelibrary.com/advanced-search/search-manager?search=7376359), searched: 2 May 2024

No.	Searches	Results
1	MeSH descriptor: [Meningitis] explode all trees	856
2	meningit*:ti,ab OR (Meningococc* NEAR/3 (disease* OR infection*)):ti,ab,kw	2 547
3	(osmotic* OR osmotic-therap* OR glycerol OR mannitol OR hypertonic-saline OR hypertonic-agent* OR sodium-lactate OR osmotic-pressure OR osmotic-diuretic OR sorbitol OR propanetriol OR sodium-chloride OR Osmolality OR Osmol*):ti,ab,kw	18 452
4	(intravenous-fluid* OR oral-fluid* OR fluid-restriction* OR fluid-management OR maintenance-fluid* OR isotonic-solution* OR fluid-therap* OR fluid-balance OR electrolyte-balance OR supportive-therap* OR restricted-fluid* OR plasma-arginine OR restricting-fluids OR rehydration OR hydrat* OR hyponatremia OR water-deprivation OR water-restriction OR dehydration OR dehydrat* OR electrolyt* OR sodium-chloride OR saline OR plasma-substitute OR hypertonic-solution* OR hyptertonic-agent* OR ors OR parenteral-nutrition-solution OR albumin OR dextran OR starch OR hemaccel OR gelofusine):ti,ab,kw	94 256
5	MeSH descriptor: [Steroids] explode all trees	75 652
6	(steroid* OR corticosteroid* OR glucocorticoids OR dexameth* OR prednisolone OR predniso* OR hydrocortisone OR adrenal-cortex-hormone*):ti,ab,kw	93 271
7	((Adjunct* OR adjuvant*) NEAR/5 (treatment* OR therap*)):ti,ab,kw	34 213
8	#1 OR #2	2 718
9	#3 OR #4 OR #5 OR #6 OR #7	259 766
10	#9 AND #8	482
11	Limits Jan 1998 to Dec 2024	474

Table WA13.A1.4 Database: ClinicalTrials.gov (https://clinicaltrials.gov/), searched on 7 February 2024

No.	Searches	Field	Results
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	(osmotic OR glycerol OR mannitol OR "hypertonic saline" OR "sodium lactate" OR sorbitol OR propanetriol OR "sodium chloride" OR Osmolality) NOT vaccine	Intervention	
3	1 and 2		15
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	("isotonic solution" OR plasma OR rehydration OR hydrate OR hydration OR hyponatremia OR dehydration OR dehydrate OR electrolyte OR saline OR hypertonic OR "parenteral nutrition" OR albumin OR dextran) NOT Vaccine	Intervention	
3	1 and 2		50
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	hemaccel OR gelofusine OR starch	Intervention	
3	1 and 2		0
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	

2	(Steroids OR steroid OR corticosteroid OR glucocorticoids OR dexamethasone OR prednisolone OR prednisone OR hydrocortisone OR “adrenal cortex hormone”)	Intervention	
3	1 and 2		47
1	Meningitis OR meningitidis OR "Meningococcal disease" OR "meningococcal infections" OR "meningococcal infection"	Condition	
2	"adjunctive treatment" OR "adjunctive treatments" OR "Adjunctive therapy" OR "Adjunctive therapies" OR "adjuvant therapy" OR "adjuvant therapies" OR "adjunctive treatments" OR "adjunctive treatment" OR "adjunct therapy"	Intervention	
3	1 and 2		7
Total			119
Duplicates			28
To screen			91

Appendix 2. Categories in the data extraction form

Study name		
Publication details	Type of study	
	Duration	
	Location	
	Type of country: LMIC/HIC	
	Date of trial	
	Date of publication	
	Sponsor and funding	
	Protocol publication (for RCTs)	
		Intervention **Comparator**
Study details	Number of participants	
	Patients who completed study	
	Reason for discontinuation	
	Missing outcomes	
	Deviation from protocol	
	Inclusion criteria	
	Exclusion criteria	
Patient demographic data	Age	
	Gender	
	Vaccination status (pneumococcal vaccine)	
	Immunocompromised	
	Source of Infection: RTA/sinus/abscess/ any other risk factor	
	Duration of illness	

Clinical features		**Intervention**	**Comparator**
	Seizures		
	Altered sensorium		
	Hemiparesis		
	Papilloedema		
	Cranial nerve palsy		
Disease details	Causative organism		
	Culture and sensitivity details		
	Severity		
	Risk assessment scale		
Comorbidity/ Confounding factors	Diabetes		
	Hypertension		
	Stroke		
	Seizure		
Corticosteroid details	Name		
	Type of corticosteroid, start of therapy from date of admission or symptoms		
	Dose		
	Frequency		
	Route		
	duration		
Other therapeutic intervention	Antimicrobial therapy		
	Other adjunctive therapies		
	Immunosuppressants		
Antimicrobial therapy		**Intervention**	**Comparator**
	Type of antibiotic		

	Dosage			
	Duration of therapy			
CSF analysis			**Intervention**	**Comparator**
	Cell count and type – at admission			
	Cell count and type – at discharge /2nd analysis			
	Protein – at admission			
	Protein – at discharge /2nd analysis			
	Glucose – at admission			
	Glucose – at discharge/2nd analysis			
	Change between the 1st and 2nd LP			
	P value			
Outcomes	Outcomes assessed in the study, with number of participants assessed for each outcome			
	Approach to primary analysis (e.g. per protocol, intention to treat)			
	Were any imputations made for missing data?			
Critical outcomes	Mortality – total study 28 to 30 days in hospital	No. of patients		
	Mortality with respect to each of the etiological organisms			
	Time to resolution of symptoms	No. of days Median (range)		
		Length of hospital stay		
	Disease complications	Sepsis		
		DIC		

		Neurological complications
		Cognitive impairment
		Seizures
		Hearing sequelae
		GI bleeding
		Infection/Fever
		Arthritis
		Behavioural changes
		Hyperglycaemia
Important outcomes	Adverse effects – antimicrobe-related adverse events like *C. difficile* infection and candidemia infection	No. of patients
		No. of events
		Drug-related adverse events
	CSF culture positivity rate	No. of patients with positive culture
		Proposition of positive culture
	Blood culture positivity rate	No. of patients
		Positivity rate
Follow-up	What was planned, way participants were followed up	
	Results, length of follow-up	
	Lost to follow-up: number and characteristics	

CSF: cerebrospinal fluid; DIC: disseminated intravascular coagulation; GI: gastrointestinal; HIC: high-income country; LMICs: low- and middle-income countries; LP: lumbar puncture; RCT: randomized controlled trial.

14. Anti-seizure medicines

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Abbreviations

ASM	anti-seizure medicine(s)
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RoB 2	Version 2 of the Cochrane risk-of-bias tool for randomized trials
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions (tool)
RR	relative risk
WHO	World Health Organization

1. Background

Acute symptomatic seizures frequently occur as a complication of acute meningitis, further complicating clinical management *(1, 2)*. Anti-seizure medicines (ASM) are commonly prescribed to control seizures and prevent recurrent episodes, but the optimal duration of their use remains unclear.

Acute symptomatic seizures in the context of meningitis pose unique challenges to health-care providers. The decision about when to initiate and, more importantly, when to discontinue ASM for these patients is of great clinical importance. Inappropriate and prolonged use of ASM may expose patients to unnecessary side-effects and drug interactions. Conversely, premature discontinuation of this medication can lead to recurrent seizures, which may lead to adverse effects on the brain – with short- and long-term medical, social and economic consequences.

To date, there is no comprehensive synthesis of existing evidence to guide the management of ASM for people with acute meningitis. As part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, this systematic review was conducted to address the question of the optimal duration for administering ASM to patients with acute bacterial meningitis who have experienced acute symptomatic seizures.

2. Methodology

The protocol for this systematic review was published on PROSPERO *(3)*.

2.1 Research question and study design

What should be the duration of anti-seizure medicines in individuals with acute meningitis who were started on this treatment for acute symptomatic seizures?

Population: Adults and children with acute meningitis experiencing acute symptomatic seizures and receiving ASM.

Intervention: Early stopping of ASM (within three months of the administration of medication).

Comparator: Late stopping (beyond three months) of ASM.

Outcomes

Critical outcomes (as prioritized by the Guideline Development Group):

- development of epilepsy
- adverse effects of medicines
- mortality.

*Important outcomes: r*ecurrence of seizure.

Study designs:

1. Experimental and quasi-experimental studies
    - Randomized controlled trials (RCTs).
2. Non-randomized studies of intervention
    - Observational studies
    - Cohort studies (retrospective, non-concurrent and prospective)
    - Case series.

Studies should have estimated the differences in the outcome between the groups receiving the intervention of interest and those receiving the comparator.

2.2 Eligible studies

Published language: The intention was to include studies published in all languages.

Exclusion criteria

The following types of studies were excluded preclinical studies (in vivo and in vitro studies); studies without a control group; and records of registered, ongoing trials with no results (e.g. those from ClinicalTrials.gov).

The following disease categories were excluded: meningitis in newborns (0–28 days); hospital-acquired, nosocomial and health-care-associated meningitis; subacute and chronic meningitis, including tuberculous, cryptococcal and eosinophilic meningitis; non-infectious meningitis (e.g. drugs, malignancy, autoimmune diseases).

2.3 Search strategy

The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and ClinicalTrials.gov. The reference lists of all the studies included were examined for additional relevant studies, as were relevant reviews (see Appendix 1).

2.4 Selection of studies

First stage: Two of the authors independently screened titles and abstracts to determine studies eligible for full-text screening. Disagreements were resolved by discussion or by referring the matter to a third author.

Second stage: Two of the authors independently reviewed the full texts of potentially eligible studies to determine the final eligible studies. Disagreements were resolved by discussion or by referring the question to a third author.

Rayyan software was used to screen titles and abstracts, as well as the full text of articles *(4)*. The reference lists of the eligible articles were retrieved and screened. Finally, a subject expert was asked to identify further eligible articles.

2.5 Data extraction and management

Data were extracted using a pilot-tested standardized data collection template. Two of the authors extracted data from the eligible records independently. In the case of any disagreement, they discussed the matter to build consensus. In the case of persistent disagreement, the opinion of a third author was considered binding.

The following were abstracted: surname of the first author, year of publication, country, region, sample size, enrolment period, details on population (etiology, mean age, % male, disease severity, type of treatment received before or during therapy), interventions (ASM, dose, duration, route), length of follow-up, outcomes reported and effect sizes with 95% confidence intervals (CIs) (see Appendix 2).

2.6 Assessment of risk of bias in studies included in the review

The risk of bias in randomized trials was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2); for non-randomized studies, the Risk Of Bias In Non-randomized Studies – of Interventions tool (ROBINS-I) was used; and the Joanna

Briggs Institute (JBI) checklist was used for case series *(5-7)*. Two of the authors independently assessed the risk of bias of the studies, with disagreements resolved by involving a third author.

2.7 Data synthesis

If there was a consistent outcome measure across two or more studies, meta-analyses for the effect estimate of the interventions were conducted. The pooled odds ratio or relative risk (RR) and 95% CIs were calculated for dichotomous outcomes. The mean difference or standardized mean difference and 95% CI were calculated for continuous outcomes.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

We used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) methodology to rate the certainty of the evidence for each outcome *(8)* (see Box WA14.1).

Box WA14.1 The certainty of evidence used in GRADE	
High ⨁⨁⨁⨁	High level of confidence that the true effect lies close to that of the estimate of the effect.
Moderate ⨁⨁⨁◯	Moderate level of confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⨁⨁◯◯	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very low ⨁◯◯◯	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

The assessment included judgments addressing risk of bias, imprecision, inconsistency, indirectness and publication bias. The evidence is summarized both narratively (section 4) and in GRADE evidence profiles (Tables WA14.2 and 3). The evidence profiles were prepared using GRADEpro software *(9)*.

Two of the authors assessed the certainty of the evidence for the synthesized estimates independently. In case of any disagreement, they discussed the matter to build consensus. In the case of persistent disagreement, the opinion of a third author was considered binding. A minimally contextualized framework within the GRADE framework was used to assist guideline development. The target for certainty rating was a non-null effect.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

Heterogeneity in the meta-analyses was assessed by visual inspection of the forest plot and by the I^2 statistic. Subgroup analyses were conducted by study design.

2.10 Deviations from the review protocol

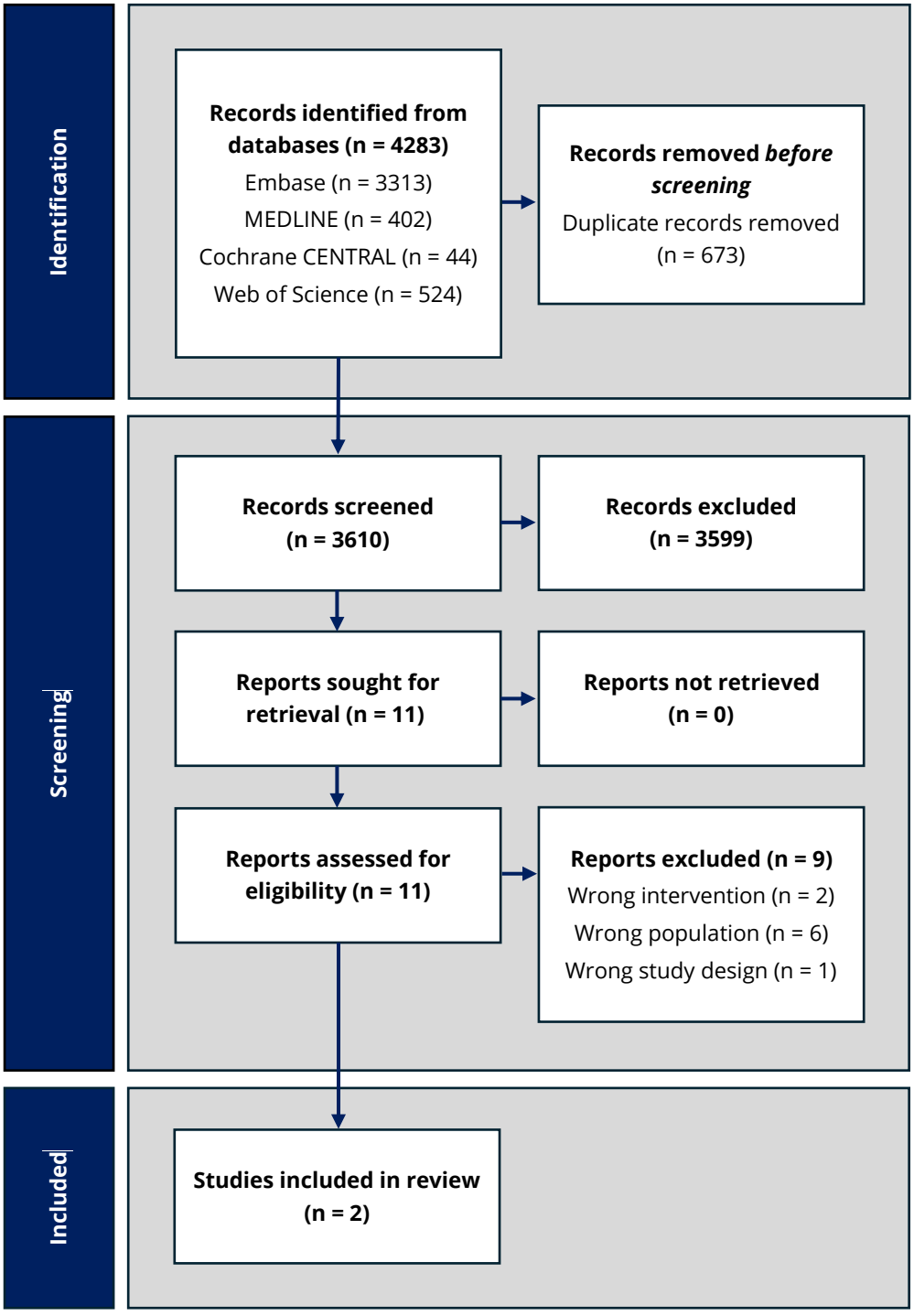
In the absence of direct evidence about patients with acute bacterial meningitis, evidence about patients experiencing acute symptomatic seizures due to other causes, such as acute encephalitis syndrome, was included.

3. Results

3.1 Studies identified by the search process

The search yielded 4283 titles and abstracts – all from the electronic database search – 3610 of which remained after duplicates were removed. A total of 3599 articles were excluded on the basis of a review of the title and abstract, leaving 11 articles for full review. Of these, nine were excluded, for the following reasons: wrong study design (n = 1), wrong intervention (n = 2), wrong population (n = 6). Two studies were included in the systematic review.

Fig. WA14.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews) and Meta-Analyses) flow diagram for the review.



3.1.1 Studies included in the review

Table WA14.1 presents the characteristics of the studies included in the GRADE evidence profile.

Table WA14.1. Characteristics of the studies included in the GRADE evidence profile

Lead author (year), country Study design	Overall risk of bias (study level)	Intervention	Population (sample size: intervention/control)	Comparator	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
Studies including patients with acute encephalitis/meningoencephalitis							
Dhawan (2021), India *(10)* RCT	Low	4 weeks ASM	Children with acute encephalitis syndrome The majority had aseptic meningitis/ meningoencephalitis (n = 29, 48.3%) Intervention: 30 Control: 30	12 weeks ASM	Seizure recurrence Adverse effects	Seizure recurrence	6, 12 and 18 months
Herzig-Nichtweiß, Germany (2023) *(11)* Cohort study	Low	ASM less than 100 days	Adults 7% bacterial meningoencephalitis or meningitis; cerebrovascular accidents formed the most prevalent group (n = 90; 75%), followed by infections with structural	ASM more than 100 days	Seizure recurrence	Seizure recurrence	12 months

Lead author (year), country Study design	Overall risk of bias (study level)	Intervention	Population (sample size: intervention/control)	Comparator	Outcome domains with available data (synthesis method/metric)	Specific outcome measure	Time point of measurement
			affection of brain tissue visible on neuroimaging (n = 14; 11%) Intervention: 53 Control: 67				

ASM: anti-seizure medicine(s).

3.1.2 Studies excluded from the review

Table WA14.2 presents the studies that were excluded from the review and gives reasons for their exclusion.

Table WA14.2 Studies excluded from the review, with reasons for exclusion

Study	Reason for exclusion
[No authors listed] 1990 *(12)*	Wrong population
Amare 2021 *(13)*	Wrong population
Amare et al. 2008 *(14)*	Wrong intervention
Chang et al. 2004 *(15)*	Wrong population
Pathak G et al. 2013 *(16)*	Wrong population
Zoons et al. 2008 *(17)*	Wrong intervention
Lepage & Dan 2013 *(18)*	Wrong study design
Pathania et al. 2022 *(19)*	Wrong population
Glass et al. 2021 *(20)*	Wrong population

4. Summary of findings

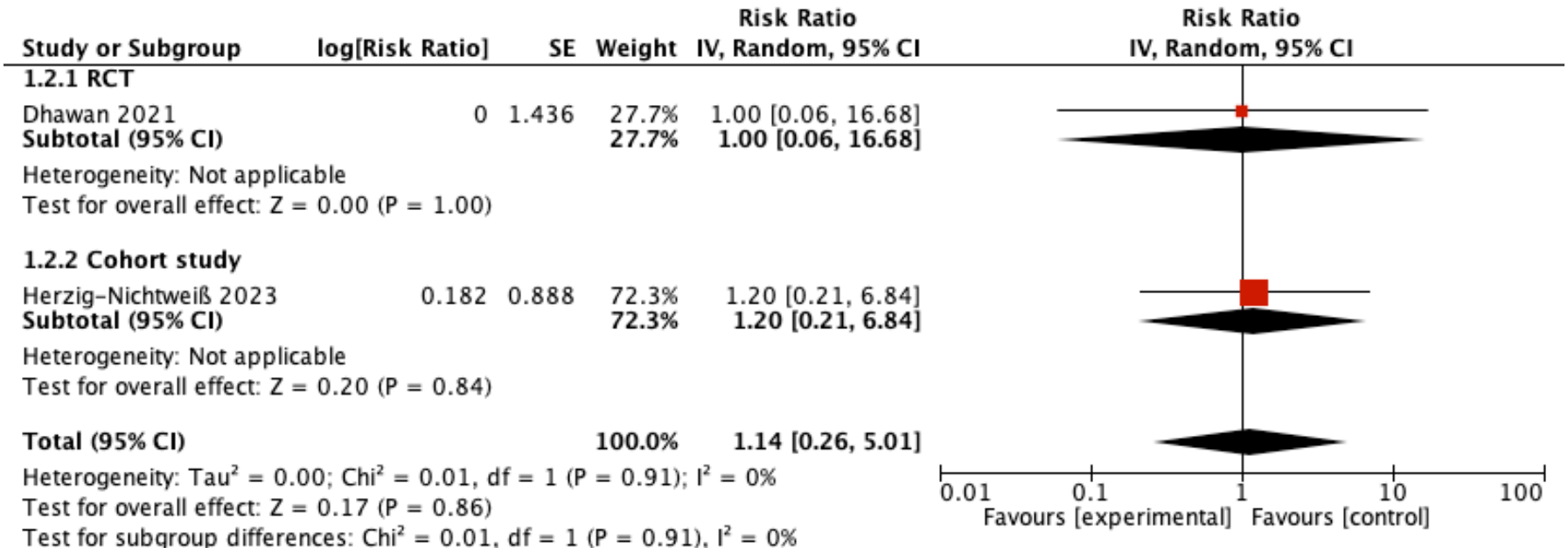
4.1 Narrative description of intervention effects

4.1.1 Outcome 1: seizure recurrence

One RCT and one cohort study reported the outcome seizure recurrence at one month. The RCT included 60 children with acute encephalitis syndrome *(10)*, and the cohort study included 141 adults with various structural and non-structural brain conditions, 7% of whom had meningitis or meningoencephalitis *(11)*. Cerebrovascular accidents formed the most prevalent group in the cohort study. The RCT compared 4 weeks versus 12 weeks of ASM, and the cohort study compared fewer than 100 days versus more than 100 days of ASM.

Very-low-certainty evidence from the RCT showed that the effect of 4 weeks of ASM on seizure recurrence at 12 months compared with 12 weeks of ASM was uncertain (RR 1.00, 95% CI 0.06–16.68). Very-low-certainty evidence from the cohort study including showed that the effect of less than 100 days of ASM on seizure recurrence at 12 months compared with more than 100 days of ASM was uncertain (RR 1.20, 95% CI 0.21–6.84). The pooled RR across these two studies was 1.14 (95% CI 0.26–5.01) (see Fig. WA14. 2).

Fig. WA14.2 Seizure recurrence at 12 months



References: Dhawan et al., 2021 *(10)*; Herzig-Nichtweiß et al., 2023 *(11)*.

4.1.2 Outcome 2: adverse events

One RCT reported measuring adverse events but reported that no patient in either arm experienced adverse events.

4.2 GRADE evidence profile

This section presents the GRADE evidence profiles of the studies included in this review (see Table WA14.3).

Table WA14.3 GRADE evidence profile

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Incon-sistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative risk (95% CI)	Anticipated absolute effects	
							With late stopping of ASM	With early stopping		Risk with late stopping of ASM	Risk difference with early stopping
Seizure recurrence at 12 months – RCT											
60 (1 RCT) *(10)*	Not serious	NA	Serious[a]	Very serious[b]	None	⨁◯◯◯ Very low	1/30 (3.3%)	1/30 (3.3%)	**RR 1.00** (0.06 to 16.68)	33 per 1000	**0 fewer per 1000** (from 31 fewer to 523 more)
Seizure recurrence at 12 months – cohort study											

Certainty assessment							Summary of findings				
141 (1 non-randomized study) *(11)*	Not serious	NA	Serious[a]	Very serious[b]	None	⊕◯◯◯ Very low	17%[c]	-/0	**RR 1.20** (0.21 to 6.84)	142 per 1000	**34 more per 1000** (134 fewer to 993 more)

ASM: anti-seizure medicine(s); NA: not applicable.

[a] Population includes patients experiencing acute symptomatic seizures due to causes apart from meningitis, such as acute encephalitis syndrome, hypoxic ischemic encephalopathy (HIE) or stroke.

[b] Confidence interval includes both important benefit and harm.

[c] Baseline risk from Zoons et al., 2008 *(17)*.

4.3 Research gaps

There is a significant lack of direct evidence regarding the efficacy and safety of early versus late stopping of ASM specifically in patients with acute meningitis. Future studies should focus on this specific population to determine the optimal timing for stopping ASM. The absence of RCTs directly comparing early versus late stopping of ASM as regards people with acute bacterial meningitis is a major research gap.

There is a need for standardized outcome measures to assess the effectiveness of early versus late stopping of ASM administered to people with acute bacterial meningitis. These measures should include seizure recurrence rates, neurological outcomes, mortality and adverse effects related to medication withdrawal.

Subgroup analysis based on factors such as age, severity of meningitis, causative pathogens and comorbidities could help identify patient populations that may benefit more from early or late stopping of ASM. Further research should explore these potential differences in treatment response.

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Appendix 1. Search strategy used to identify primary studies

Database: Ovid MEDLINE, including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to 20 Dec 2023 (https://www.wolterskluwer.com/en/solutions/ovid/ovid-medline-901), searched on 21 Dec 2023

Search strategy

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1 exp Meningitis/ (59046)

2 meningit*.mp. (81222)

3 1 or 2 (92471)

4 exp Anticonvulsants/ (154895)

5 (antiepileptic* or anti-epileptic* or antiseizure or anti-seizure or anticonvuls* or anti-convuls*).mp. (85306)

6 (Acetazolamid* or Aedon or Aethosuximide or Alodorm or Amizepin* or Ant?lepsin or Anxirloc or Arem or Ativan or Atretol or Avugane or Baceca or Barbexaclon* or Beclamid* or Biston or Bomathal or Brivaracetam or Bromid* or Calepsin or Carbagen or Carbamazepen* or Carbamazepin* or Carbatrol or Carbazepin* or Carbelan or Carisbamat* or Castilium or Celontin or Cerebyx or Chlonazepam or Chloracon or C?lorepin or C?lormethiazole or Clarmyl or Cloazepam or Clobam* or Clobator or Clobazam or Clofritis or Clonazepam* or Clonex or Clonopin or Clopax or Clorazepate or Comfyde or Convulex or Dapaz or Dasuen or Delepsine or Depacon or Depak* or Depamide or Deproic or Desitin or Diacomit or Diamox or Diastat or Diazepam or Difenilhidantoin* or Dihydantoin or Dilantin or Dimethadione or Dimethyloxazolidinedione or Diphenin* or Diphenylan or Diphenylhydantoin* or Distraneurin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilepax or Epilex or Epilim or Episenta or Epitol or Epival or Eptoin or Equanil or Equetro or Ergenyl or Erimin or Erlosamide or Eslicarbazepine or Estazolam or Ethadione or Ethosucci* or Ethosuxi* or Ethotoin or Ethylphenacemide or Etosuxi* or Euhypnos or Exalief or Excegran or Ezogabine or Fanatrex or Felbam* or Felbatol or Fenitoin* or Fenobarbit* or Fenytoin* or Finlepsin or Fosphenytoin or Frisium or Fycompa or Gabapentin* or Gabapetin* or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Grifoclobam or Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex or Lacosamid* or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigin* or Lamotrine or Landsen or Levanxol or Levetiracetam* or Lexin or Liskantin or Loraz or Lorazepam* or Losigamon* or Lucium or Luminal or Lyrica or Magnesium sulfat* or Magnesium sulphat* or Mebaral or Medazepam or Mephenytoin or Mephobarbit* or Mephyltaletten or Meprobamate or Meprospan or Mesantoin or Mesuximide or Methazolamid$ or Methsuximide or Methylacetazolamide or Methyloxazepam or Methylphenobarbit* or Midazolam or Miltown or Mogadon or Mylepsinum or Mylproin or Mysoline or Mystan or Neogab or Neptazane or Nesdonal or Neurontin or Neurotop or Nimetazepam or Nitrados or Nitrazadon or Nitrazepam or Nobrium or Nocturne or Noiafren or Norkotral or Normison or Normitab or Nortem or Novo-Clopate or Nuctalon or Nupentin or Nydrane or OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or

Oxcarbamazepin* or Oxcarbazepin* or Oxydiazepam or Pacisyn or Paraldehyde or Paramethadione or Paxadorm or Paxam or Peganone or Penthiobarbital or Pentothal or Perampanel or Petinutin or Petril or Phemiton or Phenacemide or Pheneturide or Phenobarbit* or Phensuximide or Phenylethylbarbit* or Phenylethylmalonylurea or Phenytek or Phenytoin* or Planum or Posedrine or Potiga or Pregabalin or Primidone or Prodilantin or Progabide or Prominal or Pronervon or Propofol or Prosom or Prysoline or Ravotril or Remacemide or Remestan or Remnos or Resimatil or Restoril or Retigabine or Riluzole or Rilutek or Riv?tril or Rudotel or Rufinamide or Rusedal or "RWJ-333369" or Sabril or Seclar or Sederlona or Selenica or Seletracetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or Stavzor or Stazepin* or Stedesa or Stiripentol or Sulthiam* or Sultiam* or Talampanel or Taloxa or Tasedan or Tegret?l or Telesmin or Temaze or Temazep* or Temesta or Temtabs or Tenox or Teril or Thiomebumal or Thionembutal or Thiopent* or Tiagabin* or Tiletamine or Timonil or Tiobarbit* or Tipiram* or Topamax or Topiram* or Tranmep or Tranxene or Trapanal or Tridione or Trileptal or Trimethadione or Trobalt or Urbadan or Urban?l or Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro* or Versed or Vigabatrin* or Vimpat or Visano or VPA or Xilep or "YKP 509" or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid*).tw. (288544)

7 or/4-6 (367603)

8 3 and 7 (777)

9 limit 8 to (case reports or comment or editorial or letter or "review") (375)

10 8 not 9 (402)

Database: Embase (OVID) (https://www.embase.com/#advancedSearch/), searched on 21 Dec 2023

Search strategy

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1 exp meningit*/

2 (meningit*) or (infectious meningit*)

3 1 or 2

4 exp anticonvulsive agent/

5 (antiepileptic* or anti-epileptic* or antiseizure or anti-seizure or anticonvuls* or anti-convuls*).mp.

6 (Acetazolamid* or Aedon or Aethosuximide or Alodorm or Amizepin* or Ant?lepsin or Anxirloc or Arem or Ativan or Atretol or Avugane or Baceca or Barbexaclon* or Beclamid* or Biston or Bomathal or Brivaracetam or Bromid* or Calepsin or Carbagen or Carbamazepen* or Carbamazepin* or Carbatrol or Carbazepin* or Carbelan or Carisbamat* or Castilium or Celontin or Cerebyx or Chlonazepam or Chloracon or C?lorepin or C?lormethiazole or Clarmyl or Cloazepam or Clobam* or Clobator or Clobazam or Clofritis or Clonazepam* or Clonex or Clonopin or Clopax or Clorazepate or Comfyde or Convulex or Dapaz or Dasuen or Delepsine or Depacon or Depak* or Depamide or Deproic or Desitin or Diacomit or Diamox or Diastat or Diazepam or Difenilhidantoin* or Dihydantoin or Dilantin or Dimethadione or Dimethyloxazolidinedione or Diphenin* or Diphenylan or Diphenylhydantoin* or Distraneurin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilepax or Epilex or Epilim or Episenta or Epitol or Epival or Eptoin or Equanil or Equetro or Ergenyl or Erimin or Erlosamide or Eslicarbazepine or Estazolam or Ethadione or Ethosucci* or Ethosuxi* or Ethotoin or Ethylphenacemide or Etosuxi* or Euhypnos or Exalief or Excegran or Ezogabine or Fanatrex or Felbam* or Felbatol or Fenitoin* or Fenobarbit* or Fenytoin* or Finlepsin or Fosphenytoin or Frisium or Fycompa or Gabapentin* or Gabapetin* or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Grifoclobam or Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex or Lacosamid* or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigin* or Lamotrine or Landsen or Levanxol or Levetiracetam* or Lexin or Liskantin or Loraz or Lorazepam* or Losigamon* or Lucium or Luminal or Lyrica or Magnesium sulfat* or Magnesium sulphat* or Mebaral or Medazepam or Mephenytoin or Mephobarbit* or Mephyltaletten or Meprobamate or Meprospan or Mesantoin or Mesuximide or Methazolamid$ or Methsuximide or Methylacetazolamide or Methyloxazepam or Methylphenobarbit* or Midazolam or Miltown or Mogadon or Mylepsinum or Mylproin or Mysoline or Mystan or Neogab or Neptazane or Nesdonal or Neurontin or Neurotop or Nimetazepam or Nitrados or Nitrazadon or Nitrazepam or Nobrium or Nocturne or Noiafren or Norkotral or Normison or Normitab or Nortem or Novo-Clopate or Nuctalon or Nupentin or Nydrane or OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or Oxcarbamazepin* or Oxcarbazepin* or Oxydiazepam or Pacisyn or Paraldehyde or Paramethadione or Paxadorm or Paxam or Peganone or Penthiobarbital or Pentothal or Perampanel or Petinutin or Petril or Phemiton or Phenacemide or Pheneturide or Phenobarbit* or Phensuximide or Phenylethylbarbit* or Phenylethylmalonylurea or Phenytek or Phenytoin* or Planum or Posedrine or Potiga or Pregabalin or Primidone or Prodilantin or Progabide or Prominal

or Pronervon or Propofol or Prosom or Prysoline or Ravotril or Remacemide or Remestan or Remnos or Resimatil or Restoril or Retigabine or Riluzole or Rilutek or Riv?tril or Rudotel or Rufinamide or Rusedal or "RWJ-333369" or Sabril or Seclar or Sederlona or Selenica or Seletracetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or Stavzor or Stazepin* or Stedesa or Stiripentol or Sulthiam* or Sultiam* or Talampanel or Taloxa or Tasedan or Tegret?l or Telesmin or Temaze or Temazep* or Temesta or Temtabs or Tenox or Teril or Thiomebumal or Thionembutal or Thiopent* or Tiagabin* or Tiletamine or Timonil or Tiobarbit* or Tipiram* or Topamax or Topiram* or Tranmep or Tranxene or Trapanal or Tridione or Trileptal or Trimethadione or Trobalt or Urbadan or Urban?l or Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro* or Versed or Vigabatrin* or Vimpat or Visano or Xilep or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid*).tw.

7 or/4-6

8 3 and 7

9 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

10 Animal experiment/ not (human experiment/ or human/)

11 9 or 10

12 8 not 11

Database: CENTRAL (https://pubmed.ncbi.nlm.nih.gov/), searched on 21 Dec 2023

Search strategy

ID Search hits

#1 MeSH descriptor: [Meningit*] explode all trees

#2 (meningit*)

#3 #1 or #2

#4 MeSH descriptor: [Anticonvulsants] explode all trees

#5 (antiepileptic* or anti-epileptic* or antiseizure or anti-seizure or anticonvuls* or anti-convuls*):ti,ab,kw (Word variations have been searched)

#6 (Acetazolamid* or Aedon or Aethosuximide or Alodorm or Amizepin* or Ant?lepsin or Anxirloc or Arem or Ativan or Atretol or Avugane or Baceca or Barbexaclon* or Beclamid* or Biston or Bomathal or Brivaracetam or Bromid* or Calepsin or Carbagen or Carbamazepen* or Carbamazepin* or Carbatrol or Carbazepin* or Carbelan or Carisbamat* or Castilium or Celontin or Cerebyx or Chlonazepam or Chloracon or C?lorepin or C?lormethiazole or Clarmyl or Cloazepam or Clobam* or Clobator or Clobazam or Clofritis or Clonazepam* or Clonex or Clonopin or Clopax or Clorazepate or Comfyde or Convulex or Dapaz or Dasuen or Delepsine or Depacon or Depak* or Depamide or Deproic or Desitin or Diacomit or Diamox or Diastat or Diazepam or Difenilhidantoin* or Dihydantoin or Dilantin or Dimethadione or Dimethyloxazolidinedione or Diphenin* or Diphenylan or Diphenylhydantoin* or Distraneurin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilepax or Epilex or Epilim or Episenta or Epitol or Epival or Eptoin or Equanil or Equetro or Ergenyl or Erimin or Erlosamide or Eslicarbazepine or Estazolam or Ethadione or Ethosucci* or Ethosuxi* or Ethotoin or Ethylphenacemide or Etosuxi* or Euhypnos or Exalief or Excegran or Ezogabine or Fanatrex or Felbam* or Felbatol or Fenitoin* or Fenobarbit* or Fenytoin* or Finlepsin or Fosphenytoin or Frisium or Fycompa or Gabapentin* or Gabapetin* or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Grifoclobam or Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex or Lacosamid* or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigin* or Lamotrine or Landsen or Levanxol or Levetiracetam* or Lexin or Liskantin or Loraz or Lorazepam* or Losigamon* or Lucium or Luminal or Lyrica or Magnesium sulfat* or Magnesium sulphat* or Mebaral or Medazepam or Mephenytoin or Mephobarbit* or Mephyltaletten or Meprobamate or Meprospan or Mesantoin or Mesuximide or Methazolamid$ or Methsuximide or Methylacetazolamide or Methyloxazepam or Methylphenobarbit* or Midazolam or Miltown or Mogadon or Mylepsinum or Mylproin or Mysoline or Mystan or Neogab or Neptazane or Nesdonal or Neurontin or Neurotop or Nimetazepam or Nitrados or Nitrazadon or Nitrazepam or Nobrium or Nocturne or Noiafren or Norkotral or Normison or Normitab or Nortem or Novo-Clopate or Nuctalon or Nupentin or Nydrane or OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or Oxcarbamazepin* or Oxcarbazepin* or Oxydiazepam or Pacisyn or Paraldehyde or Paramethadione or Paxadorm or Paxam or Peganone or Penthiobarbital or Pentothal or Perampanel or Petinutin or Petril or Phemiton or Phenacemide or Pheneturide or Phenobarbit* or Phensuximide or Phenylethylbarbit* or Phenylethylmalonylurea or Phenytek or Phenytoin* or Planum or Posedrine or Potiga or Pregabalin or Primidone or Prodilantin or Progabide or Prominal or Pronervon or Propofol or Prosom or Prysoline or Ravotril or Remacemide or Remestan or

Remnos or Resimatil or Restoril or Retigabine or Riluzole or Rilutek or Riv?tril or Rudotel or Rufinamide or Rusedal or Sabril or Seclar or Sederlona or Selenica or Seletracetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or Stavzor or Stazepin* or Stedesa or Stiripentol or Sulthiam* or Sultiam* or Talampanel or Taloxa or Tasedan or Tegret?l or Telesmin or Temaze or Temazep* or Temesta or Temtabs or Tenox or Teril or Thiomebumal or Thionembutal or Thiopent* or Tiagabin* or Tiletamine or Timonil or Tiobarbit* or Tipiram* or Topamax or Topiram* or Tranmep or Tranxene or Trapanal or Tridione or Trileptal or Trimethadione or Trobalt or Urbadan or Urban?l or Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro* or Versed or Vigabatrin* or Vimpat or Visano or VPA or Xilep or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid*):ti,ab,kw (Word variations have been searched)

#7 #4 or #5 or #6

#8 #3 and #7 in Trials

Appendix 2. Risk of bias assessment of studies included

Table WA14.A2.1 Risk of bias in the RCT included (assessed using RoB 2)

Lead author (year), country and outcome	1. Bias arising from the randomiza-tion process	Domain 1 justification	2. Bias due to deviations from the intended intervention	Domain 2 justification	3. Bias due to missing outcome data	Domain 3 justification	4. Bias in measureme nt of the outcome	Domain 4 justification	5. Bias in selection of the reported results	Domain 5 justification	6. Other biases (e.g. competing risks)	Domain 6 justification
Dhawan (2021), India *(10)* Seizure recurrence	Low	Randomization by computer-generated, allocation concealed, baseline characteristics seems similar	Probably high	Open label	Low	No significant loss to follow-up	Low	Outcome assessor blinded	Low	Same as published protocol	Probably low	NA

Table WA14.A2.2 Risk of bias in cohort studies included (assessed using ROBINS-I)

Outcome	Lead author (year)	Adjusted/ unadjusted analysis	ROBINS-I assessment	Confounding bias	Selection bias	Classification bias	Bias from deviations from intended intervention	Missing data bias	Measurement bias	Selective reporting bias
Seizure recurrence	Herzig-Nichtweiß (2023), Germany *(11)*	A	Low	Low	High	Low	Low	Low	Low	Low

15. Clinical assessment of sequelae in adults and children

Authors

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Abbreviations

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial

1. Background

The consequences of acute meningitis can be profound, in both children and adults, with a wide spectrum of sequelae, including cognitive deficits, motor impairment, speech and language difficulties, sensory impairments and psychological challenges *(1, 2)*. Performing a clinical review to identify sequelae following certain neurological conditions (e.g. stroke, traumatic brain injury) is generally considered an effective way of reducing the burden of unaddressed sequelae and enabling timely initiation of rehabilitation. However, whether a formal review should be performed following acute meningitis, and the optimal timing of such a review, is not yet certain.

This systematic review was conducted as part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, to assess whether a formal clinical review should be performed to identify sequelae following acute meningitis and to identify the optimal time frame in which to conduct a follow-up examination of children or adults after an episode of acute meningitis from any infectious cause.

2. Methodology

2.1 Research questions and study design, eligible studies

2.1.1 Adults

Should adults with acute meningitis (from any cause) be reviewed by a health-care provider before discharge from hospital or at follow-up, in order to identify sequelae?

Population: Adults with acute meningitis from any cause.

Intervention: Review by a health-care provider (before or at discharge from hospital versus post-discharge)[23] to identify sequelae.[24]

Comparator: No review by a health-care provider before discharge from hospital to identify sequelae. Comparison of time points when clinical review took place.

Outcomes

Critical outcomes:

- detection of sequelae
- mortality.

Important outcomes: loss to follow-up.

Study designs: The objective was to capture all relevant studies documenting the time frames within which the sequelae associated with acute meningitis (arising from all causes) might manifest. The study designs considered included observational studies, (e.g. cross-sectional studies, cohort studies, case–control studies, case series, systematic reviews and meta-analyses); and experimental studies (e.g. randomized controlled trials [RCTs]).

Published language: Only studies published in English were considered.

Exclusion criteria: Case reports, experimental studies (not RCTs), animal model studies, histopathological or physiological studies, non-peer-reviewed articles and disease modelling studies were excluded. Studies for which the full text was not accessible, an English language version was unavailable, or the quality of the literature was too low were also excluded. Any studies of subacute or chronic meningitis, or non-infectious meningitis (such as disease cause by chemical or inflammatory agents) were ruled out.

[23] Potential stratification of the post-discharge time point in the presentation of results (4–6 weeks, up to two years, etc.).
[24] Sequelae are defined as follows: hearing loss, speech and/or language impairment, seizures, neurocognitive/neurodevelopmental impairment, psychological after-effects (stress, depression, behavioural changes), hydrocephalus, motor deficits, vision impairment, and digit or limb loss.

2.1.2 Children

Should children with acute meningitis (from any cause) be reviewed by a health-care provider before discharge from hospital or at follow-up, in order to identify sequelae?

Population: Children with acute meningitis from any cause.

Intervention: Review by a health-care provider (before or at discharge from hospital vs post-discharge)[25] to identify sequelae.[26]

Comparator: No review by a health-care provider before discharge from the hospital to identify sequelae. Comparison of time points when clinical review took place.

Outcomes

Critical outcomes:

- detection of sequelae
- mortality.

Important outcomes: loss to follow-up.

Study designs: The objective was to ensure that all relevant studies documenting the time frames within which the sequelae associated with acute meningitis (from all causes) might manifest were captured. This enabled the identification of common time frames during which it is prudent to conduct follow-up or implement auditory studies, such as various audiological screenings. The study designs considered included: observational studies (e.g. cross-sectional studies, cohort studies, case-control studies, case series, systematic reviews for references, and meta-analyses for references); and experimental studies (e.g. RCTs and embedded observational studies).

Published language: Only studies in English were selected.

Exclusion criteria: Case reports, animal model studies, histopathological or physiological studies, non-peer-reviewed articles and disease modelling studies were excluded. Studies for which the full text was not accessible, an English language version was unavailable, or the quality of literature was too low were also excluded. If the central theme of any document was subacute or chronic meningitis, or meningitis with non-infectious causes (such as disease caused by chemical or inflammatory agents) were ruled out.

2.2 Search strategy

The search strategies for the research questions were structured as follows:

[25] Potential stratification of the post-discharge time point in the presentation of results (4–6 weeks, up to two years, etc.).
[26] Sequelae are defined as follows: hearing loss, speech and/or language impairment, seizures, neurocognitive/neurodevelopmental impairment, psychological after-effects (stress, depression, behavioural changes), hydrocephalus, motor deficits, vision impairment, and digit or limb amputation.

- Concept 1: General terms connected with meningitis.
- Concept 2: Terms connected with acute meningitis from all causes. The terms for bacterial, fungal, viral and parasitic meningitis were included, along with the terms for microorganisms that cause acute infectious meningitis.
- Concept 3: Terms connected with sequelae within our scope (hearing loss, speech and/or language impairment, seizures, neurocognitive/neurodevelopmental impairment, psychological after-effects [stress, depression, behavioural changes], hydrocephalus, motor deficits, vision impairment and limb loss).

The search terms, including Mesh and free text terms, are given in detail in Appendix 1.

Searches were conducted in English in the following electronic databases: PubMed, Scopus and Cochrane Library.

2.3 Data extraction and management

A list of publications that might be eligible for inclusion was compiled using the search strategy and exported to Zotero for duplicate deletion. Details of the remaining documents were uploaded to the online COVIDENCE software tool. Two of the authors screened each eligible publication in COVIDENCE, initially by title and abstract, and then by full text. Any disagreement, at either stage of the screening, was resolved by discussion among the authors.

The standardized data extraction tool in COVIDENCE was used to extract the following data: study design/type/characteristics; population, setting, context; characteristics of pathogen/disease; intervention; and outcomes.

During the study selection and data extraction stages, regular meetings were held, once or twice per week, to solve conflicts that arose during the data extraction process and to discuss questions or doubts raised by any of the authors. Appendix 2 provides the details of the data extraction categories.

2.4 Assessment of risk of bias in studies included in the review

In an Excel spreadsheet, two of the authors assessed the risk of bias independently for each included study. If there was any disagreement between them, a third author reviewed the subset of articles, and questions or doubts were discussed by the whole team.

The CLARITY tool for RCTs was used to assess the risk of bias in such studies *(3)*. For the observational studies, the risk of bias was assessed with the following tools: the Newcastle-Ottawa Cohort tool for cohort studies *(4)*, the Newcastle-Ottawa tool for case–control studies *(4)*, the Joanna Briggs Institute (JBI) checklist for case series studies *(5)*, and the AXIS tool for cross-sectional studies *(6)*.

2.5 Data synthesis

Descriptive data were synthesized into summary tables, presenting continuous data with means and categorical data with counts and proportions. This analysis was primarily conducted using Excel, and for more complex variables, using R programming software (R version 4.3.3).

The weighted average time to diagnosis was calculated for any sequelae. The time points considered to calculate this average were divided into before and after discharge. The proportion of patients diagnosed over the total number of patients assessed by a health-care provider was also calculated per time point for both research questions.

A meta-analysis of arcsine transformed proportions was conducted to identify comparative effect estimates (proportion of people with a diagnosis of sequelae screened before discharge, compared to those screened after discharge). The proportion of patients diagnosed with sequelae over the total number of patients assessed by a health-care provider was used for meta-analysis according to different time points of diagnosis: during hospitalization, at discharge, at short-term follow-up (within three months) and at long-term follow-up (after three months).

2.6 Assessment of certainty of evidence (GRADE evidence profiles)

Owing to a lack of studies with a comparator arm, a Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile could not be constructed.

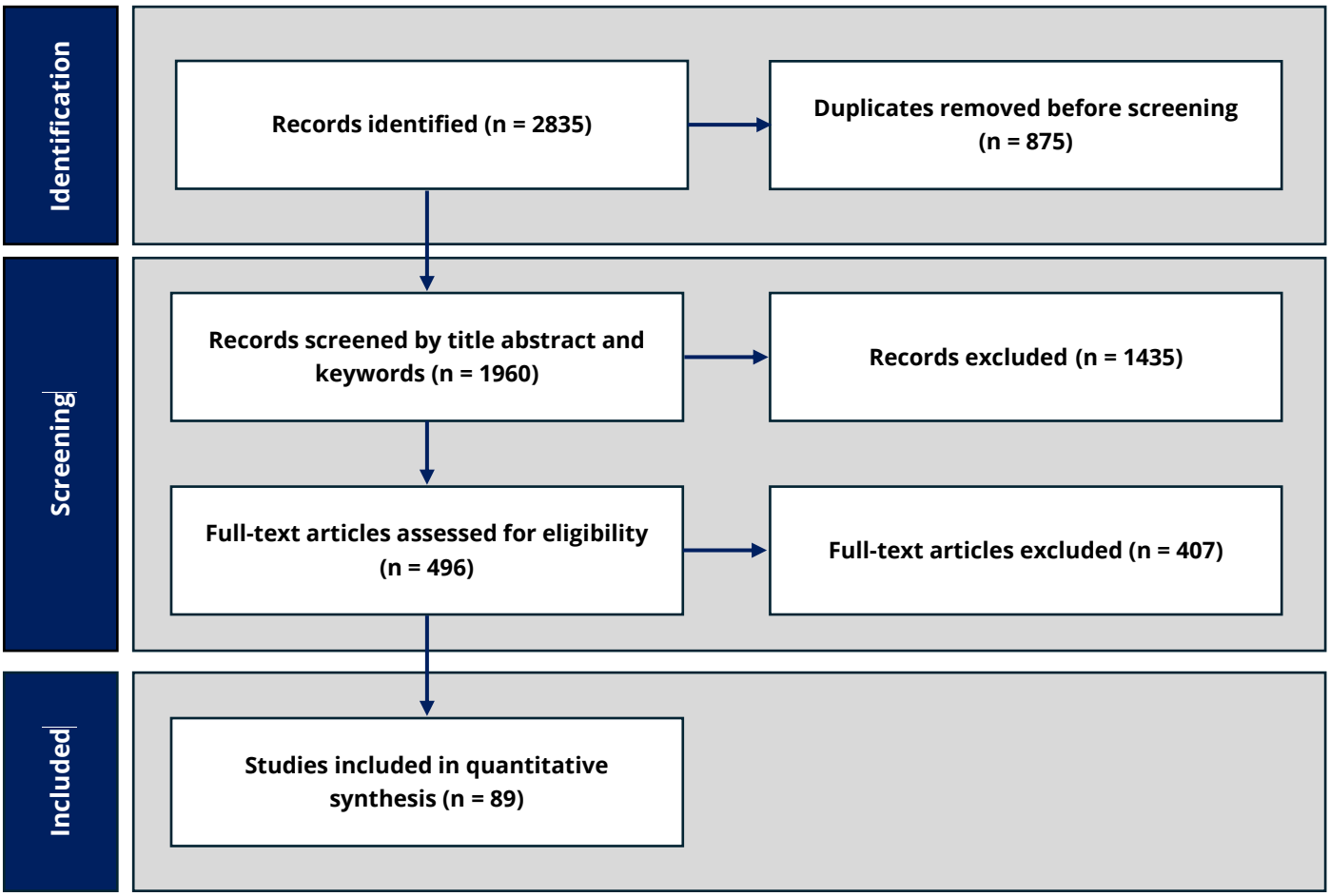
3. Results

The systematic review did not find any evidence from studies comparing having a clinical review to identify sequelae to not having a review. Moreover, no study comparing the different time points at which a review might take place (i.e. before or at discharge vs post-discharge) was identified. However, this review identified 89 observational studies providing evidence on clinical assessment for sequelae, either in children or adults, or both.

3.1 Studies identified by the search process

Figure WA15.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review.

Fig. WA15.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review

The characteristics of the studies included in this systematic review are presented in Table WA15.1a (studies involving adults only), Table WA15.1b (studies involving adults and children) and Table WA15.1c (studies involving children only).

Table WA15.1a Characteristics of studies included in the review (involving adults only)

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Auburtin (2006) *(7)* France Cohort	Low	Assessments: physical and neurological exam, Glasgow Outcome Scale – (GOS), Barthel Index	Patient population: Adults (aged > 18 years) admitted to the intensive care unit with community-acquired pneumococcal meningitis – 156 patients with meningitis – 156 patients tested for neurological sequelae 36 with neurological sequelae	No comparator	Neurological sequelae: 36 Hearing loss: 14 Behavioural disturbances: 10 Hemiparesis: 9 Speech disturbances: 8 Vegetative state: 4 Mortality: 51 Lost to follow-up: 0	Primary outcomes: neurological sequelae (motor deficit, clinically detected hearing impairment, behaviour or speech disturbance, and vegetative state), death	At discharge and 3 months after ICU admission

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Bodilsen (2013) *(8)* Denmark Cohort	Low	Assessments: physical and neurological exam, GOS	Patient population: adults (aged > 14 years) with community-acquired bacterial meningitis – 165 patients with meningitis – 165 patients tested for neurological sequelae – 5 with neurological sequelae	No comparator	Neurological sequelae: 5 Mortality: 14 Lost to follow-up: 0	Primary outcomes: neurological sequelae	1–3 months post-discharge
Cabellos (2019) *(9)* Spain Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged ≥ 14 years) with invasive meningococcal disease – 470 patients with meningitis – 445 patients tested for neurological sequelae – 37 with neurological sequelae	No comparator	Neurological sequelae: 37 Focal neurological: 6 Hearing loss: 11 Seizures: 1 Hydrocephalus: 1 Mortality: 25 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At 1 year

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Díez de los Ríos (2021) *(10)* Spain Case series (> 5 cases)	Low	Assessments: physical and neurological exam	Patient population: adults with *S. suis* infection – 5 patients with meningitis – 5 patients tested for neurological sequelae – 4 with neurological sequelae	No comparator	Neurological sequelae: 4 Focal neurological: 1 Hearing loss: 4 Mortality: 0 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At 30 days post-discharge
Deliran (2022) *(11)* Netherlands (Kingdom of the) Cohort	Low	Assessments: physical and neurological exam, GOS	Patient population: adults (aged > 16 years) with community-acquired bacterial meningitis – 2306 patients with meningitis – 1689 patients tested for neurological sequelae – 218 with neurological sequelae	No comparator	Neurological sequelae: 218 Focal neurological: 478 Hearing loss: 8 Speech: 2 Seizures: 298 Neurocognitive: 7 Mortality: 370 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Deng (2023) *(12)* China Case series (> 5 cases)	Low	Assessments: physical and neurological exam, modified Rankin scale, Activities of daily living (ADLs)	Patient population: adults with *S. suis* meningitis – 17 patients with meningitis – 17 patients tested for neurological sequelae – 12 with neurological sequelae	No comparator	Neurological sequelae: 12 Focal neurological: 1 Hearing loss: 11 Mortality: 0 Lost to follow-up: 0	Primary outcomes: neurological sequelae, disability	At discharge
Domingo (2009) *(13)* Spain Case–control	High	Assessments: physical and neurological exam	Patient population: adults with spontaneous meningitis – 299 patients with meningitis – 299 patients tested for neurological sequelae – 33 with neurological sequelae	No comparator	Neurological sequelae: 33 Focal neurological: 11 Seizures: 19 Neurocognitive: 2 Vision impairment: 1 Mortality: 27 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Domingo (2013) *(14)* Spain Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged > 14 years) with bacterial meningitis – 635 patients with meningitis – 523 patients tested for neurological sequelae – 63 with neurological sequelae	No comparator	Neurological sequelae: 63 Focal neurological: 39 Seizures: 79/607 Mortality: 112 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge
Duval (2022) *(15)* France Cohort	Low	Assessments: physical and neurological exam, modified Rankin scale, GOS, Centre for Epidemiological Studies Depression scale, Hearing Handicap Inventory for the Elderly-screening version, SF-12 Health Survey	Patient population: adults (aged ≥ 18 years) with community-acquired meningococcal meningitis – 111 patients with meningitis – 71 patients tested for neurological sequelae – 48 with neurological sequelae	No comparator	Neurological sequelae: 48 Hearing loss: 11 Neurocognitive: 7 Psychological: 24 Mortality: 7 Lost to follow-up: 33	Primary outcomes: neurological sequelae and quality of life	At 1-year follow-up

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
El-Gindy (2015) *(16)* Egypt Cohort	Low	Assessments: physical and neurological exam, mini mental state examination, Wechsler memory scale	Patient population: adults with bacterial meningitis – 61 patients with meningitis – 41 patients tested for neurological sequelae – 16 with neurological sequelae	No comparator	Neurological sequelae: 16 Focal neurological: 8 Speech: 1 Seizures: 1 Neurocognitive: 22 Hydrocephalus: 1 Mortality: 20 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge
Glimaker (2015) *(17)* Sweden Cohort	Low	Assessments: physical and neurological exam	Patient population: adults with bacterial meningitis – 712 patients with meningitis – 535 patients tested for neurological sequelae – 235 with neurological sequelae	No comparator	Neurological sequelae: 235 Mortality: 68 Lost to follow-up: 109	Primary outcomes: neurological sequelae, death	At 2–6 months post-discharge

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Grindborg (2015) *(18)* Sweden Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged > 17 years) with bacterial meningitis – 520 patients with meningitis – 379 patients tested for neurological sequelae – 150 with neurological sequelae	No comparator	Neurological sequelae: 150 Mortality: 38 Lost to follow-up: 103	Primary outcomes: neurological and audiological sequelae, death	At 2–6 months follow-up
Heckenberg (2008) *(19)* Netherlands (Kingdom of the) Cohort	Low	Assessments: physical and neurological exam, GOS	Patient population: adults (aged > 16 years) with community-acquired bacterial meningitis – 258 patients with meningitis – 238 patients tested for neurological sequelae – 28 with neurological sequelae	No comparator	Neurological sequelae: 28 Focal neurological: 12 Hearing loss: 19 Mortality: 19 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Huong (2018) *(20)* Viet Nam Case-control	Low	Assessments: physical and neurological exam, air conduction audiometry, Modified Clinical Test of Sensory Interaction and Balance, Vertigo Symptoms Scale, Hearing Handicap Inventory for Adults, Dizziness Handicap Inventory, mini mental state examination	Patient population: adults with *S. suis* infection – 76 patients with meningitis – 76 patients tested for neurological sequelae – 45 with neurological sequelae	No comparator	Neurological sequelae: 45 Focal neurological: 8 Hearing loss: 27 Neurocognitive: 5 Psychological: 10 Vision impairment: 4 Mortality: 14 Lost to follow-up: 0	Primary outcomes: neurological, audiological, vestibular sequelae	At discharge, 3 months and 9 months post-discharge
Jensen (2023) *(21)* Denmark Cohort	Low	Assessments: physical and neurological exam, audiological assessment	Patient population: adults (aged ≥ 18 years) with acute bacterial meningitis – 32 patients with meningitis – 24 patients tested for neurological sequelae – 13 with neurological sequelae	No comparator	Neurological sequelae: 13 Mortality: 4 Lost to follow-up: 4	Primary outcomes: neurological and audiological sequelae	At discharge (13 with hearing loss) and 60 days post-discharge (11 with hearing loss)

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Le Bot (2021) *(22)* France Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged ≥ 18 years) with varicella zoster virus central nervous system (CNS) infections – 21 patients with meningitis – 21 patients tested for neurological sequelae – 5 with neurological sequelae	No comparator	Neurological sequelae: 5 Focal neurological: 4 Neurocognitive: 1 Mortality: 0 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge
Moon (2010) *(23)* Republic of Korea Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged ≥ 18 years) with bacterial meningitis – 195 patients with meningitis – 154 patients tested for neurological sequelae – 41 with neurological sequelae	No comparator	Neurological sequelae: 41 Hearing loss: 5 Hydrocephalus: 7 Mortality: 10 Lost to follow-up: 64	Primary outcomes: neurological sequelae, death	At discharge and 30-day follow up

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Moon (2012) *(24)* Republic of Korea Cohort	Low	Assessments: physical and neurological exam	Patient population: adults with pneumococcal meningitis – 93 patients with meningitis – 77 patients tested for neurological sequelae – 29 with neurological sequelae	No comparator	Neurological sequelae: 29 Focal neurological: 11 Hearing loss: 6 Seizures: 7 Hydrocephalus: 2 Mortality: 29/81 Lost to follow-up: 4	Primary outcomes: neurological and audiological sequelae, death	At 30-day follow up
Navacharoen (2009) *(25)* Thailand Case series (> 5 cases)	Low	Assessments: physical and neurological exam	Patient population: all patients with *S. suis* infection – 19 patients with meningitis – 15 patients tested for neurological sequelae – 14 with neurological sequelae	No comparator	Neurological sequelae: 14 Hearing loss: 14 Mortality: 0 Lost to follow-up: 4	Primary outcomes: neurological, audiological, vestibular sequelae	Mean length of follow-up: 17 months (range 6–30 months)

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Pagliano (2017) *(26)* Italy Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged > 18 years) with bacterial meningitis and liver cirrhosis – 44 patients with meningitis – 27 patients tested for neurological sequelae – 8 with neurological sequelae	No comparator	Neurological sequelae: 8 Focal neurological: 4 Hearing loss: 2 Neurocognitive: 5 Mortality: 13 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At 8-week follow-up
Rabbani (2003) *(27)* Pakistan Cohort	Low	Assessments: physical and neurological exam	Patient population: adults with bacterial meningitis – 190 patients with meningitis – 182 patients tested for neurological sequelae – 73 with neurological sequelae	No comparator	Neurological sequelae: 73 Focal neurological: 44 Hearing loss: 11 Speech: 6 Seizures: 25 Hydrocephalus: 12 Mortality: 42 Lost to follow-up: 8	Primary outcomes: neurological sequelae, death	After discharge for unspecified follow-up period

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Raemy (2023) *(28)* Switzerland Cohort	Low	Assessments: physical and neurological exam	Patient population: adults (aged ≥ 18 years) with confirmed pneumococcal meningitis – 52 patients with meningitis – 35 patients tested for neurological sequelae – 15 with neurological sequelae	No comparator	Neurological sequelae: 15 Focal neurological: 2 Hearing loss: 14 Seizures: 1 Neurocognitive: 3 Hydrocephalus: 2 Mortality: 8 Lost to follow-up: 9	Primary outcomes: death Secondary outcomes: neurological sequelae	At discharge and 1 year post-discharge
Thomas (1999) *(29)* France; Switzerland RCT	Low	Assessments: physical and neurological exam, Glasgow Coma Scale, mini mental state examination, Simplified Acute Physiologic Score	Patient population: adults (aged 18–79 years) with bacterial meningitis – 60 patients with meningitis – 52 patients tested for neurological sequelae	No comparator	Neurological sequelae: 14 Mortality: 8 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At 30-day follow-up

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 14 with neurological sequelae				
Tubiana (2020) *(30)* France Cohort	Low	Assessments: physical and neurological exam, Center for Epidemiologic Studies Depression scale, Hearing Handicap Inventory for the Elderly screening version, SF-12 Health Survey	Patient population: adults (aged ≥ 18 years) with community-acquired bacterial meningitis – 533 patients with meningitis – 284 patients tested for neurological sequelae – 48 with neurological sequelae	No comparator	Neurological sequelae: 48 Hearing loss: 74 Psychological: 87 Mortality: 90 Lost to follow-up: not reported (NR)	Primary outcomes: neurological sequelae, disability, death	At 12-month follow-up
van Soest (2023) *(31)* Netherlands (Kingdom of the) Cohort	Low	Assessments: physical and neurological exam, Glasgow Coma Scale, Glasgow Outcome Scale	Patient population: adults (aged ≥ 16 years) with meningococcal meningitis – 442 patients with meningitis – 273 patients tested for neurological sequelae	No comparator	Neurological sequelae: 67 Focal neurological: 18 Hearing loss: 34 Mortality: 10	Primary outcomes: neurological sequelae, death	During hospitalization

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 67 with neurological sequelae		Lost to follow-up: NR		
van Veen (2016) *(32)* Netherlands (Kingdom of the) Cohort	Low	Assessments: physical and neurological exam, GOS	Patient population: adults (aged > 16 years) with community-acquired bacterial meningitis – 1449 patients with meningitis – 1194 patients tested for neurological sequelae – 115 with neurological sequelae	No comparator	Neurological sequelae: 115 Hearing loss: 114 Mortality: 1246 Lost to follow-up: NR	Primary outcomes: neurological sequelae, death	At discharge
Viale (2015) *(33)* Italy Cohort	Low	Assessments: physical and neurological exam	Patient population: adults with acute bacterial meningitis – 177 patients with meningitis – 160 patients tested for neurological sequelae	No comparator	Neurological sequelae: 26 Focal neurological: 6 Hearing loss: 3 Mortality: 17 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge and 30-day follow up

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 26 with neurological sequelae				

CNS: central nervous system; GOS: Glasgow Outcome Scale; NR: not reported; RCT: randomized controlled trial.

Table WA15.1b Characteristics of studies included in the review (involving both adults and children)

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Ostergaard (2005) *(34)* Denmark Cohort	Low	Assessments: physical and neurological exam	Patient population: All patients with pneumococcal meningitis Children: – 45 paediatric patients with meningitis – 42 paediatric patients tested for neurological sequelae – 7 children with neurological sequelae Adults: – 142 adult patients with meningitis – 96 adult patients tested for neurological sequelae	No comparator	Neurological sequelae: 57 (children: 7; adults: 50) Focal neurological: Children: 1 Adults: 21 Hearing loss Children: 5 Adults: 29 Mortality: 39 Children: 1 Adults: 38 Lost to follow-up: 10	Primary outcomes: neurological and audiological sequelae	At discharge

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			50 adults with neurological sequelae				
Bettinger (2013) *(35)* Canada Epidemio-logical surveillance	Low	Assessments: physical and neurological exam	Patient population: All invasive meningococcal cases (children aged < 20 years) – 413 patients with meningitis (Children: 278; Adults: 135) – 391 paediatric patients tested for neurological sequelae 14 with neurological sequelae	No comparator	Neurological sequelae: 14 Deafness: 28 Seizures: 10 Mortality: 22 (Children: 12; Adults: 10) Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge
Sakata (2010) *(36)* Japan Cohort	Low	Assessments: physical and neurological exam	Patient population: All patients with bacterial meningitis Children: – 342 paediatric patients with meningitis – 340 paediatric patients tested	No comparator	Neurological sequelae: 87 (Children: 64; Adults: 23) Focal neurological Children: 12 Adults: 6	Primary outcomes: neurological sequelae, death	At end of treatment, 1 month and 1 year post-discharge

Lead author (year) Country of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			for neurological sequelae – 64 children with neurological sequelae Adults: – 71 adult patients with meningitis – 71 adult patients tested for neurological sequelae 23 adults with neurological sequelae		Hearing loss Children: 5 Adults: 2 Seizures Children: 19 Adults: 4 Neurocognitive Children: 25 Adults: 1 Hydrocephalus Children: 6 Adults: 3 Mortality: 36 Children: 6 Adults: 30		

Table WA15.1c Characteristics of the studies included in the review (involving children only)

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Ahmed (2013) *(37)* Bangladesh Cohort	Low	Assessments: physical and neuro-developmental exam (head circumference, and assessments of motor, hearing, vision and cognitive functions), neurological assessment (cranial nerve palsy and motor deficits [e.g. cerebral palsy], and an initial assessment of hearing and vision), hearing assessment, visual assessment, psychological assessment (Mental Development Index of the Bayley Scales of Infant Development-II or Stanford-Binet Intelligence Scale)	Patient population: children (aged 2–59 months) with confirmed Hib meningitis Short-term follow-up cohort: 64/81 Long-term follow-up cohort: 71/107 – 188 patients with meningitis – 135 patients tested for neurological sequelae – 54 with neurological sequelae	No comparator; short-term vs long-term follow-up	Neurological sequelae: 54 Developmental deficit: 41 Vision: 3 Hearing: 13 Mental delay: 28 Psychomotor delay: 34 Mortality: 20 Lost to follow-up: 33	Primary outcomes: neurological sequelae (cranial nerve palsy, motor deficits), hearing impairment, visual impairment, IQ, psychomotor delay	Short-term: 30–40 days post-discharge Long-term: 12–24 months post-discharge
Ai (2017) *(38)* China	Low	Assessments: physical and neurological exam	Patient population: children with viral	No comparator	Neurological sequelae: 2 Headache: 1	Primary outcomes: neurological sequelae (seizure, cognitive	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Cohort			encephalitis and meningitis – 285 patients with meningitis – 285 patients tested for neurological sequelae – 2 with neurological sequelae		Speech difficulties: 1 Mortality: 0 Lost to follow-up: 0	impairment, visual impairment, hearing impairment, speech and language disorders, motor dysfunction), death	
Al Khorasani (2006) *(39)* Yemen Cohort	Low	Assessments: physical and neurological exam, hearing tests	Patient population: children (aged 1 month to 15 years) with meningitis – 160 patients with meningitis – 144 patients tested for neurological sequelae – 28 with neurological sequelae	No comparator	Neurological sequelae: 28 Cerebral palsy: 18 Epilepsy: 15 Hydrocephalus: 8 Deafness: 1 Mortality: 16 Lost to follow-up: 0	Primary outcomes: neurological sequelae (visual, hearing, speech impairment; motor deficits), death	6 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Alsubaie (2020) *(40)* Saudi Arabia Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged up to 14 years) with Salmonella meningitis – 14 patients with meningitis – 10 patients tested for neurological sequelae – 6 with neurological sequelae	No comparator	Neurological sequelae: 6 Hydrocephalus: 5 Cerebral palsy: 4 Developmental delay: 3 Epilepsy: 3 Mortality: 4 Lost to follow-up: 0	Primary outcomes: neurological sequelae (cerebral palsy or any other persistent neuromotor deficits; developmental delay, including motor and speech/language development; hydrocephalus; epilepsy; and sensorineural hearing loss), death	6 months, 1 year, 3 years after meningitis diagnosis
Anh (2006) *(41)* Viet Nam Cohort	High	Assessments: physical and neurological exam	Patient population: children (aged < 60 months) with suspected meningitis – 116 patients with meningitis – 111 patients tested for neurological sequelae	No comparator	Neurological sequelae: 12 Developmental delay: 2 Hydrocephalus: 4 Paralysis: 2 Seizure: 4 Mortality: 5	Primary outcomes: neurological sequelae (cranial nerve, motor, cognitive deficits), death	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 12 with neurological sequelae		Lost to follow-up: 0		
Antony (2017) *(42)* USA Case series (> 5 cases)	Low	Assessments: physical and neurological exam	Patient population: children with invasive non-type-b *H. influenzae* – 13 patients with meningitis – 12 patients tested for neurological sequelae – 10 with neurological sequelae	No comparator	Neurological sequelae: 10 Seizures: 9 Motor delay: 5 Hearing loss: 2 Mortality: 1 Lost to follow-up: 0	Primary outcomes: Neurological sequelae	During hospitalization
Arditi (1998) *(43)* USA Cohort	Low	Assessments: physical and neurological exam	Patient population: children with pneumococcal meningitis – 180 patients with meningitis – 166 patients tested for neurological sequelae	No comparator	Neurological sequelae: 41 Hearing loss: 48/151 (hemiparesis, quadriplegia, spasticity, ataxia, cranial nerve dysfunction, cortical blindness, vegetative state,	Primary outcomes: neurological sequelae (neurological sequelae (motor deficits) and/or neurosensory deafness)	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 41 with neurological sequelae		and obstructive hydrocephalus) Mortality: 14 Lost to follow-up: 0		
Arteta-Acosta (2022) *(44)* Chile Cross-sectional	Low	Assessments: physical and neurological exam	Patient population: children with invasive meningococcal disease – 36 patients with meningitis – 36 patients tested for neurological sequelae – 27 with neurological sequelae	No comparator	Neurological sequelae: 27 Mortality: 0 Lost to follow-up: 0	Primary outcomes: neurological sequelae (neurological impairments (psychomotor developmental delay, speech/language impairment, seizures, hypertonia/ hypotonia, nerve damage, and attention deficit hyperactivity disorder [ADHD]); hearing loss and cochlear implant; osteoarticular (movement limitation, surgical debridement, and	Range: 16–50 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
						limb amputation), and skin scarring	
Basualdo (2004) *(45)* Paraguay Cohort	Low	Assessments: physical and neurological exam, hearing test	Patient population: children (aged up to 15 years) with invasive *H. influenzae* infection – 83 patients with meningitis – 72 patients tested for neurological sequelae – 28 with neurological sequelae	No comparator	Neurological sequelae: 28 Hydrocephalus: 16 Hearing loss: 3/10 Mortality: 11 Lost to follow-up: 0	Primary outcomes: neurological sequelae (hydrocephalus, cranial nerve deficits, hearing loss and psychomotor/ mental retardation)	At discharge
Biaukula (2012) *(46)* Fiji Cohort	Low	Assessments: physical and neurological exam, vision test, Pediatric Quality of Life Inventory tool (PedsQL), pure tone audiometry, behavioural observation audiometry, auditory brainstem response testing, visual reinforcement	Patient population: children (aged 1 month to 5 years) with suspected meningitis – 70 patients with meningitis – 54 patients tested for neurological sequelae	No comparator	Neurological sequelae: 6 Hearing loss: 5/33 Mortality: 16 Lost to follow-up: 3	Primary outcomes: neurological sequelae (seizure, motor deficits, hearing impairment, visual impairment)	At discharge Short term follow-up (6–8 weeks post-discharge) Long-term follow-up (6 months post-discharge)

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
		audiometry or impedance audiometry	– 6 with neurological sequelae				
Blanco (2020) *(47)* Brazil Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 28 days to 15 years) with confirmed bacterial or meningococcal meningitis – 90 patients with meningitis – 83 patients tested for neurological sequelae – 19 with neurological sequelae	No comparator	Neurological sequelae: 19 Convulsion: 9 Visual impairment: 2 Hydrocephalus: 2 Anisocoria and hemiparesis: 1 Mortality: 5 Lost to follow-up: 2	Primary outcomes: neurological sequelae (visual impairment, convulsion, hydrocephalus, septic shock, empyema, arthritis, anisocoria and hemiparesis)	During hospitalization

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Bor (2020) *(48)* Türkiye Cohort	Low	Assessments: physical and neurological exam	Patient population: children with acute bacterial meningitis – 389 patients with meningitis – 385 patients tested for neurological sequelae – 108 with neurological sequelae	No comparator	Neurological sequelae: 108 Hydrocephalus: 25 Epilepsy: 13 Hearing loss: 5 Mortality: 4 Lost to follow-up: 0	Primary outcomes: neurological sequelae (hydrocephalus, epilepsy, cranial nerve involvement, hearing loss)	Before discharge
Bozzola (2021) *(49)* Italy Cohort	Low	Assessments: physical and neurological exam, vision and hearing tests	Patient population: children (aged under 18 years) with meningitis – 425 patients with meningitis – 419 patients tested for neurological sequelae	No comparator	Neurological sequelae: 119 Neuro: 83 Auditory: 46 Visual: 27 Mortality: 6 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge Follow-up: 6 months to 1 year

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 119 with neurological sequelae				
Buckingham (2006) *(50)* USA Cohort	High	Assessments: physical and neurological exam, audiometric tests	Patient population: children with pneumococcal meningitis – 114 patients with meningitis – 151 patients tested for neurological sequelae – 51 with neurological sequelae	No comparator	Neurological sequelae: 51 Neurological deficits: 14 Cranial nerve palsy: 6 Hemiparesis: 4 Hemiplegia: 3 Hearing loss: 37 Mortality: 10 Lost to follow-up: 27	Primary outcomes: neurological sequelae (motor or cranial nerve deficits or global encephalopathy), hearing loss	At discharge
Burton (2023) *(51)* New Zealand Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged < 15 years) with meningococcal meningitis – 425 patients with meningitis	No comparator	Neurological sequelae: 61 Hearing loss: 32 Seizures: 8 Cognitive: 35 Limb loss: 7	Primary outcomes: neurological sequelae, death	At follow-up ≥ 3 months

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 419 patients tested for neurological sequelae – 119 with neurological sequelae		Mortality: 13 Lost to follow-up: 48		
Casella (2004) *(52)* Brazil Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged > 5 weeks) with meningococcal meningitis – 81 patients with meningitis – 61 patients tested for neurological sequelae – 16 with neurological sequelae	No comparator	Neurological sequelae: 16 Focal neurological: 2 Hearing loss: 7 Speech deficits: 5 Seizures: 1 Neurocognitive: 9 Psychological: 5 Mortality: 7 Lost to follow-up: 13	Primary outcomes: neurological, psychological, auditory sequelae	Mean length of follow-up: 36.97 months (median 34.5)
Chamkhaleh (2021) *(53)*	Low	Assessments: physical and neurological exam	Patient population: children with meningitis	No comparator	Neurological sequelae: 14	Primary outcomes: neurological sequelae (motor,	Follow-up after at least 2 years

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Islamic Republic of Iran Cohort			– 202 patients with meningitis – 187 patients tested for neurological sequelae – 14 with neurological sequelae		Focal neurological: 9 Seizures: 5 Mortality: 15 Lost to follow-up: 0	sensation, audition and cognition defects, and also seizure history), death	
Chauhan (2018) *(54)* India Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 1–59 months) with acute bacterial meningitis – 81 patients with meningitis – 32 patients tested for neurological sequelae – 24 with neurological sequelae	No comparator	Neurological sequelae: 24 Focal neurological: 20 Hearing loss: 3 Seizures: 5 Hydrocephalus: 2 Vision impairment: 5 Mortality: 7 Lost to follow-up: 42	Primary outcomes: neurological sequelae, death	Up to 6 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Chen (2018) China *(55)* Cohort	Low	Assessments: physical and neurological exam, Pediatric Version of the Glasgow Outcome Scale –extended (GOS-E Peds)	Patient population: children (aged ≤ 28 days to ≥ 16 years) with acute CNS infection, including meningitis and/or encephalitis – 139 patients with meningitis – 139 patients tested for neurological sequelae – 68 with neurological sequelae	No comparator	Neurological sequelae: 68 Focal neurological: 10 Hearing loss: 6 Speech deficits: 12 Seizures: 16 Neurocognitive: 34 Psychological: 14 Vision impairment: 3 Limb loss: 15 Mortality: 8 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At 46–56 months post onset of meningitis
Dueger (2008) *(56)* Guatemala Case series	Low	Assessments: physical and neurological exam	Patient population: children (aged 1–59 months) with bacterial meningitis – 1021 patients with meningitis	No comparator	Neurological sequelae: 239 Focal neurological: 103 Seizures: 119 Hydrocephalus: 28	Primary outcomes: neurological sequelae, death	At discharge Mean length of follow-up: 14.95 days

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 387 patients tested for neurological sequelae – 239 with neurological sequelae		Mortality: 214 Lost to follow-up: 420		
Duke (2002) *(57)* Papua New Guinea RCT	Mid	Assessments: physical and neurological exam	Patient population: children (aged 1 month to 12 years) with bacterial meningitis – 346 patients with meningitis – 346 patients tested for neurological sequelae – 162 with neurological sequelae	No comparator	Neurological sequelae: 162 Focal neurological: 36 Hearing loss: 21 Seizures: 12 Hydrocephalus: 9 Vision impairment: 43 Mortality: 65 Lost to follow-up: 0	Primary outcomes: neurological sequelae, severity of sequelae Secondary outcomes: death	At discharge and 3 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Edmond (2010) *(58)* Senegal Cohort	Low	Assessments: physical and neurological exam	Patient population: children (> 4 years) with bacterial meningitis – 105 patients with meningitis – 66 patients tested for neurological sequelae – 51 with neurological sequelae	No comparator	Neurological sequelae: 51 Focal neurological: 17 Hearing loss: 38 Seizures: 14 Neurocognitive: 32 Psychological: 4 Vision impairment: 1 Mortality: 8 Lost to follow-up: 7	Primary outcomes: major and minor neurological sequelae, hearing loss	At 1 year follow-up post-discharge
Epelboin (2016) *(59)* France Cross-sectional	Low	Assessments: physical and neurological exam	Patient population: children with eosinophilic meningitis – 14 patients with meningitis – 7 patients tested for neurological sequelae	No comparator	Neurological sequelae: 3 Mortality: 5 Lost to follow-up: 2	Primary outcomes: neurological sequelae, death	At 1 year post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 3 with neurological sequelae				
Kadziszewska (2023) *(60)* Poland Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 1 month to 17 years) with bacterial meningitis – 75 patients with meningitis – 59 patients tested for neurological sequelae – 42 with neurological sequelae	No comparator	Neurological sequelae: 42 Focal neurological: 12 Hearing loss: 11 Seizures: 2 Neurocognitive: 24 Hydrocephalus: 5 Mortality: 2 Lost to follow-up: 14	Primary outcomes: neurological sequelae	Mean length of follow-up: 4.6 years (range: 1–10 years)
Khowaja (2013) *(61)* Pakistan Case–control	Low	Assessments: physical and neurological exam, Denver II scale	Patient population: children (aged < 5 years) with acute bacterial meningitis – 188 patients with meningitis	No comparator	Neurological sequelae: 45 Focal neurological: 17 Hearing loss: 19 Speech: 17 Seizures: 11	Primary outcomes: neurological, neurodevelopmental, audiological sequelae	Up to 6 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 80 patients tested for neurological sequelae – 45 with neurological sequelae		Neurocognitive: 35 Vision impairment: 11 Mortality: 64 Lost to follow-up: 44		
Klobassa (2014) *(62)* Austria Cohort	Low	Assessments: physical and neurological exam	Patient population: children (less than 5 years) with pneumococcal meningitis – 74 patients with meningitis – 57 patients tested for neurological sequelae – 20 with neurological sequelae	No comparator	Neurological sequelae: 20 Focal neurological: 8 Hearing loss: 9 Hydrocephalus: 3 Mortality: 5 Lost to follow-up: 12	Primary outcomes: neurological sequelae	At discharge and follow-up Mean (SD) length of follow-up: 20.3 (17.5) months
Lovera (2022) *(63)* Paraguay	Low	Assessments: physical and neurological exam	Patient population: children (aged < 15 years) with bacterial meningitis	No comparator	Neurological sequelae: 16 Focal neurological: 4	Primary outcomes: severe neurological sequelae (blindness,	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Cohort			– 114 patients with meningitis – 76 patients tested for neurological sequelae – 16 with neurological sequelae		Hearing loss: 6 Neurocognitive: 9 Hydrocephalus: 7 Vision impairment: 2 Mortality: 38 Lost to follow-up: 0	quadriplegia and/or paresis, hydrocephalus requiring a shunt, refractory convulsions, hypoacusis or severe psychomotor retardation), death	
Meng (2022) *(64)* China Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged ≥ 1 month) with bacterial meningitis – 283 patients with meningitis – 175 patients tested for neurological sequelae – 41 with neurological sequelae	No comparator	Neurological sequelae: 41 Focal neurological: 23 Hearing loss: 6 Speech: 13 Seizures: 19 Neurocognitive: 19 Hydrocephalus: 27 Vision impairment: 4 Mortality: 8	Primary outcomes: neurological sequelae	After discharge follow-up range: 6 months to 5 years

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
					Lost to follow-up: 100		
Molyneux (2002) *(65)* Malawi RCT	Mid	Assessments: physical and neurological exam	Patient population: children (aged 2 months to 13 years) with bacterial meningitis; HIV patients – 598 patients with meningitis – 301 patients tested for neurological sequelae – 152 with neurological sequelae	No comparator	Neurological sequelae: 152 Focal neurological: 11 Hearing loss: 127 Speech: 7 Seizures: 11 Psychological: 8 Hydrocephalus: 11 Vision impairment: 1 Limb loss: 7 Mortality: 215 Lost to follow-up: 82	Primary outcomes: neurological sequelae, death	At 1 and 6 months post-discharge
Molyneux (2014) *(66)* Malawi	Low	Assessments: physical and neurological exam	Patient population: children (aged ≥ 2 months) with bacterial meningitis	No comparator	Neurological sequelae: 127 Hearing loss: 104	Primary outcomes: visual, hearing, developmental,	At discharge, 30 and 180 days post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
RCT			– 360 patients with meningitis – 265 patients tested for neurological sequelae – 127 with neurological sequelae		Mortality: 93 Lost to follow-up: 2	neurological sequelae, death	
Namani (2011) *(67)* [1]Kosovo Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 0–16 years) with bacterial meningitis – 277 patients with meningitis – 270 patients tested for neurological sequelae – 60 with neurological sequelae	No comparator	Neurological sequelae: 60 Seizures: 31 Hydrocephalus: 7 Vision impairment: 1 Mortality: 15 (before and after follow-up) Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge and follow-up of 3 years
Pagliano (2007) *(68)* Italy	Low	Assessments: physical and neurological exam	Patient population: children with pneumococcal meningitis	No comparator	Neurological sequelae: 14	Primary outcomes: neurological sequelae, death	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Cohort			– 64 patients with meningitis – 61 patients tested for neurological sequelae – 14 with neurological sequelae		Focal neurological: 7 Hearing loss: 4 Neurocognitive: 2 Hydrocephalus: 2 Mortality: 3 Lost to follow-up: 0		
Pan (2023) *(69)* China Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged between 29 days and 14 years) with bacterial meningitis – 207 patients with meningitis – 207 patients tested for neurological sequelae – 123 with neurological sequelae	No comparator	Neurological sequelae: 123 Mortality: 21 Lost to follow-up: 0	Primary outcomes: neurological sequelae	During hospitalization

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Paulke-Korinek (2014) *(70)* Austria Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged < 5 years) with invasive pneumococcal disease – 85 patients with meningitis – 75 patients tested for neurological sequelae – 43 with neurological sequelae	No comparator	Neurological sequelae: 43 Focal neurological: 6 Hearing loss: 10 Hydrocephalus: 12 Vision impairment: 1 Mortality: 10 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge and at follow-up 6 months post-discharge
Pelkonen (2008) *(71)* Angola Cross-sectional	Low	Assessments: physical and neurological exam	Patient population: children (aged 0–12 years) with acute bacterial meningitis – 482 patients with meningitis – 270 patients tested for neurological sequelae – 95 with neurological sequelae	No comparator	Neurological sequelae: 95 Focal neurological: 21 Hearing loss: 16 Neurocognitive: 15 Vision impairment: 24 Limb loss: 21	Primary outcomes: neurological sequelae	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
					Mortality: 158 Lost to follow-up: 20		
Pelkonen (2009) *(72)* Angola Cross-sectional	Low	Assessments: physical and neurological exam	Patient population: children (aged 2 months to 12 years) with bacterial meningitis – 422 patients with meningitis – 403 patients tested for neurological sequelae – 62 with neurological sequelae	No comparator	Neurological sequelae: 62 Mortality: 133 (before and after follow-up) Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge
Pelkonen (2022) *(73)* Angola, Argentina, Brazil, Dominican Republic, Ecuador, Finland,	Low	Assessments: physical and neurological exam	Patient population: children (aged 2 months to 15 years) with suspected bacterial meningitis – 2061 patients with meningitis – 1503 patients tested for	No comparator	Neurological sequelae: 488 Focal neurological: 341 Hearing loss: 351 Mortality: 494	Primary outcomes: neurological sequelae, death	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Paraguay, Venezuela (Bolivarian Republic of) Cohort			– neurological sequelae – 488 with neurological sequelae		Lost to follow-up: NR		
Plumb (2018) *(74)* USA Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged < 10 years) with confirmed invasive *H. influenzae* serotype a infection – 15 patients with meningitis – 15 patients tested for neurological sequelae – 4 with neurological sequelae	No comparator	Neurological sequelae: 4 Focal neurological: 3 Hearing loss: 3 Speech: 2 Neurocognitive: 1 Hydrocephalus: 1 Mortality: 2 Lost to follow-up: 0	Primary outcomes: neurological sequelae	6 months to 2 years after illness
Resti (2009) *(75)* Italy Cohort	Low	Assessments: physical and neurological exam	Patient population: children and adolescents (aged 0–16 years) with invasive pneumococcal disease – 19 patients with meningitis	No comparator	Neurological sequelae: 2 Mortality: 1 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At 6 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 19 patients tested for neurological sequelae – 2 with neurological sequelae				
Rivero-Calle (2016) *(76)* Spain Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged under 15 years) with invasive meningococcal disease – 114 patients with meningitis – 114 patients tested for neurological sequelae – 19 with neurological sequelae	No comparator	Neurological sequelae: 19 Focal neurological: 1 Hearing loss: 7 Mortality: 16 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge
Roine (2015) *(77)* Angola Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 2 months to 13 years) with presumed bacterial meningitis – 361 patients with meningitis	No comparator	Neurological sequelae: 243 Focal neurological: 243 Hearing loss: 146 Seizures: 189	Primary outcomes: neurological sequelae	At Day 7 of treatment, discharge and 1 month post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 280 patients tested for neurological sequelae – 243 with neurological sequelae		Mortality: 19 Lost to follow-up: 62		
Rugemalira (2021) *(78)* Finland Cohort	Low	Assessments: physical and neurological exam, GOS, auditory brainstem response, PedsQL 4.0 Generic Core Scales, PedsQL Infant Scales	Patient population: children with bacterial meningitis – 68 patients with meningitis – 68 patients tested for neurological sequelae – 29 with neurological sequelae	No comparator	Neurological sequelae: 29 Focal neurological: 16 Hearing loss: 16 Seizures: 8 Neurocognitive: 4 Vision impairment: 1 Mortality: 0 Lost to follow-up: 0	Primary outcomes: neurological and audiologic sequelae	Median length of follow-up: 28 months
Saha (2009) *(79)* Bangladesh Cohort	Low	Assessments: physical and neurological exam	Patient population: children with pneumococcal meningitis	No comparator	Neurological sequelae: 78 Hearing loss: 11	Primary outcomes: neurological sequelae	Mean length of follow-up (weeks): 5

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 102 patients with meningitis – 102 patients tested for neurological sequelae – 78 with neurological sequelae		Neurocognitive: 27 Vision impairment: 4 Mortality: 18 Lost to follow-up: 13		Short term: 30–40 days Long term: 6–24 months
Sankar (2007) *(80)* India RCT	Low	Assessments: physical and neurological exam, Denver Developmental Scale II, audiometry, brainstem evoked auditory potential	Patient population: children (aged 2 months to 12 years) with acute bacterial meningitis – 58 patients with meningitis – 55 patients tested for neurological sequelae – 17 with neurological sequelae	No comparator	Neurological sequelae: 17 Focal neurological: 7 Hearing loss: 10 Neurocognitive: 3 Hydrocephalus: 2 Vision impairment: 2 Mortality: 3 Lost to follow-up: 7	Primary outcomes: neurological and audiological sequelae	At discharge, and 1 month and 6months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Şensoy (2009) *(81)* Türkiye Cohort	High	Assessments: physical and neurological exam	Patient population: children with enteroviral meningitis – 104 patients with meningitis – 104 patients tested for neurological sequelae – 0 with neurological sequelae	No comparator	Neurological sequelae: 0 Mortality: 0 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge
Shamsad (2009) *(82)* Bangladesh Cohort	Low	Assessments: physical and neurological exam	Patient population: children (1–12 months) with meningitis – 90 patients with meningitis – 90 patients tested for neurological sequelae – 28 with neurological sequelae	No comparator	Neurological sequelae: 28 Mortality: 7 Lost to follow-up: 0	Primary outcomes: neurological sequelae, death	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Stockmann (2013) *(83)* USA Cohort	Low	Assessments: physical and neurological exam	Patient population: children with culture-confirmed pneumococcal meningitis – 68 patients with meningitis – 59 patients tested for neurological sequelae – 37 with neurological sequelae	No comparator	Neurological sequelae: 37 Focal neurological: 31 Hearing loss: 17 Seizures: 19 Neurocognitive: 23 Hydrocephalus: 8 Vision impairment: 6 Mortality: 9 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge or follow-up Median length of follow-up: 3.1 years
Türel (2013) *(84)* Türkiye Case series (> 5 cases)	Low	Assessments: physical and neurological exam, transient evoked otoacoustic emissions, Denver Developmental Screening Test II	Patient population: children (aged < 1 month to < 5 years) with bacterial meningitis – 283 patients with meningitis – 146 patients tested for	No comparator	Neurological sequelae: 38 Focal neurological: 35 Hearing loss: 11 Speech: 21 Seizures: 26 Psychological: 20	Primary outcomes: neurological, audiological, neurodevelopmental sequelae	At 9 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– neurological sequelae – 38 with neurological sequelae		Hydrocephalus: 17 Mortality: 2 Lost to follow-up: 137		
Teixeira (2021) *(85)* Brazil Cohort		Assessments: physical and neurological exam	Patient population: children (aged 0–18 years) with bacterial meningitis – 178 patients with meningitis – 170 patients tested for neurological sequelae – 22 with neurological sequelae	No comparator	Neurological sequelae: 22 Focal neurological: 1 Hearing loss: 9 Seizures: 1 Neurocognitive: 2 Hydrocephalus: 1 Mortality: 22 (before and after follow-up) Lost to follow-up: 0	Primary outcomes: suppurative complications, neurological sequelae, death	At discharge
Tenhu (2020) *(86)* Angola	Mid	Assessments: physical and neurological exam, Glasgow and Blantyre coma scores	Patient population: children (aged 2 months to 15 years)	No comparator	Neurological sequelae: 24	Primary outcomes: neurological sequelae	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
RCT			with presumptive bacterial meningitis – 241 patients with meningitis – 177 patients tested for neurological sequelae – 24 with neurological sequelae		Mortality: 63 Lost to follow-up: 0		
Teräsjärvi (2024) *(87)* Angola Cross-sectional	Low	Assessments: physical and neurological exam, Glasgow and Blantyre coma scores	Patient population: children with bacterial meningitis – 241 patients with meningitis – 178 patients tested for neurological sequelae – 54 with neurological sequelae	No comparator	Neurological sequelae: 54 Mortality: 63 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Theodoridou (2013) *(88)* Greece Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 1 month to 14 years) with bacterial meningitis – 2477 patients with meningitis – 2207 patients tested for neurological sequelae – 73 with neurological sequelae	No comparator	Neurological sequelae: 73 Hearing loss: 23 Seizures: 24 Hydrocephalus: 12 Mortality: 95 Lost to follow-up: NR	Primary outcomes: neurological sequelae	Up to 3 months post-discharge
Tuncer (2004) *(89)* Türkiye Cohort	Low	Assessments: physical and neurological exam	Patient population: children with purulent meningitis – 48 patients with meningitis – 42 patients tested for neurological sequelae – 13 with neurological sequelae	No comparator	Neurological sequelae: 13 Hearing loss: 5 Hydrocephalus: 5 Mortality: 6 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Uppal (2017) *(90)* India RCT	Low	Assessments: physical and neurological exam	Patient population: children (aged 3 months to 12 years) with acute bacterial meningitis – 40 patients with meningitis – 40 patients tested for neurological sequelae – 6 with neurological sequelae	No comparator	Neurological sequelae: 6 Focal neurological: 7 Hydrocephalus: 3 Mortality: 0 Lost to follow-up: 0	Primary outcomes: cerebrospinal fluid concentrations of tumour necrosis factor alpha Secondary outcomes: neurological and audiological sequelae	At discharge and follow-up 3 months
Vasilopoulou (2011) *(91)* Greece Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged 1 month to 14 years) with acute bacterial meningitis – 2477 patients with meningitis – 2207 patients tested for neurological sequelae – 73 with neurological sequelae	No comparator	Neurological sequelae: 73 Focal neurological: 3 Hearing loss: 23 Seizures: 24 Hydrocephalus: 12 Mortality: 95 Lost to follow-up: NR	Primary outcomes: neurological sequelae	Up to 3 months post-discharge

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Vaswani (2021) *(92)* India RCT	Mid	Assessments: physical and neurological exam, Denver Developmental Screening Tests, Brainstem evoked responses, pure tone audiometry	Patient population: children (aged 3 months to 14 years) with acute pyogenic meningitis – 96 patients with meningitis – 96 patients tested for neurological sequelae – 20 with neurological sequelae	No comparator	Neurological sequelae: 20 Focal neurological: 9 Hearing loss: 6 Hydrocephalus: 5 Mortality: 0 Lost to follow-up: 0	Primary outcomes: treatment failure Secondary outcomes: neurological, audiological, neurodevelopmental sequelae	At 30-day and 90-day follow-up post-discharge
Wang (2019) *(93)* China Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged < 5 years) with pneumococcal meningitis – 132 patients with meningitis – 107 patients tested for neurological sequelae	No comparator	Neurological sequelae: 39 Focal neurological: 3 Hearing loss: 12 Seizures: 14 Psychological: 18 Hydrocephalus: 8 Vision impairment: 2	Primary outcomes: neurological sequelae	Every month in the first year and every 6 months thereafter

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 39 with neurological sequelae		Mortality: 25 Lost to follow-up: 0		
Wang (2022) *(94)* China Cohort	Low	Assessments: physical and neurological exam	Patient population: children (aged < 16 years) with pneumococcal meningitis – 26 patients with meningitis – 26 patients tested for neurological sequelae – 3 with neurological sequelae	No comparator	Neurological sequelae: 3 Focal neurological: 1 Neurocognitive: 1 Hydrocephalus: 1 Mortality: 12 Lost to follow-up: 0	Primary outcomes: neurological sequelae	At 6 months post-discharge
Wee (2016) *(95)* Singapore Cohort	Low	Assessments: physical and neurological exam, Glasgow coma scale	Patient population: children (aged < 18 years) with acute bacterial meningitis – 112 patients with meningitis – 73 patients tested for neurological sequelae	No comparator	Neurological sequelae: 41 Hearing loss: 12 Seizures: 20 Neurocognitive: 28 Hydrocephalus: 9 Vision impairment: 4	Primary outcomes: neurological sequelae, death	At 6 months, 1 year, 2 years and 5 years post-illness

Lead author (year) Country/area of conduct Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			– 41 with neurological sequelae		Mortality: 7 Lost to follow-up: 32		

CNS: central nervous system; GOS: Glasgow Outcome Scale; NR: not reported; PedsQL: Pediatric Quality of Life Inventory tool; RCT: randomized controlled trial.
[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244(1999).

3.2 Risk-of-bias assessment results

The results of the risk-of-bias assessments were as follows: the total sample size was 32 282, with 9794 adults (aged ≥ 8 years) and 22 413 children (aged < 18 years). A total of 89 articles were extracted, of which 30 involved adults, and 62 children. Three of the 89 articles involved both adults and children. Tables WA15.2a–2e present the results of the risk-of-bias assessments.

Table WA15.2a Risk-of-bias assessment results: case series studies

Case series (JBI checklist)	
Study	**Result**
Navacharoen 2009 *(25)*	Good quality
Dueger 2008 *(56)*	Good quality
Diez de los Rios 2021 *(10)*	Fair quality
Deng 2023 *(12)*	Good quality
Antony 2017 *(42)*	Good quality

Table WA15.2b Risk-of-bias assessment results: case–control studies

Case–control (Newcastle-Ottawa tool)	
Study	**Overall result**
Khowaja 2013 *(61)*	Good quality
Huong 2018 *(20)*	Good quality
Edmond 2010 *(58)*	Good quality

Table WA15.2c Risk-of-bias assessment results: cohort studies

Cohort studies (Newcastle-Ottawa tool)	
Study	**Overall result**
Türel 2013 *(84)*	Good quality
Viale 2015 *(33)*	Good quality

Cohort studies (Newcastle-Ottawa tool)	
Rugemalira 2021 *(78)*	Good quality
Jensen 2023 *(21)*	Good quality
Domingo 2013 *(14)*	Poor quality
Buckingham 2006 *(50)*	Good quality
Arditi 1998 *(43)*	Good quality
Wee 2016 *(95)*	Good quality
Wang 2022 *(94)*	Good quality
Wang 2019 *(93)*	Good quality
Vasilopoulou 2011 *(91)*	Fair quality
van Veen 2016 *(32)*	Good quality
van Soest 2023 *(31)*	Good quality
Tuncer 2004 *(89)*	Fair quality
Tubiana 2020 *(30)*	Good quality
Theodoridou 2013 *(88)*	Fair quality
Teixeira 2021 *(85)*	Fair quality
Stockmann 2013 *(83)*	Good quality
Shamsad 2009 *(82)*	Good quality
Sensoy 2009 *(81)*	Poor quality
Sakata 2010 *(36)*	Good quality
Saha 2009 *(79)*	Good quality
Roine 2015 *(77)*	Good quality
Rivero-Calle 2016 *(76)*	Good quality
Resti 2009 *(75)*	Good quality
Raemy 2023 *(28)*	Good quality
Rabbani 2003 *(27)*	Good quality

Cohort studies (Newcastle-Ottawa tool)	
Plumb 2018 *(74)*	Good quality
Paulke-Korinek 2014 *(70)*	Good quality
Pan 2023 *(69)*	Good quality
Pagliano 2007 *(68)*	Fair quality
Pagliano 2017 *(26)*	Fair quality
Ostergaard 2005 *(34)*	Good quality
Namani 2011 *(67)*	Good quality
Moon 2010 *(23)*	Good quality
Moon 2012 *(24)*	Good quality
Meng 2022 *(64)*	Good quality
Lovera 2022 *(63)*	Good quality
Le Bot 2021 *(22)*	Fair quality
Klobassa 2014 *(62)*	Good quality
Kadziszewska 2023 *(60)*	Good quality
Heckenberg 2008 *(19)*	Good quality
Grindborg 2015 *(18)*	Good quality
Glimaker 2015 *(17)*	Good quality
El-Gindy 2015 *(16)*	Good quality
Duval 2022 *(15)*	Good quality
Deliran 2022 *(11)*	Good quality
Chen 2018 *(55)*	Good quality
Chauhan 2018 *(54)*	Good quality
Chamkhaleh 2021 *(53)*	Good quality
Casella 2004 *(52)*	Fair quality
Cabellos 2019 *(9)*	Good quality

Cohort studies (Newcastle-Ottawa tool)	
Burton 2023 *(51)*	Good quality
Bozzola 2021 *(49)*	Fair quality
Bor 2020 *(48)*	Good quality
Bodilsen 2013 *(8)*	Fair quality
Blanco 2020 *(47)*	Good quality
Biaukula 2012 *(46)*	Good quality
Bettinger 2013 *(35)*	Good quality
Basualdo 2004 *(45)*	Good quality
Auburtin 2006 *(7)*	Good quality
Alsubaie 2020 *(40)*	Good quality
Al Khorasani 2006 *(39)*	Good quality
Ahmed 2013 *(37)*	Good quality
Anh 2006 *(41)*	Poor quality
Ai 2017 *(38)*	Fair quality
Pelkonen 2022 *(73)*	Good quality

Table WA15.2d Risk-of-bias assessment results (cross-sectional studies)

Cross-sectional studies (AXIS tool)	
Study	**Overall result**
Pelkonen 2009 *(72)*	Fair quality
Terasjarvi 2024 *(87)*	Good quality
Pelkonen 2008 *(71)*	Fair quality
Epelboin 2016 *(59)*	Fair quality
Arteta-Acosta 2022 *(44)*	Fair quality

Table WA15.2e Risk-of-bias assessment results: RCTs

Randomized controlled trials (CLARITY tool)	
Study	**Overall result**
Vaswani 2021 *(92)*	Some concerns
Uppal 2017 *(90)*	Low risk of bias
Thomas 1999 *(29)*	Low risk of bias
Tenhu 2020 *(86)*	Some concerns
Sankar 2007 *(80)*	Low risk of bias
Molyneux 2002 *(65)*	Some concerns
Molyneux 2014 *(66)*	Low risk of bias
Duke 2002 *(57)*	Some concerns

3.3 Description of results

3.3.1 Adult studies

Thirty studies involving a total of 9311 adults with a confirmed diagnosis of meningitis were identified. Three of these studies involved both children and adults. Among the adults, 99.7% had bacterial meningitis; 7301 adults (78.4%) underwent audiological screening; and 1339 (14.4%) were found to have meningitis-related sequelae. Clinical assessment to identify sequelae was conducted before discharge in one study, at discharge in 17 studies and after discharge in 18 studies. Of the adults assessed before discharge (including those assessed during hospitalization and at discharge), 16% (814/5270) were found to have sequelae; among those assessed after discharge, 29% (785/2711) were found to have at least one sequela. Figure WA15.2 and Table WA15.3 provide more detailed information on the number of adults assessed with sequelae, type of sequela and infectious etiology.

Fig. WA15.2 Overview of results from adult studies

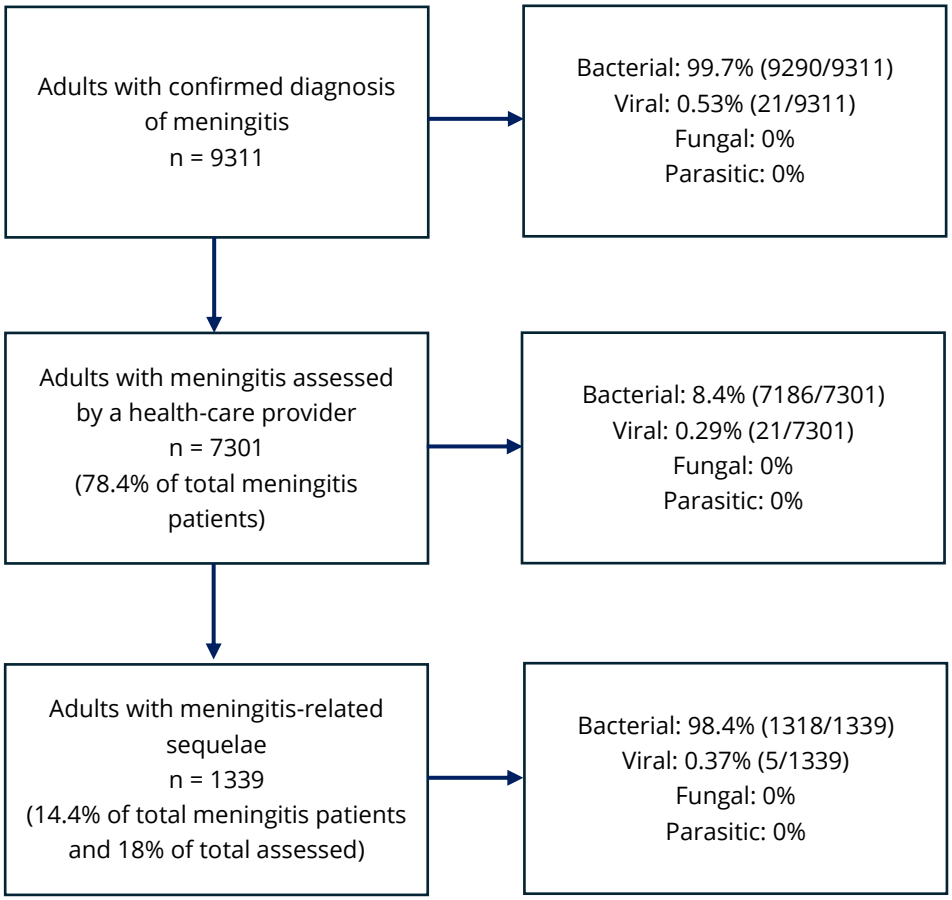


Table WA15.3 Sequelae among adults

Type of sequelae	No. of patients/total no. of patients assessed[a] (%)	Specific pathogen
Psychological after-effects	121/511 (24%)	Meningococcus > Pneumococcus
Hearing loss	395/3382 (12%)	Meningococcus > Pneumococcus
Neurocognitive/neurodevelopmental impairment	70/817 (9%)	Meningococcus > Pneumococcus
Focal neurological deficits	165/2134 (8%)	Pneumococcus > Meningococcus
Seizures	42/851 (5%)	Pneumococcus > Meningococcus
Speech	15/379 (4%)	Pneumococcus
Hydrocephalus	33/1188 (3%)	Pneumococcus > Meningococcus
Vision loss/impairment	1/299 (0.3%)	Not reported
Limb loss	0/0 (0%)	-
All neurological sequelae	1339/7301 (18%)	Pneumococcus > Meningococcus

[a] Denominators: Total number of adults with meningitis assessed by health-care provider for each sequelae.

Table WA15.4 presents the time frame for the diagnosis of sequelae in adults by time point and Table WA15.5 presents the time frame by sequela in adults.

Table WA15.4 Time frame for diagnosis of sequelae (adults)

Time of diagnosis of neurological sequelae	No. of patients/total no. patients[a] (%)	No. of articles	Mean time to diagnosis in days (months)
Before discharge	814/5270 (16%)	18	-
During hospitalization	67/273 (24%)	1	-
At discharge	747/4997 (15%)	17	14 (0.5)
After discharge	785/2711 (29%)	18	-
Within 1 month	85/303 (28%)	6	26 (0.9)
Short-term follow-up (≤ 3 months)	225/883 (25%)	13	47.8 (1.6)
Long-term follow-up (> 3 months)	588/1864 (32%)	8	172.3 (5.7)

[a] Denominators: Total number of adults assessed by a health-care provider (by complete physical or neurological exam) at each time point.

Sequelae diagnosis timing	No. of articles
After discharge (at follow-up)	18
At discharge	17
Before discharge	1

Table WA15.5 Time frame for diagnosis of sequelae, by sequela (adults)

Time of diagnosis	No. of patients/total no. of patients assessed[a] (%)	No. of articles	Mean time to diagnosis in days (months)
FOCAL NEUROLOGICAL DEFICITS			
Before discharge	139/3896 (3.6%)	15	
During hospitalization	18/273 (6.6%)	1	
At discharge	121/3623 (3.3%)	14	13.9
After discharge	61/981 (6.2%)	11	
Short-term follow-up (≤ 3 months)	97/868 (11.2%)	8	50.4 (1.7)
Within 1 month	30/236 (12.7%)	3	30 (1)
Long-term follow-up (> 3 months)	17/1478 (1.2%)	4	356 (11.8)
HEARING LOSS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	323/4753 (6.8%)		
During hospitalization	34/273 (8.7%)	1	
At discharge	289/4480 (6.4%)	13	13.5
After discharge	216/1568 (13.8%)		
Short-term follow-up (≤ 3 months)	107/718 (15%)	10	56 (1.8)
Within 1 month	17/236 (7.2%)	3	30 (1)
Long-term follow-up (> 3 months)	154/930 (16.6%)	7	305 (10.2)
SPEECH AND/OR LANGUAGE DISORDERS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	7/2337 (0.3%)	3	
During hospitalization	–	–	
At discharge	7/2337 (0.3%)	3	
After discharge	14/289 (4.8%)	2	

Short-term follow-up (≤ 3 months)	14/289 (4.8%)	2	90 (3)
Within 1 month	–	–	
Long-term follow-up (> 3 months)	–	–	
SEIZURES			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	89/3644 (2.4%)	6	
During hospitalization	–	–	
At discharge	89/3644 (2.4%)	6	
After discharge	38/819 (4.6%)	6	
Short-term follow-up (≤ 3 months)	36/339 (10.6%)	4	46.3 (1.5)
Within 1 month	28/277 (10.1%)	1	30 (1)
Long-term follow-up (> 3 months)	4/519 (0.8%)	3	367 (12.2)
NEUROCOGNITIVE/NEURODEVELOPMENTAL DISORDERS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	90/4282 (2.1%)	10	
During hospitalization	30/273 (11%)	1	
At discharge	60/4009 (1.5%)	9	12.7
After discharge	21/266 (7.9%)	5	
Short-term follow-up (≤ 3 months)	11/108 (10.2%)	3	76.4 (2.6)
Within 1 month	–	–	
Long-term follow-up (> 3 months)	20/190 (10.5%)	4	319 (10.6)
PSYCHOLOGICAL AFTER-EFFECTS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	1/170 (0.6%)	2	

During hospitalization	–	–	
At discharge	1/170 (0.6%)	2	
After discharge	131/490 (26.8%)	4	
Short-term follow-up (≤ 3 months)	20/135 (14.9%)	2	90 (3)
Within 1 month	–	–	
Long-term follow-up (> 3 months)	121/400 (30.3%)	3	357 (11.9)
HYDROCEPHALUS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	12/933 (1.3%)	5	
During hospitalization	–	–	
At discharge	12/933 (1.3%)	5	
After discharge	30/1111 (2.7%)	7	
Short-term follow-up (≤ 3 months)	26/631 (4.1%)	5	40.7 (1.4)
Within 1 month	9/231 (3.9%)	2	30 (1)
Long-term follow-up (> 3 months)	4/519 (0.2%)	3	297.5 (10)
VISION IMPAIRMENT			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	9/951 (0.9%)	3	
During hospitalization	–		
At discharge	9/951 (0.9%)	3	
After discharge	7/45 (15.5%)	1	
Short-term Follow-up (≤3 months)	4/30 (13.3%)	1	90 (3)
Within 1 month	–		
Long-term Follow-up (>3 months)	7/45 (15.5%)	1	270 (9)

[a] Denominators: Total number of adults assessed by a health-care provider (by complete physical or neurological exam) at each time point.

The forest plots below (Figs. WA15.3a–c) depict the pooled proportion of adult patients with sequelae detection over the total assessed patients in subgroups by time point of screening, using meta-analyses of arcsine transformed proportions.

Fig. WA15.3a depicts this at discharge, Fig, WA15.3b after discharge (within three months) and Fig. WA15.3c after discharge (later than three months).

Fig. WA15.3a Diagnosis of sequelae at discharge: forest plot (adults)

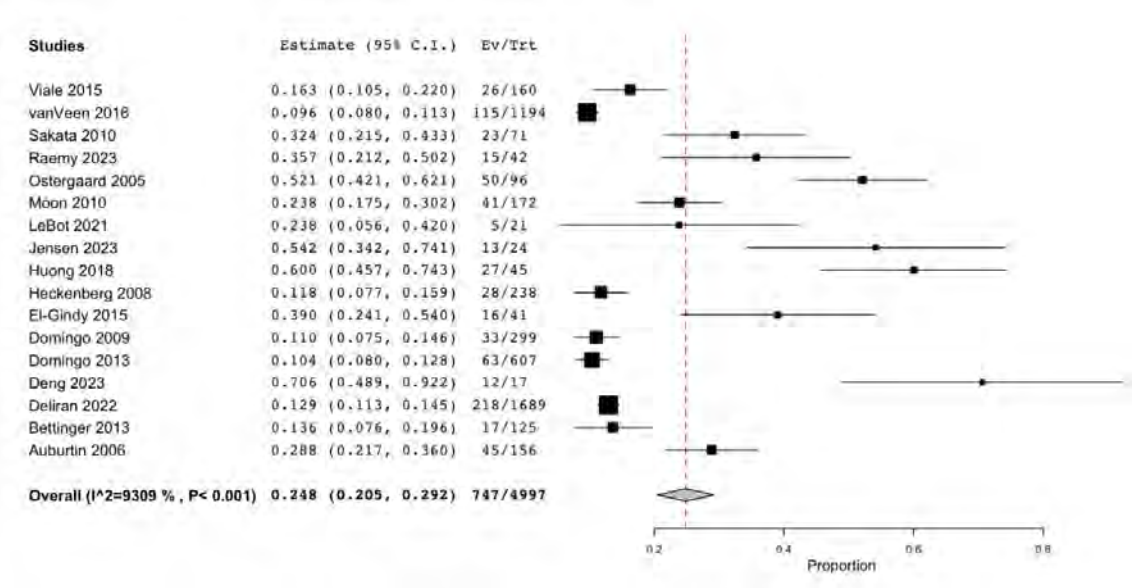


Fig. WA15.3b Diagnosis of sequelae ≤ 3 months after discharge: forest plot (adults)

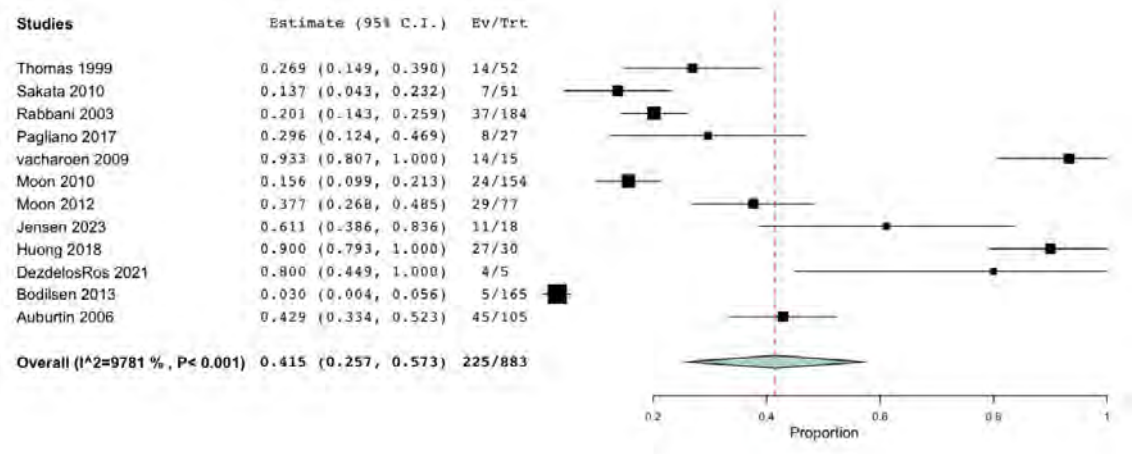
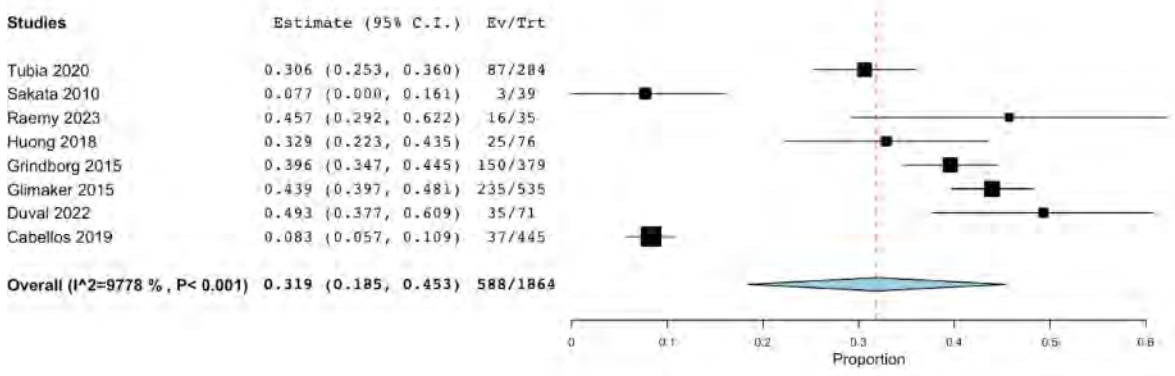


Fig. WA15.3c Diagnosis of sequelae > 3 months after discharge: forest plot (adults)



3.3.2 Child studies

Sixty-two studies involving a total of 18 658 children with a confirmed diagnosis of meningitis were identified. Three studies involved both adults and children. Among the children, 94% had bacterial meningitis, 14 826 (79%) underwent clinical assessment by a health-care provider and 3484 (19%) were diagnosed with meningitis-related sequelae.

Clinical assessment to identify sequelae was conducted before discharge in four studies, at discharge in 27 studies and after discharge in 37 studies. Of the children assessed before discharge, 34% (2473/7180) were found to have sequelae; among those assessed after discharge, 17% (1406/8298) were found to have at least one sequela. Figure WA15.4 and Table. WA15.6 provide more detailed information on the number of children assessed with sequelae, type of sequela and infectious etiology.

Fig. WA15.4 Overview of results from child studies

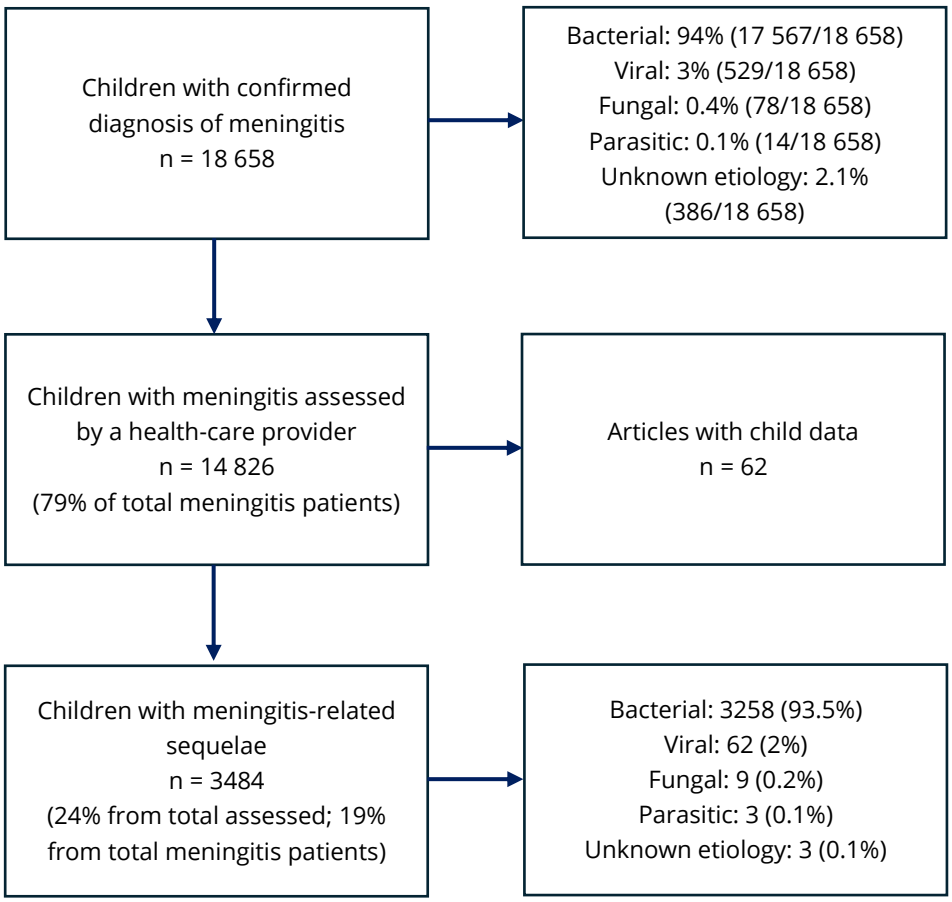


Table. WA15.6 Sequelae among children

Type of sequelae	No. patients/total no. patients assessed[a] (%)	Specific pathogen
Focal neurological deficits	1108/7288 (15%)	Pneumococcus > Meningococcus > *Haemophilus influenzae* > Group B streptococcus (GBS)
Hearing loss	1257/12624 (10%)	Pneumococcus > Meningococcus > *H. influenzae* > GBS
Neurocognitive/neurodevelopmental impairment	382/3859 (10%)	Pneumococcus > *H. influenzae* > Meningococcus > GBS
Seizures	653/9553 (7%)	Pneumococcus > *H. influenzae* > Meningococcus > GBS
Psychological after-effects	69/930 (7%)	Pneumococcus > Meningococcus
Speech	89/1423 (6%)	Pneumococcus > Meningococcus
Limb loss	53/1114 (5%)	Pneumococcus > Meningococcus > *H. influenzae* > GBS
Vision loss/impairment	167/4437 (4%)	Pneumococcus > *H. influenza*
Hydrocephalus	256/9067 (3%)	Pneumococcus > *H. influenzae* > Meningococcus > GBS
All neurological sequelae	3484/14826 (24%)	Pneumococcus > Meningococcus > *H. influenzae* > GBS

GBS: Group B streptococcus.

[a] Denominator: Total number of children with meningitis assessed by a health-care provider for each sequela.

Table. WA15.7 Time frame for diagnosis of sequelae (children)

Time of diagnosis	No. of patients/total no. of patients assessed[a] (%)	No. of articles	Mean time to diagnosis in days (months)
Before discharge	2473/7180 (34%)	34	
During hospitalization	301/885 (34%)	4	-
At discharge	2172/6296 (34.5%)	30	13.5 (0.45)
After discharge	1406/8298 (17%)	37	
Within 1 month	240/357 (67%)	3	30 (1)
Short-term follow-up (≤ 3 months)	621/5920 (10.5%)	13	62.7 (2)
Long-term follow-up (> 3 months)	879/2738 (32%)	28	551.7 (18.4)

[a] Denominators: Total number of children assessed by a health-care provider (by complete physical or neurological exam) at each time point.

Sequelae diagnosis timing	No. of studies
After discharge (at follow-up)	37
At discharge	27
Before discharge	4

Table. WA15.8 Time frame for diagnosis of sequelae, by sequela (children)

Time of diagnosis	No. of patients/total no. of patients assessed[a] (%)	No. of articles	Mean time to diagnosis in days (months)
FOCAL NEUROLOGICAL DEFICITS			
Before discharge	942/4532 (20.3%)	22	
During hospitalization	3/389 (0.78%)	1	
At discharge	939/4143 (22.7%)	21	10.62 (0.4)
After discharge	253/1781 (14.2%)	25	
Short-term follow-up (≤ 3 months)	113/877 (12.9%)	8	44.5 (1.5)
Within 1 month	66/357 (18.4%)	3	30 (1)
Long-term follow-up (> 3 months)	238/1853 (12.8%)	20	627 (20.9)
HEARING LOSS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	965/5541 (17.4%)	24	
During hospitalization	7/401 (1.7%)	2	
At discharge	959/5140 (18.7%)	22	13.2 (0.4)
After discharge	605/7545 (8%)	29	
Short-term follow-up (≤ 3 months)	212/5529 (3.8%)	10	57.3 (1.9)
Within 1 month	111/357 (31%)	3	30 (1)
Long-term follow-up (> 3 months)	402/2298 (17.5%)	21	347.4 (11.58)
SPEECH AND/OR LANGUAGE DISORDERS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	2/285 (0.7%)	1	
During hospitalization	–	0	
At discharge	2/285 (0.7%)	1	-

Time of diagnosis	No. of patients/total no. of patients assessed[a] (%)	No. of articles	Mean time to diagnosis in days (months)
After discharge	72/873 (8.24%)	7	
Short-term follow-up (≤ 3 months)	–	0	
Within 1 month	–	0	
Long-term follow-up (> 3 months)	72/873 (8.24%)	7	713 (23.4)
SEIZURES			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	264/2756 (9.6%)		
During hospitalization	14/289 (4.8%)	2	
At discharge	250/2467 (10.1%)	6	7.7 (0.3)
After discharge	354/6904 (5%)		
Short-term follow-up (≤ 3 months)	189/5307 (3.6%)	7	54.4 (1.8)
Within 1 month	108/302 (35.8%)	2	30 (1)
Long-term follow-up (> 3 months)	182/1835 (9.9%)	18	558 (18.6)
NEUROCOGNITIVE/NEURODEVELOPMENTAL DISORDERS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	53/2273 2.3%	9	
During hospitalization	5/12 (41.6%)	1	
At discharge	48/2551 (1.9%)	8	12.5 (0.4)
After discharge	312/1946 (16%)	20	
Short-term follow-up (≤ 3 months)	89/728 (12.2%)	5	60 (2)
Within 1 month	3/55 (5.4%)	1	30 (1)
Long-term follow-up (> 3 months)	269/1551 (17.3%)	18	783 (26)
PSYCHOLOGICAL AFTER-EFFECTS			

Time of diagnosis	No. of patients/total no. of patients assessed[a] (%)	No. of articles	Mean time to diagnosis in days (months)
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	–	–	
During hospitalization	–	–	
At discharge	–	–	
After discharge	69/820 (8.4%)	6	
Short-term follow-up (≤ 3 months)	18/107 (16.8%)	1	30 (1)
Within 1 month	18/107 (16.8%)	1	30 (1)
Long-term follow-up (> 3 months)	51/713 (7.15%)	5	637 (21)
HYDROCEPHALUS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	222/4192 (5.2%)		
During hospitalization	82/484 (17%)	2	
At discharge	140/3344 (4.1%)	14	13.7 (0.5)
After discharge	173/6560 (2.6%)	23	
Short-term follow-up (≤ 3 months)	50/5045 (1%)	8	67.2 (2.2)
Within 1 month	10/162 (6.2%)	2	30 (1)
Long-term follow-up (> 3 months)	130/1753 (7.42%)	17	641.3 (21.4)
VISION IMPAIRMENT			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	127/3078 (4.1%)		
During hospitalization	1/277 (0.4%)	1	
At discharge	126/2801 (4.5%)	9	17.2 (0.6)
After discharge	66/1546 (4.3%)	15	

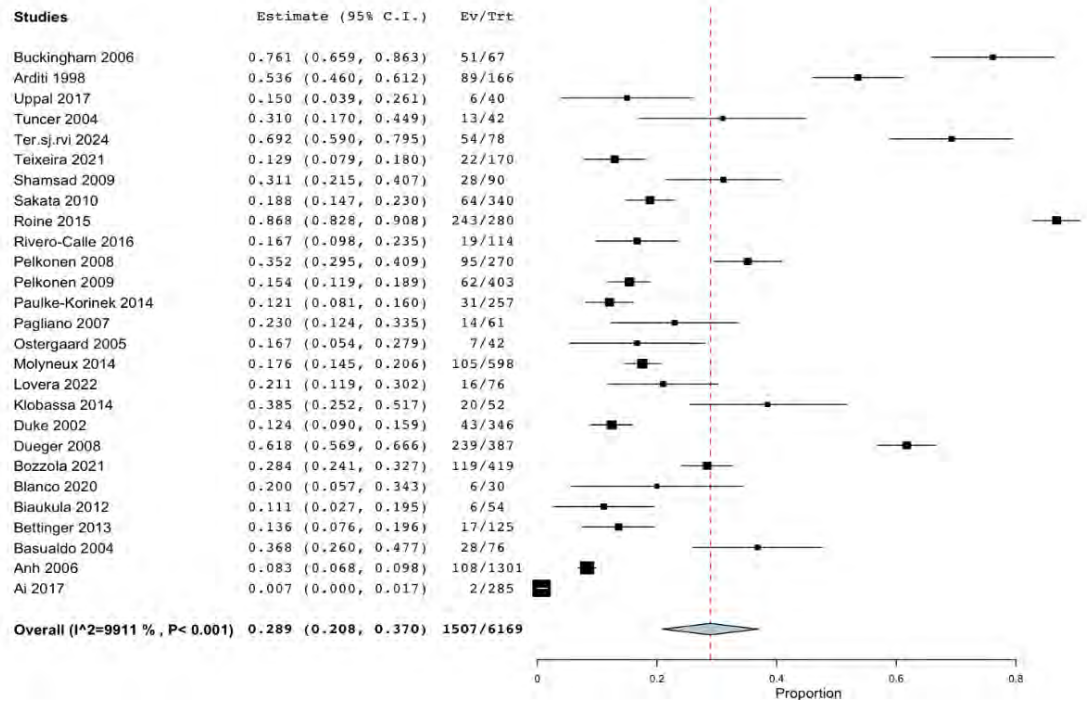
Time of diagnosis	No. of patients/total no. of patients assessed[a] (%)	No. of articles	Mean time to diagnosis in days (months)
Short-term follow-up (≤ 3 months)	16/310 (5.2%)	5	39 (1.3)
Within 1 month	4/162 (2.5%)	2	30 (1)
Long-term follow-up (> 3 months)	59/1385 (4.3%)	13	794.2 (26.5)
LIMB LOSS			
Time of diagnosis	**No. of patients (%)**	**No. of articles**	**Mean time to diagnosis in days (months)**
Before discharge	30/803 (3.7%)	4	
During hospitalization	7/389 (1.8%)	1	
At discharge	23/414 (5.5%)	3	16 (0.5)
After discharge	28/467 (6%)	3	
Short-term follow-up (≤ 3 months)	–	–	
Within 1 month	–	–	
Long-term follow-up (> 3 months)	28/467 (6%)	3	804.1 (26.8)

[a] Denominators: Total number of children assessed by a health-care provider (by complete physical or neurological exam) at each time point.

The forest plots below (Figs. WA15.5a–c) depict the pooled proportion of children with hearing loss detection over total tested patients in subgroups by time point of screening, using meta-analyses of arcsine transformed proportions.

Fig. WA15.5a depicts this at discharge, Fig, WA15.5b after discharge (within three months) and Fig. WA15.5c after discharge (more than three months).

Fig. WA15.5a Diagnosis of sequelae at discharge: forest plot (children)[a]



[a] Three studies were excluded from the meta-analysis as denominators were not reported (two studies) or no events were recorded. One study (Tenhu et al., 2020 [*(86)*]) reported zero sequelae cases among 102 patients assessed at discharge. The other two studies only provided the number of diagnosed sequelae without specifying the total number of patients assessed. For inclusion in the meta-analysis, both numerators (sequelae cases) and denominators (total patients assessed) were required.

Fig. WA15.5b Diagnosis of sequelae after ≤ 3 months discharge: forest plot (children)

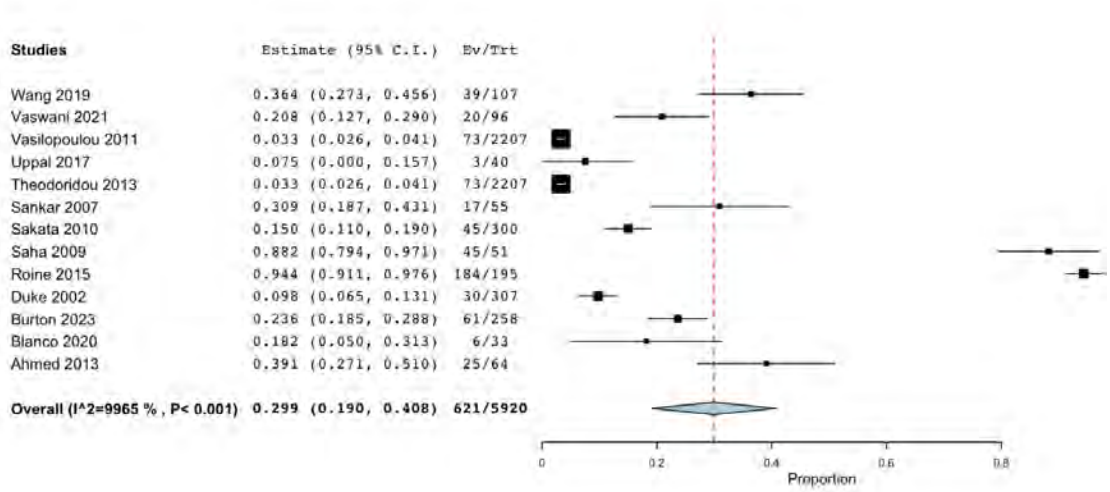
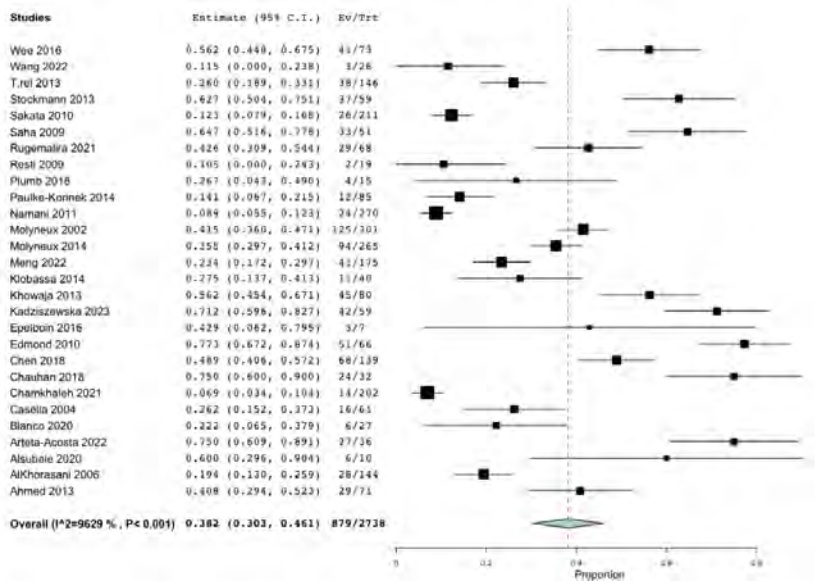


Fig. WA15.5c Diagnosis of sequelae > 3 months after discharge: forest plot (children)



4. Research gaps

The present systematic review revealed the absence of studies with comparator groups, including RCTs and cohort studies. The existing literature consists predominantly of case series and observational studies, limiting the ability to draw robust conclusions regarding the timing of performing a clinical review for sequelae identification, and highlighting the need for RCTs and cohort studies comparing different time points for a clinical assessment to identify sequelae.

The body of evidence had variable reporting, with a lack of consistency in outcome measures reported. This further reduced the suitability of the data for quantitative synthesis and highlighted the need to develop a core outcome set to guide research efforts on screening for sequelae following acute meningitis.

Furthermore, there was a notable lack of research exploring the effectiveness of interventions or assessing patient values and preferences in the context of post-meningitis rehabilitation of neurological sequelae.

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Appendix 1. Search strategy used to identify primary studies

Table WA15.A1.1 Database: Medline

Search date: 09/02/2024		
Years: 1858 to present		
#	**Search**	**Results**
#1	Meningitis/ OR meningit*.mp. OR ((meningococc*) ADJ3 (infection* OR disease*))	77047
#2	Meningitis, Bacterial/ OR Meningitis, Escherichia coli/ OR Meningitis, Haemophilus/ OR Meningitis, Listeria/ OR Meningitis, Meningococcal/ OR Meningococcal Infections/ OR Meningitis, Pneumococcal/ OR Meningitis, Fungal/ OR Meningitis, Aseptic/ OR Meningitis, Viral/ OR ((Bacterial OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired OR Acute OR fulminat* OR Fulminant OR Sudden-onset) ADJ5 (meningiti*)).ti,ab,kw,kf OR (infectious-meningiti* OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi).ti,ab,kw,kf	1411308
#3	Hearing Loss/ OR Hearing Disorders/ OR Language Disorders/ OR Hydrocephalus/ OR Vision Disorders/ OR Neurocognitive Disorders/ OR Intellectual Disability/ OR Cognitive Dysfunction/ OR Hemiplegia/ OR Paraplegia/ OR Dysarthria/ OR Deafness/ OR (hearing ADJ3 loss) OR (sequela* OR hydroceph* OR intellectual-disabilit* OR deafness OR hemiplegi* OR parapares* OR dysarthri* OR functional-disabilit* OR limb-loss OR motor-deficit*).ti,ab OR ((language* OR speech OR communication OR vision OR hearing OR psychological* OR cognitive OR neurocognitive OR development OR attention OR neurodevelopment*	744803

	OR neurologic* OR neuropsychologic*) ADJ3 (abnormal* OR disorder* OR impair* OR deficit* OR dysfunction*)).ti,ab,kw,kf OR ((neurologic* OR central-nervous-system* OR cns OR language* OR speech OR communication OR vision OR hearing OR psychological* OR paralysis) ADJ3 (complication* OR deteriorat*)).ti,ab,kw,kf OR ((neurologic* OR neurobehavo*) ADJ3 manifestat*).ti,ab,kw,kf	
#4	#1 and #2 and #3	5146
#5	((ongoing* OR long* OR persist* OR residual* OR delay* OR prolong* OR linger* OR permanent* OR nonrecover* OR non-recover* OR lasting* OR continuous* OR continual* OR continuing* OR Postmeningitic OR post-meningit* OR postacute* OR post-acute* OR postdischarg* OR post-discharg* OR postinfect* OR post-infect* OR medium*-term* OR mediumterm*) ADJ3 (sequela* OR complication* OR consequence* OR consequent* OR complexit* OR impair* OR problem* OR symptom* OR disorder* OR dysfunction* OR manifest* OR outcome* OR effect OR effects OR disturbance* OR disabilit*)).ti,ab,kw,kf OR after-effect*.ti,ab OR (after ADJ3 meningit*).ti,ab	423582
#6	(postacute* OR post-acute* OR postdischarg* OR post-discharg* OR postinfect* OR post-infect* OR post-meningiti* OR postmeningiti*).ti,ab,kw,kf	47191
#7	sequela*.ti,ab,kw,kf OR unfavourable-outcome*.ti,ab	76026
#8	((year* OR month* OR extended) ADJ3 (follow-up OR followed OR infection)).ti,ab	464948
#9	#5 OR #6 OR #7 OR #8	946762
#10	#4 AND #9	2411
#11	(auto-inflamm* OR autoimmun* OR auto-immun* OR Rheumatoid OR Parkison* OR Dementia OR tubercul* OR vaccin* OR cryptococc* OR Sarcoid* OR Lupus).ti	632074
#12	#10 NOT #11	2202
#13	(letter or historical article or comment or editorial or news or case reports).pt.	4474001
#14	#12 NOT #13	1728
#15	animals/ not (animals/ and humans/)	5157355
#16	#14 not #15	1595
#17	limit 15 to yr="2003 -Current"	891

Table WA15.A1.2 Database: Embase

Search date: 09/02/2024		
Years: 1858 to present		
#	**Search**	**Results**
#1	('meningitis'/exp OR (meningiti* OR (Meningococc* NEAR/3 (infection* OR disease*))):ti,ab)	152478
#2	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR 'fungal meningitis'/exp OR 'HIV-associated meningitis'/exp OR 'parasitic meningitis'/exp OR 'virus meningitis'/exp OR 'aseptic meningitis'/exp OR 'Staphylococcus aureus'/exp OR 'Staphylococcus'/exp OR 'Enterobacteriaceae'/exp OR 'Streptococcus agalactiae'/exp OR 'Streptococcus pyogenes'/exp OR 'Enterovirus'/exp OR 'Herpesviridae'/exp OR 'herpes virus infection'/exp OR 'Simplexvirus'/exp OR 'Flavivirus'/exp OR 'West Nile virus'/exp OR 'Togaviridae'/exp OR 'Mumps'/exp OR 'Mumps virus'/exp OR 'Orthomyxoviridae'/exp OR 'HIV'/exp OR 'Adenoviridae'/exp OR 'Rubella'/exp OR 'Lymphocytic Choriomeningitis'/exp OR 'Rickettsiales'/exp OR 'Spirochaetales'/exp OR 'Leptospira'/exp OR 'Brucella'/exp OR 'Treponema pallidum'/exp OR 'Coxiella'/exp OR 'Mycoplasma'/exp OR 'Naegleria'/exp OR 'Angiostrongylus'/exp OR 'Coccidioides'/exp OR 'Candida'/exp OR 'Histoplasma'/exp OR 'Blastomyces'/exp OR 'Aspergillus'/exp OR 'Syphilis'/exp OR 'Lyme Disease'/exp OR 'Scrub Typhus'/exp OR ((Bacterial OR bacteraemia OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired OR Acute OR fulminat* OR Fulminant OR Sudden-onset) NEAR/5 (meningiti*)):ti,ab,kw,de OR (infectious-meningiti* OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR	2792455

	Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi):ti,ab,kw,de	
#3	hearing impairment'/exp OR 'hearing disorder'/exp OR 'speech disorder'/exp OR 'language disability'/exp OR 'hydrocephalus'/exp OR 'visual disorder'/exp OR 'behavior disorder'/exp OR 'intellectual disabilities'/exp OR 'cognitive defect'/exp OR 'hemiplegia'/exp OR 'paraplegia'/exp OR 'dysarthria'/exp OR 'deafness'/exp OR ((hearing NEAR/3 loss):ti,ab OR (sequela* OR hydroceph* OR intellectual-disabilit* OR deafness OR hemiplegi* OR parapares* OR dysarthri* OR functional-disabilit* OR limb-loss OR motor-deficit*):ti,ab OR ((language* OR speech OR communication OR vision OR hearing OR psychological* OR cognitive OR neurocognitive OR development OR attention OR neurodevelopment* OR neurologic* OR neuropsychologic*) NEAR/3 (abnormal* OR disorder* OR impair* OR deficit* OR dysfunction*)):ti,ab OR ((neurologic* OR 'central nervous system*' OR cns OR language* OR speech OR communication OR vision OR hearing OR psychological* OR paralysis) NEAR/3 (complication* OR deteriorat*)):ti,ab OR ((neurologic* OR neurobehavo*) NEAR/3 manifestat*)):ti,ab,de,kw	2260289
#4	#1 AND #2 AND #3	18646
#5	((ongoing* OR long* OR persist* OR residual* OR delay* OR prolong* OR linger* OR permanent* OR nonrecover* OR non-recover* OR lasting* OR continuous* OR continual* OR continuing* OR Postmeningitic OR post-meningit* OR postacute* OR post-acute* OR postdischarg* OR post-discharg* OR postinfect* OR post-infect* OR medium*-term* OR mediumterm*) NEAR/3 (sequela* OR complication* OR consequence* OR consequent* OR complexit* OR impair* OR problem* OR symptom* OR disorder* OR dysfunction* OR manifest* OR outcome* OR effect OR effects OR disturbance* OR disabilit*)):ti,ab,kw,de OR after-effect*:ti,ab OR (after NEAR/3 meningit*):ti,ab	716968
#6	(postacute* OR post-acute* OR postdischarg* OR post-discharg* OR postinfect* OR post-infect* OR post-meningiti* OR postmeningiti*):ti,ab,kw,de	83914
#7	sequela*:ti,ab,kw,de OR unfavourable-outcome*:ti,ab	118171
#8	((year* OR month* OR extended) NEAR/3 (follow-up OR followed OR infection)):ti,ab	758984
#9	#5 OR #6 OR #7 OR #8	1541843
#10	#4 AND #9	5523
#11	(auto-inflamm* OR autoimmun* OR auto-immun* OR Rheumatoid OR Parkison* OR Dementia OR tubercul* OR vaccin* OR cryptococc* OR Sarcoid* OR Lupus):ti	888233
#12	#10 NOT #11	4980

#13	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR 'case report':ti,kw,de	11321860
#14	#12 NOT #13	3083
#15	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6462262
#16	#14 NOT #15	2820
#17	#16 AND [2003-2024]/py	1851

Table WA15.A1.3 Database: Cochrane Library

Search date: 09/02/2024		
1984 - present		
Search Name: Meningitis Sequalae PICO 15 and 16		
Date Run: 5/2/24 8:52		
ID	**Search**	**Hits**
#1	MeSH descriptor: [Meningitis] explode all trees	856
#2	(meningiti*):ti,ab,kw	2706
#3	Meningococc* NEAR/3 (infection* OR disease*)	670
#4	MeSH descriptor: [Meningitis, Bacterial] explode all trees	524
#5	MeSH descriptor: [Meningitis, Aseptic] explode all trees	10
#6	MeSH descriptor: [Meningitis, Viral] explode all trees	18
#7	MeSH descriptor: [Meningitis, Fungal] explode all trees	134
#8	MeSH descriptor: [Meningitis, Meningococcal] explode all trees	214
#9	MeSH descriptor: [Meningitis, Pneumococcal] explode all trees	60
#10	MeSH descriptor: [Meningitis, Haemophilus] explode all trees	74
#11	MeSH descriptor: [Meningitis, Listeria] explode all trees	0
#12	MeSH descriptor: [Staphylococcus aureus] explode all trees	1173
#13	MeSH descriptor: [Enterobacteriaceae] explode all trees	1789
#14	MeSH descriptor: [Enterobacter] explode all trees	42
#15	MeSH descriptor: [Escherichia coli] explode all trees	982
#16	MeSH descriptor: [Streptococcus agalactiae] explode all trees	148
#17	MeSH descriptor: [Streptococcus pyogenes] explode all trees	325
#18	MeSH descriptor: [Enterovirus] explode all trees	244
#19	MeSH descriptor: [Herpesviridae] explode all trees	1273
#20	MeSH descriptor: [Herpesviridae Infections] explode all trees	3711

#21	MeSH descriptor: [Simplexvirus] explode all trees	435
#22	MeSH descriptor: [Flavivirus] explode all trees	280
#23	MeSH descriptor: [West Nile virus] explode all trees	11
#24	MeSH descriptor: [Togaviridae] explode all trees	110
#25	MeSH descriptor: [Mumps] explode all trees	131
#26	MeSH descriptor: [Mumps virus] explode all trees	39
#27	MeSH descriptor: [Orthomyxoviridae] explode all trees	1363
#28	MeSH descriptor: [HIV] explode all trees	4211
#29	MeSH descriptor: [Adenoviridae] explode all trees	282
#30	MeSH descriptor: [Rubella] explode all trees	206
#31	MeSH descriptor: [Lymphocytic Choriomeningitis] explode all trees	1
#32	MeSH descriptor: [Rickettsiales] explode all trees	49
#33	MeSH descriptor: [Spirochaetales] explode all trees	246
#34	MeSH descriptor: [Leptospira] explode all trees	12
#35	MeSH descriptor: [Brucella] explode all trees	18
#36	MeSH descriptor: [Treponema pallidum] explode all trees	29
#37	MeSH descriptor: [Coxiella] explode all trees	10
#38	MeSH descriptor: [Mycoplasma] explode all trees	122
#39	MeSH descriptor: [Naegleria fowleri] explode all trees	0
#40	MeSH descriptor: [Angiostrongylus] explode all trees	4
#41	MeSH descriptor: [Coccidioides] explode all trees	5
#42	MeSH descriptor: [Candida] explode all trees	587
#43	MeSH descriptor: [Histoplasma] explode all trees	1
#44	MeSH descriptor: [Blastomyces] explode all trees	0
#45	MeSH descriptor: [Aspergillus] explode all trees	112
#46	MeSH descriptor: [Syphilis] explode all trees	214

#47	MeSH descriptor: [Lyme Disease] explode all trees	184
#48	MeSH descriptor: [Scrub Typhus] explode all trees	20
#49	((Bacterial OR bacteraemia OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired OR Acute OR fulminat* OR Fulminant OR Sudden-onset) NEAR/5 (meningiti*)) OR (infectious-meningiti* OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi):ti,ab,kw	67049
#50	#1 OR #2 OR #3	3028
#51	#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 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	70584
#52	#50 AND #51	2320
#53	MeSH descriptor: [Hearing Loss] explode all trees	1867
#54	MeSH descriptor: [Speech Disorders] explode all trees	1254
#55	MeSH descriptor: [Language Disorders] explode all trees	2011
#56	MeSH descriptor: [Hydrocephalus] explode all trees	306
#57	MeSH descriptor: [Vision Disorders] explode all trees	2079
#58	MeSH descriptor: [Neurobehavioral Manifestations] explode all trees	11773

#59	MeSH descriptor: [Intellectual Disability] explode all trees	1999
#60	MeSH descriptor: [Cognitive Dysfunction] explode all trees	3818
#61	MeSH descriptor: [Hearing Disorders] explode all trees	2858
#62	MeSH descriptor: [Deafness] explode all trees	476
#63	MeSH descriptor: [Hemiplegia] explode all trees	967
#64	MeSH descriptor: [Paresis] explode all trees	1101
#65	MeSH descriptor: [Dysarthria] explode all trees	91
#66	((hearing NEAR/3 loss) OR (sequela* OR hydroceph* OR intellectual-disabilit* OR deafness OR hemiplegi* OR parapares* OR dysarthri* OR functional-disabilit* OR limb-loss OR motor-deficit*) OR ((language* OR speech OR communication OR vision OR hearing OR psychological* OR cognitive OR neurocognitive OR development OR attention OR neurodevelopment* OR neurologic* OR neuropsychologic*) NEAR/3 (abnormal* OR disorder* OR impair* OR deficit* OR dysfunction*)) OR ((neurologic* OR 'central nervous system*' OR cns OR language* OR speech OR communication OR vision OR hearing OR psychological* OR paralysis) NEAR/3 (complication* OR deteriorat*)) OR ((neurologic* OR neurobehavo*) NEAR/3 manifestat*))	72576
#67	#53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66	83278
#68	#52 AND #67	236
#69	((ongoing* OR long* OR persist* OR residual* OR delay* OR prolong* OR linger* OR permanent* OR nonrecover* OR non-recover* OR lasting* OR continuous* OR continual* OR continuing* OR medium-term* OR mediumterm*) NEAR/3 (sequela* OR complication* OR consequence* OR consequent* OR complexit* OR impair* OR problem* OR symptom* OR disorder* OR dysfunction* OR manifest* OR outcome* OR effect OR effects OR disturbance* OR disabilit*)) OR after-effect* OR (after NEAR/3 meningit*)	84124
#70	(postacute* OR post-acute* OR postdischarg* OR post-discharg* OR postinfect* OR post-infect*OR post-meningiti* OR postmeningiti*)	5838
#71	sequela* OR unfavourable-outcome*	6691
#72	((year* OR month* OR extended) NEAR/3 (follow-up OR followed OR infection)):ti,ab	120777
#73	#69 OR #70 OR #71 OR #72	200918

#74	#68 AND #73	138
#68	Jan 2003 to Dec 2024	93

Appendix 2. Extraction tool

The forms below show which data were extracted for the review.

Information about the study

Study period(s)

When was the study conducted? If it was conducted in one year, fill with single number (e.g. 2015).

Study period #2

If the study has more than one period, write the second period. If not, write NA

Study design

1.	Case-control study
2.	Case series (> 5 cases)
3.	Cohort study
4.	Cross-sectional study
5.	Randomized controlled trial
6.	I don't know
7.	Other

Population and disease information

Country

1.	Afghanistan
2.	Algeria
3.	Angola
4.	Argentina
5.	Bangladesh
6.	Brazil
7.	Canada
8.	China
9.	Colombia
10.	Congo (Democratic Republic)
11.	Egypt
12.	Ethiopia
13.	France
14.	Germany
15.	Ghana
16.	India
17.	Indonesia
18.	Iran (Islamic Republic of)
19.	Iraq
20.	Italy

21. Japan
22. Kenya
23. Malaysia
24. Mexico
25. Morocco
26. Mozambique
27. Myanmar (Burma)
28. Nepal
29. Nigeria
30. Pakistan
31. Peru
32. Philippines
33. Poland
34. Russia
35. Saudi Arabia
36. South Africa
37. Republic of Korea
38. Spain
39. Sudan
40. Tanzania
41. Thailand
42. Türkiye
43. Uganda
44. Ukraine
45. United Kingdom of Great Britain and Northern Ireland
46. United States of America
47. Uzbekistan
48. Venezuela (Bolivarian Republic of)
49. Viet Nam
50. Other

Total sample size

Study population

Copy/paste any unusual features of patient population if applicable. If not, write NA.

Number of patients identified per age range from the total sample size

Write NA, not zero

	Children < 18 y.o	**Adults > 18 y.o**
# of patients		

For ADULTS (> 18 y.o) → please fill in the following information:

Number of patients with acute meningitis and meningitis-related sequelae

	# patients with meningitis	# patients with meningitis that were followed up	# patients with any meningitis sequelae
Patients			

If mortality is reported, write down # of patients who died

Mortality should be from meningitis. If not reported, please write NR.

If mortality is reported, at what time did it happen?

→ Before discharge could be before admission, at admission, during hospitalization, etc.
→ After discharge could be in follow-up.

1. Before discharge
2. After discharge
3. Unknown

Select the starting point of sequelae time frame detection

What is the point of time at which you should start counting the days until diagnosis?

e.g. diagnosis of hearing loss was done at the follow-up 30 days after admission -> "ADMISSION" would be starting point.

1. From symptom onset
2. From meningitis diagnosis
3. From admission
4. From treatment
5. From discharge
6. Unknown
7. Other

Select the time of detection of meningitis sequelae

Before discharge could be at admission (Day 1), or during hospitalization before discharge.
e.g. if diagnosis of hearing loss was done at follow-up 30 days after admission -> "FOLLOW-UP" would be time of detection

1. Before discharge
2. At discharge
3. After discharge (at follow-up)
4. Unknown
5. Other

Copy and paste the section from the article that describes the timing of meningitis sequelae diagnosis (starting point to detection)

Type of sequelae per timing of detection

1. Please identify how many patients had EACH sequela.
2. Please use mean time frame or median (in days). You can also write the range of follow-up if applicable; for example "follow-up was done within 3–9 months", so you can write in the column of timing → 90–270 days.

If neurological sequelae are not stratified, please select those that are mentioned:

1. Focal neurological deficits
2. Hearing loss
3. Speech and/or language disorders
4. Seizures
5. Neurocognitive/neurodevelopmental disorders
6. Psychological after-effects (stress, depression, behavioural changes)
7. Hydrocephalus
8. Vision impairment
9. Limb loss

Number of patients with acute meningitis and meningitis-related sequelae PER pathogen macro category

	# patients with meningitis	# patients with meningitis that were followed up	# patients with meningitis-related sequelae
Bacterial			
Viral			
Fungal			
Parasitic			
Unknown etiology			

	# patients	Mean time frame (DAYS)	# patients additional time frame	Mean time frame (DAYS)	# patients additional time frame	Mean time frame (DAYS)
Focal neurological deficits						
Hearing loss						
Speech and/or language disorders						
Seizures						
Neurocognitive/neurodevelopmental impairment						
Psychological after-effects (stress, depression, behavioural changes)						
Hydrocephalus						
Vision impairment						
Limb loss						
TOTAL without stratification of sequelae						

Type of sequelae, identified PER pathogen macro category

If number of patients with EACH sequela are not listed per type of pathogen, fill in only the last row of TOTAL patients with ANY sequelae. If provided for EACH sequela, then sum up the total per pathogen.

	Bacterial	Viral	Fungal	Parasitic	Unknown etiology
Focal neurological deficits					
Hearing loss					
Speech and/or language disorders					
Seizures					
Neurocognitive/neurodevelopmental impairment					
Psychological after-effects (stress, depression, behavioural changes)					
Hydrocephalus					
Vision impairment					
Limb loss					
TOTAL without stratification of sequelae					

Type of sequelae per specific pathogen

If number of patients with EACH sequela are not listed per type of pathogen, fill in only the last row of TOTAL patients with ANY sequelae. If provided for EACH sequela, then sum up the total per pathogen.

	Neisseria meningitis	***Streptococcus pneumoniae***	***Haemophilus influenzae type b (Hib)***	***Streptococcus agalactiae (GBS)***
Focal neurological deficits				
Hearing loss				
Speech and/or language disorders				
Seizures				
Neurocognitive/neurodevelopmental impairment				
Psychological after-effects (stress, depression, behavioural changes)				
Hydrocephalus				
Vision impairment				
Limb loss				
TOTAL without stratification of sequelae				

For CHILDREN (< 18 y.o) → please fill in the following information:

Number of patients with acute meningitis and meningitis-related sequelae

If CHILDREN are not stratified per age, fill in only the not stratified column. If provided for EACH age range, fill in per age, and then sum up the total in the not stratified column.

	CHILDREN (NOT STRATIFIED)	1 mo. – 1 y.o	>1 y.o – 5.y o	> 5 y.o –18 y.o
# patients with meningitis				
# patients with meningitis that were followed up				
# patients with any meningitis-related sequelae				

If mortality is reported, write down # of patients that died

Mortality should be from meningitis. If not reported, please write NR.

If mortality is reported, at what time did it happen?

→ Before discharge could be before admission, at admission, during hospitalization, etc.
→ After discharge could be in follow-up.

1. Before discharge
2. After discharge
3. Unknown

Select the starting point of sequelae time frame detection

What is the point of time at which you should start counting the days until diagnosis?

e.g. if diagnosis of hearing loss was done at the follow-up 30 days after admission ≥ "ADMISSION" would be starting point.

1. From symptom onset
2. From meningitis diagnosis
3. From admission
4. From treatment
5. From discharge
6. Unknown
7. Other

Select the time of detection of meningitis sequelae diagnosis

e.g. if diagnosis of hearing loss was done at follow up 30 days after admission ≥ "FOLLOW-UP" would be time of detection

1. Before discharge
2. At discharge
3. After discharge (at follow-up)
4. Unknown
5. Other

Copy and paste the section from the article that describes the timing of meningitis sequelae diagnosis (starting point to detection)

Type of sequelae per timing of detection

CHILDREN (NOT STRATIFIED)

1. Please identify how many patients had EACH sequela.
2. Please use mean time frame or median (in days). You can also write the range of follow-up if applicable; for example "follow-up was done within 3–9 months", so you can write in the column of timing → 90–270 days.

	# patients	Mean time frame (DAYS)	# patients additional time frame	Mean time frame (DAYS)	# patients additional time frame	Mean time frame (DAYS)
Focal neurological deficits						
Hearing loss						
Speech and/or language disorders						
Seizures						
Neurocognitive/neurodevelopmental impairment						
Psychological after-effects (stress, depression, behavioural changes)						
Hydrocephalus						
Vision impairment						
Limb loss						
TOTAL without stratification of sequelae						

If neurological sequelae are not stratified, please select those that are mentioned:

1. Focal neurological deficits
2. Hearing loss
3. Speech and/or language disorders
4. Seizures
5. Neurocognitive/neurodevelopmental impairment
6. Psychological after-effects (stress, depression, behavioural changes)
7. Hydrocephalus

8. Vision impairment
9. Limb loss

Number of patients with acute meningitis PER pathogen macro category

If CHILDREN are not stratified per age, fill in only the not stratified column. If provided for EACH age range, fill in per age, and then sum up the total in the not stratified column.

	Children (not stratified)	**1 mo. – 1 y.o**	**> 1 y.o – 5.y o**	**> 5 y.o –18 y.o**
Bacterial				
Viral				
Fungal				
Parasitic				
Unknown etiology				

Number of patients with meningitis-related sequelae PER pathogen macro category

If CHILDREN are not stratified per age, fill in only the not stratified column. If provided for EACH age range, fill in per age, and then sum up the total in the not stratified column.

	Children (not stratified)	**1 mo. – 1 y.o**	**> 1 y.o – 5.y o**	**> 5 y.o –18 y.o**
Bacterial				
Viral				
Fungal				
Parasitic				
Unknown etiology				

Type of sequelae, identified per pathogen macro category

CHILDREN (NOT STRATIFIED)

If number of patients with EACH sequela are not listed per type of pathogen, fill in only the last row of TOTAL patients with ANY sequelae. If provided for EACH sequela, then sum up the total per pathogen.

	Bacterial	Viral	Fungal	Parasitic	Unknown etiology
Focal neurological deficits					
Hearing loss					
Speech and/or language disorders					
Seizures					
Neurocognitive/neurodevelopmental impairment					
Psychological after-effects (stress, depression, behavioural changes)					
Hydrocephalus					
Vision impairment					
Limb loss					
TOTAL without stratification of sequelae					

Type of sequelae PER specific pathogen

CHILDREN (NOT STRATIFIED)

If number of patients with EACH sequela are not listed per type of pathogen, fill in only the last row of TOTAL patients with ANY sequelae. If provided for EACH sequela, then sum up the total per pathogen.

	Neisseria meningitis	***Streptococcus pneumoniae***	***Haemophilus influenzae type b (Hib)***	***Streptococcus agalactiae (GBS)***
Focal neurological deficits				
Hearing loss				
Speech and/or language disorders				
Seizures				
Neurocognitive/neurodevelopmental impairment				
Psychological after-effects (stress, depression, behavioural changes)				
Hydrocephalus				
Vision impairment				
Limb loss				
TOTAL without stratification of sequelae				

16. (a). Rehabilitation for sequelae in adults

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Abbreviations

ADL	activities of daily living
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
RCT	randomized controlled trial
SMD	standardized mean difference
WHO	World Health Organization

1. Background

The consequences of acute meningitis can be profound, with a wide spectrum of sequelae, including cognitive deficits, motor impairment, speech and language difficulties, sensory impairments and psychological challenges *(1, 2)*. Rehabilitation plays a crucial role in addressing the diverse and complex sequelae that may follow acute meningitis in adults. The aim of rehabilitation is to optimize functional recovery, reduce disability and enhance the overall quality of life for the individuals affected. As outlined by the WHO *Package of interventions for rehabilitation*, sequelae rehabilitation includes a variety of interventions, such as physical therapy, occupational therapy, speech and language therapy, neuropsychological rehabilitation and psychological support *(3)*. These interventions are designed to address specific impairments and to promote the reintegration of survivors into their communities.

Despite the wide array of rehabilitation interventions available, the optimal strategy for sequelae rehabilitation in the context of acute meningitis in adults is not yet well defined. This gap has implications for both clinical practice and health-care policy, as it affects the ability to provide targeted and evidence-based care to this vulnerable patient population. As part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*, this systematic review aims to address the question of what constitutes effective rehabilitation for adults experiencing sequelae as a result of acute meningitis.

The protocol for this systematic review was published on PROSPERO *(4)*.

2. Methodology

2.1 Research question and study design

Among adult cases of acute meningitis from any cause (excluding cases of isolated hearing loss), should rehabilitation for sequelae be provided to improve outcomes?

Population: Adults with, or who have had, acute meningitis arising from any cause and are experiencing sequelae (excluded if isolated hearing loss).

Intervention: Rehabilitation (neurological, psychological or physical rehabilitation, including occupational therapy, assistive technology provision and training, speech and language therapy and/or vision assistance).

Comparator: Care without rehabilitation.

Outcomes

Critical outcomes:

- quality of life;
- functioning (ability to perform activities of daily living – e.g. those measured by Barthel Index, disability measured on scales such as Modified Rankin Scale or Glasgow Outcome Scale);
- participation (defined as involvement in a life situation, e.g. going to school, undertaking work, having a family);
- career burden.

Important outcomes:

- mortality
- secondary consequences.

Study designs: These study designs were considered for inclusion:

1. Experimental and quasi-experimental studies
    - Randomized controlled trials (RCTs).
2. Non-randomized studies of intervention
    - Observational studies
    - Cohort studies (retrospective, non-concurrent and prospective)
    - Case-series.

Studies should have estimated the differences between the outcomes of the groups receiving the intervention of interest and those in the comparator arm.

2.2 Eligible studies

Published language: The intention was to include studies published in all languages.

Exclusion criteria: Studies that did not include a comparator group and any studies with incomparable groups (e.g. milder and severe cases in different arms) were excluded. Case reports, reviews, letters, expert opinions, commentaries, editorials as well as unpublished, non-peer-reviewed literature, and records of registered, ongoing trials with no results (e.g. those from ClinicalTrials.gov) were also excluded.

2.3 Search strategy

The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The reference lists of all the studies included were reviewed, and we examined relevant studies for additional references (see Appendix 1).

2.4 Selection of studies

First stage: Two of the authors independently screened titles and abstracts to determine which studies were eligible for full-text screening. Disagreements were resolved by discussion or by referring the matter to a third author.

Second stage: Two of the authors independently reviewed the full texts of potentially eligible studies to determine which studies would be eligible for consideration for the final selection. Disagreements were resolved by discussion or by referring the question to a third author.

Covidence software was used to screen the titles and abstracts as well as the full text of the articles. The reference lists of the eligible articles were retrieved and screened. Finally, a subject expert was asked to identify further eligible articles.

2.5 Data extraction and management

The data were extracted using a pilot-tested, standardized data collection template. Two of the authors extracted data from the selected studies. In the case of any disagreement, they tried to build consensus through discussion. If there was persistent disagreement, the opinion of a third author was considered binding.

The following data were extracted: surname of the first author, year of publication, country, region, sample size, enrolment period, details of population (etiology, mean age, % male, disease severity, type of treatment received before or during therapy, time since acute meningitis diagnosis), interventions (type of rehabilitation interventions – e.g. physical therapy, occupational therapy, speech therapy, neuropsychological

rehabilitation, description of the intervention protocol, duration of rehabilitation, frequency and duration of therapy sessions), length of follow-up, outcomes reported and effect sizes with a 95% confidence interval (CI).

2.6 Assessment of risk of bias in studies included in the review

Assessment of risk of bias was not performed as the search strategy did not identify any eligible studies.

2.7 Data synthesis

A narrative synthesis of indirect evidence from five systematic reviews was conducted in accordance with the SWiM (synthesis without meta-analysis) guidance *(5)*.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

No studies with a comparator group were identified.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles were not developed for this systematic review as no eligible evidence was identified. Please refer to the review protocol for a description of the preplanned methods *(4)*.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

This analysis was not applicable to this review.

2.10 Deviations from the review protocol

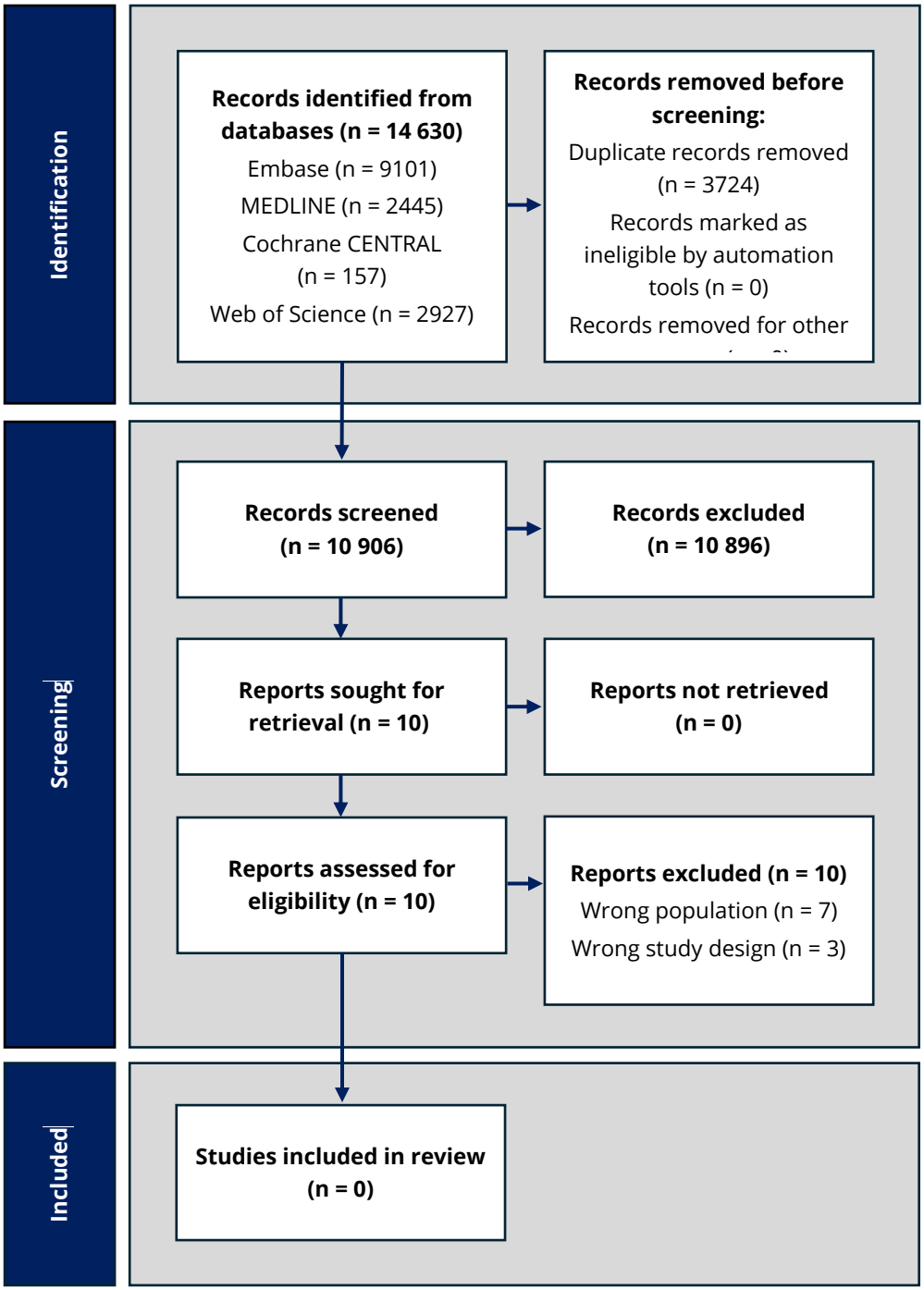
This was not applicable to this review.

3. Results

Figure WA16a.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the review.

The search yielded 14 630 titles and abstracts, all of which were identified as a result of the electronic database search. After duplicates were removed there were 10 906 articles remaining, of which 10 896 were excluded on the basis of a review of the title and abstract. This left 10 articles for full-text review. Of these, all 10 were excluded either because they had the wrong population (n = 7) or wrong study design (n = 3).

Fig. WA16a.1 PRISMA flow diagram for the systematic review



3.1 Studies included in the review

The literature search did not identify any studies eligible for this review. However, five high-quality systematic reviews on rehabilitation following infectious encephalitis, stroke and other brain injuries were identified and included as indirect evidence to inform this research question *(6-10)*.

3.2 Studies excluded from the review

Ten studies were considered as indirect evidence to inform the research question but eventually excluded mainly due to having the wrong population *(11-20)*.

3.3 Narrative summary of the effect of intervention from studies that provide indirect evidence

3.3.1 Indirect evidence from infectious encephalitis

A systematic review by Christie et al. *(6)* of 20 studies was identified, involving a total of 37 adults and 5 children, and looking at rehabilitation outcomes in cases of infectious encephalitis. It showed that a variety of interventions have been used to alleviate sequelae resulting from infectious encephalitis, including cognitive therapy (nine studies), behavioural therapy (five studies) and physical therapy (two studies), or a combination of these (four studies). The study design included one RCT, two cohort studies and 16 case series or case reports. All the studies had sample sizes of less than 25 patients. About 50% of the studies were assessed as having a high risk of bias. Most of the studies (10 out of 20) focused on evaluating the effectiveness of interventions aimed at addressing the sequelae of herpes simplex virus encephalitis.

The evidence suggested that rehabilitation interventions might have a beneficial effect on patients experiencing sequelae resulting from infectious encephalitis across all outcomes. Rehabilitation outcomes were assessed using various approaches, including functional measures, neuropsychological-based measures, behaviour-based measures, and combinations of these. This systematic review was limited by the clinical and methodological heterogeneity across included studies and inconsistencies in outcomes reported, for these reasons meta-analyses were not performed.

3.3.2 Indirect evidence from stroke and other non-progressive acquired brain damage

Physical rehabilitation

Indirect evidence for physical rehabilitation following a stroke was provided by a systematic review by Pollock et al. of 96 studies involving 10 401 participants *(8)*. More than half of the studies (50 of 96) were conducted in China. The studies demonstrated considerable heterogeneity, with many being inadequately reported.

In terms of functional recovery after a stroke, physical rehabilitation had a beneficial effect compared to no treatment, as evidenced by 27 studies involving 3423 participants and assessing measures of independence using activities of daily living [ADL] scales (standardized mean difference [SMD] 0.78, 95% CI 0.58 to 0.97). Furthermore, this effect persisted beyond the intervention period, as indicated by nine studies involving 540 participants (SMD 0.58, 95% CI 0.11 to 1.04). Subgroup analysis indicated a significant difference based on dose of intervention ($P < 0.0001$ for measures of independence in ADL), suggesting that an intervention duration of 30–60 minutes per day, 5–7 days per week, was most effective. Additionally, subgroup analyses that suggested significant benefits were associated with a shorter time since stroke ($P = 0.003$ for *independence* in ADL).

Compared to usual care or attention control, physical rehabilitation proved more effective in enhancing motor function (12 studies, 887 participants; SMD 0.37, 95% CI 0.20 to 0.55), balance (5 studies, 246 participants; SMD 0.31, 95% CI 0.05 to 0.56) and gait velocity (14 studies, 1126 participants; SMD 0.46, 95% CI 0.32 to 0.60). Subgroup analysis revealed a significant difference based on intervention dosage ($P = 0.02$ for motor function), indicating that a dosage of 30–60 minutes per day, 5–7 days per week, provided significant benefit. Subgroup analyses also suggested that significant benefit was associated with a shorter time since stroke ($P = 0.05$ for *independence* in ADL).

No particular physical rehabilitation approach demonstrated superiority or inferiority to others in improving independence in ADL (8 studies, 491 participants; test for subgroup differences: $P = 0.71$) or motor function (9 studies, 546 participants; test for subgroup differences: $P = 0.41$). These conclusions were supported by subgroup analyses comparing intervention versus no treatment or usual care, which found no significant effects of different treatment components or intervention categories.

Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage

Indirect evidence for cognitive rehabilitation is provided by a systematic review by Chung et al. including 19 studies (907 participants) in stroke and other non-progressive acquired brain damage *(7)*. Meta-analyses were conducted with 13 studies (770 participants), encompassing 417 traumatic brain injury cases, 304 stroke cases and 49 other acquired

brain injury cases. After excluding non-included intervention groups from three- and four-group studies, the total participant count was reduced to 660.

Among the studies included, three (134 participants) compared cognitive rehabilitation with sensorimotor therapy. None of these studies reported global executive function as an outcome. However, one study provided data on secondary outcomes such as concept formation and ADL.

Six studies (333 participants) compared cognitive rehabilitation with either no treatment or a placebo. Like the group of studies mentioned above, none of these studies reported on the global executive function as an outcome. All six studies included measures of components of executive function, including concept formation (Wisconsin Card Sorting Test), planning (the Everyday Descriptions Task) and flexibility (the Stroop Test). Three studies included measures of working memory (the Trail Making Test and the Paced Auditory Serial Attention Test). Data from four studies did not show any statistically significant effect of cognitive rehabilitation on executive function component outcomes.

Ten studies (448 participants) compared two different cognitive rehabilitation approaches. Two of these studies (82 participants) reported on global executive function as an outcome, but no statistically significant effect was observed. Data from the remaining eight studies did not demonstrate any statistically significant effect on executive function component outcomes either.

Finally, the review explored the effects of restorative interventions (10 studies, 468 participants) and compensative interventions (4 studies, 128 participants). However, no statistically significant effect was found when these were compared with other interventions.

Overall, there was insufficient high-quality evidence to reach any generalized conclusions about the effect of cognitive rehabilitation on executive function, or about any secondary outcome measures.

Task-specific practice (also known as task-oriented practice or repetitive task practice) in stroke

Task-specific practice encompasses the conduct of complete tasks or preparatory movements for an entire limb or limb segment, such as grasping, gripping or executing movements along a path, to aid in ADL or mobility. These movements may encompass actions involving both upper and lower limbs, as well as activities related to maintaining balance while seated or standing, transferring between positions or engaging in functional mobility tasks like navigating stairs or moving around the home.

A systematic review conducted by French et al. *(9)* presented evidence of moderate quality endorsing this recommendation. It synthesized data from 32 RCTs and one quasi-RCT that examined the effectiveness of repetitive task practice versus standard or usual care.

The inclusion criteria stipulated that trials focusing on repetitive activity needed to involve complex, multi-joint, functional movement patterns, as opposed to exercises targeting a single joint or muscle group aimed at strengthening a limb. The duration of training varied from 2 to 20 weeks across the studies included.

The findings revealed statistically significant enhancements in ADLs among stroke patients undergoing task-specific practice compared to those receiving the usual care, across different stages of recovery following a stroke. Importantly, this improvement persisted beyond six months of follow-up and was still evident in a subset of studies even at the four-year follow-up appointment.

Cardiovascular exercise to increase maximum walking speed after stroke

Cardiovascular exercise and/or training, such as walking, aquatic exercises or rowing, have been shown to enhance the maximum walking speed among patients who have had a stroke. A systematic review by Saunders et al. *(10)* specifically addressing cardiovascular training identified within the evidence review encompassed 75 RCTs. These trials investigated critical outcomes, including maximum and preferred walking speeds, preferred gait speed for mobility, disability measured by the Barthel Index and Functional Independence Measures, and quality of life assessed through the Stroke Adapted-Sickness Impact Profile.

The systematic review showed that death was not influenced by any intervention, while disability scores improved with cardiorespiratory training and mixed training.

3.4 GRADE evidence profile

Owing to a lack of studies with a comparator group, a GRADE evidence profile could not be constructed.

4. Research gaps

The present systematic review revealed the absence of studies looking at post-meningitis sequelae with or without comparator groups. While conducting placebo-controlled trials may not be feasible, further research could address the need to clarify the magnitude of effect through observational studies. Furthermore, identification of core outcome measures and standardized reporting of outcomes would aid in maintaining consistency in reporting effects across studies.

There is a need to conduct observational studies and RCTs studying the effect of rehabilitation interventions on post-meningitis sequelae in adults. Furthermore, identification of relevant subgroups that may benefit to a greater or lesser extent requires exploration in order to aid better risk stratification and tailored approaches to rehabilitation.

There is also a notable absence of research exploring the effectiveness of interventions or assessing patient values and preferences in the context of post-meningitis rehabilitation.

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Appendix 1. Search strategy used to identify primary studies

Database: Ovid MEDLINE, including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to 20 December 2023

Search strategy

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2 meningit*.mp. (81339)

3 1 or 2 (92595)

4 exp Rehabilitation/ (357698)

5 ((occupational or speech or language) adj3 therap*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (37518)

6 rehab*.mp. (384674)

7 exp Self-Help Devices/ (13441)

8 (Self-help-device* or assistive-device*).mp. (8589)

9 assistive technology.mp. (2998)

10 vision*.mp. (215823)

11 exp Hearing Loss/ (78933)

12 (hear or hearing or deaf* or communicat* or auditor*).mp. (805326)

13 or/4-12 (1599940)

14 3 and 13 (4381)

15 limit 14 to (case reports or comment or editorial or "review") (1936)

16 14 not 15 (2445)

Database: Embase (Ovid), 1974 to 19 December 2023

Search strategy

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1 exp meningitis/ (109903)

2 meningit*.mp. (114236)

3 1 or 2 (137495)

4 exp rehabilitation/ (496413)

5 ((occupational or speech or language) adj3 therap*).mp. (60312)

6 rehab*.mp. (462338)

7 rehabilitation equipment/ or exp self help device/ (3972)

8 (Self-help-device* or assistive-device*).mp. (7267)

9 assistive technology.mp. or assistive technology/ (5869)

10 vision*.mp. (330423)

11 exp hearing impairment/ (120762)

12 (hear or hearing or deaf* or communicat* or auditor*).mp. (1135685)

13 or/4-12 (2155142)

14 3 and 13 (11001)

15 limit 14 to (editorial or letter or "review") (1764)

16 14 not 15 (9237)

17 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1234951)

18 Animal experiment/ not (human experiment/ or human/) (2594124)

19 17 or 18 (2664622)

20 16 not 19 (9101)

16. (b). Rehabilitation for sequelae in children

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Abbreviations

ADL	activities of daily living
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
RCT	randomized controlled trial
RoB 2	Version 2 of the Cochrane risk-of-bias tool for randomized trials
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions (tool)

1. Background

The neurological and functional sequelae of acute meningitis in children and adolescents are varied and can include a wide range of impairments *(1, 2)*. These sequelae encompass cognitive deficits, motor impairments, speech and language difficulties, sensory deficits and psychological challenges. The extent and nature of these sequelae can be influenced by factors such as the causative organism, the timeliness of treatment and individual patient characteristics.

Rehabilitation is fundamental to addressing these sequelae and supporting the recovery and reintegration of children and adolescents who have survived acute meningitis *(3)*. As outlined by the WHO *Package of interventions for rehabilitation*, rehabilitation for sequelae includes a variety of interventions, such as physical therapy, occupational therapy, speech and language therapy, neuropsychological rehabilitation and psychological support *(4)*. These interventions are designed to address specific impairments and promote the overall well-being and quality of life of the individuals affected.

Despite the wide array of rehabilitation interventions available, the optimal strategy for rehabilitation for sequelae resulting from acute meningitis in children and adolescents is not yet well defined. This gap has implications for both clinical practice and health-care policy, as it affects the ability to provide targeted and evidence-based care to this vulnerable patient population.

As part of the development of the *WHO guidelines on meningitis diagnosis treatment and care*, this systematic review aims to address the question of what constitutes effective rehabilitation for children and adolescents experiencing sequelae as a result of acute meningitis.

The protocol for this systematic review was registered on PROSPERO *(5)*.

2. Methodology

2.1 Research question and study design

Among child and adolescent cases of acute meningitis from any cause (excluding cases with isolated hearing loss), should rehabilitation for sequelae be provided to improve outcomes?

Population: Children and adolescents with, or who have had, acute meningitis from any cause and are experiencing sequelae (excluded if isolated hearing loss).

Intervention: Rehabilitation (neurological, psychological or physical rehabilitation, including occupational therapy, assistive technology provision and training, speech and language therapy and vision assistance).

Comparator: Care without rehabilitation.

Outcomes

Critical outcomes:

- quality of life;
- functioning (ability to perform activities of daily living – e.g. Barthel Index – disability measured on scales such as Modified Rankin Scale or Glasgow Outcome Scale);
- participation (defined as involvement in a life situation – e.g. going to school, undertaking work, having a family);
- caregiver burden.

Important outcomes:

- mortality
- secondary consequences.

Study designs: These study designs were considered for inclusion:

1. Experimental and quasi-experimental studies
   - Randomized controlled trials (RCTs).
2. Non-randomized studies of intervention
   - Observational studies
   - Cohort studies (retrospective, non-concurrent and prospective)
   - Case-series.

Studies should have estimated the differences between the outcomes of the groups receiving the intervention of interest and those in the comparator arm.

2.2 Eligible studies

Published language: Studies published in all languages were considered for inclusion.

Exclusion criteria: Studies that did not include a comparator group and any studies with incomparable groups (e.g. milder and severe cases in different arms) were excluded. Case reports, reviews, letters, expert opinions, commentaries, editorials as well as unpublished, non-peer-reviewed literature, and records of registered, ongoing trials with no results (e.g. those from ClinicalTrials.gov) were excluded.

2.3 Search strategy

Information sources: The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The reference lists of all the studies included were searched, and relevant reviews were checked for additional references (see Appendix 1).

2.4 Selection of studies

First stage: Two of the authors independently screened titles and abstracts to determine which studies were eligible for full-text screening. Any disagreements were resolved by discussion or by referring the matter to a third author.

Second stage: Two of the authors independently reviewed the full texts of potentially eligible studies to determine which studies would be eligible for consideration for the final selection. Any disagreements were resolved by discussion or by referring the issue to a third author.

Covidence software was used to screen the titles and abstracts as well as the full text of the articles. The reference lists of the eligible articles were retrieved and screened. Finally, a subject expert was asked to identify further eligible articles.

2.5 Data extraction and management

The data were extracted using a pilot-tested, standardized data collection template. Two of the authors extracted data from the eligible records independently. In the case of any disagreement, they tried to build consensus through discussion. In the case of persistent disagreement, the opinion of a third author was considered binding.

The following data were extracted: surname of the first author, year of publication, country, region, sample size, enrolment period, details of population (etiology, mean age, % male, disease severity, type of treatment received before or during therapy, time since acute meningitis diagnosis), interventions (type of rehabilitation interventions – e.g.

physical therapy, occupational therapy, speech therapy, neuropsychological rehabilitation, description of the intervention protocol, duration of rehabilitation, frequency and duration of therapy sessions), length of follow-up, outcomes reported and effect sizes with a 95% confidence interval (CI).

2.6 Assessment of risk of bias in studies included in the review

Assessment of risk of bias was not performed as the search strategy did not identify any eligible studies.

2.7 Data synthesis

Since a meta-analysis of treatment effects was not possible, the results of the studies included were synthesized narratively and in tabular form. SWiM (synthesis without meta-analysis) guidance was used for synthesizing results narratively *(6)*.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles were not developed for this systematic review as no eligible evidence was identified.

Please refer to the review protocol for the description of the preplanned methods *(5)*.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

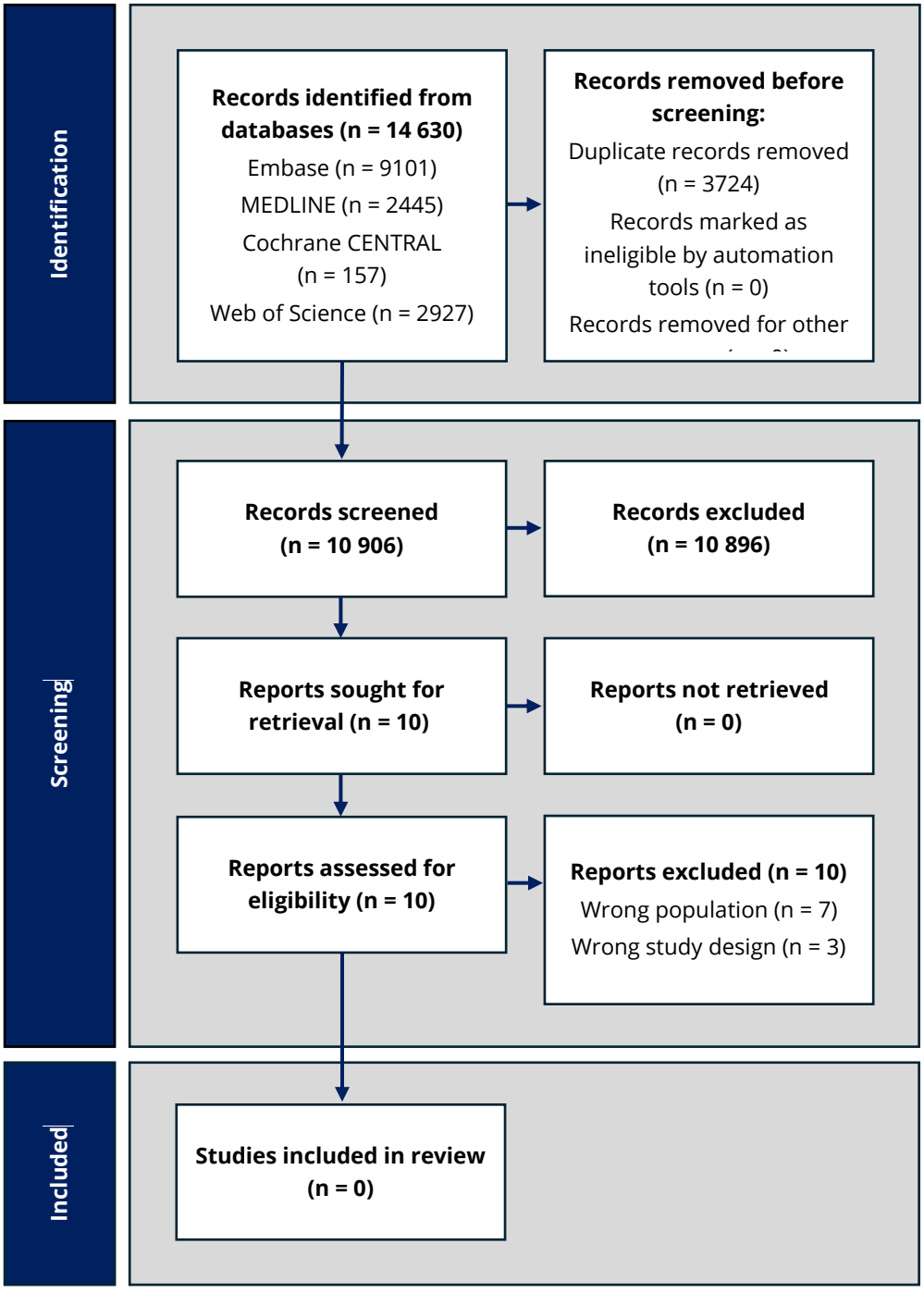
This analysis was not applicable to this review.

3. Results

Figure WA16b.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review.

The search yielded 14 630 titles and abstracts, all of which were identified as a result of the electronic database search. After duplicates were removed, there were 10 906 articles remaining, 10 896 of which were excluded on the basis of a review of the title and abstract. This left 10 articles for full-text review. Of these, all 10 were excluded either because they had the wrong population (n = 7) or wrong study design (n = 3).

Fig. WA16b.1 PRISMA flow diagram for the systematic review



3.1 Studies included in the review

The literature search did not identify any studies eligible for this review. However, three high-quality studies, including one systematic review on infectious encephalitis and two systematic reviews on cerebral palsy, were identified and included as indirect evidence to inform this research question *(7-9)*.

3.2 Studies excluded from the review

Ten studies were considered as indirect evidence to inform the research question but eventually excluded *(10-19)*.

3.3. Narrative summary of the effect of intervention from studies that provide indirect evidence

3.3.1 Indirect evidence from infectious encephalitis

A systematic review by Christie et al. *(7)* of 20 studies was identified, involving a total of 37 adults and five children, and looking at rehabilitation outcomes in cases of infectious encephalitis. It showed that a variety of interventions have been applied to alleviate sequelae resulting from infectious encephalitis, including cognitive therapy (nine studies), behavioural therapy (five studies) and physical therapy (two studies), or a combination of these (four studies).

Three studies (with only five participants in total) in this review focused on paediatric participants, one being a cohort study and the other two case series. Baseline assessment varied across the three studies, with one study using two neuropsychological tests (the Children's Orientation and Amnesia Test and the McCarthy Scale of Children's Abilities) to assess the cognitive status of the patient. The other two studies did not specify a standard tool that measured the severity of the sequelae at baseline.

The rehabilitation outcomes of these paediatric patients were reported using functional measures. As none of the studies included had a follow-up assessment after discharge from rehabilitation, improvements resulting from the rehabilitation intervention were not assessed.

3.3.2 Indirect evidence from cerebral palsy

A systematic review of guidelines for the rehabilitation of children following a diagnosis of cerebral palsy, by Damiano et al., provides indirect evidence for acute meningitis *(8)*. A summary of the recommendations in the guidelines included in the review is presented in Table WA16b.1.

Evidence-based guidelines by Demont et al. *(9)* corroborate the evidence outlined above. Gait training and physical activities are strongly advised for all children with cerebral palsy; however, the evidence supporting these interventions was notably more robust for individuals with unilateral cerebral palsy and those who were ambulatory. Insufficient evidence was available to determine the optimal dosage (duration, intensity and frequency) of these interventions.

Passive joint mobilization, muscle stretching, prolonged stretching with fixed limbs, and neurodevelopmental therapies like the traditional Bobath concept, which is aimed at reducing muscle contractions and spasticity or enhancing gross motor function, were conditionally not recommended. Comparing neurodevelopmental therapies with other interventions was challenging, owing to inadequate detail provided in the articles.

Among intensive rehabilitation programmes, hand–arm bimanual intensive therapy (HABIT) and variations incorporating the lower extremities (HABIT-ILE) were strongly endorsed for both ambulatory and non-ambulatory children with unilateral cerebral palsy, and conditionally recommended for those with bilateral cerebral palsy to enhance gross motor function, upper limb motor function, bimanual skills and self-care abilities. Constraint-induced movement therapy was weakly recommended for ambulatory children with unilateral cerebral palsy. For ambulatory children with unilateral or bilateral cerebral palsy exhibiting equinus gait, the utilization of ankle–foot orthoses was strongly advised to enhance gait speed and increase ankle dorsiflexion range of motion during walking. However, there was inadequate evidence to either recommend or discourage the use of biofeedback-based exercises, treadmill and backward walking training, constraint-induced movement therapy, and their modified versions for children with bilateral cerebral palsy.

Table WA16b.1 Summary of interventions in guidelines for rehabilitation of children with cerebral palsy

Guideline	No. of guidelines	Outcomes addressed	Summary of main results
NICE: cerebral palsy (CP) in adults	103	Spasticity motor function	• Electronic assistive technology may be useful • Physical activity is important • Spasticity has positive and negative effects • CONSIDER oral baclofen • DO NOT OFFER diazepam except in emergency • ONLY CONSIDER SDR and ITB if other less invasive options fail • OFFER vaccinations • DO NOT OFFER prophylactic antibiotics unless there is a high risk of respiratory infections • OFFER chest PT • CONSIDER in-home ventilation • CONSIDER more invasive support if needed (e.g. tracheostomy)
NICE: spasticity in under-19s	117	Spasticity motor function	• CONSIDER: upper and lower limb orthoses for gait and contractures • 24-hour postural management and stretching during daily routines • GMFCS IV–V; oral baclofen, diazepam, ITB; GMFCS II–III; BotA, orthosurgery, SDR • Muscle strengthening • CIMT or bimanual training • PT after BotA or surgeries

AACPDM care pathway: dystonia	9	Muscle tone	• 1 recommendation had evidence for effectiveness (ITB/DBS). All others were expert opinion (level U) and related to medication (1 on BotA for focal dystonia)
AACPDM care pathway: osteoporosis	5	Bone mineral density (fracture risk)	• Increase CA intake. Class III for increasing BMD, no evidence for decreasing fracture risk. If BMD low, prescribe vitamin D. Class III for BMD, none for fracture risk • PT weight-bearing programme: class I–II for and against increased BMD • Consider bisphosphonates and side-effects: class I–III support for increasing BMD, 1 class I against; less certainty for fracture risk
NICE: assessment and management of CP in the under-25s	159	Feeding Communication BMD Drooling Pain Sleep disorders Mental health Postoperative care Comorbidities	• Develop individual feeding plans with families • Early intervention important for communication • OFFER speech therapy to improve intelligibility • CONSIDER augmentative communication • CONSIDER medication, then BotA, then surgery for drooling • CONSIDER management plan for BMD in those at risk • DO NOT OFFER standing frames or vibration plates for BMD only • Treat pain, by cause; if not known use stepped approach • Manage sleep problems but DO NOT OFFER regular sedation or sleep positioning systems • Manage mental health problems recognize unique CP challenges • Ensure pain management, PT and equipment are in place after surgery • Manage comorbidities by cause

AACPDM: American Academy for Cerebral Palsy and Developmental Medicine; BMD: bone mineral density; BotA: Botulinum Toxin A; CA: calcium; CIMT: constraint-induced movement therapy; CP: cerebral palsy; DBS: deep brain stimulation; GMFCS: Gross Motor Function Classification System; ITB: intra-thecal baclofen; NICE: National Institute for Health and Care Excellence (UK); PT: physical therapy; SDR: selective dorsal rhizotomy.
Source: Damiano et al. (2021) *(8)*.

3.4 GRADE evidence profile

Owing to a lack of studies with a comparator group, a GRADE evidence profile could not be constructed.

4. Research gaps

The present systematic review revealed the absence of studies looking at post-meningitis sequelae with or without comparator groups. While conducting placebo-controlled trials may not be feasible, further research could address the need to clarify the magnitude of effect through observational studies. Furthermore, identification of core outcome measures and standardized reporting of outcomes would aid in maintaining consistency in reporting effects across studies.

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14 3 and 13 (4381)

15 limit 14 to (case reports or comment or editorial or "review") (1936)

16 14 not 15 (2445)

Database: Embase (Ovid), 1974 to 20 December 2023

Search strategy

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1 exp meningitis/ (109903)

2 meningit*.mp. (114236)

3 1 or 2 (137495)

4 exp rehabilitation/ (496413)

5 ((occupational or speech or language) adj3 therap*).mp. (60312)

6 rehab*.mp. (462338)

7 rehabilitation equipment/ or exp self help device/ (3972)

8 (Self-help-device* or assistive-device*).mp. (7267)

9 assistive technology.mp. or assistive technology/ (5869)

10 vision*.mp. (330423)

11 exp hearing impairment/ (120762)

12 (hear or hearing or deaf* or communicat* or auditor*).mp. (1135685)

13 or/4-12 (2155142)

14 3 and 13 (11001)

15 limit 14 to (editorial or letter or "review") (1764)

16 14 not 15 (9237)

17 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1234951)

18 Animal experiment/ not (human experiment/ or human/) (2594124)

19 17 or 18 (2664622)

20 16 not 19 (9101

17. Hearing loss screening

Authors

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Abbreviations

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SOAE	spontaneous otoacoustic emissions (test)
TEOAE	transient-evoked otoacoustic emissions (test)

1. Background

Hearing loss is one of the most common sequelae of acute meningitis and can significantly impact the quality of life of the individuals affected *(1, 2)*. Unaddressed hearing loss in individuals who have had acute meningitis has a potentially devastating impact on their communication, education, employment and social well-being.

Formal audiological screening is generally considered an effective way of reducing the burden of unaddressed hearing loss arising from a variety of conditions (e.g. age-related sensorineural degeneration) and of enabling timely initiation of hearing rehabilitation *(3)*.

However, whether formal audiological screening should be performed following acute meningitis, and the optimal timing of such an intervention, is not yet certain.

2. Methodology

2.1 Research question and study design

Among children and adults with acute meningitis (from any cause), should a formal audiological screening test be conducted before discharge or within four weeks of discharge?

Population: People with acute meningitis from any cause.

Subgroup analysis: Age group (child [< 18 years of age], adult).

Intervention: Formal audiological screening test before discharge or within four weeks of discharge. The following hearing tests could be considered:

- acoustic impedance test
- audiometry/pure-tone audiometry
- auditory brainstem response audiometry
- auditory steady-state response
- behavioural observational audiometry
- computer-conditioned play audiometry
- conditioned play audiometry
- evoked response audiometry
- immittance audiometry
- speech discrimination tests
- spontaneous otoacoustic emissions (SOAEs)
- transient-evoked otoacoustic emissions (TEOAEs)
- visual reinforcement audiometry.

Comparator: No formal audiological screening test before discharge or within four weeks of discharge.

Outcomes

Critical outcomes:

- detection of hearing loss
- time to access hearing rehabilitation services where indicated.

Important outcomes:

- quality of life

- functioning (including developmental outcomes for children) and participation[30]
- loss to follow-up.

Study designs: The objective was to capture all relevant studies documenting the time frames within which hearing loss secondary to acute meningitis (arising from all causes) may manifest. This enabled the identification of the common time frames during which it is prudent to implement auditory examinations, including various audiological screening tests.

The study designs considered included observational studies, particularly cross-sectional studies, cohort studies, case-control studies, case series (> 5 cases), systematic reviews (included to identify key primary studies-references) and meta-analyses (included to identify key primary studies-references). They also included experimental studies, namely randomized controlled trials (RCTs), which were included in order to identify embedded observational studies.

2.2 Eligible studies

Published language: Only studies published in English were considered.

Exclusion criteria: Case reports (< 5 cases), experimental studies (not RCTs), animal model studies, histopathological or physiological studies, and disease modelling studies were excluded. Studies for which the full text was not accessible, or an English language was unavailable were excluded. If the central theme of any document was subacute, chronic or non-infectious causes of meningitis (such as chemical or inflammatory causes), or encephalitis/meningoencephalitis, they were also ruled out. Studies with newborns as the patient population were also excluded.

2.3 Search strategy

The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase) and the Cochrane Library. All the databases were searched for studies published from 2000 to January 2024. Reviews, systematic reviews and meta-analyses were also reviewed for references.

The search strategy was structured as follows:

- Concept 1: General terms connected with meningitis.
- Concept 2: Terms connected with acute meningitis arising from all causes. The terms for bacterial, fungal, viral and parasitic meningitis were included, along with the terms for microorganisms that cause acute infectious meningitis.

[30] Participation is defined as involvement in a life situation, e.g. going to school, undertaking work or having a family.

- Concept 3: Terms connected with audiological screening. The terms for the different types of audiological tests were included.

Details of the search strategy, including search terms for each database, can be found in Appendix 1.

2.4 Data extraction and management

A list of publications that might be eligible for inclusion was compiled using the search strategy and exported to Zotero for duplicate deletion. Details of the remaining documents were uploaded to the online COVIDENCE software tool. Two of the authors screened each eligible publication in COVIDENCE, initially by title and abstract, and then by full text. Any disagreement, at either stage of the screening, was resolved by discussion among the team. The extraction tool was then created and used in COVIDENCE to extract the following data:

- study design/type/characteristics
- population, setting, context
- characteristics of pathogen/disease
- intervention
- outcomes.

During the study selection and data extraction stages, team meetings were held once or twice per week to solve conflicts that arose in the data extraction process and to discuss questions or doubts raised by team members. Appendix 2 provides details of the data extraction categories.

2.5 Assessment of risk of bias in studies included in the review

In an Excel spreadsheet, two of the authors independently assessed the risk of bias for each included study. Any disagreement between them was resolved by a third author, and any questions or doubts were discussed by the whole review team.

The CLARITY tool was used to assess bias in the RCTs *(4)*. For the observational studies included, the most appropriate tools to assess the risk of bias were the Newcastle-Ottawa Cohort (for cohort studies) *(5)*, the Newcastle-Ottawa CC tool (for case-control studies) *(5)*, the Joanna Briggs Institute (JBI) checklist (for case series studies) *(6)* and the AXIS tool (for cross-sectional studies) *(7)*.

2.6 Data synthesis

Descriptive data were synthesized into summary tables, presenting continuous data with means and categorical data with counts and proportions. This descriptive analysis was primarily conducted using Excel and R programming software (R version 4.3.3).

The weighted average time to diagnosis was calculated for hearing loss diagnosis. The time points considered to calculate this average were put into two categories: before and after discharge. The proportion of patients diagnosed with hearing loss over the total number of patients tested with a formal audiological screening test was also calculated per time point.

A proportional meta-analysis was conducted to identify comparative effect estimates (the proportion of people diagnosed with sequelae screened before discharge, compared to those screened after discharge). The proportion of patients diagnosed with any degree of hearing loss over the total number of patients tested with a formal audiological test was used for meta-analysis by time point: at admission, during hospitalization/at discharge, at short-term follow-up and at long-term follow-up.

2.7 Assessment of certainty of evidence (GRADE evidence profiles)

Owing to a lack of studies with a comparator group, a Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile could not be constructed.

2.8 Analysis of subgroups or subsets and investigation of heterogeneity

Sensitivity analyses were performed, excluding studies with an assessed high risk of bias if necessary.

The following sources of heterogeneity were considered:

- age (adults versus children and the subgroups for each category)
- causative pathogen
- sequelae identified
- time at which sequelae were identified after diagnosis and/or discharge.

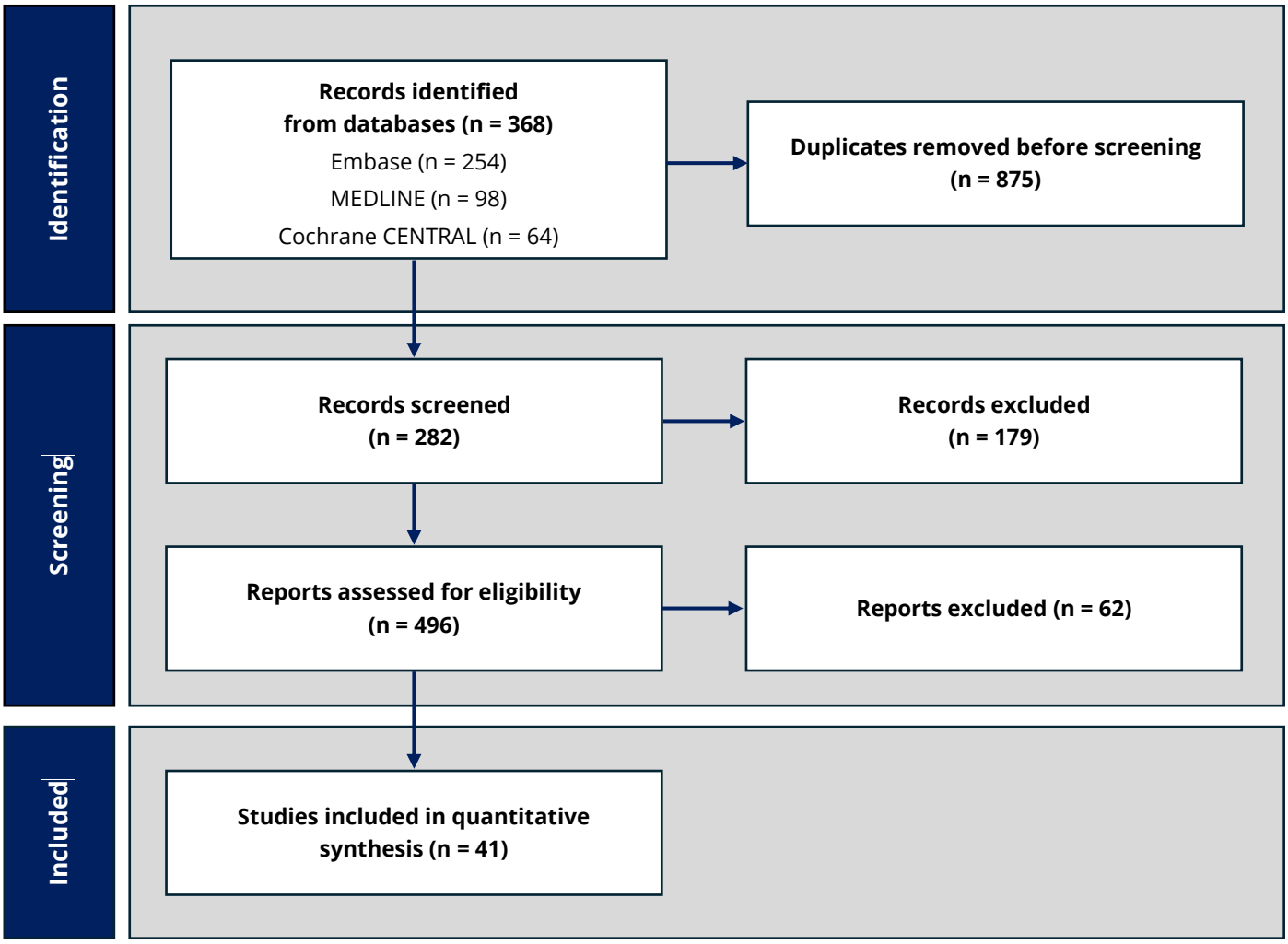
3. Results

The systematic review did not identify any evidence comparing formal audiological screening tests conducted before discharge or within four weeks of discharge to no audiological screening. However, the review identified 41 observational studies providing evidence on audiological screening. These studies were limited by numerous factors, including variability in the time points when hearing loss was assessed, differences in the screening tests used, and lack of clarity in determining whether the hearing loss was developed after acute meningitis or whether it was an ongoing condition.

3.1 Studies identified by the search process

Figure WA17.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review.

Fig. WA17.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review

Table WA17.1 presents the characteristics of the studies included in this review.

Table WA17.1 Characteristics of studies included in the review

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Arditi (1998) *(8)* United States of America (USA)	Cohort	Low	Auditory brainstem response audiometry; Behavioural observational audiometry	Patient population: children with pneumococcal meningitis – 181 patients with meningitis – 151 patients tested for hearing loss – 48 with hearing loss	No comparator	Hearing loss detection: 48 Mortality: 14 Loss to follow-up: NR	Primary outcomes: neurological sequelae (motor deficits) and/or neurosensory deafness	At discharge
Asadi-Pooya (2008) *(9)* Islamic Republic of Iran	Cohort	Low	Audiometry/Pure-tone audiometry	Patient population: children (aged 5–15 years) with confirmed bacterial and aseptic meningitis – 115 patients with meningitis	No comparator	Hearing loss detection: 49 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing impairment	At discharge

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 115 patients tested for hearing loss – 49 with hearing loss				
Biaukula (2012) *(10)* Fiji	Cohort	Low	Acoustic impedance test; Audiometry/pure-tone audiometry; auditory brainstem response audiometry; behavioural observational audiometry; visual reinforcement audiometry	Patient population: children (aged 1 month to less than 5 years) with suspected (bacterial, viral, unknown etiology) meningitis – 70 patients with meningitis – 33 patients tested for hearing loss – 5 with hearing loss	No comparator	Hearing loss detection: 48 Mortality: 16 Loss to follow-up: 21	Primary outcomes: neurological sequelae, hearing loss, visual impairment, Pediatric Quality of Life Inventory	Mean length of follow-up (weeks): 7 Short and long-term morbidities were assessed at approximately 6–8 weeks and 6 months following discharge
Buckingham (2006) *(11)* USA	Cohort	High	Audiometry/pure-tone audiometry	Patient population: children with pneumococcal meningitis – 114 patients with meningitis – 67 patients tested for hearing loss	No comparator	Hearing loss detection: 37 Mortality: 10 Loss to follow-up: 27	Primary outcomes: death, moderate to profound sensorineural hearing loss, and other	At discharge

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 37 with hearing loss			neurological deficits	
Chandrashekar (2015) *(12)* India	Cohort	High	Auditory brainstem response audiometry	Patient population: children (aged 3 months to 12 years) with acute bacterial meningitis – 30 patients with meningitis – 30 patients tested for hearing loss – 6 with hearing loss	No comparator	Hearing loss detection: 6 Mortality: 0 Loss to follow-up: 0	Primary outcomes: sensorineural hearing loss	At discharge
Cherian (2002) *(13)* India	Case series	Low	Brainstem evoked response audiometry (BERA)	Patient population: children (aged 1 month to 12 years) with acute bacterial meningitis – 32 patients with meningitis – 32 patients tested for hearing loss – 9 with hearing loss	No comparator	Hearing loss detection: 9 Mortality: 0 Loss to follow-up: 0	Primary outcomes: sensorineural hearing loss	At discharge
Choong (2021) *(14)*	Cohort	Low	Transient-evoked otoacoustic emissions (TEOAEs)	Patient population: children (aged 15 years and younger)	No comparator	Hearing loss detection: 24 Mortality: 0	Primary outcomes: hearing loss	Mean length of follow-up (weeks): 8

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Singapore				with non-polio enteroviral meningitis – 179 patients with meningitis – 179 patients tested for hearing loss – 24 with hearing loss		Loss to follow-up: 0		Hearing and developmental assessment at 8–10 weeks post-discharge
De Barros (2014) *(15)* France	Case series	Low	Audiometry/Pure-tone audiometry; auditory brainstem response audiometry	Patient population: paediatric patients with severe or bilateral profound deafness following bacterial meningitis – 5 patients with meningitis – 5 patients tested for hearing loss – 5 with hearing loss	No comparator	Hearing loss detection: 5 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	Before discharge and 7 months post-discharge
de Gans (2002) *(16)* Austria, Belgium, Denmark, Germany,	RCT	Low	Audiological examination; test not specified	Patient population: patients (aged 17 years and older) with suspected bacterial meningitis – 301 patients with meningitis	No comparator	Hearing loss detection: 48 Mortality: 32 Loss to follow-up: 7	Primary outcomes: Glasgow Outcome Scale (GOS) Secondary outcomes:	Before discharge (27 with hearing loss) and 8 weeks post-discharge

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Kingdom of the Netherlands				– 262 patients tested for hearing loss – 27 with hearing loss			death, focal neurological abnormalities (defined as aphasia, cranial nerve palsy, monoparesis, hemiparesis and severe ataxia), hearing loss, gastrointestinal bleeding, fungal infection, herpes zoster and hyperglycaemia	(27 with hearing loss)
Drake (2000) *(17)* New Zealand	Case series	Low	Auditory brainstem response audiometry; behavioural observational audiometry; conditioned play audiometry; visual reinforcement audiometry; Other: distraction testing	Patient population: children (aged 6 weeks to 15 years) with confirmed meningococcal meningitis – 65 patients with meningitis – 49 patients tested for hearing loss – 15 with hearing loss	No comparator	Hearing loss detection: 15 Mortality: 0 Loss to follow-up: 16	Primary outcomes: hearing loss	Follow-up within 6 weeks of discharge 34 tested within 6 weeks, 8 within 12 weeks, 7 greater than 12 weeks

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
François (1997) *(18)* France	Cohort	Low	Acoustic impedance test; auditory brainstem response audiometry; TEOAEs; visual reinforcement audiometry	Patient population: children (aged 6–24 months) recovering from purulent meningitis with TEOAEs testing results – 39 patients with meningitis – 39 patients tested for hearing loss – 4 with hearing loss	No comparator	Hearing loss detection: 4 Mortality: 0 Loss to follow-up: 0	Primary outcomes: feasibility and cost-effectiveness of TEOAEs as a hearing assessment for infants recovering from meningitis	Mean length of follow-up (days): 41
Gohar (2021) *(19)* Pakistan	Cross-sectional	Low	Audiometry/pure-tone audiometry; auditory brainstem response audiometry; BERA	Patient population: children (aged 2–144 months) with acute bacterial meningitis – 149 patients with meningitis – 149 patients tested for hearing loss – 10 with hearing loss	No comparator	Hearing loss detection: 10 Mortality: 0 Loss to follow-up: 0	Primary outcomes: sensorineural hearing loss	Before discharge
Heckenberg (2012) *(20)*	Cohort	Low	Pure-tone audiometry	Patient population: adult survivors of pneumococcal meningitis	No comparator	Hearing loss detection: 73 Mortality: 0	Primary outcomes: GOS, hearing loss	At discharge Audiograms performed

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Kingdom of the Netherlands				– 531 patients with meningitis – 531 patients tested for hearing loss – 73 with hearing loss		Loss to follow-up: 0		within 1 year of admission
Herrmann (2024) *(21)* USA	Case series	Low	Auditory brainstem response audiometry	Patient population: survivors (aged ≤ 18 years) of non-type b *H. influenzae* meningitis – 11 patients with meningitis – 10 patients tested for hearing loss – 4 with hearing loss	No comparator	Hearing loss detection: 4 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss and neurological sequelae	Before discharge
Jensen (2023) *(22)* Denmark	Cohort	Low	Otoacoustic emissions; pure-tone audiometry	Patient population: adults (aged ≥ 18 years) with acute bacterial meningitis – 32 patients with meningitis – 28 patients tested for hearing loss – 22 with hearing loss	No comparator	Hearing loss detection: 22 Mortality: 4 Loss to follow-up: 4	Primary outcomes: sensorineural hearing loss	At admission (22 with hearing loss); at discharge (13 with hearing loss); and 60 days post-discharge (11 with hearing loss)

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Karanja (2014) *(23)* Kenya	Cohort	Low	Audiometry/Pure-tone audiometry; Behavioural observational audiometry; conditioned play audiometry	Patient population: children (aged 6 months to 12 years) with bacterial meningitis – 83 patients with meningitis – 83 patients tested for hearing loss – 36 with hearing loss	No comparator	Hearing loss detection: 36 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	At discharge and 2 weeks post-discharge (no data available for post-discharge)
Karppinen (2015) *(24)* Angola	RCT	Low	Auditory brainstem response audiometry	Patient population: children who survived bacterial meningitis – 723 patients with meningitis – 351 patients tested for hearing loss – 65 with hearing loss	No comparator	Hearing loss detection: 65 Mortality: 272 Loss to follow-up: 100	Primary outcomes: hearing impairment	Before discharge on day 7 (±1) of hospitalization
Kastenbauer (2003) *(25)* Germany	Case series	Low	Audiometry	Patient population: adults (aged ≥ 16 years) with pneumococcal meningitis – 87 patients with meningitis	No comparator	Hearing loss detection: 17 Mortality: 20 Loss to follow-up: 1	Primary outcomes: GOS, hearing loss, mortality	During hospitalization

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 66 patients tested for hearing loss – 17 with hearing loss				
Koomen (2003) *(26)* Kingdom of the Netherlands	Cohort	Low	Acoustic impedance test; audiometry/pure-tone audiometry; auditory brainstem response audiometry; Other: distraction method	Patient population: surviving children of non-*H. influenzae* type b (Hib) bacterial meningitis – 578 patients with meningitis – 395 patients tested for hearing loss – 43 with hearing loss	No comparator	Hearing loss detection: 43 Mortality: 0 Loss to follow-up: 183	Primary outcomes: hearing loss	At 6 months post-discharge
Kopelovich (2011) *(27)* USA	Cohort	Low	Audiometry/Pure-tone audiometry; auditory brainstem response audiometry; SOAEs; TEOAEs	Patient population: children (aged 3 months to 18 years) with bacterial meningitis – 23 patients with meningitis – 23 patients tested for hearing loss – 8 with hearing loss	No comparator	Hearing loss detection: 8 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	Before discharge

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Kuschke (2018) *(28)* South Africa	Cohort	Low	SOAEs	Patient population: children with meningitis – 16 patients with meningitis – 14 patients tested for hearing loss – 6 with hearing loss	No comparator	Hearing loss detection: 6 Mortality: 0 Loss to follow-up: 2	Primary outcomes: hearing loss	Mean length of follow-up: 17 weeks (range 1–60)
Kutz (2006) *(29)* USA	Cohort	Low	Audiometry/Pure-tone audiometry; auditory brainstem response audiometry; behavioural observational audiometry	Patient population: children (aged 3 months to 17 years) with bacterial meningitis – 171 patients with meningitis – 134 patients tested for hearing loss – 41 with hearing loss	No comparator	Hearing loss detection: 41 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	Mean length of follow-up (weeks): 42
Lempinen (2022) *(30)* Angola	RCT	Low	Auditory brainstem response audiometry; SOAEs; TEOAEs	Patient population: children with confirmed acute bacterial meningitis with and without otitis media	No comparator	Hearing loss detection: 136 Mortality: 0 Loss to follow-up: 121	Primary outcomes: hearing loss	Mean length of follow-up (weeks): 4 Hearing tests by auditory

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 512 patients with meningitis – 391 patients tested for hearing loss – 136 with hearing loss				brainstem response were performed within 24 h of admission (136/391 with hearing loss); on Day 7 ± 1 of the treatment (92/310); and at follow-up visits at 1 month post-discharge (43/168); 3 months post-discharge (6/78); and 6 months post-discharge (15/47)
McCulloch (2003) *(31)* United Kingdom of Great Britain and Northern Ireland	Cohort	Low	Other: formal audiological screening	Patient population: children (aged < 16 years) with bacterial meningitis – 27 patients with meningitis – 27 patients tested for hearing loss – 3 with hearing loss	No comparator	Hearing loss detection: 3 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	Mean length of follow-up (weeks): 6

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Molyneux (2002) *(32)* Malawi	RCT	Low	Behavioural observational audiometry; TEOAEs	Patient population: children (aged 2 months to 13 years) with bacterial meningitis; HIV-positive patients – 598 patients with meningitis – 341 patients tested for hearing loss – 127 with hearing loss	No comparator	Hearing loss detection: 127 Mortality: 211 Loss to follow-up: 46	Primary outcomes: mortality, hearing loss	Mean length of follow-up (weeks): 4
Molyneux (2003) *(33)* Malawi	RCT	Low	Evoked response audiometry; TEOAEs	Patient population: children (aged 2 months to 13 years) with bacterial meningitis – 598 patients with meningitis – 442 patients tested for hearing loss – 71 with hearing loss	No comparator	Hearing loss detection: 71 Mortality: 215 Loss to follow-up: 36	Primary outcomes: mortality, neurological sequelae, hearing loss	Mean length of follow-up (weeks): 4 Follow-up visits were requested at 1 month and 6 months after discharge
Orman (2020) *(34)*	Case-control	Low	Audiometry/Pure-tone audiometry; auditory steady-state response;	Patient population: infants (aged < 1 year)	No comparator	Hearing loss detection: 16	Primary outcomes:	Median length of follow up: 323.2 days

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
USA			SOAEs; TEOAEs; visual reinforcement audiometry	with confirmed bacterial meningitis – 115 patients with meningitis – 115 patients tested for hearing loss – 16 with hearing loss		Mortality: 0 Loss to follow-up: 0	sensorineural hearing loss	(range, 0–2268 days)
Ozen (2008) *(35)* Türkiye	Case-control	Low	Acoustic impedance test; audiometry/pure-tone audiometry	Patient population: children with pneumococcal meningitis – 55 patients with meningitis – 55 patients tested for hearing loss – 11 with hearing loss	No comparator	Hearing loss detection: 11 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	Mean length of follow-up (weeks): 6
Pelkonen (2011) *(36)* Angola	RCT	Low	Auditory brainstem response audiometry; TEOAEs	Patient population: children (aged 2 months to 13 years) with confirmed bacterial meningitis – 723 patients with meningitis	No comparator	Hearing loss detection: 141 Mortality: 272 Loss to follow-up: 77	Primary outcomes: death or severe neurological sequelae (defined as blindness, quadriplegia or paresis, hydrocephalus	At discharge

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 374 patients tested for hearing loss – 141 with hearing loss			requiring a shunt, or severe psychomotor retardation) Secondary outcomes: deafness	
Richardson (1997) *(37)* United Kingdom	Cohort	Low	Auditory brainstem response audiometry; TEOAEs	Patient population: children (aged 4 weeks to 16 years) with bacterial meningitis – 124 patients with meningitis – 83 patients tested for hearing loss – 21 with hearing loss	No comparator	Hearing loss detection: 21 Mortality: 0 Loss to follow-up: 40	Primary outcomes: hearing loss	At discharge (8 with hearing loss) and 9 months post-discharge (3 with hearing loss)
Rodenburg-Vlot (2018) *(38)* Kingdom of the Netherlands	Cohort	Low	Pure-tone audiometry; auditory brainstem response audiometry	Patient population: All patients with bacterial meningitis with audiometry – 252 patients with meningitis – 228 patients tested for hearing loss – 69 with hearing loss	No comparator	Hearing loss detection: 69 Mortality: 0 Loss to follow-up: 142	Primary outcome: hearing loss	Median follow-up: 24 days after diagnosis

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Roine (2013) *(39)* Angola	Cohort	Low	Auditory brainstem response audiometry	Patient population: children with bacterial meningitis – 124 patients with meningitis – 124 patients tested for hearing loss – 33 with hearing loss	No comparator	Hearing loss detection: 33 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	At 3 months after admission
Saha (2009) *(40)* Bangladesh	Case-control	Low	Auditory brainstem response audiometry; SOAEs; TEOAEs; Other: tympanometry	Patient population: children with pneumococcal meningitis – 102 patients with meningitis – 102 patients tested for hearing loss – 17 with hearing loss	No comparator	Hearing loss detection: 17 Mortality: 18 Loss to follow-up: NR	Primary outcomes: neurodevelopmental sequelae (neurological, hearing, visual, psychological)	Mean length of follow-up (weeks): 5 Short term: 30–40 days Long term: 6–24 months
Sankar (2007) *(41)* India	RCT	Low	Audiometry/Pure-tone audiometry; auditory brainstem response audiometry	Patient population: children (aged 2 months to 12 years) with acute bacterial meningitis – 58 patients with meningitis	No comparator	Hearing loss detection: 10 Mortality: 3 Loss to follow-up: 0	Primary outcomes: hearing loss and neurological sequelae	Mean length of follow-up (weeks): 4

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 55 patients tested for hearing loss – 10 with hearing loss				
Shi (2021) *(42)* USA	Cohort	Low	Auditory brainstem response audiometry; behavioural observational audiometry; Other: tympanometry	Patient population: children (aged 3 months to 18 years) with bacterial meningitis – 42 patients with meningitis – 42 patients tested for hearing loss – 12 with hearing loss	No comparator	Hearing loss detection: 12 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	Mean length of follow-up: 7.5 days
Singhi (2002) *(43)* India	RCT	Low	Audiometry/Pure-tone audiometry; behavioural observational audiometry; evoked response audiometry	Patient population: children (aged 3 months to 12 years) with bacterial meningitis – 69 patients with meningitis – 69 patients tested for hearing loss – 15 with hearing loss	No comparator	Hearing loss detection: 15 Mortality: 0 Loss to follow-up: 0	Primary outcomes: neurological sequelae, hearing loss	At discharge (15 with hearing loss) and 1-month post-discharge (14 with hearing loss)

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Singhi (2007) *(44)* India	Cohort	Low	Audiometry/Pure-tone audiometry; evoked response audiometry	Patient population: children (aged 2 months to 12 years) with bacterial meningitis – 80 patients with meningitis – 80 patients tested for hearing loss – 5 with hearing loss	No comparator	Hearing loss detection: 5 Mortality: 0 Loss to follow-up: 0	Primary outcomes: neuro-motor status (active and passive tone, reflexes and asymmetry), neurobehavioral status (seizures, hyper-excitability and lethargy), neuro-sensory status (vision and hearing test audiometry and BERA, as indicated). Vineland Social Maturity Scale, Nagpur modification 20 was used for psychomotor testing	Mean length of follow-up (months): 15
Turel 2013 *(45)* Türkiye	Cohort	Low	Acoustic impedance test; auditory brainstem response audiometry; TEOAEs	Patient population: children (aged < 1 month to < 5 years) with bacterial meningitis	No comparator	Hearing loss detection: 11 Mortality: 2	Primary outcomes: neurological sequelae, hearing loss	Mean length of follow-up: 2 years post-discharge

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				– 283 patients with meningitis – 146 patients tested for hearing loss – 11 with hearing loss		Loss to follow-up: 137		
Wellman (2003) *(46)* Canada	Cohort	Low	Auditory brainstem response audiometry; Other: cortical electrical response audiometry	Patient population: surviving children (aged 1 day to 18 years) with confirmed bacterial meningitis – 79 patients with meningitis – 68 patients tested for hearing loss – 11 with hearing loss	No comparator	Hearing loss detection: 11 Mortality: 0 Loss to follow-up: 11	Primary outcomes: hearing loss	Mean length of follow-up: 2.5 weeks Range: 0–7 weeks Before discharge (22 with hearing loss) and post discharge (11 with hearing loss)
Worsøe (2010) *(47)* Denmark	Cohort	Low	Audiometry/Pure-tone audiometry; auditory brainstem response audiometry; behavioural observational audiometry; visual	Patient population: all patients with pneumococcal meningitis – 343 patients with meningitis	No comparator	Hearing loss detection: 129 Mortality: 107 Loss to follow-up: 0	Primary outcomes: hearing loss	1 year after symptom onset

Lead author (year) Country	Study design	Overall risk of bias (study level)	Intervention	Population (sample size: Intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			reinforcement audiometry; other	– 240 patients tested for hearing loss – 129 with hearing loss				
Zeeshan (2018) *(48)* Pakistan	Cohort	Low	Other: otoacoustic emissions	Patient population: children (aged 1 month to 13 years) with bacterial meningitis – 175 patients with meningitis – 175 patients tested for hearing loss – 38 with hearing loss	No comparator	Hearing loss detection: 38 Mortality: 0 Loss to follow-up: 0	Primary outcomes: hearing loss	2 weeks after admission

BERA: brainstem evoked response audiometry (test); GOS: Glasgow Outcome Scale; NR: not reported; RCT: randomized controlled trial; SOAE: spontaneous otoacoustic emissions (test); TEOAE: transient-evoked otoacoustic emissions (test).

3.1.2 Studies excluded from the review

Studies were excluded for the following reasons: time frames (i.e. the time to detection of hearing loss sequela) was not mentioned; follow-up time was outside the scope of the review; it involved the wrong patient population (i.e. people already experiencing hearing loss); the intervention was not relevant (i.e. cochlear implants); the study was not in English; or there was no full text available.

3.2 Risk-of-bias assessment results

Tables WA17.2a to 2e present the results of the risk-of-bias assessments for the different types of studies.

Table WA17.2a Risk-of-bias assessment results: case series studies

Case series (JBI checklist)	
Study	**Result**
Drake 2000 *(17)*	Good quality
Kastenbauer 2003 *(25)*	Good quality
Cherian 2002 *(13)*	Good quality
Herrmann 2024 *(21)*	Good quality
De Barros 2014 *(15)*	Fair quality

Table WA17.2b Risk-of-bias assessment results: case control studies

Case-control (Newcastle-Ottawa)	
Study	**Overall result**
Saha 2009 *(40)*	Good quality
Ozen 2008 *(35)*	Fair quality
Orman 2020 *(34)*	Good quality

Table WA17.2c Risk-of-bias assessment results: cohort studies

Cohort studies (Newcastle-Ottawa)	
Study	**Overall result**
Arditi 1998 *(8)*	Good quality
Francois 1997 *(18)*	Fair quality
Richardson 1997 *(37)*	Good quality
Zeeshan 2018 *(48)*	Good quality
Worsøe 2010 *(47)*	Good quality
Wellman 2003 *(46)*	Good quality
Turel 2013 *(45)*	Fair quality
Singhi 2007 *(43)*	Fair quality
Shi 2021 *(42)*	Good quality
Roine 2013 *(39)*	Good quality
Rodenburg-Vlot 2018 *(38)*	Good quality
McCulloch 2003 *(31)*	Poor quality
Kutz 2006 *(29)*	Fair quality
Kuschke 2018 *(28)*	Good quality
Kopelovich 2011 *(27)*	Good quality
Koomen 2003 *(26)*	Good quality
Karanja 2014 *(23)*	Good quality
Jensen 2023 *(22)*	Good quality
Heckenberg 2012 *(20)*	Good quality
Choong 2021 *(14)*	Good quality
Chandrashekar 2015 *(12)*	Poor quality
Buckingham 2006 *(11)*	Poor quality
Biaukula 2012 *(10)*	Good quality

Cohort studies (Newcastle-Ottawa)	
Asadi-Pooya 2008 *(9)*	Fair quality

Table WA17.2d Risk-of-bias assessment results: RCTs

Randomized controlled trial (CLARITY tool)	
Study	**Overall result**
de Gans 2002 *(16)*	Low risk of bias
Molyneux 2003 *(33)*	Some concerns
Pelkonen 2011 *(36)*	Low risk of bias
Singhi 2002 *(43)*	Low risk of bias
Sankar 2007 *(41)*	Some concerns
Molyneux 2002 *(32)*	Some concerns
Lempinen 2022 *(30)*	Low risk of bias
Karppinen 2015 *(24)*	Low risk of bias

Table WA17.2e Risk-of-bias assessment results: cross-sectional studies

Cross-sectional studies (AXIS tool)	
Study	**Overall result**
Gohar 2021 *(19)*	Fair quality

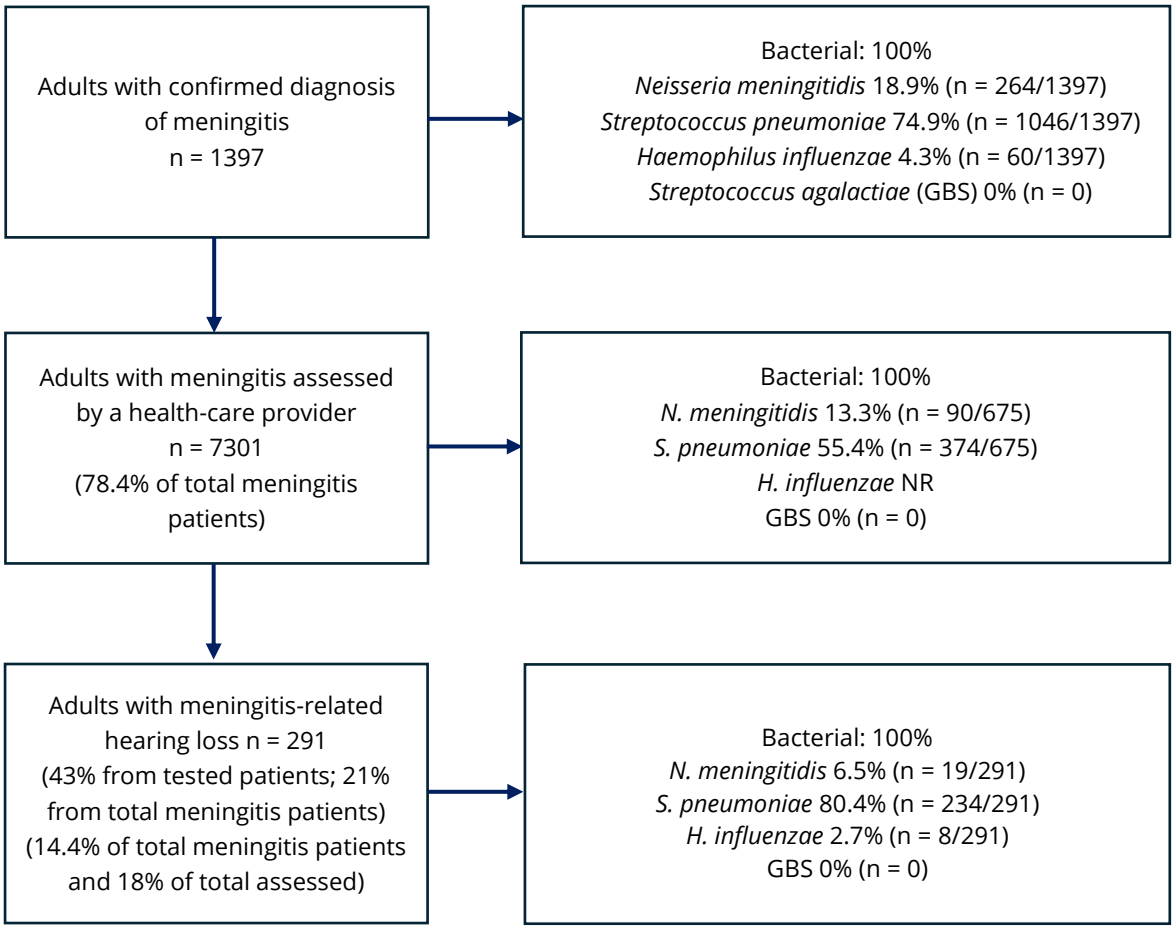
3.3 Description of results

Forty-one studies were included in the descriptive analysis and systematic review. Most studies were observational cohort studies (n = 24), involving paediatric populations (n = 37/41), and six studies involved adult populations. Two studies had both child and adult populations. The majority of the studies (n = 35/41) were published in and concerned populations in high-income regions.

3.3.1 Adult studies

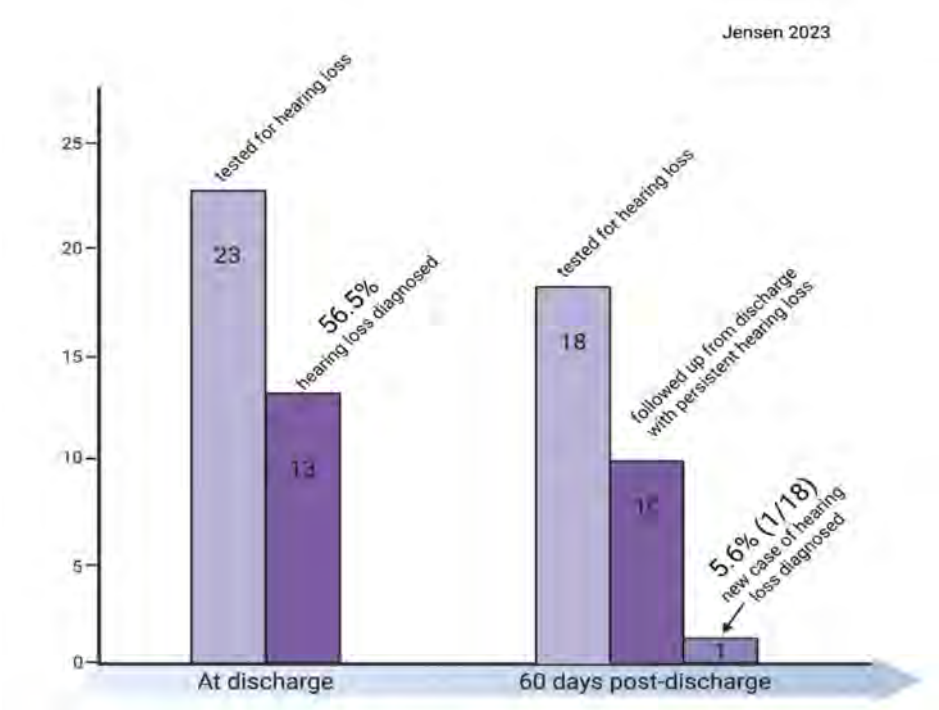
Six studies including a total of 1397 adults with acute meningitis were identified. Two studies included both adults and children. All adults had bacterial meningitis: 1046 (75%) had pneumococcal meningitis and 264 had meningococcal meningitis (19%). Among the adults, 675 (48%) underwent audiological screening and 291 (43%) were found to have meningitis-related hearing loss. Of these, 234 (80%) had pneumococcal meningitis. Figure WA17.2 presents an overview of results of adult studies.

Fig. WA17.2 Overview of results from adult studies



Of the 1397 adults with meningitis, 675 (48%) were screened with a formal audiological test, and 291 of the 675 (43%) had evidence of hearing loss. All the adult populations encompassed individuals who had had bacterial meningitis, predominantly *Streptococcus pneumoniae* and *Neisseria meningitidis*. Pure tone audiometry was the most common test performed. Only two studies, one of which was a case series, included data on hearing tests performed before and after discharge (Jensen et al., 2023 *(22)*). In that study sensorineural hearing loss > 20 dB was present in 13 of 23 people (57%) at discharge and in 11 of 18 patients (61%) 60 days after discharge. Figure WA17.3 presents the results of the study by Jensen et al.

Fig. WA17.3 Hearing detection before and after discharge



Source: Jensen et al. 2023 *(22)*.

Audiological screening test was conducted before discharge in three studies and after discharge in five studies, while two studies conducted the test at both time points. Of the 145 adults screened before discharge, 66 (46%) were found to have hearing loss. Of the 530 adults screened after discharge, 225 (43%) were found to have hearing loss. Table WA17.3 presents the different time points at which hearing loss was diagnosed.

Table WA17.3 Time points at which hearing loss arising from meningitis was diagnosed in adults

Time of hearing loss test	No. of patients/total no. of patients tested[a] (%)	No. of studies	Mean time to hearing loss diagnosis in days (months)
Before discharge	66/145 (45.5%)	3	
At admission	36/56 (64.3%)	2[b]	
During hospitalization	17/66 (25.8%)	1	
At discharge	13/23 (56.4%)	1[b]	
After discharge	225/530 (42.5%)	5	188 (6.2)
Within 1 month	15/24 (62%)	1	24 (0.8)
Short-term follow-up (1–3 months)	38/280 (13.6%)	2[b]	57 (1.9)
Long-term follow-up (< 3 months)	172/226 (76.1%)	2	365 (12)

[a] Denominators: Total number of adults with meningitis tested with formal audiological test at each time point.
[b] Studies with assessment data before and after discharge.

3.3.2 Child studies

Thirty-seven studies including a total of 6708 children with acute meningitis were identified. Two studies included both adults and children. Among the children, 90.4% had bacterial meningitis, 5351 (80%) underwent audiological screening and 1198 (22%) were found to have meningitis-related hearing loss. Nearly all of the children (95%) had bacterial meningitis, with *Streptococcus pneumoniae* being isolated in 32% of cases. Figure WA17.4 presents an overview of the results of children studies.

Fig. WA17.4 Overview of results from child studies

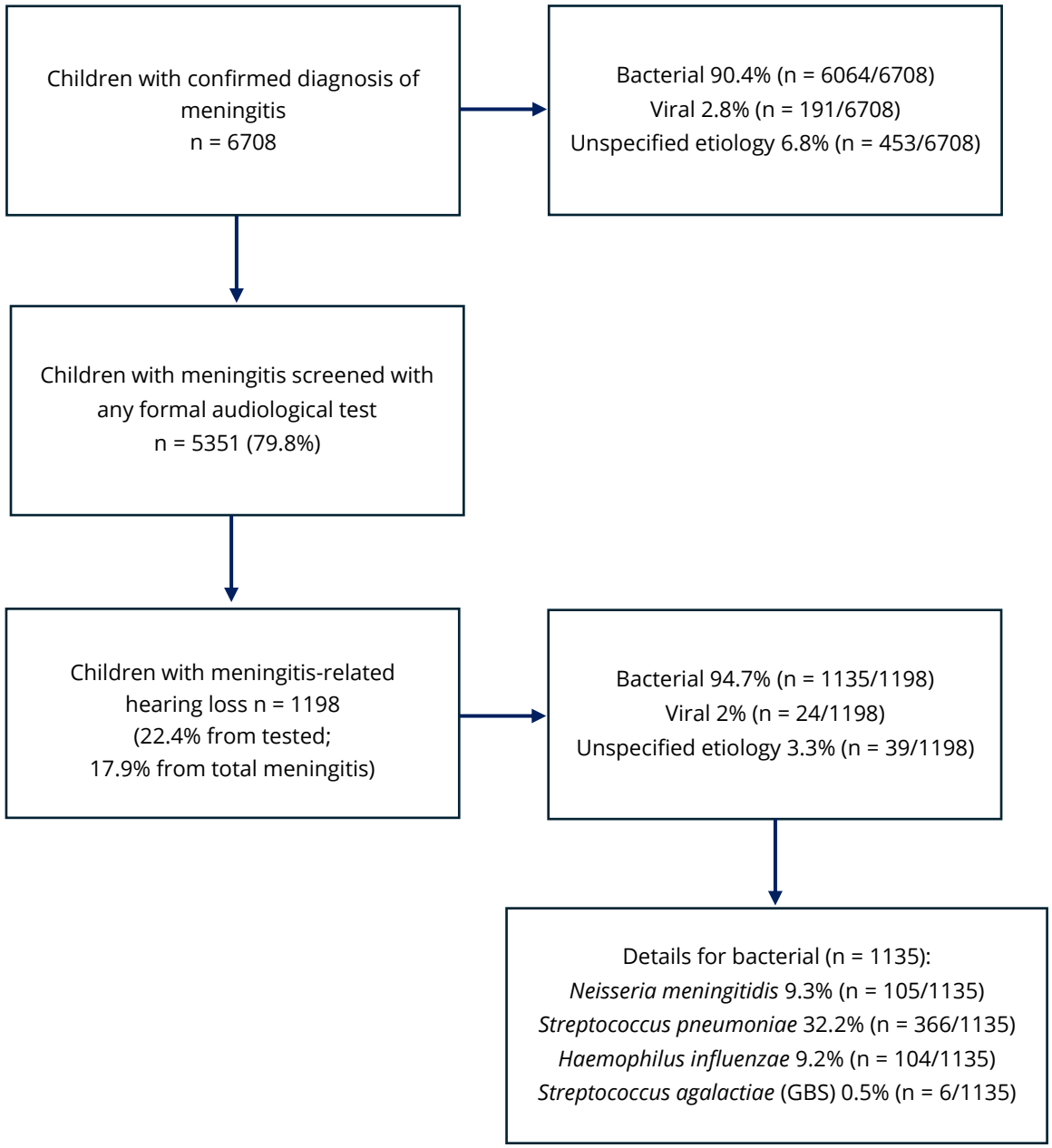


Table WA17.4 presents the different time points at which hearing loss was diagnosed in children.

Table WA17.4 Time taken to diagnose hearing loss arising from meningitis in children

Time of hearing loss test	No. of patients/total no. patients tested[a] (%)	No. of studies	Mean time to hearing loss diagnosis in days (months)
Before discharge	611/1975 (30.9%)	18	4.9
At admission	59/258 (22.8%)	2[b]	1
During hospitalization	249/973 (25.6%)	7[b]	8
At discharge	441/1312 (33.6%)	9[b]	14.2
After discharge	756/3340 (22.6%)	24	94.3 (3.1)
Within 1 month	384/1518 (25.3%)	7[b]	28 (0.9)
Short-term follow-up (1–3 months)	123/688 (17.8%)	9[b]	35.9 (1.2)
Long-term follow-up (< 3 months)	270/1259 (21.5%)	9[b]	284.9 (9.5)

[a] Denominators: Total number of children with meningitis tested with formal audiological test at each time point.
[b] Studies with assessment data before and after discharge.

The forest plots (Figs. WA17.5a to 5d) depict the pooled proportion of children with hearing loss detected over the total number patients tested in subgroups by time point of screening, using meta-analyses of arcsine transformed proportions.

Fig. WA17.5a Hearing loss diagnosis during hospitalization or at discharge: forest plot (children)

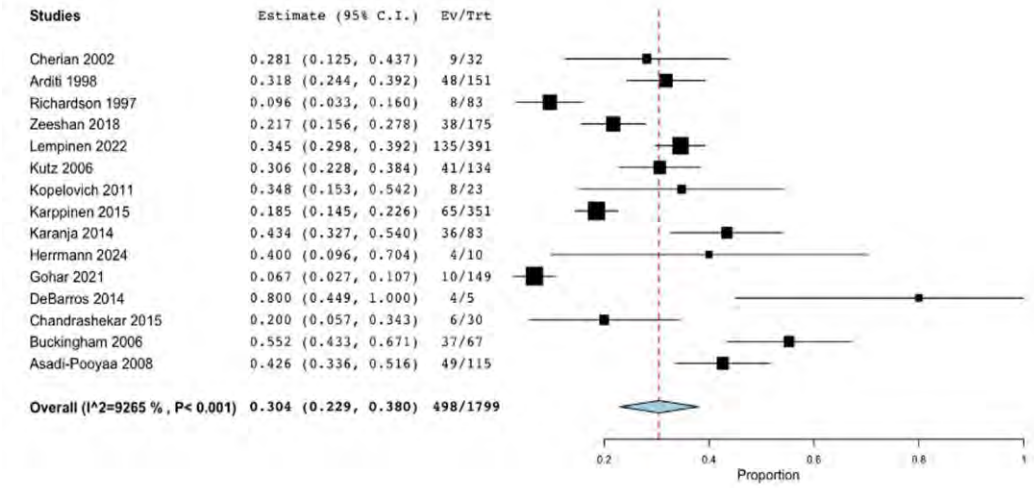


Fig. WA17.5b Hearing loss diagnosis 1–2 months after discharge: forest plot (children)

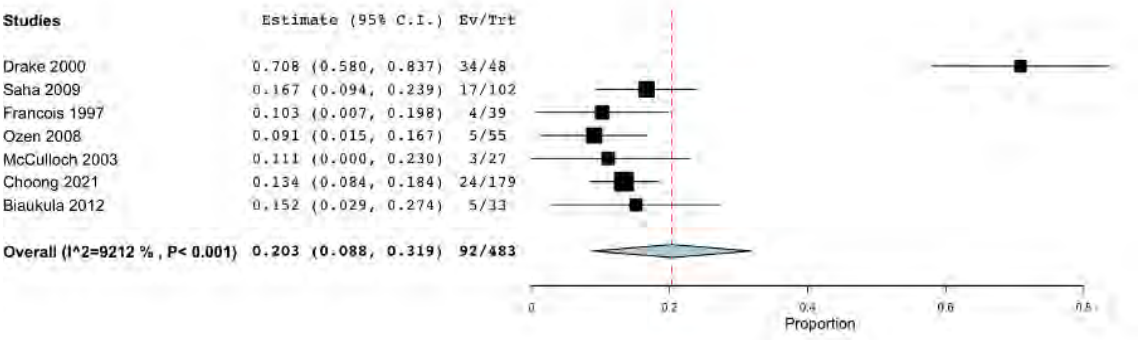


Fig. WA17.5c Hearing loss diagnosis 2–6 months discharge: forest plot(children)

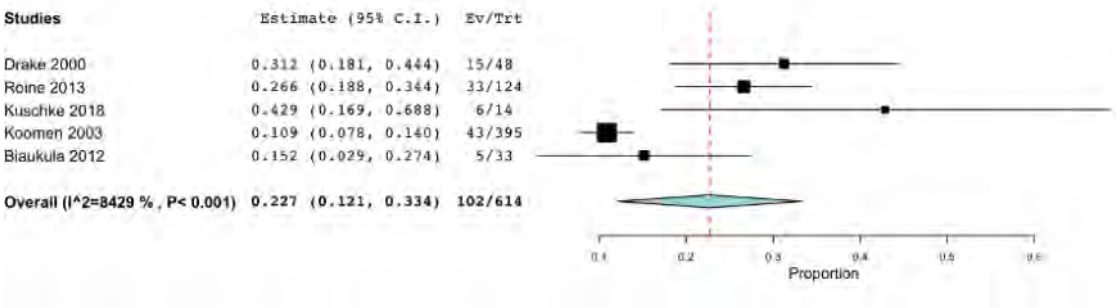
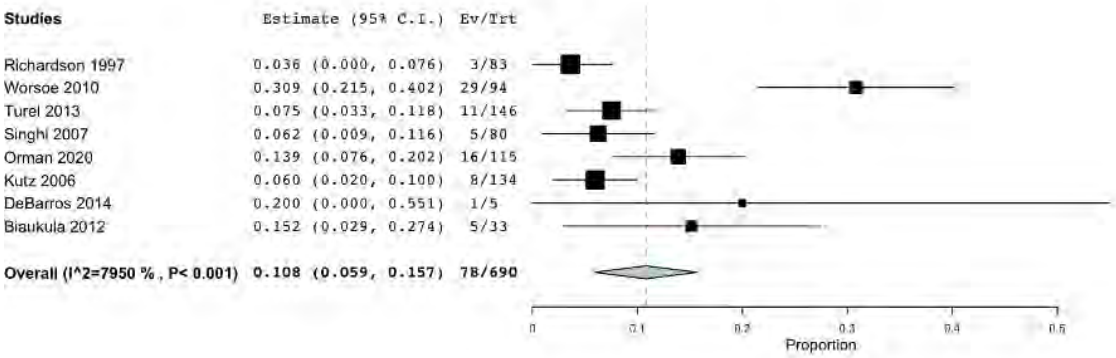


Fig. WA17.5d Hearing loss diagnosis > 6 months after discharge: forest plot (children)



4. Research gaps

The present systematic review revealed the absence of studies with comparator arms, including RCTs and cohort studies. The existing literature consists predominantly of case series and other observational studies, limiting the ability to draw robust conclusions regarding the efficacy of hearing rehabilitation interventions. While conducting placebo-controlled trials may not be feasible, further research could address the need to obtain the magnitude of effect through observational studies.

The body of evidence had variable reporting, with lack of consistency in the outcome measures reported. This further reduced the suitability of the data for quantitative synthesis. The risk-of bias-assessment for the case series was unclear or not reported for a number of domains.

Furthermore, there was a notable absence of research exploring the effectiveness of interventions or assessing patient values and preferences in the context of post-meningitis hearing loss rehabilitation.

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Appendix 1. Search terms used to identify primary studies

Table WA17.A1.1 Database: Ovid MEDLINE,1946 to January Week 4 2024, searched on 9 February 2024

No.	Search	Results
1	Meningitis/ OR meningit*.mp. OR ((meningococc*) ADJ3 (infection* OR disease*))	77 047
2	Meningitis, Bacterial/ OR Meningitis, Escherichia coli/ OR Meningitis, Haemophilus/ OR Meningitis, Listeria/ OR Meningitis, Meningococcal/ OR Meningococcal Infections/ OR Meningitis, Pneumococcal/ OR Meningitis, Fungal/ OR Meningitis, Aseptic/ OR Meningitis, Viral/ OR ((Bacterial OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired OR Acute OR fulminat* OR Fulminant OR Sudden-onset) ADJ5 (meningiti*)).ti,ab,kw,kf OR (infectious-meningiti* OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi).ti,ab,kw,kf	1 413 432
3	Hearing Tests/ OR Acoustic Impedance Tests/ OR Audiometry/ OR ((Audiophonologic* OR otolaryngology OR auditory OR deafness OR acoustic* OR audiometr* OR hearing OR Speech OR audiologic* OR otoacoustic*) ADJ3 (investigation* OR examin* OR consultation* OR test* OR screening OR evaluation* OR assess* OR impedance* OR immittance* OR response* OR emission* OR diagnostic*)).ti,ab,kw,kf OR (audiologic-result* OR tympanomet* OR Audiogram* OR Audiometr* OR OAE-screening OR "visual reinforcement audiometry" OR "Behavioral observational audiometry" OR "auditory steady state response" OR "auditory brainstem response audiometry" OR "immittance audiometry"	76 036

	OR "Auditory brainstem response" OR "electric response audiometry").ti,ab,kw,kf	
4	1 and 2 and 3	273
5	(auto-inflamm* or autoimmun* or auto-immun* or Rheumatoid or Parkison* or Dementia or tubercul* or vaccin* or cryptococc* or Sarcoid* or Lupus).ti.	632 074
6	4 not 5	269
7	(letter or historical article or comment or editorial or news or case reports).pt.	4 474 001
8	6 not 7	212
9	animals/ not (animals/ and humans/)	5 157 355
10	8 not 9	190
11	limit 10 to yr="2003 -Current"	98

Table WA17.A1.2 Database: Embase (Elsevier), 1858 to present, searched on 9 February 2024

No.	Search	Results
1	('meningitis'/exp OR (meningiti* OR (Meningococc* NEAR/3 (infection* OR disease*))):ti,ab)	152 375
2	bacterial meningitis'/de OR 'epidemic meningitis'/exp OR 'Escherichia coli meningitis'/exp OR 'group B streptococcal meningitis'/exp OR 'Haemophilus meningitis'/exp OR 'leptospiral meningitis'/exp OR 'Listeria meningitis'/exp OR 'Lyme meningitis'/exp OR 'pneumococcal meningitis'/exp OR 'fungal meningitis'/exp OR 'HIV-associated meningitis'/exp OR 'parasitic meningitis'/exp OR 'virus meningitis'/exp OR 'aseptic meningitis'/exp OR 'Staphylococcus aureus'/exp OR 'Staphylococcus'/exp OR 'Enterobacteriaceae'/exp OR 'Streptococcus agalactiae'/exp OR 'Streptococcus pyogenes'/exp OR 'Enterovirus'/exp OR 'Herpesviridae'/exp OR 'herpes virus infection'/exp OR 'Simplexvirus'/exp OR 'Flavivirus'/exp OR 'West Nile virus'/exp OR 'Togaviridae'/exp OR 'Mumps'/exp OR 'Mumps virus'/exp OR 'Orthomyxoviridae'/exp OR 'HIV'/exp OR 'Adenoviridae'/exp OR 'Rubella'/exp OR 'Lymphocytic Choriomeningitis'/exp OR 'Rickettsiales'/exp OR 'Spirochaetales'/exp OR 'Leptospira'/exp OR 'Brucella'/exp OR 'Treponema pallidum'/exp OR 'Coxiella'/exp OR 'Mycoplasma'/exp OR 'Naegleria'/exp OR 'Angiostrongylus'/exp OR 'Coccidioides'/exp OR 'Candida'/exp OR 'Histoplasma'/exp OR 'Blastomyces'/exp OR 'Aspergillus'/exp OR 'Syphilis'/exp OR 'Lyme Disease'/exp OR 'Scrub Typhus'/exp OR ((Bacterial OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired OR Acute OR fulminat* OR Fulminant OR Sudden-onset) NEAR/5 (meningiti*)):ti,ab,kw,de OR (infectious-meningiti* OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix*	2 792 412

	OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi):ti,ab,kw,de	
3	acoustic impedance'/exp OR 'audiometry'/exp OR 'speech discrimination test'/exp OR 'hearing test'/exp OR 'spontaneous otoacoustic emission'/exp OR ((Audiophonologic* OR otolaryngology OR auditory OR deafness OR acoustic* OR audiometr* OR hearing OR Speech OR audiologic* OR otoacoustic*) NEAR/3 (investigation* OR examin* OR consultation* OR test* OR screening OR evaluation* OR assess* OR impedance* OR immittance* OR response* OR emission* OR diagnostic*)):ti,ab,kw,de OR (audiologic-result* OR tympanomet* OR Audiogram* OR Audiometr* OR OAE-screening OR "visual reinforcement audiometry" OR "Behavioral observational audiometry" OR "auditory steady state response" OR "auditory brainstem response audiometry" OR "immittance audiometry" OR "Auditory brainstem response" OR "electric response audiometry"):ti,ab,kw,de	136 577
4	#1 AND #2 AND #3	796
5	(auto-inflamm* OR autoimmun* OR auto-immun* OR Rheumatoid OR Parkison* OR Dementia OR tubercul* OR vaccin* OR cryptococc* OR Sarcoid* OR Lupus):ti	888 233
6	#4 NOT #5	686
7	[letter]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [note]/lim OR 'case report':de	11 307 131
8	#6 NOT #7	403
9	([animals]/lim NOT ([animals]/lim AND [humans]/lim))	6 459 575
10	#8 NOT #9	401
11	#10 AND [2003-2024]/py	254

Table WA17.A1.3 Database: Cochrane Library, 1995–present, searched on 9 February 2024

No.	Search	Results
1	MeSH descriptor: [Meningitis] explode all trees	856
2	(meningiti* OR (Meningococc* NEAR/3 (infection* OR disease))):ti,ab,kw	2985
3	MeSH descriptor: [Meningitis, Bacterial] explode all trees	524
4	MeSH descriptor: [Meningitis, Aseptic] explode all trees	10
5	MeSH descriptor: [Meningitis, Viral] explode all trees	18
6	MeSH descriptor: [Meningitis, Fungal] explode all trees	134
7	MeSH descriptor: [Meningitis, Meningococcal] explode all trees	214
8	MeSH descriptor: [Meningitis, Pneumococcal] explode all trees	60
9	MeSH descriptor: [Meningitis, Haemophilus] explode all trees	74
10	MeSH descriptor: [Meningitis, Listeria] explode all trees	0
11	MeSH descriptor: [Staphylococcus aureus] explode all trees	1173
12	MeSH descriptor: [Enterobacteriaceae] explode all trees	1789
13	MeSH descriptor: [Enterobacter] explode all trees	42
14	MeSH descriptor: [Escherichia coli] explode all trees	982
15	MeSH descriptor: [Streptococcus agalactiae] explode all trees	148
16	MeSH descriptor: [Streptococcus pyogenes] explode all trees	325
17	MeSH descriptor: [Enterovirus] explode all trees	244
18	MeSH descriptor: [Herpesviridae] explode all trees	1273
19	MeSH descriptor: [Herpesviridae Infections] explode all trees	3711
20	MeSH descriptor: [Simplexvirus] explode all trees	435
21	MeSH descriptor: [Flavivirus] explode all trees	280
22	MeSH descriptor: [West Nile virus] explode all trees	11

23	MeSH descriptor: [Togaviridae] explode all trees	110
24	MeSH descriptor: [Mumps] explode all trees	131
25	MeSH descriptor: [Mumps virus] explode all trees	39
26	MeSH descriptor: [Orthomyxoviridae] explode all trees	1363
27	MeSH descriptor: [HIV] explode all trees	4211
28	MeSH descriptor: [Adenoviridae] explode all trees	282
29	MeSH descriptor: [Rubella] explode all trees	206
30	MeSH descriptor: [Lymphocytic Choriomeningitis] explode all trees	1
31	MeSH descriptor: [Rickettsiales] explode all trees	49
32	MeSH descriptor: [Spirochaetales] explode all trees	246
33	MeSH descriptor: [Leptospira] explode all trees	12
34	MeSH descriptor: [Brucella] explode all trees	18
35	MeSH descriptor: [Treponema pallidum] explode all trees	29
36	MeSH descriptor: [Coxiella] explode all trees	10
37	MeSH descriptor: [Mycoplasma] explode all trees	122
38	MeSH descriptor: [Naegleria fowleri] explode all trees	0
39	MeSH descriptor: [Angiostrongylus] explode all trees	4
40	MeSH descriptor: [Coccidioides] explode all trees	5
41	MeSH descriptor: [Candida] explode all trees	587
42	MeSH descriptor: [Histoplasma] explode all trees	1
43	MeSH descriptor: [Blastomyces] explode all trees	0
44	MeSH descriptor: [Aspergillus] explode all trees	112
45	MeSH descriptor: [Syphilis] explode all trees	214
46	MeSH descriptor: [Lyme Disease] explode all trees	184

47	MeSH descriptor: [Scrub Typhus] explode all trees	20
48	((Bacterial OR bacteraemia OR Viral OR Fungal OR Aseptic OR Parasitic OR community-acquired OR Acute OR fulminat* OR Fulminant OR Sudden-onset) NEAR/5 (meningiti*)) OR (infectious-meningiti* OR Meningococc* OR Neisseria-meningit* OR N-Meningitidis OR Pneumococc* OR S-pneumoniae* OR Haemophilus-influenzae OR Listeri* OR L-monocytogenes OR Staphylococc* OR Staph-aureus OR Enterobacter* OR Enterococc* OR Escherichia-coli OR E-coli OR Streptococc* OR S-agalactiae* OR S-pyogenes OR Enterovir* OR Coxsackieviruses OR Herpesviridae OR Herpesvirus* OR herpes-virus* OR Varicella-zoster OR flavi-virus* OR Japanese-encephal* OR Tick-borne-encephal* OR Powassan-virus* OR West-Nile-virus OR Togaviridae OR Toga-virus* OR Togavir* OR equine-encephal* OR Bunyavirus* OR crosse-encephal* OR Toscana-virus* OR Reovirus* OR tick-fever* OR paramyxovir* OR Mumps OR morbillivirus* OR parainfluenza* OR Orthomyxovir* OR Influenza OR HIV OR human-immuno-deficienc* OR Adenoviridae OR adenovirus* OR Arenavir* OR Choriomeningit* OR LCMV OR Rickettsi* OR Orientia-spp OR Ehrlichia-spp OR spirochet* OR Borrelia-spp OR B-burgdorferi OR leptospir* OR Treponema-pallidum OR Brucell* OR Coxiella OR Mycoplasma OR spirillum* OR Naegleria OR angiostrongyl* OR Trichinella-spiralis* OR Candida OR Coccidioid* OR Histoplasm* OR Blastomyc* OR Sporothrix* OR Aspergill* OR Lyme OR Syphili* OR Scrub-Typhus OR tsutsugamushi)	67 049
49	#1 OR #2	3022
50	#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 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	235 770
51	#49 AND #50	2364
52	MeSH descriptor: [Acoustic Impedance Tests] explode all trees	186
53	MeSH descriptor: [Audiometry] explode all trees	1036
54	MeSH descriptor: [Audiometry, Evoked Response] explode all trees	51
55	MeSH descriptor: [Speech Discrimination Tests] explode all trees	109

56	MeSH descriptor: [Hearing Tests] explode all trees	1420
57	MeSH descriptor: [Otoacoustic Emissions, Spontaneous] explode all trees	102
58	((Audiophonologic* OR otolaryngology OR auditory OR deafness OR acoustic* OR audiometr* OR hearing OR Speech OR audiologic* OR otoacoustic*) NEAR/3 (investigation* OR examin* OR consultation* OR test* OR screening OR evaluation* OR assess* OR impedance* OR immittance* OR response* OR emission* OR diagnostic*)) OR (audiologic-result* OR tympanomet* OR Audiogram* OR Audiometr* OR OAE-screening OR "visual reinforcement audiometry" OR "Behavioral observational audiometry" OR "auditory steady state response" OR "auditory brainstem response audiometry" OR "immittance audiometry" OR "Auditory brainstem response" OR "electric response audiometry")	7085
59	#52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60	7239
60	#51 AND #61	16

Appendix 2. Extraction tool

The forms below show which data were extracted for the review.

Information about the study

Study period(s)

When was the study conducted?

e.g. 1990–1995

If it was conducted in one year, fill with single number (e.g. 2015).

Study period #2

If the study has more than one period, write the second period. If not, write NA.

Study design

Case-control study
Case series (> 5 cases)
Cohort study
Cross-sectional study
Randomized controlled trial
I don't know
Other

Population and disease information

Country

Afghanistan
Algeria
Angola
Argentina
Bangladesh
Brazil
Canada
China
Colombia
Congo (Democratic Republic of the)
Egypt
Ethiopia
France
Germany
Ghana
India
Indonesia

Islamic Republic of Iran
Iraq
Italy
Japan
Kenya
Malaysia
Mexico
Morocco
Mozambique
Myanmar
Nepal
Nigeria
Pakistan
Peru
Philippines
Poland
Republic of Korea
Russian Federation
Saudi Arabia
South Africa
Spain
Sudan
Thailand
Türkiye
Uganda
Ukraine
United Kingdom of Great Britain and Northern Ireland
United Republic of Tanzania
United States of America
Uzbekistan
Venezuela
Viet Nam
Other

Total sample size

Study population

Copy and paste any unusual features of patient population

Number of patients identified per age range

	Children < 18 y.o.	Adults > 18 y.o.
# of patients		

For ADULTS (> 18 y.o.) → please fill in the following information:

Number of patients with acute meningitis and meningitis-related hearing loss (HL)

	# of patients with meningitis	# of patients with meningitis TESTED for HL	# of patients with meningitis-related HL
Patients			

Timing of hearing loss diagnosis

Please select the option(s) of HL detection mentioned in the article.

before discharge
after discharge
unknown

Select the starting point from which hearing loss diagnosis was made

What is the point considered Day zero?

(e.g. If diagnosis of hearing loss was done 7 days after admission ≥ "ADMISSION" would be starting point)

from symptom onset
from meningitis diagnosis
from admission
from treatment
from discharge
other

Copy and paste the section from the article that describes the timing of hearing loss detection after the starting point.

Number of patients with acute meningitis and hearing loss (HL) by type of pathogen

Number of patients by infectious macro category

	# patients with meningitis	# patients with meningitis TESTED for HL	# patients with meningitis-related HL
Bacterial meningitis			
Viral meningitis			
Fungal meningitis			
Parasitic meningitis			
Unspecified meningitis (no etiology)			

Pathogen frequency in meningitis-related hearing loss (HL)

	# patients with meningitis	# patients with meningitis TESTED for HL	# patients with meningitis-related HL
Neisseria meningitidis			
Streptococcus pneumoniae			
***Haemophilus influenzae* type b (Hib)**			
***Streptococcus agalactiae* (GBS)**			

Method of diagnosing hearing loss

acoustic impedance test
audiometry/pure-tone audiometry
auditory brainstem response audiometry
auditory steady-state response
behavioural observational audiometry
computer conditioned play audiometry
conditioned play audiometry
evoked response audiometry
immittance audiometry
speech discrimination tests

spontaneous otoacoustic emissions (SOAEs)
transient-evoked otoacoustic emissions (TEOAEs)
visual reinforcement audiometry
other

Time to diagnosis of hearing loss

	# patients at admission	Admission time frame (DAYS)	# patients before discharge	Before discharge time frame (DAYS)	# of patients at discharge	Discharge timeframe (DAYS)	# patients after discharge	After discharge timeframe (DAYS)
Meningitis symptom onset								
Admission								
Meningitis diagnosis								
Treatment								
Discharge								

For CHILDREN (< 18 y.o.) → please fill in the following information

Fill in the blanks, according to each age group.

Number of patients with acute meningitis and meningitis-related hearing loss (HL) by AGE GROUP

	Children (not stratified)	1 mo. – 1 y.o.	> 1 y.o. - 5.y o.	> 5 y.o. –18 y.o.
# of patients with meningitis				
# of patients with meningitis TESTED for HL				
# of patients with meningitis-related HL				

Timing of hearing loss diagnosis

Please select the type(s) of HL detection mentioned in the article.

before discharge
after discharge
unknown

Select the starting point from which hearing loss diagnosis was made.

What is the point considered Day zero??

(e.g. if diagnosis of hearing loss was done 7 days after admission ≥ "ADMISSION" would be starting point)

from symptom onset
from meningitis diagnosis
from admission
from treatment
from discharge
other

Copy and paste the section from the article that describes the timing of hearing loss detection after the starting point.

Number of patients with ACUTE MENINGITIS by type of pathogen

Number of patients by infectious macro category

	Children (not stratified)	1 mo. – 1y.o.	> 1 y.o. – 5 y.o.	> 5 y.o. – 18 y.o.
Bacterial meningitis				
Viral meningitis				
Fungal meningitis				
Parasitic meningitis				
Unspecified meningitis (no etiology)				

Number of patients with meningitis-related hearing loss by type of pathogen

	Children (not stratified)	1 mo. – 1y.o.	> 1 y.o. – 5 y.o.	> 5 y.o. – 18 y.o.
Bacterial meningitis				
Viral meningitis				
Fungal meningitis				
Parasitic meningitis				
Unspecified meningitis (no etiology)				

Pathogen frequency in meningitis-related hearing loss

	Children (not stratified)	1 mo. – 1y.o.	> 1 y.o. – 5 y.o.	> 5 y.o. – 18 y.o.
Neisseria meningitis				
Streptococcus pneumoniae				
***Haemophilus influenzae* type b (Hib)**				

Group B streptococcus (GBS)	

Method of diagnosing hearing loss

acoustic impedance test
audiometry/pure-tone audiometry
auditory brainstem response audiometry
auditory steady-state response
behavioural observational audiometry
computer conditioned play audiometry
conditioned play audiometry
evoked response audiometry
immittance audiometry
speech discrimination tests
spontaneous otoacoustic emissions (SOAEs)
transient-evoked otoacoustic emissions (TEOAEs)
visual reinforcement audiometry
other

Time to hearing loss diagnosis

	#of patients at admission	Admission time frame (DAYS)	#of patients before discharge	Before discharge time frame (DAYS)	# of patients at discharge	Discharge time frame (DAYS)	# after discharge	After discharge time frame (DAYS)
Meningitis symptom onset								
Admission								
Meningitis diagnosis								
Treatment								
Discharge								

18. Rehabilitation for hearing loss

Authors

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Abbreviations

CAP	categories of auditory performance
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	Health-related Quality of Life scale
JBI	Joanna Briggs Institute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
WHO	World Health Organization

1. Background

Hearing loss is one of the most common sequelae of acute bacterial meningitis and can significantly impact the quality of life of individuals affected *(1, 2)*. Given the potentially devastating impact of hearing loss on an individual's communication, education, employment and social well-being, effective hearing rehabilitation is a crucial aspect of care for individuals recovering from acute meningitis. The field of hearing rehabilitation offers a wide array of interventions and strategies. However, the optimal strategies for hearing rehabilitation in the context of acute meningitis are not yet well defined.

This systematic review was conducted to address the critical question of hearing rehabilitation in individuals recovering from acute meningitis, as part of the development of the *WHO guidelines on meningitis diagnosis, treatment and care*. This systematic review aims to synthesize existing evidence on the efficacy of hearing rehabilitation interventions for people with hearing loss as a sequela following acute meningitis.

The protocol for this systematic review was published on PROSPERO *(3)*.

2. Methodology

2.1 Research question and study design

Among children and adults with hearing loss following acute meningitis from any cause, should hearing rehabilitation be provided to improve outcomes?

Population: Children and adults with acute meningitis from any cause, experiencing hearing loss as a sequela. Subgroups: Age group (child; adult).

Intervention: Hearing rehabilitation, defined as interventions to support optimal hearing and communication, including provision of and training in the use of assistive products for communication or hearing, as well as education, counselling and support, communication skills training, and education for caregivers.

Comparator: Care without hearing rehabilitation.

Outcomes

Critical outcomes (as prioritized by the Guideline Development Group):

1. functioning: speech perception (word and sentence) scores, categories of auditory performance (CAP), hearing test, speech production performance;
2. participation, defined as involvement in a life situation, e.g. going to school, undertaking work, having a family;
3. quality of life;
4. caregiver burden.

Important outcomes: secondary consequences (including speech delays or regression, behavioural issues).

Study designs: The following study designs were considered for inclusion:

1. Experimental and quasi-experimental studies
    - randomized controlled trials (RCTs).
2. Non-randomized studies of intervention
    - observational studies
    - cohort studies (retrospective, non-concurrent, and prospective).

Studies should have estimated the differences between the outcomes in the groups receiving the intervention of interest and those in the comparator arm.

2.2 Eligible studies

Published language: The intention was to include studies published in all languages.

Exclusion criteria: Studies that did not include a comparator group and any studies with incomparable groups (e.g. milder and severe cases in different arms) were excluded. Case reports, reviews, letters, expert opinions, commentaries and editorials, as well as unpublished, non-peer-reviewed literature, and records of registered, ongoing trials with no results (e.g. those from ClinicalTrials.gov) were also excluded.

2.3 Search strategy

The following databases were searched: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The reference lists of all the studies included were reviewed, and relevant studies were checked for additional references (see Appendix 1).

2.4 Selection of studies

First stage: Two of the authors independently screened titles and abstracts to determine which studies were eligible for full-text screening. Any disagreements were resolved by discussion or by referring to a third author.

Second stage: Two of the authors independently reviewed the full texts of potentially eligible studies to determine which studies would be eligible for the final selection. Any disagreements were resolved by discussion or by referring the matter to a third author.

Covidence software was used to screen the titles and abstracts, as well as the full text of the articles. The reference lists of the eligible articles were retrieved and screened. Moreover, a subject expert was asked to identify further articles that might be eligible for inclusion.

2.5 Data extraction and management

The data were extracted using a pilot-tested standardized data collection template. Two authors independently extracted data from the eligible records. In case of any disagreement, they discussed the matter in order to build consensus. If there was persistent disagreement, the opinion of a third author was considered binding.

The following data were extracted: surname of the first author, year of publication, country, region, sample size, enrolment period, details on population (eligibility criteria, number of post-meningitis patients, age group, mean age at diagnosis, mean duration of deafness, mean age at implantation, number of patients with neurological sequalae or learning disabilities) details on intervention (surgical technique, cochlear implant device, speech processing strategy, number with full or partial insertion, insertion method), length of follow-up, and outcomes reported.

2.6 Assessment of risk of bias in studies included in the review

The Joanna Briggs Institute (JBI) checklist was used for case series *(4-6)*. Two of the review authors independently assessed the risk of bias, with disagreements resolved by involving a third author.

2.7 Data synthesis

A meta-analysis of treatment effects could not be conducted due to a lack of appropriate studies. The results of the studies included were synthesized narratively and in tabular form in accordance with the SWiM (synthesis without meta-analysis) guidance *(7)*. Firstly, a study-specific table was constructed, detailing the effects of interventions and any potential influencing factors, as estimated in each study included. Next, information was aggregated across the studies to formulate a summary of findings for each intervention category and primary outcome *(7)*.

2.8 Assessment of certainty of evidence (GRADE evidence profiles)

Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles were not developed for this systematic review as no eligible evidence was identified. Please refer to the systematic review protocol for the description of the preplanned methods *(3)*.

2.9 Analysis of subgroups or subsets and investigation of heterogeneity

This analysis was not applicable to this review.

2.10 Deviations from the review protocol

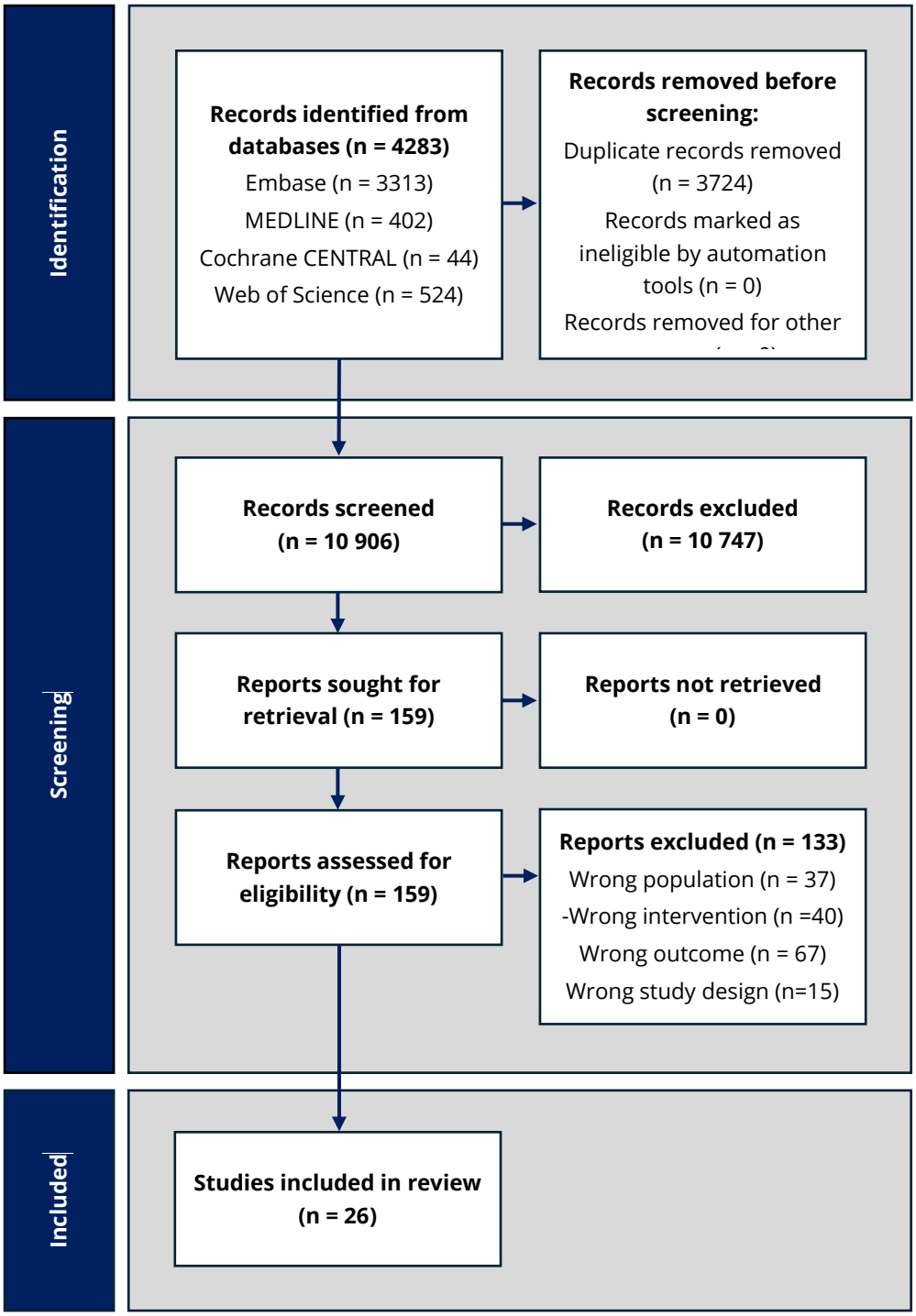
In the absence of studies with a comparator group, case series without a comparator group were included in the systematic review.

3. Results

3.1 Studies identified by the search process

The search yielded 14 630 titles and abstracts, all of which came from the electronic database search. After duplicates had been removed, 10 906 remained. Subsequently, 10 747 articles were excluded on the basis of the title and abstract, leaving 159 articles for review of the full text. Of these, 134 were excluded for the following reasons: wrong population (n = 37), wrong intervention (n = 40), wrong outcome (n = 68), wrong study design (n = 15). Twenty-six studies were included in the systematic review. The risk of bias assessment was performed using the JBI checklist for case series (see Appendix 2). Figure WA18.1 provides the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for this review.

Fig. WA18.1 PRISMA flow diagram for the systematic review



3.1.1 Studies included in the review

Table WA18.1 presents the characteristics of the studies included in the review.

Table WA18.1 Characteristics of studies included in the review

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Alshaikh (2019) *(8)*	Cross-sectional study	High	The operation was done on the right side; prosthesis was of the MED-EL type in 61.5% of cases, and Cochlear™ Nucleus for the remainder	Thirteen patients post-meningitis with profound degree of SNHL; No preoperative otitis media effusion; 93% males	No comparator	Functioning	Intraoperative and postoperative auditory response Speech recognition threshold	NA
Beadle (2005) *(9)*	Case series	Low	Surgical technique: not specified; Cochlear implant device: Nucleus 22; Pre-operative imaging (CT/MRI): not specified; Insertion method: not specified; Bilateral implantations: not specified	Eligibility criteria: bilateral profound deafness; Number of meningitis patients: 22; Subgroups: none; Prelingual deafness: not specified; Causative organism: not specified; Age group: children; Mean age at diagnosis (months): 20.4; Mean duration of deafness	No comparator	Functioning	Primary outcomes: CAP, SIR, mode of communication Secondary outcomes: re-implantation, schooling	Mean length of follow-up (months): 360 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				(months): not specified; Mean age at implantation (months): 60; Ossification: not specified; Number of patients with neurological sequalae or learning disabilities: 2				
Bertram (1995) *(10)*	Case series	High	Surgical technique: not specified; Cochlear implant device: Nucleus mini, Combi, Claricon Double Array; Speech processing strategy: not specified; Full insertion: not specified; Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: not specified	Eligibility criteria: obliteration of cochlea within first year of meningitis, age < 2 years at implantation; Number of meningitis patients: 33; Subgroups: none; Prelingual deafness: not specified; Causative organism: not specified; Age group: children; Mean age at diagnosis (months): 9.8 (n = 26); Mean duration of deafness (months): not specified; Mean age at implantation (months): 17.5 (n=26); Ossification:	No comparator	Functioning	Primary outcomes: modified Hannover hearing test (consists of 4 closed-set tests and 3 open-set tests) Secondary outcomes: intra-operative complications; post-operative complications; reimplantation	Mean length of follow-up (months): 36 months Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				26; Number of patients with neurological sequelae or learning disabilities: not specified				
Bille (2014) *(11)*	Case series	High	Surgical technique: not specified; Cochlear implant device: Nucleus CI24RE (n = 8), Nucleus C24CA (n = 1), Nucleus CI24R (n = 6), Nucleus Ci512 (n = 3), Nucleus CI24m (n = 3), CI+11+11+2M (n = 1); Speech processing strategy: not specified; Full insertion: 22 ears; Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: 10	Eligibility criteria: children < 15 years who underwent CI between December 1996 and January 2012; Number of meningitis patients: 22 (32 ears); Prelingual deafness: 18; Causative organism: *S. pneumoniae;* Age group: children; Mean age at diagnosis (months): 15; Mean duration of deafness (months): 32; Mean age at implantation (months): 46.9; Ossification: 8; Number of patients with neurological sequelae or learning disabilities: 7	No comparator	Functioning	Primary outcomes: CAP; SIR Secondary outcomes: post-operative complications	Mean length of follow-up (months): 41.6 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Cordero (2004) *(12)*	Case series	High	Surgical technique: not specified; Cochlear implant device: not specified; Speech processing strategy: not specified; Full insertion: 33 patients (permeable cochlea and partial ossification); Pre-operative imaging (CT/MRI): not specified; Insertion method: scala vestibuli (n = 2); Bilateral implantations: none	Eligibility criteria: not specified; Number of meningitis patients: 44; Subgroups: none; Prelingual deafness: 36; Causative organism: *S. pneumoniae* (n = 18), *N. meningitides* (n = 16), *H. influenzae* (n = 4), unknown (n = 6); Age group: children; Mean age at diagnosis (months): not specified; Mean duration of deafness (months): 55.5; Ossification: 15 (partial = 4, total = 11); Number of patients with neurological sequalae or learning disabilities: mild = 14, moderate = 6, severe = 8	No comparator	Functioning, participation	Primary outcomes: open-set speech perception measured using ESP and IT-MAIS Secondary outcomes: schooling	Mean length of follow-up (months): 36 Losses to follow-up: 16
Cushing (2009) *(13)*	Case series	Low	Nucleus 22, 24M, 24RCS, 24CA and 24RE devices (Cochlear	Study participants: 9 children with profound SNHL from confirmed bacterial	No comparator	Functioning	Vestibular end-organ function	NR

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			Corporation, Melbourne, Australia) were inserted by 2 staff oto-laryngologists. No child demonstrated middle ear effusion	meningitis; 1 was pending CI surgery, 6 had had CI surgery on the right, and 2 had had CI surgery on the left. The 2 boys and 7 girls ranged in age from 4.5 to 17.5 years (K, 10.1 T 4.6 years [SD]). At time of testing, those with CI were experienced users with ≥ 1 year of implant use (K, 6.5 T 2.9 years [SD]). Mean age at implantation was 2.6 years (T1.8 years [SD])			Horizontal canal function: caloric testing Horizontal canal function: rotational chair testing Saccular function: VEMP testing Static and dynamic balance Temporal bone imaging	
de Brito (2013) *(14)*	Retrospective cohort	Low	Nucleus-22 or Nucleus-24 cochlear implants for at least 1 year	26 post-meningitis patients; Male: (n = 14); Mean age (years) at the time of surgery: 30.5; Mean time (years) since the onset of deafness: 12.6 Nucleus-22 (7) Nucleus-24 (19)	No comparator	Functioning	Closed- and open-set speech recognition tests	NA

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Duarte (2014) *(15)*	Cross-sectional study	High	15 devices manufactured by Cochlear (Nucleus CI24M and 24M Contour) and 8 Advanced Bionics (Clarion) cochlear implants were used in group 1, while 42 Nucleus and 47 Clarion cochlear implants were used in group 2	Included 3 children with post-meningitis hearing loss	No comparator	Functioning, quality of life	Health-related Quality of Life (HRQoL) scale: Kidscreen-52	NA
Durisin (2008) *(16)*	Case series	Low	Surgical technique: mastoidectomy posterior tympanotomy; Cochlear implant device: not specified; Speech processing strategy: MPEAK (n = 2), ACE (n= 3), CIS/SAS (n = 22); Full insertion: 40 patients (group 1 = 17, group 2 = 23); Pre-operative imaging (CT/MRI): not specified; Insertion method: scala tympani; Bilateral implantations: 15	Eligibility criteria: not specified Number of meningitis patients: 60 (75 ears); Subgroups: group 1 = duration of deafness < 6 months (n=26), group 2 = duration of deafness > 6 months (n=34); Prelingual deafness: not specified; Causative organism: not specified; Age group: children; Mean age at diagnosis (months): group 1 = 31.2, group 2 = 9.48;	No comparator	Functioning	Primary outcomes: MAIS; MUSS; open- set test (common phrases); closed-set test (monosyllable words) Secondary outcomes: none	Mean length of follow-up (months): 36 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			(group 1 = 12, group 2 = 3)	Mean duration of deafness (months): group 1 = 2.4, group 2 = 45.6; Mean age at implantation (months): not specified; Ossification: not specified; Number of patients with neurological sequalae or learning disabilities: 22				
El-Kashlan (2003) *(17)*	Case series	Low	Surgical technique: facial recess approach; Cochlear implant device: not specified Speech processing strategy: not specified; Full insertion: 9 patients (group 1) Pre-operative imaging (CT/MRI): not specified; Insertion method: scala tympani (n = 9), circumodiolar drill-out (n = 7); Bilateral implantations: not specified	Eligibility criteria: perioperative documentation of cochlear ossification, pre-lingual onset of deafness, min. 2 years' experience with cochlear implant; Number of meningitis patients: 21; Subgroups: group 1 = minimal ossification (n=9), group 2 = partial insertion (n=5), group 3 = circumodiolar drill-out (n = 7); Prelingual deafness: 21; Causative organism:	No comparator	Functioning	Primary outcomes: pure-tone average; SPC; open-set speech perception Secondary outcomes: none	Mean length of follow-up (months): 24 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				S. pneumoniae. Age group: children; Mean age at diagnosis (months): group 1 = 15.6, group 2 = 13.2, group 3 = 13.2; Mean duration of deafness (months): 63.6 (group 1 = 56.4, group 2 = 67.2, group 3 = 69.6); Mean age at implantation (months): not specified; Ossification: 21 (partial = 8, total = 12); Number of patients with neurological sequalae or learning disabilities: not specified				
Francis (2004) *(18)*	Case series	Low	Surgical technique: not specified; Cochlear implant device: ABC clarion (n = 9), ABC HiFocus (n = 2), Nucleus 22 (n = 13), Nucleus 24 (n = 6); Speech processing strategy:	Eligibility criteria: severe to profound deafness, no benefit from hearing aids; Number of meningitis patients: 30; Subgroups: none; Prelingual deafness: 23; Causative	No comparator	Functioning	Primary outcomes: open-set speech discrimination measured using GASP, PBK and LNT; closed-set speech discrimination	Mean length of follow-up (months): 20.8 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			not specified; Full insertion: 26 patients; Pre-operative imaging (CT/MRI): not specified; Insertion method: not specified; Bilateral implantations: not specified	organism: *S. pneumoniae* (n = 12), *H. influenzae* (n = 1), *N. meningitidis* (n = 1), group B strep (n = 1), unknown (n = 15); Age group: children; Mean age at diagnosis (months): 16.8; Mean duration of deafness (months): 34.8; Mean age at implantation (months): 51.6; Ossification: 9			measured using WIPI, ESP, NU-CHIPS Secondary outcomes: none	
Helmstaedter (2018) *(19)*	Case series	Low	Surgical technique: mastoidectomy with posterior tympanotomy; Cochlear implant device: CI24M, CI24R, CI24REA; Speech processing strategy: not specified; Full insertion: 27 patients; Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: 8	Eligibility criteria: unilateral or bilateral deafness secondary to bacterial meningitis, no learning or motor disabilities, no bilateral sequential cochlear implantation, no syndromic conditions; Number of meningitis patients: 27 (35 ears); Subgroups: none; Prelingual deafness: not specified; Causative	No comparator	Functioning	Primary outcomes: open-set speech perception measured using Freiburger monosyllabic word test and HSM- sentence test	Mean length of follow-up (months): not specified (median = 103.2) Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				organism: not specified; Age group: children; Mean age at implantation (months): 103.2; Ossification: 15 ears; Number of patients with neurological sequalae or learning disabilities: none				
Lesinski-Schiedat (2004) *(20)*	Case series	High	15 devices manufactured by Cochlear (Nucleus CI24M and 24M Contour) and 8 Advanced Bionics (Clarion) cochlear implants were used in group 1, while 42 Nucleus and 47 Clarion cochlear implants were used in group 2	Mean age at time of implantation: 0.8 years (0.4–12 months) in group 1 and 1.6 years (1.0–2.0 years) in group 2; Etiology of deafness not identified in 40% of children in group 1 and 75% of those in group 2; Meningitis had occurred prior to implantation in 7 (30%) children in group 1 and 15 (15%) in group 2. Of the children in groups 1 and 2, 72.9% and 88% respectively had prior experience of	No comparator	Functioning	Speech understanding (open and closed set), MAIS, MUSS questionnaire	3, 6, 12, 18 and 24 months

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				conventional hearing aids				
Liu (2015) *(21)*	Case series	High	Surgical technique: not specified; Cochlear implant device: not specified; Speech processing strategy: not specified; Full insertion: 32 patients; Pre-operative imaging (CT/MRI): not specified Insertion method: scala tympani (n = 34), scala vestibuli (n = 1), circumodiolar drill-out (n = 4); Bilateral implantations: none	Eligibility criteria: deafness secondary to bacterial meningitis; Number of meningitis patients: 39; Subgroups: group 1 = ossified cochlea (n = 19), group 2 = non-ossified cochlea (n = 20); Age group: children; Mean age at diagnosis (months): group 1 = 18.54, group 2 = 32.35; Mean duration of deafness (months): group 1 = 20.15, group 2 = 38.92; Mean age at implantation (months): group 1 = 38.64, group 2 = 73.76; Ossification: 19; Number of patients with neurological sequalae or learning disabilities: not specified	No comparator	Functioning, participation	Primary outcomes: SPC; open-set speech perception Secondary outcomes: schooling	Mean length of follow-up (months): 89.8 Losses to follow-up: 3

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Mitchell (2000) *(22)*	Case series	Low	Surgical technique: not specified; Cochlear implant device: Nucleus 22; Speech processing strategy: MSP (n = 9), Spectra (n = 27); Full insertion: not specified; Pre-operative imaging (CT/MRI): not specified; Insertion method: not specified; Bilateral implantations: not specified; Bilateral implantations: not specified	Eligibility criteria: not specified; Number of meningitis patients: 36; Subgroups: group 1 = deafened by meningitis before age 2 years (n = 22), group 2 = deafened by meningitis after age 2 years (n = 14); Prelingual deafness: not specified; Causative organism: not specified; Age group: children; Mean age at diagnosis (months): group 1 = 14.3, group 2 = 48; Mean duration of deafness (months): group 1 = 20.9, group 2 = 17.9; Mean age at implantation (months): not specified; Ossification: not specified; Number of patients with neurological sequalae or learning disabilities: not specified	No comparator	Functioning	Primary outcomes: open-set speech perception; speech production performance Secondary outcomes: none	Mean length of follow-up (months): group 1 = 52.3, group 2 = 69.0 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
Mosnier (2012) *(23)*	Case series	Low	Surgical technique: not specified; Cochlear implant device: Nucleus 24 (n = 13), Freedom (n = 5), Hires 90K (n = 3), Combi 40+ (n = 2), Pulsar (n = 2); Speech processing strategy: Spectra 22 (n = 1), Sprint TM (n = 5), ESPrit TM (n = 5), ESPrit 3G (n = 2), Freedom (n = 5), Harmony (n=3), Tempo+ (n = 2), Opus 2 (n = 2); Full insertion: 20 patients (23 ears); Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: 5	Eligibility criteria: not specified; Number of meningitis patients: 22 (27 ears); Subgroups: group 1 = implanted between 1995 and 2001 (n = 11 ears), group 2 = implanted between 2002 and 2008 (n = 14 ears); Prelingual deafness: 0; Causative organism: not specified; Age group: adults; Mean age at diagnosis (months): not specified; Mean duration of deafness (months): 180; Mean age at implantation (months): group 1 = 564, group 2 = 492; Ossification: not specified; Number of patients with neurological sequalae or learning disabilities: 3	No comparator	Functioning	Primary outcomes: open-set test of speech comprehension (disyllabic words) Secondary outcomes: re-implantation	Mean length of follow-up (months): 42 Losses to follow-up: 2
Nikolopoulos (1997) *(24)*	Case series	Low	Surgical technique: not specified; Cochlear implant	Eligibility criteria: Not specified; Number of meningitis patients:	No comparator	Functioning	Primary outcomes: LiP scale	Mean length of follow-up (months): 12

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			device: Nucleus-22 channel; Speech processing strategy: not specified; Full insertion: not specified; Pre-operative imaging (CT/MRI): not specified; Insertion method: not specified; Bilateral implantations: not specified	47; Subgroups: none; Prelingual deafness: 47; Causative organism: not specified; Age group: children; Mean age at diagnosis (months): 16.8; Mean duration of deafness (months): 42; Mean age at implantation (months): 58.8; Ossification: not specified				Losses to follow-up: 0
Nikolopoulos (2006) *(25)*	Case series	Low	Surgical technique: not specified; Cochlear implant device: Nucleus; Speech processing strategy: not specified; Full insertion: not specified; Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: none	Eligibility criteria: prelingual deafness (onset < 3 years) bilateral profound deafness, age at implantation < 5.6 years, implanted with ≥ 15 electrodes; Number of meningitis patients: 46; Subgroups: none; Prelingual deafness: 46; Causative organism: not specified; Age group: children; Mean age at diagnosis (months): not specified (range: 12–	No comparator	Functioning, participation	Primary outcomes: CAP score; open-set speech perception measured using CDT; mode of communication Secondary outcomes: schooling	Mean length of follow-up (months): 60 Losses to follow-up: 2 for CAP measurements, 6 for CDT measurements

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				18); Mean duration of deafness (months): not specified; Mean age at implantation (months): 39.6; Ossification: not specified; Number of patients with neurological sequalae or learning disabilities: 11				
Parisier (1993) *(26)*	Case series	Low	Surgical technique: canal wall-up mastoidectomy and facial recess approach; Cochlear implant device: Nucelus-22 channel (n=20), 3M/House (n=2); Speech processing strategy: not specified; Full insertion: 17 patients; Pre-operative imaging (CT/MRI): yes; Insertion method: scala tympani; Bilateral implantations: not specified	Eligibility criteria: profound deafness; Number of meningitis patients: 22; Subgroups: none; Prelingual deafness: not specified; Causative organism: *S. pneumoniae* (n=13), *H. influenzae* (n=9); Age group: children; Mean age at diagnosis (months): 34.8; Mean duration of deafness (months): 44.4; Mean age at implantation (months): 91.2; Ossification: 19 (partial = 16, total = 3); Number of	No comparator	Functioning	Primary outcomes: modified CAP Secondary outcomes: none	Mean length of follow-up (months): 24 Losses to follow-up: 2

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				patients with neurological sequalae or learning disabilities: not specified				
Philippon (2010) *(27)*	Case series	Low	Surgical technique: not specified; Cochlear implant device: not specified; Speech processing strategy: Full insertion: 31 patients (group 1 = 20, group 2 = 11); Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: 2	Eligibility criteria: profound bilateral deafness; Number of meningitis patients: 40 (42 ears); Subgroups: group 1 = children (n = 27), group 2 = adults (n = 13); Prelingual deafness: not specified; Causative organism: *S. pneumoniae* (group 1 = 22, group 2 = 2), *N. meningitidis* (group 1 = 3), *H. influenzae* type b (group 1 = 1), *M. tuberculosis* (group 2 = 2), group B strep (group 2 = 2), unknown (group 1 = 1, group 2 = 8); Age group: children and adults; Mean age at diagnosis (months): not specified; Mean duration of deafness	No comparator	Functioning, participation	Primary outcomes: open-set speech discrimination measured using CAP score Secondary outcomes: none	Mean length of follow-up (months): 12 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				(months): group 1 = 25, group 2 = 336				
Rotteveel (2005) *(28)*	Case series	Low	Surgical technique: cochleostomy; Cochlear implant device: Nucleus 22 or Nucleus 24; Speech processing strategy: MPEAK, SPEAK, ACE (n = 4); Insertion: 18 patients; Pre-operative imaging (CT/MRI): yes; Insertion method: scala tympani; Bilateral implantations: not specified	Age at onset of deafness 0–3 years; hearing thresholds at 1, 2 and 4 kHz exceeding 95 dB HL, and no open-set speech perception; no/minor additional disabilities; normal non-verbal intelligence; 25 children	No comparator	Functioning	Open-set speech discrimination, overall equivalent hearing loss	Mean length of follow-up (months): 36 Losses to follow-up: 0
Roukema (2011) *(29)*	Case series	High	All patients were implanted with a Nucleus Freedom with Contour Advance electrode (C124RE [CA], Cochlear limited, Australia)	Patients younger than 9 months, who were selected for CI because of profound post-meningitis SNHL; Mean age at implantation: 6.5 months (range 4–8 months); All patients were implanted within a month of	No comparator	Functioning	Speech intelligibility rating (SIR) criteria CAP scores	48 weeks

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				diagnosis of SNHL (range 15–31 days)				
Saldaña (2019) *(30)*	Case series	Low	Surgical technique: promontory cochleostomy (n = 20); Cochlear implant device: not specified; Full insertion: 15 patients; Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: not specified	Eligibility criteria: severe or profound deafness, follow-up of at least 1 year (exclusion criteria: > 80% missing data); Number of meningitis patients: 21; Subgroups: group 1 = ossification (n = 11), group 2 = no ossification (n = 10); Prelingual deafness: not specified; Causative organism: *S. pneumoniae* (n = 18), viral (n = 2), unknown (n = 1); Age group: children; Mean age at diagnosis (months): not specified (group 1 median = 10, group 2 median = 27); Mean duration of deafness (months): not specified (group 1 median = 102, group 2 median =	No comparator	Functioning	Primary outcomes: CAP score; Ling + vowel test score; open-set test of word recognition Secondary outcomes: post-operative complication, schooling	Mean length of follow-up (months): 12 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				69); Mean age at implantation (months): not specified (group 1 median = 108, group 2 median = 390); Ossification: 11 (partial = 11); Number of patients with neurological sequalae or learning disabilities: 4				
Steenerson (1990) *(31)*	Case series	Low	Surgical technique: Gantz procedure used for patients with total ossification; Cochlear implant device: Nucleus 22; Speech processing strategy: Spectra/ SPEAK (n = 16), MPeak (n = 12); Full insertion: not specified; Pre-operative imaging (CT/MRI): yes; Insertion method: not specified; Bilateral implantations: not specified	Eligibility criteria: profound deafness, received a cochlear implant at the age of 2–17; Number of meningitis patients: 28; Subgroups: group 1 = no ossification (n = 6), group 2 = partial ossification (n = 16), group 3 = total ossification (n = 6); Prelingual deafness: not specified; Causative organism: *S. pneumoniae* (n = 6), *N. meningitidis* (n = 1), *H. influenzae* (n = 1), unknown	No comparator	Functioning	Primary outcomes: open-set speech perception measured using GASP; closed-set speech perception measured using WIPI; ESP category Secondary outcomes: re-implantation	Median length of follow-up (months): 69.96 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
				(n = 20); Age group: children; Mean age at diagnosis (months): 27, Mean duration of deafness (months): not specified (group 1 median = 62, group 2 median = 57, group 3 median = 18)				
Tokat (2017) *(32)*	Case series	High	Surgical technique: Retro auricular approach, simple mastoidectomy and posterior tympanotomy	27 (9 females and 18 males); Median age at implantation: 68 months); Median length of hearing aid use: 34 months	No comparator	Functioning	Speech intelligibility rating (SIR) criteria CAP scores	Median follow-up time after implantation: 60 to 210 months (median: 133 months).
van den Borne (1999) *(33)*	Case series	Low	Surgical technique: canal wall-up mastoidectomy; Cochlear implant device: Nucleus 22-channel; Speech processing strategy: not specified; Full insertion: 20 patients Pre-operative imaging (CT/MRI): yes; Insertion method: scala tympani; Bilateral	Eligibility criteria: profound bilateral deafness, no benefit from hearing aids; Number of meningitis patients: 25; Subgroups: group 1 = no ossification (n = 10), group 2 = partial ossification (n = 10), group 3 = total ossification (n = 5); Prelingual deafness: not specified; Causative organism:	No comparator	Functioning	Primary outcomes: overall equivalent hearing loss, mode of communication Secondary outcomes: middle or inner ear abnormalities,	Mean length of follow-up (months): 36 Losses to follow-up: 0

Lead author (year)	Study design	Overall risk of bias (study level)	Key details of intervention	Population (sample size: intervention/ control)	Comparator	Outcome domains with available data	Specific outcome measure	Time point of measurement
			implantations: not specified	*S. pneumoniae* (n = 18), *H. influenzae* type b (n = 5), *N. meningitidis* (n = 2); Age group: children; Mean age at diagnosis (months): 28.8; Mean duration of deafness (months): 46.8; Mean age at implantation (months): 75.6; Ossification: 15 (partial = 10, total = 5); Number of patients with neurological sequalae or learning disabilities: not specified			post-operative complications	

ACE: advanced combination encoders; CAP: categories of auditory performance; CAT: Callsign Acquisition Test; CDT: Connected Discourse Tracking; CI: cochlear implantation; CT: computed tomography; ESP: early speech perception; GASP: Glendonald auditory screening procedure; HRQoL: Health-related Quality of Life; HSM: Hochmair-Schulz-Moser test; IT-MAIS: infant-toddler meaningful auditory integration scale; LiP: listening profile; MRI: Magnetic Resonance Imaging; MPEAK: multi-peak coding strategy; MUSS: meaningful use of speech scale; NA: not applicable; NR; not reported; NU-CHIPS: Northwestern University Children's Perception of Speech ; SNHL: sensorineural hearing loss; SPC: statistical process control; SD: standard deviation; SIR: speech intelligibility rating; SPEAK: Spectral Peak coding Strategy; WIPI: Word Intelligibility by Picture Identification.

3.1.2 Studies excluded from the review

The following studies were excluded from the review: Adachi et al. *(34)*, Adoga et al. *(35)*, Ahmed et al. *(36)*, Aithal et al. *(37)*, Ajallouyean et al. *(38)*, Altuntaş et al. *(39)*, Amaral et al. *(40)*, Amirsalari et al. *(41)*, Arditi et al. *(42)*, Arndt et al. *(43)*, Arteta-Acosta et al. *(44)*, Aschendorff et al. *(45)*, Babjee et al. *(46)*, Badenhorst et al. *(47)*, Baig et al. *(48)*, Baker et al. *(49)*, Baldwin et al. *(50)*, Baraff et al. *(51)*, Battmer et al. *(52)*, Becker et al. *(53)*, Beijen et al. *(54)*, Bent et al. *(55)*, Bento et al. *(56)*, Berg et al. *(57)*, Bergman et al. *(58)*, Bergman et al. *(59)*, Berliner et al. *(60)*, Berlow et al. *(61)*, Bessa et al. *(62)*, Beynon et al. *(63)*, Bille et al. *(11)*, Boivin et al. *(64)*, Bozzola et al. *(65)*, Briand et al. *(66)*, Bringas et al. *(67)*, Brookhouser et al. *(68)*, Bruijnzeel et al. *(69)*, Bucci et al. *(70)*, Byckova et al. *(71)*, Calháu et al. *(72)*, Callanan et al. *(73)*, Carroll & Carroll *(74)*, Caye-Thomasen et al. *(75)*, Charuvanij et al. *(76)*, Chen et al. *(77)*, Chiesa Estomba et al. *(78)*, Chin et al. *(79)*, Chinchankar et al. *(80)*, Christie et al. *(81)*, Christie et al. *(82)*, Ciorba et al. *(83)*, Damico et al. *(84)*, Daneshi et al. *(85)*, Daneshi et al. *(86)*, Da Silva et al. *(87)*, Dhawan et al. *(88)*, Dodds et al. *(89)*, Dodge et al. *(90)*, Doherty & Luxford *(91)*, Douglas et al. *(92)*, Dowell et al. *(93)*, Dupuis et al. *(94)*, Edmond et al. *(95)*, Edmond et al. *(96)*, Edwards & Roberts *(97)*, El Tahir et al. *(98)*, Enteria & Florschutz *(99)*, Faber & Grøntved *(100)*, Farinetti et al. *(101)*, Fraga et al. *(102)*, Francis et al. *(18)*, Geier et al. *(103)*, Grayeli et al. *(104)*, Green et al. *(105)*, Gröger et al. *(106)*, Gunes et al. *(107)*, Halawani et al. *(108)*, Hasanalifard et al. *(109)*, Haßkamp et al. *(110)*, Heman-Ackah et al. *(111)*, Jadia et al. *(112)*, Jesus et al. *(113)*, Jiang et al. *(114)*, Kanchanalarp et al. *(115)*, Kazemi et al. *(116)*, Kecskeméti et al. *(117)*, Khanna et al. *(118)*, Khowaja et al. *(119)*, Kileny & Zwolan *(120)*, Krakow *(121)*, Lemnos et al. *(122)*, Loundon et al. *(123)*, Lundin et al. *(124)*, Mason et al. *(125)*, McCulloch et al. *(126)*, Miotto *(127)*, Niparko et al. *(128)*, Onifade et al. *(129)*, Pandey et al. *(130)*, Pappas *(131)*, Patarapak et al. *(132)*, Peixoto et al. *(133)*, Percy-Smith et al. *(134)*, Persson et al. *(135)*, Proops et al. *(136)*, Rachovitsas et al. *(137)*, Rajati et al. *(138)*, Ratnayake et al. *(139)*, Reynard et al. *(140)*, Richardson et al. *(141)*, Rubin & Papsin *(142)*, Ruffin et al. *(143)*, Rugemalira et al. *(144)*, Stark et al. *(145)*, Stolle et al. *(146)*, Sumpter et al. *(147)*, Thomas & Cheshire *(148)*, Tobey et al. *(149)*, Tomioka et al. *(150)*, Trotić et al. *(151)*, Tubiana et al. *(152)*, Türel et al. *(153)*, Tzortzi et al. *(154)*, Uppal et al. *(155)*, Waltzman et al. *(156)*, Welch et al al. *(157)*, West et al. *(158)*, Yetiser & Karaman *(159)*, Yücel et al. *(160)*, Zaidman-Zait et al. *(161)*, Zanoni et al. *(162)* and Zhu et al. *(163)*.

4. Summary of findings

4.1 Narrative description of intervention effects

The systematic review included 26 studies conducted between 1990 and 2019, all of which were case series. A total of 715 patients with post-meningitis hearing loss were included, and more than 720 cochlear implants were issued. All except two studies involved children, and one study included both children and adults. In terms of methodological quality, 17 studies were considered to have a low risk of bias.

The most commonly reported outcome measures included open speech perception and categories of auditory performance (CAP), which assess factors such as sound detection, discrimination and speech recognition. Speech intelligibility ratings, which evaluate the clarity and understanding of speech following cochlear implantation, were also reported.

4.1.1 Outcome 1: Functioning (auditory performance)

Across all 26 studies reporting audiological outcomes, the effect of cochlear implantation was observed to be consistently positive in improving auditory outcomes. The reporting methods and follow-up durations varied considerably.

The most commonly used outcome measures were open-set speech perception scores (16 studies) and CAP (8 studies). Notably, two studies indicated a statistically significant inclination towards better audiological outcomes with full electrode insertion compared to partial insertion.

Only 10 studies provided information on pre-implantation hearing status, thereby allowing a comparison of pre- and post-implantation status.

4.1.2 Outcome 2: Participation

Educational outcomes following cochlear implantation were reported in four studies; specifically, participation in mainstream schooling or specialized educational settings. In studies that reported participation, the majority of children transitioned to mainstream education, with some progressing to higher-level education and securing full-time employment after more than 10 years of cochlear implant use.

4.1.3 Outcome 3: Quality of life

One study (61 participants, 44 patients with hearing loss, of which three acquired it following a bout of meningitis) reported on the quality of life after cochlear implantation. This was a cross-sectional study that included three groups: prelingually implanted deaf children and adolescents; prelingually deaf children and adolescents without implants; and normal-hearing children and adolescents. All the subjects included were aged 8–18 years and attended school in Portugal. The researchers used Kidscreen 52 for assessing

the health-related quality of life (HRQoL) of the children and adolescents and concluded that cochlear implantation appeared to improve their perceived quality of life. The HRQoL scores reported were higher in hearing children, followed by deaf children with implants and finally by deaf children without implants, in almost all dimensions.

4.1.4 Complications

Post-operative complications were rare. Five studies documented complications such as implant infection, facial nerve stimulation and otitis media, all of which occurred in less than 0.5% of the study population. Device failure and reimplantation were also rare, occurring in a total of 13 and 15 patients respectively out of the total (0.2%).

Evidence on other hearing rehabilitation interventions, such as hearing aids, assistive listening devices and bone conduction hearing devices, was not reported in post-meningitis patients.

Despite the lack of comparative studies, the collective findings suggest the potential efficacy of cochlear implantation in enhancing auditory function among individuals with post-meningitis hearing loss.

4.1.5 Changes in outcomes after intervention

Table WB18.2 presents the outcomes reported in studies reporting changes in outcomes after intervention.

Table WB18.2 Outcomes reported for studies reporting changes in outcomes after intervention

Lead author (year), Country	Pre-operative outcome	Post-operative outcome	Direction of effect
Beadle (2005), United Kingdom of Great Britain and Northern Ireland *(9)*	CAP score: 0 SIR score: 1.2	CAP score: 6.1 SIR score: 3.9 Mode of communication (no. of patients): oral: 15 Re-implantation: 7 (device failure = 7) Schooling: mainstream school or college: 7; unit or special class within mainstream school: 4; special school or college: 7; university: 2; engineer = 1	Positive
Durisin (2008), Germany *(16)*	MAIS (% alert to sound): group 1: 1; group 2: 18$ MUSS (% with vocal control): group 1: 32.5; group 2: 25 group 1: 17.5; group 2: 5 MUSS (% use of communication strategies): group 1: 17.5; group 2: 2.5 Open-set test of common phrases (% correct): group 1: 0, group 2: 0 Open-set test of monosyllable words (% correct): group 1: 0; group 2: 7.5	MAIS (% alert to sound): group 1: 70; group 2: 92.5 MUSS (% with vocal control): group 1: 72.5; group 2: 92.5 MUSS (% use of speech only): group 1: 55; group 2: 77.5 MUSS (% use of communication strategies): group 1: 55; group 2: 65 Open-set test of common phrases (% correct): group 1: 60; group 2: 45 Open-set test of monosyllable words (% correct): group 1: 57; group 2: 63	Positive
El-Kashlan (2003), USA *(17)*	SPC category: overall: 0.7; group 1: 0.8; group 2: 0.6; group 3: 0.6 Pure-tone average (dB): overall: no response; group 1: no response; group 2 = 116; group 3 = 115	SPC category: overall: 3.3; group 1 = 3.6; group 2 = 3.2; group 3 = 3.0; SPC category (long-term follow-up): group 1: 3.8 (follow-up: 7.3 years); group 2 = 3.6 (follow-up: 9.3 years); group 3 = 3.7 (follow-up: 7.1 years) Open-set speech perception (no. of patients who achieved): 0	Positive

Lead author (year), Country	Pre-operative outcome	Post-operative outcome	Direction of effect
Francis (2004), USA *(18)*	Closed-set speech perception (no. of patients who achieved categories 1–4 inclusive): 27 (category 1: 25; category 2: 2; category 3: 0; category 4: 0) Open-set speech perception (no. of patients who achieved category 5 or 6): 2 (category 5: 2; category 6: 0)	Closed-set speech perception (no. of patients who achieved categories 1–4 inclusive): 16 (category 1: 7; category 2: 0; category 3: 1; category 4: 8). 9 of 13 (69.2%) patients with neurological sequelae achieved close-set speech perception. Open-set speech perception (no. of patients who achieved category 5 or 6): 14 (category 5: 1; category 6: 13). 5 of 11 (45.5%) patients with neurological sequelae achieved open-set speech perception.	Positive
Liu (2015), USA *(21)*	SPC category: overall: 0.82 (n = 34); group 1: 0.65 (n = 17); group 2: 1.00 (n = 17)	SPC category: overall: 4.25; group 1: 3.35; group 2: 5.05 Open-set speech perception (no. of patients who achieved): 18 (group 1: 5; group 2: 13) Schooling: group 1: mainstream school: 4; special school: 13; group 2: mainstream school: 12; special school: 6 (n = 35)	Positive
Mitchell (2000), Australia *(22)*	Detection of phenomes: group 1: 36.1% (95% CI: 28.1–44.0); group 2: 48.8% (95% CI: 36.1–61.6)	Open-set speech perception (no. of patients who achieved): group 1: 11; group 2: 14 Good speech production performance at 3–4 years (no. of patients who achieved A or B rating): group 1: 11; group 2: 14	Positive
Mosnier (2013), France *(23)*	Open-set test of identification of disyllabic words (% correct): group 1: 2 (SD: 1.7); group 2: 5 (SD: 3.4)	Open-set test of identification of disyllabic words (% correct): group 1: 32; group 2: 70 Re-implantation: 1 (device failure = 1)	Positive
Nikolopoulos (2006), United Kingdom and Greece *(25)*	Open-set speech perception measured using CDT (correct words/min): 0 CAP score: 0	Open-set speech perception measured using CDT (correct words/min) at 3 years: 22 (n = 40) CAP score at 5 years: 6 (n = 44) Mode of communication at 5 years (no. of patients): oral communication: 29 (67%); sign communication: 14 (33%)	Positive

Lead author (year), Country	Pre-operative outcome	Post-operative outcome	Direction of effect
		Open-set speech perception of patients with neurological sequalae or learning disabilities measured using CDT at 5 years (correct words/min): no neurological sequalae or learning disabilities: 60 (range: 0–91); neurological sequalae or learning disabilities: 38 (range: 0–58) Schooling: mainstream school: 13; unit or special class within mainstream school: 27; special school: 4	
Rotteveel (2005), the Kingdom of the Netherlands *(28)*	Open-set speech perception (no. of patients who achieved): 0	Open-set speech perception (no. of patients who achieved): 4 Overall equivalent hearing loss (dB HL): group 1: 112; group 2: 79.5	Positive
Saldaña (2019), Argentina *(30)*	Open-set test of word recognition (% correct): group 1: 0; group 2: 0 CAT score: group 1: 0.36 (SD: 0.5); group 2: 0.60 (SD: 0.52) Ling + vowel test score: group 1: 0.18 (SD: 0.6); group 2: 0.30 (SD: 0.48)	Open-set test of word recognition (% correct): group 1: 27.6 (SD: 36.4); group 2: 52.0 (SD: 31.1) CAT score: group 1: 2.73 (SD: 1.62); group 2 = 4.70 (SD = 2.31); *P* = 0.036 Ling + vowel test score: group 1: 1.55 (SD: 0.69); group 2: 1.70 (SD: 0.67) Post-operative complications: tinnitus (n = 1) Schooling: special school: 10 (group 1: 8; group 2: 2)	Positive

CAP: categories of auditory performance; CAT: Callsign Acquisition Test; CDT: Connected Discourse Tracking; CI: confidence interval; ESP: early speech perception; GASP: Glendonald auditory screening procedure; HSM: Hochmair-Schulz-Moser test; IT-MAIS: infant-toddler meaningful auditory integration scale; LiP: listening profile; MUSS: meaningful use of speech scale; SD: standard deviation; SIR: speech intelligibility rating; SPC: statistical process control; WIPI: Word Intelligibility by Picture Identification.

4.2 GRADE evidence profile

Due to a lack of studies with a comparator group, a GRADE evidence profile could not be constructed.

4.3 Research gaps

The present systematic review revealed the absence of studies with comparator groups, including RCTs and cohort studies. The existing literature consists predominantly of case series on cochlear implants, which limits the ability to draw robust conclusions regarding the efficacy of hearing rehabilitation interventions. While conducting placebo-controlled trials may not be feasible, further research could address the need to obtain the magnitude of effect through observational studies.

The body of evidence has variable reporting, with a lack of consistency in the outcome measures reported. This further reduced the amenability of the data to be synthesized quantitatively. The risk-of-bias assessment for the case series was unclear for a number of domains (Appendix 2).

Furthermore, there is a notable absence of research exploring the effectiveness of interventions or assessing patient values and preferences in the context of post-meningitis hearing loss rehabilitation. Research gaps also include case control studies on the use of hearing aids and on caregiver burden.

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Appendix 1. Search strategy used to identify primary studies

Database: MEDLINE (Ovid), including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE, 1946 to 20 December 2023

Search strategy

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1 exp Meningitis/ (59072)

2 meningit*.mp. (81339)

3 1 or 2 (92595)

4 exp Rehabilitation/ (357698)

5 ((occupational or speech or language) adj3 therap*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] (37518)

6 rehab*.mp. (384674)

7 exp Self-Help Devices/ (13441)

8 (Self-help-device* or assistive-device*).mp. (8589)

9 assistive technology.mp. (2998)

10 vision*.mp. (215823)

11 exp Hearing Loss/ (78933)

12 (hear or hearing or deaf* or communicat* or auditor*).mp. (805326)

13 or/4-12 (1599940)

14 3 and 13 (4381)

15 limit 14 to (case reports or comment or editorial or "review") (1936)

16 14 not 15 (2445)

Database: Embase (OVID), 1974 to 20 December 2023

Search strategy

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1 exp meningitis/ (109903)

2 meningit*.mp. (114236)

3 1 or 2 (137495)

4 exp rehabilitation/ (496413)

5 ((occupational or speech or language) adj3 therap*).mp. (60312)

6 rehab*.mp. (462338)

7 rehabilitation equipment/ or exp self help device/ (3972)

8 (Self-help-device* or assistive-device*).mp. (7267)

9 assistive technology.mp. or assistive technology/ (5869)

10 vision*.mp. (330423)

11 exp hearing impairment/ (120762)

12 (hear or hearing or deaf* or communicat* or auditor*).mp. (1135685)

13 or/4-12 (2155142)

14 3 and 13 (11001)

15 limit 14 to (editorial or letter or "review") (1764)

16 14 not 15 (9237)

17 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1234951)

18 Animal experiment/ not (human experiment/ or human/) (2594124)

19 17 or 18 (2664622)

20 16 not 19 (9101)

Appendix 2. Risk of bias of studies included, assessed using JBI checklist

Table WA18.A2.1 Risk-of-bias assessment of studies included (using JBI checklist)

Lead author (year)	Criteria for inclusion	Condition measured in a standard, reliable way	Valid methods used for identification of the condition	Consecutive inclusion of participants	Complete inclusion of participants	Clear reporting of the demographics of the participants	Clear reporting of clinical information	Outcomes or follow-up results of cases clearly reported	Clear reporting of the presenting site(s)/ clinic(s) demographic information	Statistical analysis appropriate
Alshaikh (2019) *(8)*	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes
Beadle (2005) *(9)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Bertram (1995) *(10)*	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Bille (2014) *(11)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Cordero (2004) *(12)*	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Cushing (2009) *(13)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
de Brito (2013) *(14)*	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes

Lead author (year)	Criteria for inclusion	Condition measured in a standard, reliable way	Valid methods used for identification of the condition	Consecutive inclusion of participants	Complete inclusion of participants	Clear reporting of the demographics of the participants	Clear reporting of clinical information	Outcomes or follow-up results of cases clearly reported	Clear reporting of the presenting site(s)/ clinic(s) demographic information	Statistical analysis appropriate
Duarte (2014) *(15)*	Yes	Yes	Yes	No	Unclear	Yes	Yes	No	Yes	Yes
Durisin (2008) *(16)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
El-Kashlan (2003) *(17)*	Unclear	Unclear	Unclear	No	No	Yes	Yes	Unclear	Unclear	Yes
Francis (2004) *(18)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Helmstaedter (2018) *(19)*	Yes	Yes	Yes	unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Lesinski-Schiedat (2004) *(20)*	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes
Liu (2015) *(21)*	No	Yes	Yes	No	No	Yes	Yes	Unclear	Unclear	Yes
Mitchell (2000) *(22)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Mosnier (2012) *(23)*	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Nikolopoulos (1997) *(24)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Lead author (year)	Criteria for inclusion	Condition measured in a standard, reliable way	Valid methods used for identification of the condition	Consecutive inclusion of participants	Complete inclusion of participants	Clear reporting of the demographics of the participants	Clear reporting of clinical information	Outcomes or follow-up results of cases clearly reported	Clear reporting of the presenting site(s)/ clinic(s) demographic information	Statistical analysis appropriate
Nikolopoulos (2006) *(25)*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Parisier (1993) *(26)*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Philippon (2010 *(27)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Rotteveel (2005) *(28)*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Roukema (2011) *(29)*	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes
Saldaña (2019) *(30)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Steenerson (1999) *(31)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Tokat (2017) *(32)*	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
van den Borne (1993) *(33)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes

These studies are the same (and in the same order) as references nos. 8–33 in the main reference list (see also Table WA18.1).

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