National Institute for Health and Care Excellence

Final

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

[E6] Evidence review for antibiotics for bacterial meningitis caused by Neisseria meningitidis

NICE guideline NG240

Evidence review underpinning recommendations 1.6.4, 1.6.15 and 1.6.16 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Antibiotics for bacterial meningitis caused by Neisseria meningitidis

Review question

What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Introduction

Bacterial meningitis is a rare but serious infection. The causative organism is usually confirmed by tests performed on cerebrospinal fluid or blood samples. Neisseria meningitidis is a common cause of bacterial meningitis in all age groups.

The aim of this review is to determine what antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis caused by Neisseria meningitidis
Intervention	Antibiotic agent of interest: • Cefotaxime • Ceftriaxone • Benzylpencillin sodium • Amoxicillin • Ampicillin • Ciprofloxacin • Moxifloxacin • Levofloxacin • Chloramphenicol • Meropenem
Comparison	**Stage 1 (all antibiotic agents of interest):** • Antibiotic agent A (single or combination) vs Antibiotic agent B (single or combination) **Stage 2 (antibiotic agents identified during stage 1 as most effective/for use where there are contraindications)** • Antibiotic agent A – Dose A vs Antibiotic agent A – Dose B • Antibiotic agent A – Duration of administration A vs Antibiotic agent A – Duration of administration B • Antibiotic agent A – Short infusion vs Antibiotic agent A – Extended infusion
Outcome	**Critical** Population: adults, children and infants • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural

	deficits*; measured from discharge up to 1 year after discharge) Population: adults • Functional impairment (measured by any validated scale at any time point) Population: children and infants • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) **Important** Population: adults, children and infants • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • CSF sterilisation (defined as treatment failure, time-to-sterilisation or delay). Population: adults • Intracranial collections as a complication (defined as abscess or empyema) Population: children and infants • Functional impairment (measured by any validated scale at any time point) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

CSF: cerebrospinal fluid; MDI: mental development index; PDI: psychomotor development index; SD: standard deviation

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

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

Effectiveness evidence

Included studies

Four studies were included for this review: 1 retrospective cohort study (Isaacs 1988), and 3 randomised controlled trials (RCTs: Marhoum el Filali 1993; Molyneux 2011; Tuncer 1988).

The included studies are summarised in Table 2.

Two studies compared ceftriaxone to benzylpenicillin sodium (Marhoum el Filali 1993; Tuncer 1988). One study compared 5-day benzylpenicillin sodium therapy to >5-day benzylpenicillin sodium therapy (Isaacs 1988) and did not adjust for confounding factors. One study compared 5-day ceftriaxone therapy to 10-day ceftriaxone therapy (Molyneux 2011).

Two studies were conducted in babies and children (Molyneux 2011; Tuncer 1988), and 1 study was conducted in adults (Marhoum el Filali 1993). One study was conducted in both children and adults (Isaacs 1988).

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Isaacs 1988 Retrospective cohort study New Zealand	N=35 Patients aged ≥14 years with meningitis caused by N. meningitidis Age in years (mean; SD): 28 (14) Case-fatality: 0%	5-day benzylpenicillin sodium therapy IV benzylpenicillin sodium for 5 days	>5-day benzylpenicillin sodium therapy IV benzylpenicillin sodium for average duration of 8.5 days	• All-cause mortality • Any long-term neurological impairment • Hearing impairment	Frequency and dose of medication were not described.
Marhoum el Filali 1993 RCT Morocco	N=36 Adults aged >16 years with meningitis caused by N. meningitidis Age in years (mean; SD): 29 (14) Case-fatality: 6%	Ceftriaxone IV ceftriaxone 2g once daily for 2 days	Benzylpenicillin sodium IV penicillin G 300,000 IU/kg/day every 4 hours for 6 days	• All-cause mortality • Any long-term neurological impairment • CSF sterilisation	Population is indirect due to 28% of population with unknown cause of meningitis
Molyneux 2011 RCT Bangladesh, Egypt, Malawi, Pakistan and Vietnam	N. meningitidis N=73 (whole study N=1004) Babies and children aged 2 months to 12 years with meningitis	5-day ceftriaxone therapy IV ceftriaxone 80-100 mg/kg once daily for 5 days	10-day ceftriaxone therapy IV ceftriaxone 80-100 mg/kg once daily for 10 days	• All-cause mortality • Any long-term neurological impairment • Developme-ntal delay • Hearing impairment • Serious	Population is indirect for all outcomes except for all-cause mortality and CSF sterilisation due to 93% of population

Study	Population	Intervention	Comparison	Outcomes	Comments
	caused by H. influenzae, S. pneumoniae, or N. meningitidis* Age in months (mean; SD): 38 (42) Case-fatality: 4% *N. meningitidis is causative organism of interest for this review			intervention-related adverse effects • CSF sterilisation	with meningitis caused by organisms other than N. meningitidis
Tuncer 1988 RCT Turkey	N=42 Babies and children aged 1 month to 12 years with N. meningitidis infection Age (range): 1 month to 12 years Case-fatality: 7%	Ceftriaxone IV ceftriaxone 80-100 mg/kg once daily for 4 days	Benzylpenicillin sodium IV penicillin G 500,000 units/kg/day in 6 divided doses for 5 days	• All-cause mortality • CSF sterilisation	Population is indirect due to 33% of population with meningo-coccaemia alone

CSF: cerebrospinal fluid; IV: intravenous; RCT: randomised controlled trial; SD: standard deviation

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

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

The evidence was assessed as being very low quality due to risk of bias (arising from the randomisation process due to lack of information about allocation concealment, subjective measurement of the outcome, deviations from the intended interventions, missing outcome data and failure to adjust for confounding factors), seriously imprecise findings due to small

number of events and the inclusion of indirect populations and outcomes. The evidence was stratified by age.

The evidence showed no important differences between ceftriaxone and benzylpenicillin sodium for mortality or cerebrospinal fluid (CSF) sterilisation in babies and children, or for mortality, neurological impairment, or CSF sterilisation in adults.

The evidence also showed no important differences between 5-day and 10-day ceftriaxone treatment for all-cause mortality, neurological impairment, developmental delay, hearing impairment, serious intervention-related adverse effects, or CSF sterilisation in babies and children.

Finally, the evidence showed no important differences between shorter (5-day) and longer (>5 day) durations of benzylpenicillin sodium therapy for mortality, neurological impairment, or hearing impairment in children and adults.

No eligible studies were identified that reported functional impairment, or intracranial collections as a complication (for example, abscess or empyema).

See appendix F for full GRADE tables.

Economic evidence

Included studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Bacterial meningitis is associated with high rates of mortality and morbidity, and antibiotics are the mainstay of treatment for bacterial meningitis. Therefore, all-cause mortality and long-term neurological impairment were prioritised as critical outcomes due to the severity of these outcomes. Severe developmental delay was prioritised over functional impairment in children and babies, as it is a more relevant and important outcome for this population. Functional impairment was prioritised as a critical outcome in adults due to the concern about the potential long-term limitations of bacterial meningitis on the ability to carry out certain activities of daily life.

In addition to functional impairment (in children and babies), hearing impairment, serious intervention-related adverse effects, and CSF sterilisation were selected as important outcomes in all age groups as these are relatively common after bacterial meningitis and may be related to antibiotic therapy. Intracranial collections as a complication was also included as an important outcome for adults as this is a rare but severe and life threatening complication of bacterial meningitis that may require prolonged antibiotic treatment.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence for all outcomes identified in this review was very low quality, and the main reasons for downgrading the evidence were risk of bias (for example, arising from the randomisation process due to lack of information on allocation concealment, subjective measurement of the outcome, deviations from the intended interventions, missing outcome data due to attrition and failure to adjust for confounding factors), imprecision (due to wide confidence intervals and small number of events), and indirectness (of either population, outcome or both).

No evidence was found that reported functional impairment or intracranial collections as a complication.

Benefits and harms

The committee considered the evidence comparing ceftriaxone and benzylpenicillin sodium for the treatment of meningitis caused by Neisseria meningitidis (meningococcal meningitis), that showed no important differences for mortality, neurological impairment, or CSF sterilisation. However, the committee noted that this evidence came from 2 small and old RCTs. No other evidence was identified comparing the effectiveness of different antibiotics for the treatment of meningococcal meningitis. Given the limitations of the evidence, the committee agreed to make recommendations based on their clinical knowledge and experience, and on current practice, and recommended ceftriaxone in line with the BNF (Joint Formulary Committee 2022) and BNFC (Paediatric Formulary Committee 2022), for the treatment of meningococcal meningitis. The committee were aware that insufficient dose can increase the risk of treatment failure and antibiotic resistance; therefore, they agreed to use the maximum dose recommended by the BNF or BNFC or follow local antimicrobial guidance.

The committee highlighted the potential practical and resource-use advantages associated with ceftriaxone because the long half-life means that it can be given only once a day. The committee acknowledged some concerns with once daily administration in that a second dose might need to be delayed if the first dose of ceftriaxone was administered outside of routine working hours; however, they were aware that a second dose can be given earlier, to shift the administration time, if there is a minimum of 12 hours between doses (Gbesemete 2019).

The committee discussed some reasons why in clinical practice (particularly in intensive care units) cefotaxime might be given instead of ceftriaxone. For instance, to minimise the time that intravenous lines are being used for administering antibiotics, which might be needed for other medications, due to ceftriaxone typically being infused over 30 minutes intravenous and cefotaxime being given as a bolus. However, the committee agreed that this practice is not necessary, as ceftriaxone can be given as bolus. Sometimes there may be a reaction (for example, vomit reflex) if ceftriaxone is administered too quickly, but in the committee's experience this is relatively rare, which was supported by a recent study (Patel 2021). The committee agreed that ceftriaxone should be given as first-line treatment for meningococcal meningitis, unless contraindicated in which case cefotaxime can be considered.

The committee were aware that the previous NICE guideline (NICE 2010) recommended 7-day antibiotic treatment for meningococcal meningitis. However, the committee noted that the evidence reviewed showed no important difference between 5 and 10 days of ceftriaxone therapy, although this study was unlikely to have been adequately powered to be taken as definitive evidence of equivalence. The committee acknowledged that practice has changed since the previous NICE guideline, and that the previous recommendations were consensus rather than evidence based and pre-dated the widespread use of cephalosporins. The committee discussed that, in some instances, practice has moved to shorter (5-day) courses of antibiotics for the treatment of meningococcal meningitis without apparent impact on clinical outcomes, although they acknowledged that there is variation in practice. Based on

their clinical knowledge and experience, the committee agreed that meningococcus is more sensitive to antibiotics compared with other organisms, particularly cephalosporins such as ceftriaxone. The committee were also aware of evidence from low- and middle-income countries, suggesting that shorter length of treatment may be effective. The committee recommended that people with meningococcal meningitis should be treated for 5 days with ceftriaxone (or cefotaxime if ceftriaxone contraindicated). The committee agreed that advice from an infection specialist should be sought if the person had not recovered after 5 days.

There was no evidence found on antibiotic use for meningococcal meningitis in people with an antibiotic allergy, but the committee agreed it was important to make a recommendation for this population. Based on their knowledge and experience, the committee agreed that cephalosporin-induced anaphylaxis is rare, and the risk-benefit balance of a cephalosporin (relative to chloramphenicol as an alternative) is favourable in most patients with non-severe allergy. Therefore, the committee agreed that clinicians should seek information about the nature of the allergy and advice from an infection specialist (a microbiologist or infectious diseases specialist) before making a treatment decision, particularly for people who are pregnant. The committee acknowledged that it is important that treatment is not delayed; however, they agreed that information about the nature of allergy is often readily available from the patient's family. The committee agreed that a cephalosporin should still be considered if the nature of the allergic reaction they get is not severe, in accordance with the first line treatment recommended above. However, if the allergic reaction is severe, alternatives to ceftriaxone or cefotaxime will be needed. The committee discussed that chloramphenicol is commonly used in the case of severe beta-lactam (penicillin, amoxicillin, or cephalosporin) allergy. Based on clinical knowledge and experience, the committee recommended chloramphenicol for people with meningococcal meningitis and severe antibiotic allergy.

The committee were aware that the previous NICE guideline on bacterial meningitis (NICE 2010) recommended to treat people who have travelled outside the UK with vancomycin (in addition to the cephalosporin). However, they discussed that practice has changed since the previous NICE guideline. The committee were aware that current practice is to use rifampicin or linezolid in addition to a cephalosporin where the cephalosporin itself might be insufficient due to resistance. However, the committee highlighted that there is not enough evidence to support recommending them. Therefore, the committee recommended that clinicians should seek advice from an infection specialist for all cases of bacterial meningitis, but this was particularly important if cephalosporin resistance is suspected in people who have recently travelled abroad.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee considered that it would be cost-effective to facilitate the option of a shorter course of antibiotics than in previous NICE guidance (NICE 2010) for meningococcal meningitis as some practice has moved in this direction without any apparent adverse impact on clinical outcomes. However, given the absence of evidence supporting shorter courses in developed countries they did not want to mandate this. The committee believed that by facilitating the option of a shorter course of antibiotics that their recommendation could lead to some small cost savings for the NHS.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.4, 1.6.15, and 1.6.16. Other evidence supporting the recommendations 1.6.4 and 1.6.16 can be found in evidence reviews on antibiotic regimens for bacterial meningitis before or in the absence of identifying causative infecting organism (see evidence reviews D1 to D3) and for specific causative organisms (see evidence reviews E1 to E5).

References – included studies

Effectiveness

Isaacs 1988

Isaacs, R. D., Howden, C. W., Lang, W. R. et al. (1988) Short course chemotherapy for meningococcal meningitis. Australian and New Zealand journal of medicine 18(5): 731-2

Marhoum el Filali 1993

Marhoum el Filali, K., Noun, M., Chakib, A. et al. (1993) Ceftriaxone versus penicillin G in the short-term treatment of meningococcal meningitis in adults. European journal of clinical microbiology & infectious diseases 12(10): 766-768

Molyneux 2011

Molyneux, Elizabeth, Nizami, Shaikh Qamaruddin, Saha, Samir et al. (2011) 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. Lancet (London, England) 377(9780): 1837-45

Tuncer 1988

Tuncer, A. M., Gür, I., Ertem, U. et al. (1988) Once daily ceftriaxone for meningococcemia and meningococcal meningitis. Pediatric infectious disease journal 7(10): 711-713

Economic

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

Other

Gbesemete 2019

Gbesemete, D., Faust, S. (2019). Prescribing in infection: antibacterials. In. Barker, C., Turner, M., Sharland, M. (Eds.) Prescribing Medicines for Children: From drug development to practical administration, Pharmaceutical Press, London: UK

Joint Formulary Committee 2022

Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Available at: http://www.medicinescomplete.com [Accessed 04/04/2022]

NICE 2010

National Institute for Health and Care Excellence (2010). Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg102 [Accessed 04/04/2022]

Paediatric Formulary Committee 2022

Paediatric Formulary Committee. BNF for Children (online). London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. Available at: http://www.medicinescomplete.com [Accessed 29/03/2022]

Patel 2021

Patel, S., Green. H., Gray, J., Rutter, M., Bevan, A., Hand, K., Jones, C. E., Faust, S. N. (2021). Evaluating Ceftriaxone 80 mg/kg Administration by Rapid Intravenous Infusion—A Clinical Service Evaluation. The Pediatric Infectious Disease Journal, 40(2), 128-129

Appendices

Appendix A Review protocols

Review protocol for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021276597
Review title	Antibiotics for bacterial meningitis caused by Neisseria meningitidis
Review question	What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?
Objective	This review aims to find out what is the optimal antibiotic treatment regimen in improving outcomes for people with bacterial meningitis caused by Neisseria meningitidis
Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: Date limitations: 1980 English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.

Field	Content
Condition or domain being studied	Bacterial meningitis caused by Neisseria meningitidis
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis caused by Neisseria meningitidis Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Intervention/Exposure/Test	• Cefotaxime • Ceftriaxone • Benzylpencillin sodium • Amoxicillin • Ampicillin • Ciprofloxacin • Moxifloxacin • Levofloxacin • Chloramphenicol • Meropenem
Comparator/Reference standard/Confounding factors	Stage 1 (all antibiotic agents of interest): Antibiotic agent A (single or combination) vs Antibiotic agent B (single or combination) Stage 2 (antibiotic agents identified during stage 1 as most effective/for use where there are contraindications)

Field	Content
	Comparisons: 1. Antibiotic agent A – Dose A vs Antibiotic agent A – Dose B 2. Antibiotic agent A – Duration of administration A vs Antibiotic agent A – Duration of administration B 3. Antibiotic agent A – Short infusion vs Antibiotic agent A – Extended infusion
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: • Co-morbidity • Severity of infection at presentation (including sepsis) Exclude: • Conference abstracts
Other exclusion criteria	Cohort studies from low income countries. Studies conducted prior to 1980 as currently used antibiotics were not in common usage prior to this date. Studies published not in English-language
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	Adults • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point)

Field	Content
	Children and infants • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Secondary outcomes (important outcomes)	Adults • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • CSF sterilisation (defined as treatment failure, time-to-sterilisation or delay). • Intracranial collections as a complication (defined as abscess or empyema) Children and infants • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant

Field	Content
	• CSF sterilisation (defined as treatment failure, time to sterilisation or delay)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through sensitivity

Field	Content
	analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • CSF sterilization: statistical significance • Intracranial collections: statistical significance • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	Evidence will be stratified by: **Stage 1** Age: • Younger Infants, older infants and children: >28 days to <18* years of age • Adults: ≥18* years of age **Stage 2** Age: • Younger Infants: >28 days to ≤3 months of age • Older infants and children: >3 months to <18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds should be treated as adults or children.

Field	Content		
	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Young and middle aged adults • Older adults* *There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold. Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.		
Type and method of review		☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
Language	English		
Country	England		
Anticipated or actual start date	12/01/2021		
Anticipated completion date	07/12/2023		

Field	Content		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in		

Field	Content		
	line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.		
Other registration details	None		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021276597		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.		
Keywords	Bacterial meningitis, antibiotic, anti-bacterial, mortality, impairments		
Details of existing review of same topic by same authors	None		
Current review status	☐	Ongoing	
	☒	Completed but not published	
	☐	Completed and published	
	☐	Completed, published and being updated	
	☐	Discontinued	
Additional information	None		
Details of final publication	www.nice.org.uk		

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CSF: cerebrospinal fluid; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MDI: mental development index; MEDLINE: Medical Literature Analysis and Retrieval System Online; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; PDI: psychomotor development index; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies – of interventions; ROBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Clinical Search

This was a combined search to cover both this review (E6) and D1, D2, D3, E1, E2, E3, E4, E5 and F1 on antibiotic regimens for bacterial meningitis (before or in the absence of identifying causative infecting organism and for specific causative organisms) and meningococcal disease.

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococ* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococ* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis*).ti,ab.
9	exp Neisseria meningitidis/ use ppez
10	neisseria meningitidis/ use emczd
11	(Neisseria* mening* or n mening*).ti,ab.
12	or/2,4-11
13	Meningococcal Infections/ use ppez
14	meningococcosis/ or meningococcemia/
15	14 use emczd
16	(meningococ* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
17	(meningococcus* or meningococci* or meningococ?emi?).ti,ab.
18	or/13,15-17
19	exp Anti-Bacterial Agents/ or exp Penicillins/ or exp Cephalosporins/ or exp Cefotaxime/ or exp Amoxicillin/ or exp Ampicillin/
20	19 use ppez
21	exp antibiotic agent/ or antibiotic therapy/ or exp penicillin derivative/ or exp cephalosporin derivative/
22	21 use emczd
23	(anti?biotic* or anti?bacterial* or anti?biotherap*).ti,ab.
24	(empiric* adj2 (therap* or treatment*)).ti,ab.
25	(abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin* or aminoglycosid* or amox?cillin* or amoxil* or ampicillin* or ancef or anticepim or apogen or axepim* or ayercillin or azithrom?cin* or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or carbapenem* or cedax or ceftazidim* or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftaroline* or ceftin or ceftolozane* or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephalosporin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol* or ciprofloxacin* or claforan or clamoxyl or clarithromycin* or clindamycin* or colistin* or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or delafloxacin* or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or erythromycin* or flucloxacillin* or fluoroquinolon* or fosfomycin* or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or glycopeptid* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or levofloxacin* or linezolid* or longacef or longaceph or lyphocin or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or moxifloxacin* or ofloxacin* or oftagen* or omnipen or optigen* or pefloxacin* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or

#	Searches
	polymyxin*or primafen or principen or quinolon* or refobacin* or ribom?cin* or rifampicin or rifampin* or rocefalin or rocefin or rocephin* or roscillin or rufloxacin* or sagestam* or spectrobid or sulm?cin* or supen or tazobactam* or terram?cin* or tetracycline* or tobramycin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin* or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at).mp.
26	or/20,22-25
27	(12 or 18) and 26
28	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
29	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
30	meta-analysis/
31	meta-analysis as topic/
32	systematic review/
33	meta-analysis/
34	(meta analy* or metanaly* or metaanaly*).ti,ab.
35	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
36	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
41	cochrane.jw.
42	((pool* or combined) adj2 (data or trials or studies or results)).ab.
43	letter/
44	editorial/
45	news/
46	exp historical article/
47	Anecdotes as Topic/
48	comment/
49	case report/
50	(letter or comment*).ti.
51	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	randomized controlled trial/ or random*.ti,ab.
53	51 not 52
54	animals/ not humans/
55	exp Animals, Laboratory/
56	exp Animal Experimentation/
57	exp Models, Animal/
58	exp Rodentia/
59	(rat or rats or mouse or mice).ti.
60	53 or 54 or 55 or 56 or 57 or 58 or 59
61	letter.pt. or letter/
62	note.pt.
63	editorial.pt.
64	case report/ or case study/
65	(letter or comment*).ti.
66	61 or 62 or 63 or 64 or 65
67	randomized controlled trial/ or random*.ti,ab.
68	66 not 67
69	animal/ not human/
70	nonhuman/
71	exp Animal Experiment/
72	exp Experimental Animal/
73	animal model/
74	exp Rodent/
75	(rat or rats or mouse or mice).ti.
76	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77	60 use ppez
78	76 use emczd
79	77 or 78
80	28 use ppez
81	29 use emczd
82	80 or 81
83	(or/30-31,34,36-41) use ppez
84	(or/32-35,37-42) use emczd
85	83 or 84
86	27 not 79
87	limit 86 to English language

#	Searches
88	limit 87 to yr="1980 -Current"
89	limit 88 to (conference abstract or conference paper or conference review or conference proceeding) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
90	89 use emczd
91	88 not 90
92	82 or 85
93	91 and 92 [SR/RCT data]
94	91 not 93 [Non-RCT data]

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 11 of 12, November 2022, **Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2022
Date of last search: 10 November 2022

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	MeSH descriptor: [Neisseria meningitidis] explode all trees
#10	((bacter* or infect*) near/3 (mening* or leptomening* or subarachnoid space*)):ti,ab,kw
#11	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or (h next influenz*) or listeria* or pneumococc* or (gram next negativ* next bacill*) or streptococc* or GBS or (s next pneumon*)) near/3 (septic* or sepsis* or bacteraemi* or bacteremi* or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or (mening* next encephalitis*)).:ti,ab,kw
#13	((neisseria* next mening*) or (n next mening*)):ti,ab,kw
#14	MeSH descriptor: [Meningococcal Infections] this term only
#15	meningococc*:ti,ab,kw
#16	{or #1-#15}
#17	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#18	((antibiotic* or antibacterial* or antibiotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*")):ti,ab,kw
#19	((empiric* near/2 (therap* or treatment*))):ti,ab,kw
#20	((abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin* or aminoglycosid* or amox?cillin* or amoxil* or ampicillin* or ancef or anticepim or apogen or axepim* or ayercillin or azithrom?cin* or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or carbapenem* or cedax or ceftazidim* or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftaroline* or ceftin or ceftolozane* or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephalosporin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol* or ciprofloxacin* or claforan or clamoxyl or clarithromycin* or clindamycin* or colistin* or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or delafloxacin* or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or erythromycin* or flucloxacillin* or fluoroquinolon* or fosfomycin* or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or glycopeptid* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or levofloxacin* or linezolid* or longacef or longaceph or lyphocin or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or moxifloxacin* or ofloxacin* or oftagen* or omnipen or optigen* or pefloxacin* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or polymyxin*or primafen or principen or quinolon* or refobacin* or ribom?cin* or rifampicin or rifampin* or rocefalin or rocefin or rocephin* or roscillin or rufloxacin* or sagestam* or spectrobid or sulm?cin* or supen or tazobactam* or terram?cin* or tetracycline* or tobramycin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin* or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at)):ti,ab,kw
#21	{or #17-#20}
#22	#16 and #21
#23	"conference":pt or (clinicaltrials or trialsearch):so
#24	#22 not #23

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface
Date of last search: 12 February 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN DARE,HTA
2	MeSH DESCRIPTOR meningitis, bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA

#	Searches
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	MeSH DESCRIPTOR Meningococcal infections IN DARE,HTA
10	(((((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))))) IN DARE, HTA
11	(meningit*) IN DARE, HTA
12	((((meningencephalitis* or meningoencephalitis*)))) IN DARE, HTA
13	((((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))))) IN DARE, HTA
14	((((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)))) IN DARE, HTA
15	((Neisseria* NEAR1 mening*)) IN DARE, HTA
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES IN DARE,HTA
18	MeSH DESCRIPTOR Penicillins EXPLODE ALL TREES IN DARE,HTA
19	MeSH DESCRIPTOR Cephalosporins EXPLODE ALL TREES IN DARE,HTA
20	MeSH DESCRIPTOR Cefotaxime EXPLODE ALL TREES IN DARE,HTA
21	MeSH DESCRIPTOR Amoxicillin EXPLODE ALL TREES IN DARE,HTA
22	MeSH DESCRIPTOR Ampicillin EXPLODE ALL TREES IN DARE,HTA
23	(((antibiotic* or antibacterial* or antibiotherap* or anti-biotic* or anti-bacterial* or anti-biotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*"))) IN DARE, HTA
24	(((empiric* NEAR2 (therap* or treatment*)))) IN DARE, HTA
25	(((abbbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy-28142 or bmy28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or co-trimoxazol or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at))) IN DARE, HTA
26	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27	#16 AND #26

Economic Search

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

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

Date of last search: 11 March 2021

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

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

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

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

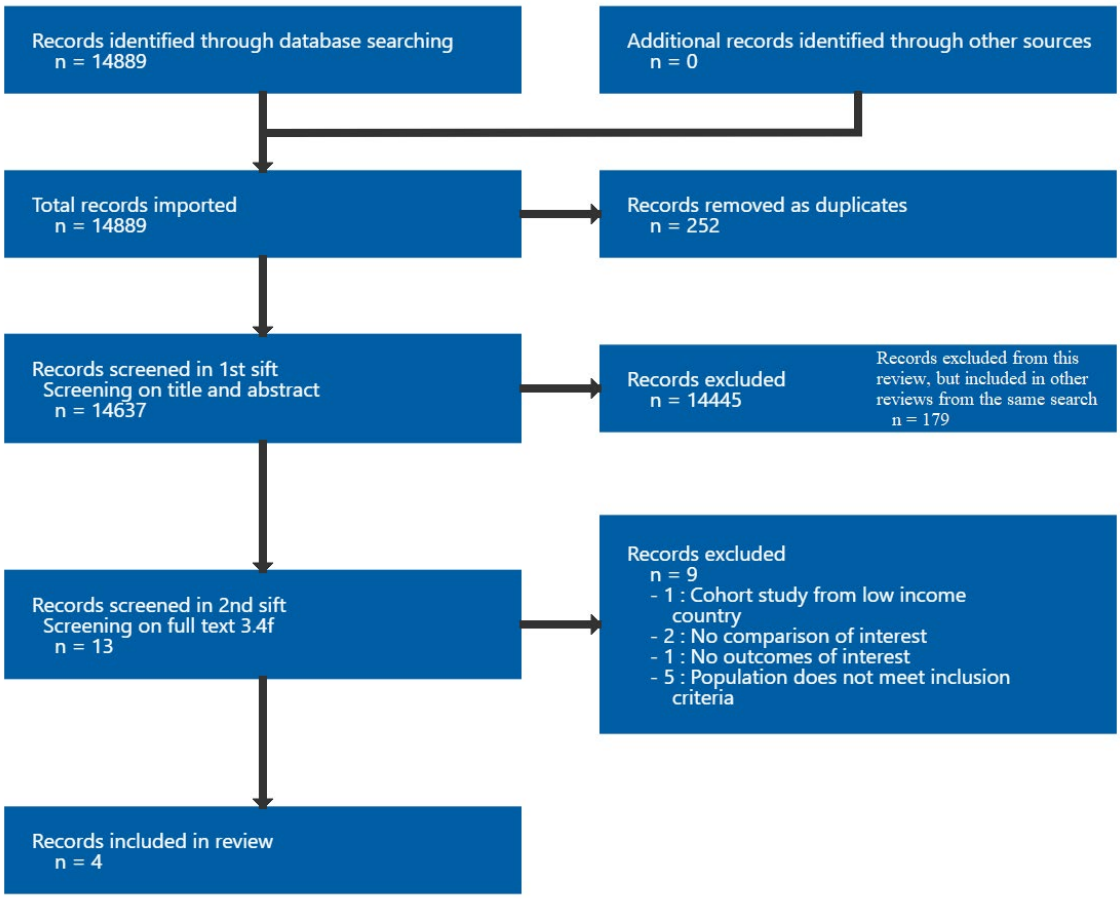
#	Searches
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd

#	Searches
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

Appendix C Effectiveness evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Table 4: Evidence tables – effectiveness evidence

Isaacs, 1988

Bibliographic Reference	Isaacs, R. D.; Howden, C. W.; Lang, W. R.; Ellis-Pegler, R. B.; Short course chemotherapy for meningococcal meningitis; Australian and New Zealand journal of medicine; 1988; vol. 18 (no. 5); 731-2

Study details

Country/ies where study was carried out	New Zealand
Study type	Retrospective cohort study
Study dates	1974 – 1986
Inclusion criteria	Patients aged ≥14 years with bacterial meningitis caused by Neisseria meningitidis (CSF culture, CSF Gram stain or blood culture) and received at least 5 days antibiotic therapy but not treated with antibiotics before admission
Exclusion criteria	Not reported
Patient characteristics	N=35 Age (years in mean; SD in parentheses): 28 (14) Sex: male: 21 (60%); female: 14 (40%) Etiology: Neisseria meningitidis: 35 (100%)

Intervention(s)/control	5-day benzylpenicillin sodium therapy: Intravenous benzylpenicillin sodium alone (n=16) or chloramphenicol alone (n=1) or ceftriaxone alone (n=1) for 5 days >5-day benzylpenicillin sodium therapy: Intravenous benzylpenicillin sodium alone (n=13) or benzylpenicillin sodium in combination (n=4) for average duration of 8.5 days
Duration of follow-up	During hospitalisation and between 2 weeks and 3 months after discharge
Sources of funding	Not reported
Sample size	N=35
Other information	Frequency and dose were not described.

CSF: cerebrospinal fluid; SD: standard deviation

Outcomes

5-day benzylpenicillin sodium therapy versus >5-day benzylpenicillin sodium therapy: All-cause mortality, any long-term neurological impairment and hearing impairment

Outcome	**5-day benzylpenicillin sodium therapy, N = 18**	**>5-day benzylpenicillin sodium therapy, N = 17**
All-cause mortality (up to 3 months after discharge) No of events	n = 0	n = 0
Any long-term neurological impairment (facial nerve palsy and cerebral infarction; up to 3 months after discharge) No of events	n = 1	n = 1
Hearing impairment (sensorineural hearing loss; up to 3 months after	n = 2	n = 1

Outcome	5-day benzylpenicillin sodium therapy, N = 18	>5-day benzylpenicillin sodium therapy, N = 17
discharge) No of events		

Critical appraisal - ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Critical *(Data not adjusted for potential confounding factors. Age, sex, Glasgow coma scale, blood culture and temperature were comparable but rates of comorbidity and severity of infection at presentation that could have caused confounding were not reported.)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious *(37% of patients were not followed after discharge.)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious *(Intervention status is not well defined.)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(No deviations from intended interventions)*
5. Bias due to missing data	Risk of bias judgement for missing data	No information *(No information is reported about missing data or the potential for data to be missing.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Serious *(Low (all-cause mortality): The outcome measure was not influenced by knowledge of the intervention received. Serious (any long-term neurological impairment and hearing impairment): The outcome measures were subjective.)*

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(No indication of selection of the reported analysis from among multiple analyses)*
Overall bias	Risk of bias judgement	Critical
Overall bias	Risk of bias variation across outcomes	None
Overall bias	Directness	Directly applicable *(All-cause mortality and hearing impairment are directly applicable. However, any long-term neurological impairment is indirect outcome as it is a composite outcome including cerebral infarction.)*

ROBINS-I: risk of bias in non-randomised studies – of interventions

Marhoum el Filali, 1993

Bibliographic Reference Marhoum el Filali, K.; Noun, M.; Chakib, A.; Zahraoui, M.; Himmich, H.; Ceftriaxone versus penicillin G in the short-term treatment of meningococcal meningitis in adults; European journal of clinical microbiology & infectious diseases; 1993; vol. 12 (no. 10); 766-768

Study details

Country/ies where study was carried out	Morocco
Study type	Randomised controlled trial (RCT)
Study dates	March 1989 – December 1990

Inclusion criteria	Adults aged >16 years with meningococcal meningitis (clinical criteria, positive CSF culture, meningococcal polysaccharide antigen in the CSF and purulent CSF)
Exclusion criteria	Adults with a history of hypersensitivity reaction to penicillin
Patient characteristics	N=36 Age (years in mean; SD in parentheses): 29 (14) Sex: male: 25 (69%); female: 11 (31%) Etiology: Neisseria meningitidis: 26 (72%); unknown (unconfirmed cases): 10 (28%)
Intervention(s)/control	Ceftriaxone: Intravenous ceftrixone 2g once daily for 2 days Benzylpenicillin sodium: Intravenous penicillin G 300,000 IU/kg/day every 4 hours for 6 days
Duration of follow-up	During hospitalisation and 2 months after discharge
Sources of funding	Not reported
Sample size	N=36
Other information	Population is indirect as it included participants with unconfirmed meningococcal meningitis (28%).

CSF: cerebrospinal fluid; RCT: randomised controlled trial; SD: standard deviation

Outcomes

Ceftriaxone versus benzylpenicillin sodium: All-cause mortality, any long-term neurological impairment and CSF sterilisation

Outcome	**Ceftriaxone, N = 16**	**Benzylpencillin sodium, N = 20**
All-cause mortality (during hospitalisation) No of events	n = 1	n = 1

Outcome	Ceftriaxone, N = 16	Benzylpencillin sodium, N = 20
Any long-term neurological impairment (neurological sequelae; 2 months after discharge) No of events	n = 0	n = 0
CSF sterilisation (negative CSF culture at 24 h after starting treatment) No of events	n = 16	n = 20

CSF: cerebrospinal fluid

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(No information about allocation concealment. Baseline characteristics, such as age, symptoms, temperature, consciousness and cerebrospinal fluid findings of the intervention groups were comparable except for sex (15% of benzylpenicillin sodium group were females compared with 50% of ceftriaxone group).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information on blinding. No information on whether deviations arose because of the trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data was available for all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Low (all-cause mortality and CSF sterilisation): Measurement did not differ between groups. Knowledge of the assigned intervention could not influence*

Section	Question	Answer
		the outcome. High (any long-term neurological impairment): Measurement did not differ between groups. Knowledge of the assigned intervention was likely to influence outcome assessment.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Analysis intentions are not available.)*
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one domain (bias arising from the randomisation process and measurement of the outcome).)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Molyneux, 2011

Bibliographic Reference	Molyneux, Elizabeth; Nizami, Shaikh Qamaruddin; Saha, Samir; Huu, Khanh Truong; Azam, Matloob; Bhutta, Zulfiqar Ahmad; Zaki, Ramadan; Weber, Martin Willi; Qazi, Shamim Ahmad; Group, C. S. F. Study; 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study; Lancet (London, England); 2011; vol. 377 (no. 9780); 1837-45

Study details

Country/ies where study was carried out	Bangladesh, Egypt, Malawi, Pakistan and Vietnam
Study type	Randomised controlled trial (RCT)

Study dates	September 2001 – December 2006
Inclusion criteria	Children aged 2 months to 12 years with bacterial meningitis caused by Haemophilus influenzae, Streptococcus pneumoniae, or Neisseria meningitidis who were alive on day 5 after the start of treatment and clinically stable or improving. Meningitis caused by the study organisms was defined as positive CSF culture or latex agglutination, or positive blood culture plus >10 white blood cells per mL of CSF, or >100 white blood cells per mL of CSF with >50% granulocytes plus CSF glucose <1.66 mml/L or <50% of blood glucose, or >100 white blood cells per mL of CSF with 75% polymorphonuclear leukocytes.
Exclusion criteria	Exclusion criteria at enrolment: Age ≤2 months, body weight ≤3 kg, pre-existing neurosurgical conditions, cerebral palsy, seizure disorders, degenerative neurological conditions, skull fractures, active viral infections, known immunodeficiency, symptomatic AIDS, known hypersensitivity reaction to cephalosporins, cyanotic congenital heart disease, inaccessibility for follow-up, children treated with any parenteral antibiotics for 24 h before admission, and children randomly assigned on more than one occasion in this study Exclusion criteria for random assignment at day 5: Criteria listed above, ceftriaxone-resistant bacteria, serious adverse reactions to the drug given, presence of or growth of bacteria from cerebrospinal fluid taken 48 to 72 h after admission, pyogenic brain abscess, intracranial suppurative thrombophlebitis, subdural empyema, presence of another infection during admission that needed another injectable antibiotic, and meningitis caused by any bacteria other than Haemophilus influenzae, Streptococcus pneumoniae, or Neisseria meningitidis
Patient characteristics	Neisseria meningitidis N=73 (study also included bacterial meningitis with other causes (N=931) but these were not of interest for the current review); 5-day ceftriaxone therapy: 46; 10-day ceftriaxone therapy: 27 Age[1] (months in mean; SD in parentheses): 38 (42) Sex[1]: male: 565 (56%); female: 439 (44%) Etiology[1]: Haemophilus influenzae: 266 (27%); Streptococcus pneumoniae: 335 (33%); Neisseria meningitidis: 73 (7%); unknown: 330 (33%) Children infected with HIV[2]: 117 (12%) [1]Reported for whole study, not based on causative organism [2]Although HIV is listed as an exclusion criteria in the protocol, the evidence was not considered indirect as those with HIV accounted for <25% of the population

Intervention(s)/control	5-day ceftriaxone therapy: Intravenous ceftriaxone 80-100 mg/kg once daily for 5 days followed by placebo for 5 days 10-day ceftriaxone therapy: Intravenous ceftriaxone 80-100 mg/kg once daily for 10 days
Duration of follow-up	Daily during hospitalisation, at discharge on day 10, and on day 40 and day 190 after enrolment
Sources of funding	Industry funded
Sample size	N=1004[1] [1]Reported for whole study, not based on causative organism
Other information	437 children (5-day ceftriaxone therapy: 209; 10-day ceftriaxone therapy: 228) received dexamethasone therapy[1] [1]Reported for whole study, not based on causative organism

AIDS: acquired immunodeficiency syndrome; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; RCT: randomised controlled trial; SD: standard deviation

Outcomes

5-day ceftriaxone therapy versus 10-day ceftriaxone therapy: All-cause mortality, any long-term neurological impairment, developmental delay, hearing impairment, serious intervention-related adverse effects and CSF sterilisation

Outcome	**5-day ceftriaxone therapy, N = 496**	**10-day ceftriaxone therapy, N = 508**
All-cause mortality (up to 6 months after discharge) Custom value	1/46	0/27
Any long-term neurological impairment (neurological sequelae including motor deficit, cranial nerve palsy and afebrile seizures; up to 6 months after discharge) Custom value	21/496	30/508

Outcome	5-day ceftriaxone therapy, N = 496	10-day ceftriaxone therapy, N = 508
Any long-term neurological impairment (visual loss; up to 6 months after discharge) Custom value	4/496	10/508
Developmental delay (assessed using the age and stages questionnaire; up to 6 months after discharge) Custom value	25/496	33/508
Hearing impairment (up to 6 months after discharge) Custom value	105/496	106/508
Serious intervention-related adverse effects (adverse events to the study drug; up to 6 months after discharge) Custom value	0/496	0/508
CSF sterilisation (positive cerebrospinal fluid or blood cultures on days 6-40) Custom value	1/46	0/27

CSF: cerebrospinal fluid

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computer-generated randomisation, process of allocation controlled by an external unit, sealed opaque envelopes used for allocation concealment. No substantial differences between groups at baseline.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and intervention staff were not aware of intervention. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Loss to follow up greater in 10-day ceftriaxone therapy compared with other arm for all outcomes (5.3% vs 4% on day 40; 11% vs 6.5% at 6-month follow-up) and could be related to participants' health status or death.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low/High *(Methods of measuring the outcomes were appropriate, and no difference in measurement of the outcomes between intervention groups. No information if outcome assessors were blinded to intervention status. Low risk for all-cause mortality, hearing impairment, CSF sterilisation and serious intervention-related adverse effects outcomes as outcome measurement would not be influenced by knowledge of assigned intervention, and high risk for neurological impairment, including visual loss, and developmental delay outcomes as they are somewhat subjective and may be influenced by knowledge of assigned intervention.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses in the protocol.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *for all-cause mortality, hearing impairment, CSF sterilisation and serious intervention-related adverse effects.* *High risk for any long-term neurological impairment and developmental delay.*
Overall bias and Directness	Overall Directness	Indirectly applicable *(All outcomes other than all-cause mortality and CSF sterilisation, data is*

Section	Question	Answer
		presented for the whole study rather than the subgroup of interest. Therefore, population is very seriously indirect (<50% had bacterial meningitis caused by organism of interest). Also, developmental delay is an indirect outcome (because no indication of severity).)
Overall bias and Directness	Risk of bias variation across outcomes	Yes, see "Risk of bias judgement" cell above.

CSF: cerebrospinal fluid; RoB: risk of bias

Tuncer, 1988

Bibliographic Reference	Tuncer, A. M.; Gür, I.; Ertem, U.; Ece, A.; Türkmen, S.; Deniz, B.; Gürman, I.; Tuncer, S.; Once daily ceftriaxone for meningococcemia and meningococcal meningitis; Pediatric infectious disease journal; 1988; vol. 7 (no. 10); 711-713

Study details

Country/ies where study was carried out	Turkey
Study type	Randomised controlled trial (RCT)
Study dates	January 1987 – June 1987
Inclusion criteria	Babies and children aged 1 month to 12 years with meningococcal disease. Meningococcal disease defined as positive CSF or blood culture for N. meningitidis, or identification of Gram-negative diplococci in CSF, or meningitis with or without purpura
Exclusion criteria	Not reported
Patient characteristics	N=42

	Age (range): 1 month to 12 years Sex: male: 23 (55%); female: 19 (45%) Etiology: Neisseria meningitidis group B: 2 (5%); Neisseria meningitidis group C: 40 (95%)
Intervention(s)/control	Ceftriaxone: Intravenous ceftriaxone single daily dose of 80-100 mg/kg for 4 days Benzylpenicillin sodium: Intravenous penicillin G 500,000 units/kg/day in 6 divided doses for 5 days
Duration of follow-up	Babies and children were assessed during hospitalisation.
Sources of funding	Not reported
Sample size	N=42
Other information	No clear information on steroid therapy but it states: Twelve patients with poor prognostic score received methylprednisolone, volume expanders, dopamine and naloxone. Population is indirect as it included participants with meningococcaemia alone (33%).

CSF: cerebrospinal fluid; RCT: randomised controlled trial

Outcomes

Ceftriaxone versus benzylpenicillin sodium: All-cause mortality and CSF sterilisation

Outcome	Ceftriaxone, N = 20	Benzylpenicillin sodium, N = 22
All-cause mortality (during hospitalisation) Custom value	1/20	2/22
CSF sterilisation (sterile CSF culture on day 3 of treatment) Custom value	15/15	13/13

CSF: cerebrospinal fluid

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information about allocation concealment was provided. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information on blinding. No information on whether deviations arose because of the trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data was available for all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

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

Appendix F GRADE tables

GRADE tables for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Table 5: Evidence profile for comparison: ceftriaxone versus benzylpenicillin sodium in babies and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Benzylpenicillin sodium	Relative (95% CI)	Absolute		
All-cause mortality: babies and children (during hospitalisation)												
1 (Tuncer 1988)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/20 (5%)	2/22 (9.1%)	RR 0.55 (0.05 to 5.61)	41 fewer per 1000 (from 86 fewer to 419 more)	VERY LOW	CRITICAL
CSF sterilisation (sterile CSF culture on day 3 of treatment): babies and children												
1 (Tuncer 1988)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15/15 (100%)	13/13 (100%)	RR 1 (0.87 to 1.14)	0 fewer per 1000 (from 130 fewer to 140 more)	VERY LOW	IMPORTANT

CI: confidence interval; CSF: cerebrospinal fluid; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to participants with meningococcaemia alone (33%)
[3] <150 events

Table 6: Evidence profile for comparison: 5-day ceftriaxone therapy versus 10-day ceftriaxone therapy in babies and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-day ceftriaxone therapy	10-day ceftriaxone therapy	Relative (95% CI)	Absolute		

All-cause mortality: babies and children (follow-up 0-6 months)												
1 (Molyneux 2011)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/46 (2.2%)	0/27 (0%)	RR 1.79 (0.08 to 42.39)	20 more per 1000 (from 50 fewer to 90 more)[3]	VERY LOW	CRITICAL
Any long-term neurological impairment (neurological sequelae including motor deficit, cranial nerve palsy and afebrile seizures): babies and children (follow-up 0-6 months)												
1 (Molyneux 2011)	randomised trials	very serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	21/496 (4.2%)	30/508 (5.9%)	RR 0.72 (0.42 to 1.23)	17 fewer per 1000 (from 34 fewer to 14 more)	VERY LOW	CRITICAL
Any long-term neurological impairment (visual loss): babies and children (follow-up 0-6 months)												
1 (Molyneux 2011)	randomised trials	very serious[4]	no serious inconsistency	very serious[7]	very serious[8]	none	4/496 (0.81%)	10/508 (2%)	RR 0.41 (0.13 to 1.3)	12 fewer per 1000 (from 17 fewer to 6 more)	VERY LOW	CRITICAL
Developmental delay (assessed using the age and stages questionnaire): babies and children (follow-up 0-6 months)												
1 (Molyneux 2011)	randomised trials	very serious[4]	no serious inconsistency	very serious[9]	very serious[8]	none	25/496 (5%)	33/508 (6.5%)	RR 0.78 (0.47 to 1.29)	14 fewer per 1000 (from 34 fewer to 19 more)	VERY LOW	CRITICAL
Hearing impairment: babies and children (follow-up 0-6 months)												
1 (Molyneux 2011)	randomised trials	serious[1]	no serious inconsistency	very serious[7]	very serious[8]	none	105/496 (21.2%)	106/508 (20.9%)	RR 1.01 (0.8 to 1.29)	2 more per 1000 (from 42 fewer to 61 more)	VERY LOW	IMPORTANT
Serious intervention-related adverse effects (adverse events to the study drug): babies and children (follow-up 0-6 months)												
1 (Molyneux 2011)	randomised trials	serious[1]	no serious inconsistency	very serious[7]	no serious imprecision	none	0/496 (0%)	0/508 (0%)	RD 0.00 (-0.0039 to 0.0039)	0 fewer per 1000 (from 3.9 fewer to 3.9 more)[3]	VERY LOW	IMPORTANT
CSF sterilisation (positive cerebrospinal fluid or blood cultures on days 6-40): babies and children												
1 (Molyneux 2011)	randomised trials	serious[1]	no serious inconsistency	serious[10]	very serious[2]	none	1/46 (2.2%)	0/27 (0%)	RR 1.79 (0.08 to 42.39)	20 more per 1000 (from 50 fewer to 90 more)[3]	VERY LOW	IMPORTANT

CI: confidence interval; CSF: cerebrospinal fluid; POR: Peto odds ratio; RD: risk difference; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] <150 events
[3] Absolute effect calculated based on risk difference
[4] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[5] Outcome is indirect as it is a composite outcome including afebrile seizures, and population is indirect due to 93% of population with meningitis caused by organisms other than N. meningitidis
[6] 95% CI crosses 1 MID
[7] Population is indirect due to 93% of population with meningitis caused by organisms other than N. meningitidis
[8] 95% CI crosses 2 MIDs
[9] Outcome is indirect as it is a composite outcome that could include mild or moderate developmental delay, and population is indirect due to 93% of population with meningitis caused by organisms other than N. meningitidis
[10] Outcome is indirect as it is a composite outcome including positive blood culture

Table 7: Evidence profile for comparison: 5-day benzylpenicillin sodium therapy versus >5-day benzylpenicillin sodium therapy in children and adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**5-day benzylpenicillin sodium therapy**	**>5-day benzylpenicillin sodium therapy**	**Relative (95% CI)**	**Absolute**		
All-cause mortality: children and adults (follow-up 0-3 months)												
1 (Isaacs 1988)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/18 (0%)	0/17 (0%)	RD 0 (-0.10 to 0.10)	0 fewer per 1000 (from 100 fewer to 100 more)[3]	VERY LOW	CRITICAL
Any long-term neurological impairment (facial nerve palsy and cerebral infarction): children and adults (follow-up 0-3 months)												
1 (Isaacs 1988)	observational studies	very serious[1]	no serious inconsistency	serious[4]	very serious[5]	none	1/18 (5.6%)	1/17 (5.9%)	RR 0.94 (0.06 to 13.93)	4 fewer per 1000 (from 55 fewer to 761 more)	VERY LOW	CRITICAL
Hearing impairment (sensorineural hearing loss): children and adults (follow-up 0-3 months)												
1 (Isaacs 1988)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/18 (11.1%)	1/17 (5.9%)	RR 1.89 (0.19 to 18.97)	52 more per 1000 (from 48 fewer to 1000 more)	VERY LOW	IMPORTANT

CI: confidence interval; RD: risk difference; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[2] Sample size <200
[3] Absolute effect calculated based on risk difference
[4] Outcome is indirect as it is a composite outcome including cerebral infarction
[5] 95% CI crosses 2 MIDs

Table 8: Evidence profile for comparison: ceftriaxone versus benzylpenicillin sodium in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Benzylpenicillin sodium	Relative (95% CI)	Absolute		
All-cause mortality: adults (during hospitalisation)												
1 (Marhoum el Filali 1993)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/16 (6.3%)	1/20 (5%)	RR 1.25 (0.08 to 18.46)	13 more per 1000 (from 46 fewer to 873 more)	VERY LOW	CRITICAL
Any long-term neurological impairment (neurological sequelae): adults (follow-up 2 months)												
1 (Marhoum el Filali 1993)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/16 (0%)	0/20 (0%)	RD 0 (-0.10 to 0.10)	0 fewer per 1000 (from 100 fewer to 100 more)[5]	VERY LOW	CRITICAL
CSF sterilisation (negative CSF culture at 24 h after starting treatment): adults												
1 (Marhoum el Filali 1993)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	16/16 (100%)	20/20 (100%)	RR 1 (0.9 to 1.11)	0 fewer per 1000 (from 100 fewer to 110 more)	VERY LOW	IMPORTANT

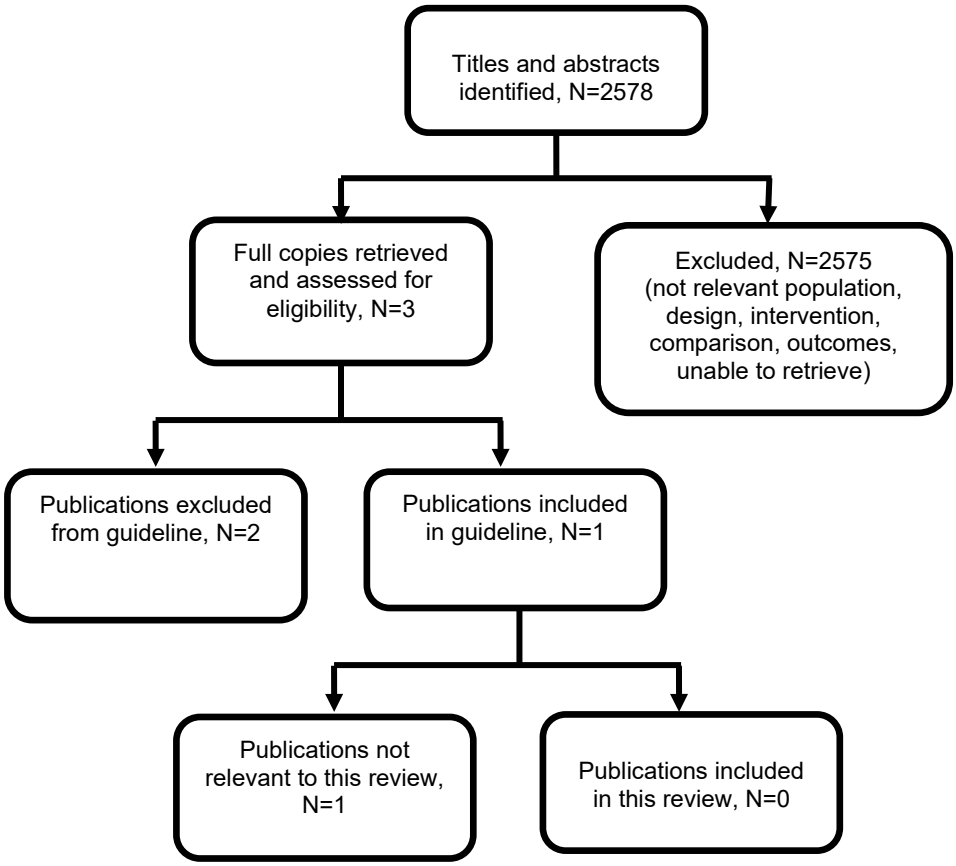
CI: confidence interval; CSF: cerebrospinal fluid; RD: risk difference; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to 28% of population with unconfirmed meningococcal meningitis
[3] <150 events
[4] Sample size <200
[5] Absolute effect calculated based on risk difference

Appendix G Economic evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

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

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

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

Appendix I Economic model

Economic model for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

Excluded effectiveness studies

The excluded studies table only lists the studies that were considered and then excluded at the full-text stage for this review (N=9) and not studies (N=179) that were considered and then excluded from the search at the full-text stage as per the PRISMA diagram in Appendix C for the other review questions in the same search.

Table 9: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Boisivon, A., Berardi-Grassias, L., Guiomar, C. et al. (1987) Bacteriostatic and bactericidal effect of ceftriaxone on Hemophilus, Neisseria meningitidis, and Proteus. Chemioterapia : international journal of the Mediterranean Society of Chemotherapy 6(2suppl): 83-84	- No comparison of interest
Congeni, B. L. (1984) Comparison of ceftriaxone and traditional therapy of bacterial meningitis. Antimicrobial agents and chemotherapy 25(1): 40-44	- Population does not meet inclusion criteria
Crosswell, Julie M.; Nicholson, W. Ross; Lennon, Diana R. (2006) Rapid sterilisation of cerebrospinal fluid in meningococcal meningitis: Implications for treatment duration. Journal of paediatrics and child health 42(4): 170-3	- No comparison of interest
Goldwater, Paul N. (2005) Cefotaxime and ceftriaxone cerebrospinal fluid levels during treatment of bacterial meningitis in children. International journal of antimicrobial agents 26(5): 408-11	- No outcomes of interest
Hussein, A. A. and Abdel Rahman, S. I. (2003) Meningococcal meningitis epidemic: A new role for single-dose oily chloramphenicol. Neurosciences 7(3): 171-175	- Cohort study from low income country
Nathan, N., Borel, T., Djibo, A. et al. (2005) Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics:	- Population does not meet inclusion criteria

Study	Code [Reason]
a randomised non-inferiority study. Lancet (London, England) 366(9482): 308-13	
Peltola, H.; Anttila, M.; Renkonen, O. V. (1989) Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Finnish Study Group. Lancet (london, england) 1(8650): 1281-1287	- Population does not meet inclusion criteria
Roine, I., Ledermann, W., Foncea, L. M. et al. (2000) Randomized trial of four vs. seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery. Pediatric infectious disease journal 19(3): 219-222	- Population does not meet inclusion criteria
Singhi, P., Kaushal, M., Singhi, S. et al. (2002) Seven days vs. 10 days ceftriaxone therapy in bacterial meningitis. Journal of tropical pediatrics 48(5): 273-279	- Population does not meet inclusion criteria

Excluded economic studies

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

Appendix K Research recommendations – full details

Research recommendations for review question: What antibiotic treatment regimens are effective in treating bacterial meningitis caused by Neisseria meningitidis?

No research recommendation was made for this review.