National Institute for Health and Care Excellence

Final

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

[G4] Evidence review for corticosteroids for treatment of bacterial meningitis

NICE guideline NG240

Evidence review underpinning recommendations 1.8.1 to 1.8.5 and the recommendation for research on corticosteroid treatment in neonates with bacterial meningitis in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Review question

What is the effectiveness of corticosteroid treatment in bacterial meningitis?

Introduction

Bacterial meningitis is a rare but serious infection, which can occur in any age group, and can result in significant complications including hearing loss and neurological deficits. Treatment with corticosteroids has been shown to result in a reduction of the inflammatory response in the cerebrospinal fluid and reversal of brain oedema.

The aim of this review is to establish the effectiveness of corticosteroid treatment in the initial management of bacterial meningitis.

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 (including neonates defined as aged 28 days old and younger) with confirmed bacterial meningitis.

Intervention	Corticosteroids (administered via any route): • Dexamethasone • Hydrocortisone • Prednisolone • Methylprednisolone
Comparison	• Head-to-head comparisons between the above corticosteroids • Placebo • No corticosteroid treatment

Outcome	**Critical** Population: adults, infants, and children • 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: infants and children • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayley's 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, infants, and children • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • 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 Population: adults • Length of hospitalisation Population: infants and children • 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.

SD: standard deviation; MDI: mental development index; PDI: psychomotor development index

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

Included studies

Two Cochrane systematic reviews (SRs; Brouwer 2015; Ogunlesi 2015), and 1 additional randomised controlled trial (RCT; Khan 2016) were included in this review.

The included studies are summarised in Table 2.

The Cochrane SRs included data from 27 RCTs, 2 RCTs were included in Ogunlesi 2015, and 25 RCTs in Brouwer 2015. One RCT (Scarborough 2007) included in the Cochrane SR by Brouwer 2015 was excluded from the review as 89% of the study population were HIV positive.

One Cochrane SR assessed neonates only (Ogunlesi 2015), 1 Cochrane SR assessed children and adults (Brouwer 2015), and the additional RCT assessed adults (Khan 2016). Not all outcomes in Brouwer 2015 were stratified into children and adults as indicated in our review protocol. Where data from adults, children and babies were combined in a meta-analysis for outcomes of interest in our review protocol, the data for each age group was extracted from the SR and meta-analysed separately for this review.

Twenty-five RCTs compared dexamethasone to placebo (22 RCTs included in Brouwer 2015; 2 RCTs included in Ogunlesi 2015; Khan 2016). Three RCTs compared hydrocortisone, prednisolone or combination of both to placebo (3 RCTs included in Brouwer 2015).

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 K.

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	Comparisons	Outcomes	Comments
Brouwer 2015 Systematic review	Number of adults, children and babies N=4121 Number of RCTs N=25 (n=17 0 - 17 years old; n=1 > 14 years old; n=1 >15 years old; >16 years old; n=5 all age groups) Countries included in SR n=15 high or middle-income n=10 low and lower middle-income Steroid administered	<u>Dexamethasone versus placebo (with antibiotics)</u> 22 RCTs (Belsey 1969; Bhaumik 1998; Ciana 1995; De Gans 2002; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Marthur 2013; Molyneux 2002; Nguyen 2007; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Scarborough 2007; Schaad 1993; Thomas 1999; Wald 1995) <u>Hydrocortisone or prednisolone or combination of both versus placebo (with antibiotics)</u> 3 RCTs (Bademosi 1979; Bennet 1963; DeLemos 1969)	• All-cause mortality • Long-term neurological impairment • Hearing impairment • Serious intervention-related adverse events	Scarborough 2007 excluded from review as 89% of population were HIV positive See evidence tables for steroid and antibiotic regimes used

Study	Population	Comparisons	Outcomes	Comments
	before or with antibiotic n=13 studies, after antibiotic n= 9 studies, and not stated n=3 studies Case-fatality range: 0%-54%			
Khan 2016 RCT Pakistan	Adults N=480 Age in mean years (SD): 40.98 (14.28) Timing of steroid in relation to antibiotics: NR Case-fatality: 20%	<u>Dexamethasone and antibiotics (n=240) versus placebo and antibiotics (n=240)</u> Dexamethasone regime: 10mg IV every 6 hours for 4 days Antibiotic regime: cefotaxime 2g IV every 8 hours plus vancomycin 1g every 12 hours	• All-cause mortality	None
Ogunlesi 2015 Systematic review	Number of neonates (≤28 days old) N=132 Number of RCTs N=2 Countries included in SR n=2 middle-income countries Steroid administered before antibiotic n=2 RCTs Case-fatality range: 25%	<u>Dexamethasone versus placebo (with antibiotics alone or antibiotic with placebo solution)</u> 2 RCTs (Daoud 1999; Marthur 2013)	• All-cause mortality • Developmental delay • Seizures • Hearing loss •	See evidence tables for steroid and antibiotic regimes used

HIV: human immunodeficiency virus; IV: intravenous; NR: not reported; SD: standard deviation; SR: systematic review; RCT: randomised controlled trial.

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

Summary of the evidence

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

All of the evidence was assessed as being moderate to very low quality due to risk of bias (arising from selective reporting, missing outcome data, non-blinding, and the randomisation process), imprecision (due to low event rates), and heterogeneity. The findings were seriously or very seriously imprecise for all outcomes, except mortality and serious intervention related adverse events (recurrent fever during hospitalisation) in babies and children; therefore, they should not be taken as definitive evidence of effectiveness, or lack of effectiveness. Evidence was stratified by age. See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

Evidence showed that corticosteroids had an important benefit over placebo in adults with bacterial meningitis on mortality and hearing impairment. In addition, corticosteroids were possibly associated with a lower rate of neurological impairment assessed at discharge to 6 weeks in adults compared to placebo (90% CI 0.43 to 0.93). However, the difference was not statistically significant, and no important difference was shown for neurological impairment assessed at 6 weeks to 1 year or gastrointestinal bleeding.

Evidence showed that a lower rate of hearing impairment and persistent fever in babies and children receiving corticosteroids relative to placebo. However, there was a higher rate of gastrointestinal bleeding and recurrent fever for corticosteroids compared to placebo in babies and children. No important difference was shown for mortality or neurological impairment at any time point.

In neonates aged less than 28 days, there was a lower rate of hearing loss (assessed at 4-10 weeks after discharge) for those receiving corticosteroids relative to placebo, however this evidence came from a single study. No important difference was shown between corticosteroids and placebo for mortality, developmental delay, or seizures in neonates.

There were a number of outcomes in the protocol that were not reported by any studies, including functional impairment and length of hospitalisation. Additionally, all of the evidence identified compared corticosteroids against a placebo; there was no evidence available for head-to-head comparisons between different types of corticosteroids or comparing corticosteroids to no treatment.

See the GRADE tables in appendix F for the certainty of the evidence for each individual outcome.

Economic evidence

Included studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because corticosteroids are not expensive.

Unit costs

Table 3: Unit costs for corticosteroid treatment in bacterial meningitis

Resource	Unit cost	Source
Dexamethasone 3.3 mg per ml	£2.40 per ampoule	BNF January 2023

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, 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), epilepsy or seizures, hearing impairment and serious intervention-related adverse effects were selected as important outcomes as these are relatively common after bacterial meningitis and may be related to corticosteroid use. Length of hospitalisation was also included as an important outcome for adults as this may be considered as an indicator of treatment effectiveness and was expected to be commonly reported in trials.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence varied from very low to moderate quality and was largely downgraded for risk of bias (due to lack of information on the randomisation process or the stratified results were not reported), and imprecision (due to wide confidence intervals or small number of events).

There was no evidence identified for functional impairment or length of hospitalisation. Additionally, there was no evidence available for head-to-head comparisons between different types of corticosteroids or comparing corticosteroids to no treatment.

Benefits and harms

The committee considered the evidence comparing corticosteroid treatment to placebo and noted that benefits were shown in terms of lower rates of mortality and hearing impairment (and possibly neurological impairment) in adults. For babies and children, the evidence showed a lower rate of hearing impairment in those receiving corticosteroids compared to placebo. However, there was a higher rate of gastrointestinal bleeding and recurrent fever for corticosteroids compared to placebo. Based on this evidence, and their clinical knowledge and experience, the committee recommended that corticosteroids should be used in the treatment of strongly suspected or confirmed bacterial meningitis. The committee agreed to make this recommendation despite the potential harms identified in this evidence review, because neurosensory deafness is a long-term significant morbidity that has serious implications whereas gastrointestinal bleeding and fever are usually short term and are typically not serious. No evidence was available for head-to-head comparisons between

different corticosteroids, however, the committee agreed to recommend intravenous dexamethasone as the corticosteroid of choice as the majority of studies included in the review used this corticosteroid. The committee were aware that in practice dexamethasone is used in people over 3 months of age and it is in line with the BNFC (British National Formulary for Children 2023). Therefore, the committee agreed to give intravenous dexamethasone to people over 3 months of age. The committee were not aware of any evidence that supports or refutes the use of dexamethasone in children between 28 days and 3 months. In the absence of evidence, the committee agreed that infection specialist advice should be sought because there is less certainty around the balance of benefits and harms in this group. The committee noted that this was an off-label use of dexamethasone (in January 2024) and doses, frequency, and duration in the BNF (British National Formulary 2023) and BNFC (British National Formulary for Children 2023) for severe infections should be followed. The committee acknowledged that 10 mg intravenous dexamethasone every 6 hours for 4 days for adults with bacterial meningitis treatment and 0.15 mg/kg (maximum 10 mg) intravenous dexamethasone every 6 hours for 4 days for babies, children and young people with bacterial meningitis treatment is in line with BNF and BNFC.

The evidence review did not directly address differential effectiveness of corticosteroids based on the causative organism or the use of corticosteroids for treatment when the causative agent is not found. However, the committee were aware of subgroup analyses in the Cochrane review that is included in this review (Brouwer 2015) showing clinical benefits of corticosteroids for pneumococcal meningitis and Haemophilus influenzae type b (Hib) but not for other causative organisms. Based on this evidence, and their clinical knowledge and experience, the committee recommended continuing dexamethasone treatment if the causative agent is pneumococcal or Hib, discontinuing dexamethasone treatment for all other causative organisms, and seeking advice from an infection specialist to determine whether dexamethasone should be continued if the causative organism of bacterial meningitis is not identified.

The evidence review did not directly address the optimal timing of corticosteroid administration, but the committee agreed this was an important issue and had included timing in the protocol as a factor to investigate in the event of significant heterogeneity across studies. The majority of studies included in the review administered corticosteroids before or with antibiotics. The committee agreed that this is in line with current clinical practice and made a recommendation to highlight the importance of early administration. However, the committee recognised that the priority in the treatment of bacterial meningitis is urgent initiation of antibiotic treatment (see evidence report C1), and the committee recommended that antibiotic administration should not be delayed waiting for dexamethasone to be started. The committee were aware that the previous NICE guideline on bacterial meningitis (NICE 2010) recommended not to administer corticosteroids if more than 12 hours had lapsed since the administration of antibiotics. The committee recommended that if corticosteroids could not be started before or with antibiotics then they should be administered at the earliest opportunity within the 12-hour window since the start of antibiotics. The committee discussed the 12-hour threshold in the previous guideline and noted that the previous recommendation was based on 12 hours being the latest time point after antibiotic administration in the evidence reviewed for the previous guideline. The committee noted that there is an absence of evidence beyond this timeframe, however, they agreed based on their clinical knowledge and experience that there are situations where a patient may benefit from corticosteroids even if more than 12 hours have elapsed since the administration of antibiotic. Therefore, the committee recommended that if corticosteroid administration is delayed for more than 12 hours after the start of antibiotics, advice from an infection specialist should be sought, and the decision to commence corticosteroids should be individualised to the patient and based on the potential for clinical benefit at this point.

The committee agreed to not include recommendations on the use of corticosteroids in neonates due to insufficient evidence. The committee discussed that extrapolating from the evidence for older age groups would not be appropriate because the spectrum of organisms

causing infection in neonates is different, and the impact on the developing brain of the causative organisms during inflammation may not be the same. The committee agreed to include a research recommendation to investigate the effectiveness of corticosteroids as an adjunct to antibiotic treatment in neonates with suspected or confirmed bacterial meningitis (see Appendix K).

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. Given the evidence on benefits and harms and the low costs of intervention the committee concluded that corticosteroids would be cost-effective for adults with strongly suspected or confirmed bacterial meningitis. The committee noted that this recommendation was in line with current NHS practice and therefore would not have a significant resource implication.

Similarly, the committee reasoned that corticosteroids were likely to be cost-effective in babies, children and young people whilst noting there was an increased risk of gastrointestinal bleeding which they did not think offset the clinical benefits of reduced hearing impairment and persistent fever. The recommendations made are in line with current practice and therefore no significant resource impact is expected.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.1 to 1.8.5 and the recommendation for research on corticosteroid treatment in neonates with bacterial meningitis.

References – included studies

Effectiveness

Brouwer 2015

Brouwer, M. C., McIntyre, P., Prasad, K., van de Beek, D. Corticosteroids for acute bacterial meningitis. Cochrane Database of Systematic Reviews Cochrane Database Syst Rev, CD004405, 2015

Khan 2016

Khan, D. M., Ather, ChAA, Khan, I. M. Comparison of dexamethasone versus placebo for management of bacterial meningitis. Pakistan journal of medical and health sciences, 10, 1296-1299, 2016

Ogunlesi 2015

Ogunlesi, T. A., Odigwe, C. C., Oladapo, O. T. Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis. Cochrane Database of Systematic Reviews Cochrane Database Syst Rev, CD010435, 2015

Economic

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

Other

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]

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42021232481
Review title	Corticosteroid treatment in bacterial meningitis
Review question	What is the effectiveness of corticosteroid treatment in bacterial meningitis?
Objective	To determine the effectiveness of corticosteroid treatment in bacterial meningitis
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.
Condition or domain being studied	Bacterial meningitis
Population	Inclusion: All adults, young people, children and babies (including neonates defined as aged 28 days old and

Field	Content
	younger) with confirmed bacterial meningitis. Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis. • with confirmed viral meningitis or viral encephalitis. • with confirmed tuberculous meningitis. • with confirmed fungal meningitis.
Intervention/Exposure/Test	Corticosteroids (administered via any route): • Dexamethasone • Hydrocortisone • Prednisolone • Methylprednisolone
Comparator/Reference standard/Confounding factors	• Head-to-head comparisons between the above corticosteroids • Placebo • No corticosteroid treatment
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 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.

Field	Content

	• Studies published not in English-language
	• Non-randomised studies be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason:
	  ○ Infective organism
	  ○ Severity of illness at presentation
	  ○ Comorbidity

Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	**Population: adults** • 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) **Population: infants and children** • 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)	**Population: adults** • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • 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

Field	Content
	life threatening or otherwise considered medically significant • Length of hospitalisation **Population: infants and children** • Diagnosis of epilepsy or occurrence of seizures during hospitalisation • 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
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. 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 intervention 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.

Field	Content
	Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Length of hospitalisation: 1 day • 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:
	Age:
	• Neonates
	  ○ Extremely preterm: <28 weeks
	  ○ Very preterm: ≥28 weeks to <32 weeks
	  ○ Preterm: ≥32 weeks to <37 weeks
	  ○ Term: ≥37 weeks
	• 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.
	
	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:

Field	Content	
	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. Corticosteroid dose • Timing of starting course of corticosteroids relative to timing of starting course of antibiotics: • Before antibiotics • At the same time • After antibiotics 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	29/01/2021	
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		

Field	Content	
	inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=232481	
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, corticosteroid, dexamethasone, hydrocortisone, 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; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IV: intravenous; MDI: mental development index; 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 is the effectiveness of corticosteroid treatment in bacterial meningitis?

Clinical Search

This was a combined search to cover both this review and evidence review H on corticosteroids for 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 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*.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	9 or 17
19	exp Adrenal Cortex Hormones/ or Dexamethasone/ or Hydrocortisone/ or Prednisolone/ or Methylprednisolone/
20	19 use ppez
21	exp corticosteroid/ or corticosteroid therapy/ or dexamethasone/ or hydrocortisone/ or prednisolone/ or methylprednisolone/
22	21 use emczd
23	(adrenal adj2 (hormone* or steroid*)).ti,ab,kw.
24	(corticosteroid* or corticoid*).ti,ab,kw.
25	(prednison* or Rayos* or Cortan* or Deltason* or Orason* or Intensol* or Sterapred* or methylprednisolon* or Medrol* or A-Methapred* or Depo-Medrol* or Solu-Medrol* or hydrocortison* or Cortef* or Cortril* or Hydrocortone* or A-Hydrocort* or Solu-Cortef* or dexamethason* or Decadron* or Intensol* or Dexpak* or Taperpak*).ti,ab,kw.
26	20 or 22 or 23 or 24 or 25
27	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.

#	Searches
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/ not human/
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
88	82 or 85
89	87 and 88 [RCT data]
90	87 not 89 [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

#	Searches
#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: [Adrenal Cortex Hormones] explode all trees
#18	((adrenal near/2 (hormone* or steroid*))):ti,ab,kw
#19	(corticosteroid* or corticoid* or corticotherap* or glucocorticoid*):ti,ab,kw
#20	(prednisolon* or Rayos* or Cortan* or Deltason* or Orason* or Intensol* or Sterapred* or methylprednisolon* or Medrol* or A-Methapred* or "Depo Medrol*" or "Solu Medrol*" or hydrocortison* or Cortef* or Cortril* or Hydrocortone* or A-Hydrocort* or "Solu Cortef*" or dexamethason* or Decadron* or Intensol* or Dexpak* or Taperpak*):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: 13 January 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
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	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))) IN DARE, HTA
10	((meningencephalitis* or meningoencephalitis* or meningit*)) IN DARE, HTA
11	MeSH DESCRIPTOR Neisseria meningitidis IN DARE,HTA
12	((Neisseria* NEXT mening*)) IN DARE, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN DARE,HTA
14	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN DARE, HTA
15	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) 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 Adrenal Cortex Hormones EXPLODE ALL TREES IN DARE,HTA
18	MeSH DESCRIPTOR Dexamethasone IN DARE,HTA
19	MeSH DESCRIPTOR Hydrocortisone IN DARE,HTA
20	MeSH DESCRIPTOR Prednisolone IN DARE,HTA
21	MeSH DESCRIPTOR Methylprednisolone IN DARE,HTA
22	((adrenal NEAR2 (hormone* or steroid*))) IN DARE, HTA
23	((corticosteroid* or corticoid*)) IN DARE, HTA
24	((prednison* or Rayos* or Cortan* or Deltason* or Orason* or Intensol* or Sterapred* or methylprednisolon* or Medrol* or A-Methapred* or Depo-Medrol* or Solu-Medrol* or hydrocortison* or Cortef* or Cortril* or Hydrocortone* or A-Hydrocort* or Solu-Cortef* or dexamethason* or Decadron* or Intensol* or Dexpak* or Taperpak*)) IN DARE, HTA
25	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	#16 AND #25

Economic Search

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

Database(s): NHS Economic Evaluation Database (NHS EED), HTA Database – CRD interface
Date of last search: 11 March 2021

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

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

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

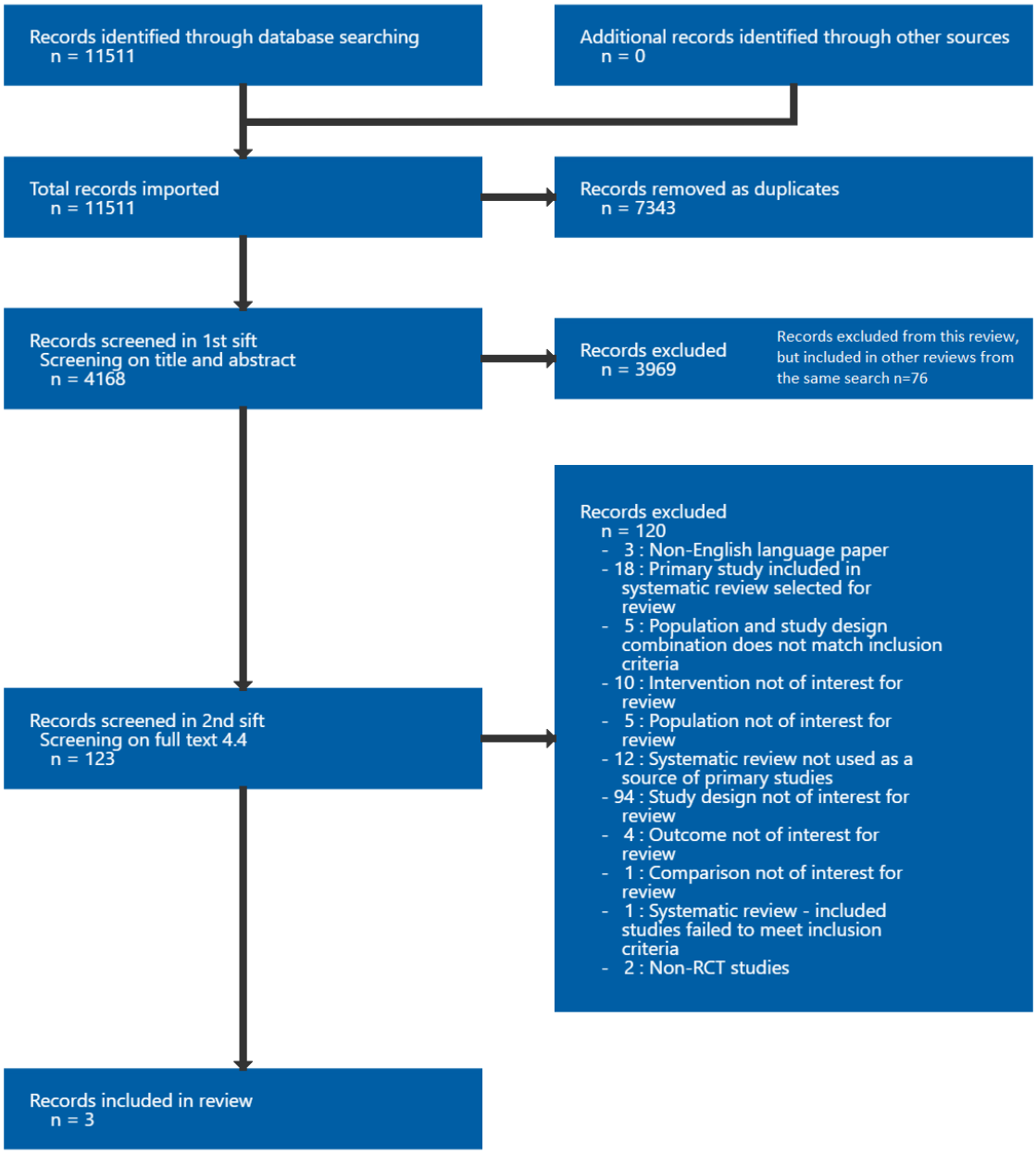
#	Searches
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
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

#	Searches
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

Table 5: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment using ROBIS or Cochrane RoB 2
Full citation Brouwer, M. C., McIntyre, P., Prasad, K., van de Beek, D., Corticosteroids for acute bacterial meningitis, Cochrane Database of Systematic Reviews Cochrane Database Syst Rev, CD004405, 2015 **Ref Id** 1135252 **Country/ies where the study was carried out** • USA (Belsey 1969, Bennett 1963, DeLemos 1969, Lebel 1988a, Lebel 1988b, Lebel 1989, Odio 1991, Wald 1995) – high income country • India (Bhaumik 1998, Mathur 2013, Sankar 2007) – lower middle income country • Malawi (Molyneux 2002, Scarborough 2007) – low income country • Netherlands, Belgium, Denmark, Austria, Germany (de Gans 2002) - high income countries • Argentina, Ecuador, Venezuela, Dominican Republic, Paraguay and Brazil (Peltola 2007) - middle income countries (except Venezuela, which is not categorised) • France and Switzerland (Thomas 1999) - high income countries • Canada (King 1994) - high income country • Egypt (Girgis 1989) - lower middle income country • Finland (Kilpi 1995) - high income country • Mozambique (Ciana 1995) - low income country • Nigeria (Bademosi 1979) - lower middle income country • Pakistan (Qazi 1996) - lower middle income country • Switzerland (Schaad 1993) - high income country • Turkey (Kanra 1995) - middle income country	**Results** Outcome: All-cause mortality Adults: Data from 6 RCTs (Bennet 1963; Bhaumik 1998; de Gans 2002; Girgis 1989; Nguyen 2007; Thomas 1999) extracted from analysis 3.1 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Children and babies: Corticosteroid = 167/1269 (13.1%) Placebo = 182/1242 (14.7%) (RR 0.89, 95% CI 0.74 to 1.07) Outcome: Long-term neurological impairment (discharge to 6 weeks) Adults: Data from 3 RCTs (Bhaumik 1998; de Gans 2002; Thomas 1999) extracted from analysis 3.3 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Children and babies: Data from 9 RCTs (Ciana 1995; Kanra 1995; Lebel 1988a; Lebel 1989b; Lebel 1989; Molyneux 2002; Peltola 2007; Sankar 2007; Wald 1995) extracted from analysis 1.4 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Outcome: Long-term neurological impairment (6 weeks to 1 year)

Study details	Results and risk of bias assessment using ROBIS or Cochrane RoB 2
• Vietnam (Nguyen 2007) - lower middle income country **Study type** Systematic review of RCTs **Study dates** 1963 to 2013 **Inclusion criteria** RCTs with participants of any age with either proven or suspected community-ABM treated with antibacterial agents and any adjuvant corticosteroid therapy **Exclusion criteria** Not reported **Patient characteristics** N=4121 Age: 0 to 17 years: 17 studies (Belsey 1969; Ciana 1995; DeLemos 1969; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Mathur 2013; Molyneux 2002; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Schaad 1993; Wald 1995) >14: 1 study (Nguyen 2007) >15: 1 study (Scarborough 2007) >16: 1 study (de Gans 2002) All ages: 5 studies (Bademosi 1979; Bennett 1963; Bhaumik 1998; Girgis 1989; Thomas 1999) Sex (reported in 20/25 studies): male 1930/3322 (58.1%); female 1392/3322 (41.9%) Proven meningitis: 6 studies (Bademosi 1979; Belsey 1969; Bennett 1963; DeLemos 1969; Kanra 1995) Suspected bacterial meningitis: 12 studies (Bhaumik 1998; Ciana 1995; de	Adults: Data from 2 RCTs (Girgis 1989; Nguyen 2007) extracted from analysis 1.5 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Children and babies: Data from 11 RCTs (De Lemos 1969; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1989b; Lebel 1989; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995) extracted from analysis 1.5 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Outcome: Any hearing loss: Adults: Data from 3 RCTs (Bhaumik 1998; de Gans 2002; Nguyen 2007) extracted from analysis 3.2 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Children and babies: Corticosteroid = 146/1001 (14.6%) Placebo = 196/960 (20.4%) (RR 0.73, 95% CI 0.61 to 0.86) Outcome: Serious intervention related events – gastrointestinal bleeding Adults: Data from 3 RCTs (de Gans 2002; Nguyen 2007; Thomas 1999) extracted from analysis 1.6 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Children and babies: Data from 12 RCTs (Kilpi 1995; King 1994; Lebel 1988a; Lebel 1989b; Lebel 1989; Marthur 2013; Odio 1991; Qazi 1996; Sankar 2007; Schaad 1993; Wald 1995) extracted from analysis 1.6 in SR; see Cochrane review

Study details	Results and risk of bias assessment using ROBIS or Cochrane RoB 2
Gans 2002; Kilpi 1995; King 1994; Mathur 2013; Molyneux 2002; Qazi 1996; Sankar 2007; Scarborough 2007; Thomas 1999; Wald 1995) Proven or suspected bacterial meningitis: 7 studies (Lebel 1988a; Lebel 1988b; Lebel 1989; Nguyen 2007; Odio 1991; Peltola 2007; Schaad 1993) Case-fatality range: 0%-54% **Interventions** **Corticosteroid:** Dexamethasone 0.4 to 1.5 mg/kg/d administered between 2 to 4 days (22 studies); hydrocortisone, prednisolone or a both administered for 3 to 14 days (3 studies: (Bademosi 1979; Bennett 1963; DeLemos 1969) **Placebo:** Specific details were not reported Steroid administered before or with antibiotic: 13 studies (Bademosi 1979; de Gans 2002; Girgis 1989; Kanra 1995; Kilpi 1995; Mathur 2013; Molyneux 2002; Nguyen 2007; Odio 1991; Peltola 2007; Qazi 1996; Scarborough 2007; Schaad 1993) Steroid administered after antibiotic: 9 studies (Bennett 1963; Bhaumik 1998; DeLemos 1969; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Thomas 1999; Wald 1995) Timing of antibiotic administration not stated: 3 studies (Belsey 1969; Ciana 1995; Sankar 2007) **Follow-up** Not reported	https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Outcome: Serious intervention related-events – persistent fever Children and babies Data from 3 RCTs (King 1994; Odio 1991; Schaad 1993) extracted from analysis 1.6 in SR; Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full Outcome: Serious intervention related-events – recurrent fever Children and babies Data from 11 RCTs (Ciana 1995; Kanra 1995; Kilpi 1995; Lebel 1988a; Lebel 1989b; Lebel 1989; Odio 1991; Peltola 2007; Qazi 1996; Schaad 1993; Wald 1995) extracted from analysis 1.6 in SR; see Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full **Risk of bias rating for SR using ROBIS** **Study eligibility criteria**: Low: objectives and eligibility criteria were pre-specified in a published protocol and they were adhered to throughout the review. **Identification and selection of studies:** Low: study identification and selection were appropriate and robust **Data collection and study appraisal:** Low: Data collection and study appraisal were done in a way that minimised error. Although data collection could be more extensively done, the reviewers do not consider this a source of bias **Synthesis and findings:** Low: Funnel plots and sensitivity analyses were carried out on all the included studies (regardless of age) where possible, however, this result is not relevant to our review as our review will analyse the adult and paediatric

Study details	Results and risk of bias assessment using ROBIS or Cochrane RoB 2
	studies separately **Overall risk of bias**: Low **Risk of bias rating for RCTs in SR using RoB** See Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full **Source of funding** Part-industry funded: 10 studies Non-industry funded: 9 studies Not reported: 9 studies **Other information** Scarborough 2007 excluded from review as 89% of the population were HIV positive
Full citation Khan, D. M., Ather, ChAA, Khan, I. M., Comparison of dexamethasone versus placebo for management of bacterial meningitis, Pakistan journal of medical and health sciences, 10, 1296-1299, 2016 **Ref Id** 1282657 **Country/ies where the study was carried out** Pakistan **Study type** RCT **Study dates** Not reported	**Results** Outcome: All-cause mortality Corticosteroid: 13/240 (5.4%) Control: 42/240 (17.5%) **1. Bias arising from the randomisation process (Low/High/Some concerns)** High: Randomisation was done by the lottery method, however, there was no mention of allocation concealment. Non-purposive sampling technique used, however no details of the methods. **2. Bias arising due to deviations from intended interventions (Low/High/Some concerns)** Unclear: not reported **3. Bias due to missing outcome data (Low/High/Some concerns)** Low: all participant data were accounted for

Study details	Results and risk of bias assessment using ROBIS or Cochrane RoB 2
Inclusion criteria Not reported **Exclusion criteria** Not reported **Patient characteristics** N = 480 Age in years (mean, SD) = 40.98, 14.28 Sex = male 67%, female 33% Aetiology = not reported Case-fatality: 20% **Interventions** **Corticosteroid** (n=240): 10mg IV dexamethasone every 6h for four days + standard regime (Cefotaxime 2g IV every 8 hours + Vancomycin 1g IV every 12 hours) **Control** (n=240): Placebo + standard regimen **Follow-up** During hospital stay	**4. Bias in measurement of the outcome (Low/High/Some concerns)** Unclear: Blind outcome assessment was not reported **5. Bias in selection of the reported result (Low/High/Some concerns)** Some concerns: Results were stratified by age, sex, duration of disease, TLC count at admission. However, not all stratified results were reported **Overall risk of bias (Low/High/Some concerns)** High **Source of funding** Not reported
Full citation Ogunlesi, T. A., Odigwe, C. C., Oladapo, O. T., Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis, Cochrane Database of Systematic Reviews. Cochrane Database Syst Rev, CD010435, 2015 **Ref Id** 1136192 **Country/ies where the study was carried out** Jordan (Daoud 1999) and India (Mathur 2013) - middle income countries	**Results** Outcome: All-cause mortality (until discharge) Corticosteroid: 11/67 (16.4%); Control: 23/65 (35.4%) Outcome: Severe neurological deficits or developmental delay (2 years) using “optimality sore”: assessed based on tone, posture, spontaneous motility, elicited motility interaction and reflexes (>20 = normal, 17 to 20 = mild deficit; <17 = moderate to severe deficit) Corticosteroid: 6/20; Control: 7/18 Outcome: Seizures persisting 5 days after treatment: Corticosteroid n=2/27; Control: n=1/25

Study details	Results and risk of bias assessment using ROBIS or Cochrane RoB 2
Study type Systematic review of RCTs **Study dates** 1999 and 2013 **Inclusion criteria** RCTs and quasi-RCTs on neonates up to 28 days of age with confirmed bacterial meningitis or suspected meningitis treated with adjunctive parenteral corticosteroid **Exclusion criteria** Neonates with tuberculous meningitis **Patient characteristics** N=132 Age: neonates with gestational age ranging between 37 weeks to full term Case-fatality range: 25% **Interventions** **Corticosteroid:** Cefotaxime and steroid 10 to 15 minutes before antibiotic administration. Dexamethasone (0.15 mg/kg body weight) was administered every 6hours for four days (n=2 RCTs). Ceftriaxone and amikacin were administered initially followed by the addition of meropenem for severely ill neonates. **Control:** Neonates were given either antibiotic alone (Daoud 1999) or adjuvant saline placebo (Mathur 2013) **Follow-up** 28 days (Mathur 2015) to 2 years (Daoud 1999)	Outcome: Hearing loss (four to 10 weeks after discharge) Corticosteroid: 6/35; Control: 10/24 **Risk of bias rating for SR using ROBIS** **Study eligibility criteria:** Low: objectives and eligibility criteria were pre-specified in a published protocol and they were adhered to throughout the review. **Identification and selection of studies:** Unclear: The search was restricted by date, however, this was not justified. **Data collection and study appraisal:** Low: There are no concerns regarding methods used to collect data and appraise studies **Synthesis and findings:** Low: There are no concerns regarding the synthesis of findings **Overall risk of bias:** Unclear **Risk of bias rating for RCTs in SR using RoB** See Cochrane review https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010435.pub2/epdf/full **Source of funding** Unclear: Mathur 2013 Non-industry funded: Daoud 1999

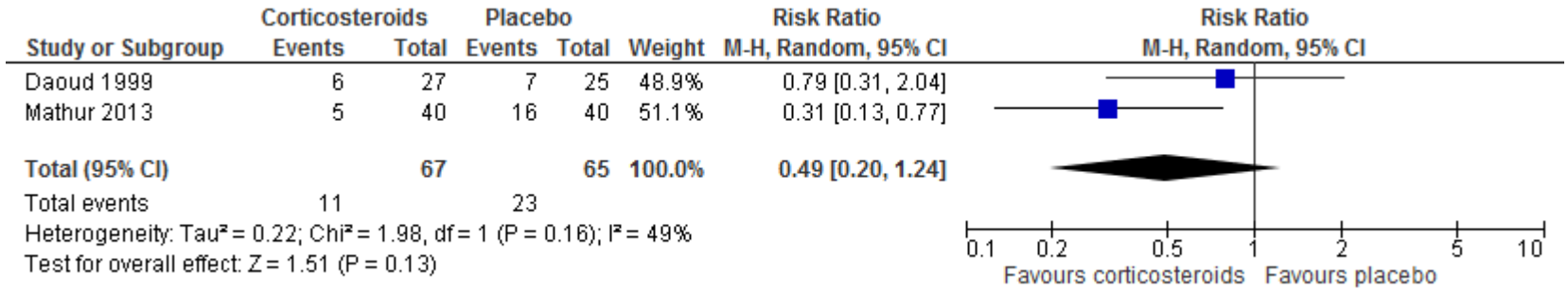
ABM: acquired bacterial meningitis; CI: confidence interval; HIV: human immunodeficiency virus; IV: intravenous; RCTs: randomised controlled trial; RoB: risk of bias; ROBIS; risk of bias assessment tool for systematic reviews; RR: risk ratio; SD: standard deviation; SR: systematic review; TLC: Total Leukocyte Count.

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

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

Figure 2: Corticosteroid versus placebo: Mortality in neonates (<28 days of age)

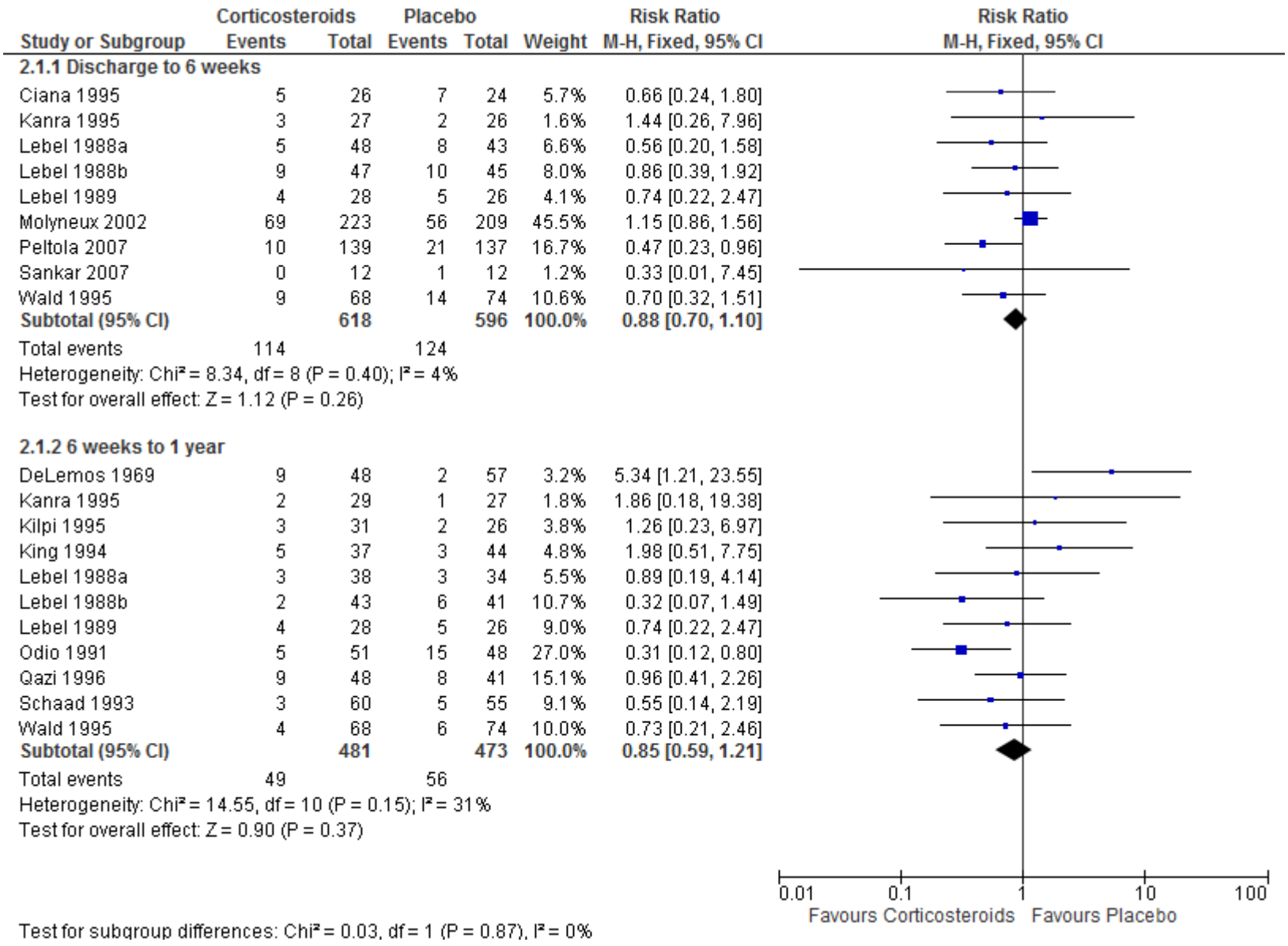


**All RCTs extracted from Cochrane SR (Ogunlesi 2015)*
CI: confidence interval; M-H: Mantel-Haenszel

Figure 3: Corticosteroid versus placebo: Mortality in babies and children

See analysis 2.1 in Cochrane review (Brouwer 2015) https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full

Figure 4: Corticosteroid versus placebo: Long-term neurological impairment in babies and children

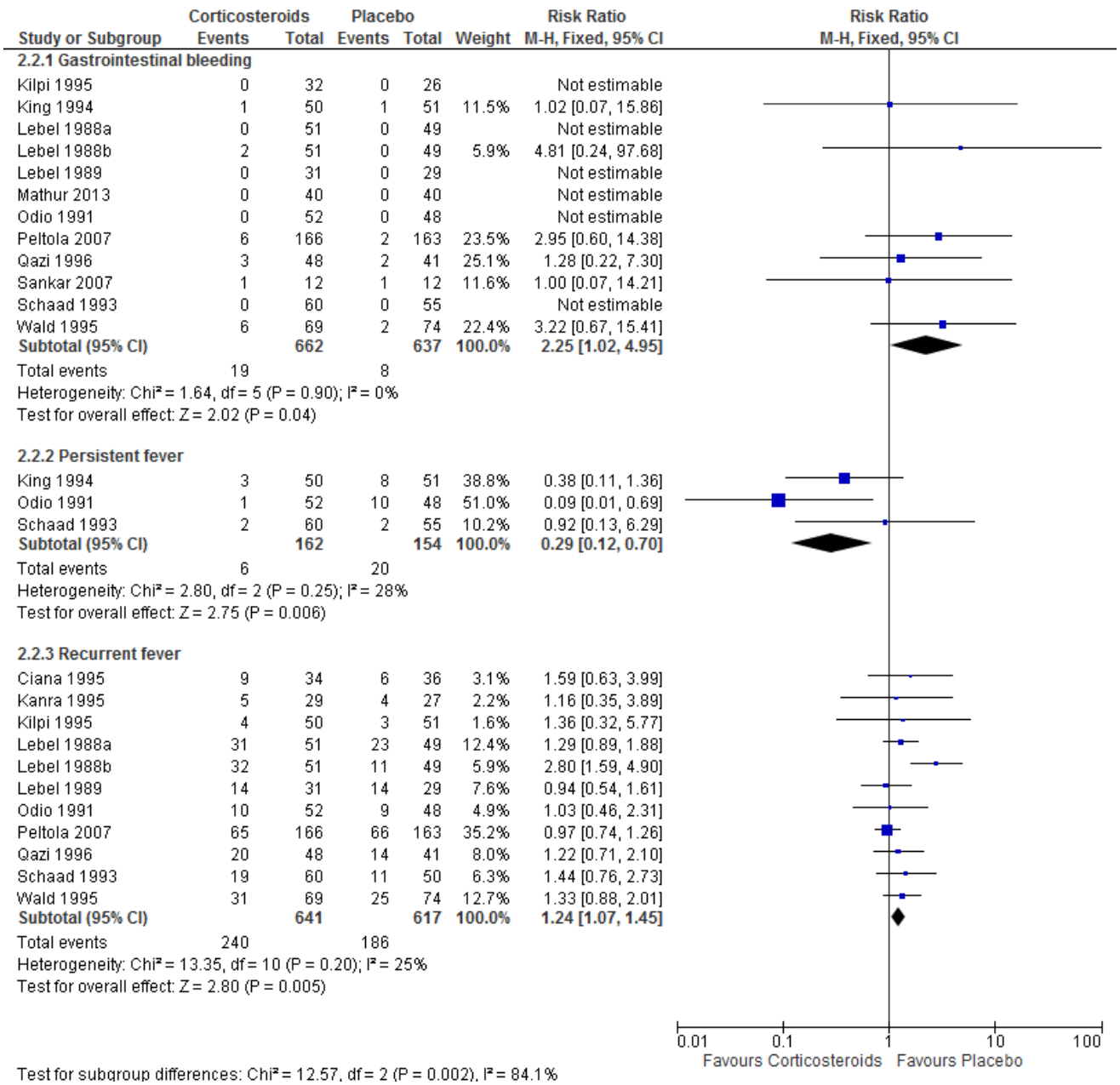


**All RCTs extracted from Cochrane SR (Brouwer 2015)*
CI: confidence interval; M-H: Mantel-Haenszel

Figure 5: Corticosteroid versus placebo: Any hearing impairment in babies and children

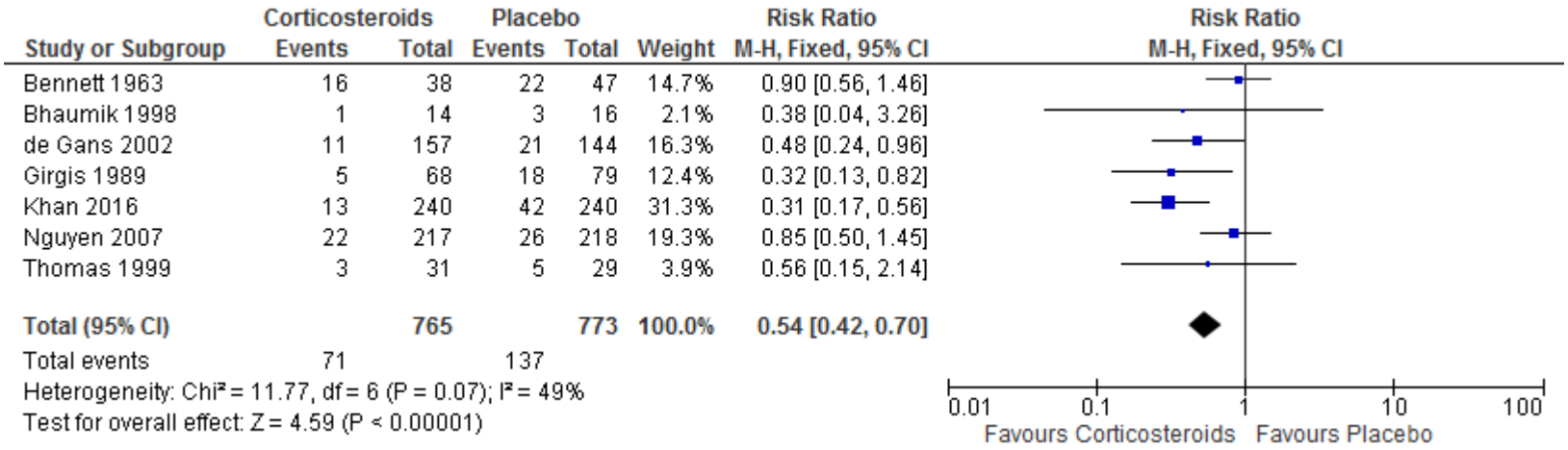
See analysis 2.3 in Cochrane review (Brouwer 2015) https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004405.pub5/epdf/full

Figure 6: Corticosteroid versus placebo: Serious intervention related adverse events - Gastrointestinal bleeding, persistent fever, and recurrent fever during hospitalisation in babies and children*


Corticosteroids
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.2.1 Gastrointestinal bleeding
Kilpi 1995 0 32 0 26 Not estimable
King 1994 1 50 1 51 11.5% 1.02 [0.07, 15.86]
Lebel 1988a 0 51 0 49 Not estimable
Lebel 1988b 2 51 0 49 5.9% 4.81 [0.24, 97.68]
Lebel 1989 0 31 0 29 Not estimable
Mathur 2013 0 40 0 40 Not estimable
Odio 1991 0 52 0 48 Not estimable
Peltola 2007 6 166 2 163 23.5% 2.95 [0.60, 14.38]
Qazi 1996 3 48 2 41 25.1% 1.28 [0.22, 7.30]
Sankar 2007 1 12 1 12 11.6% 1.00 [0.07, 14.21]
Schaad 1993 0 60 0 55 Not estimable
Wald 1995 6 69 2 74 22.4% 3.22 [0.67, 15.41]
Subtotal (95% CI) 662 637 100.0% 2.25 [1.02, 4.95]
Total events 19 8
Heterogeneity: Chi² = 1.64, df = 5 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)
2.2.2 Persistent fever
King 1994 3 50 8 51 38.8% 0.38 [0.11, 1.36]
Odio 1991 1 52 10 48 51.0% 0.09 [0.01, 0.69]
Schaad 1993 2 60 2 55 10.2% 0.92 [0.13, 6.29]
Subtotal (95% CI) 162 154 100.0% 0.29 [0.12, 0.70]
Total events 6 20
Heterogeneity: Chi² = 2.80, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 2.75 (P = 0.006)
2.2.3 Recurrent fever
Ciana 1995 9 34 6 36 3.1% 1.59 [0.63, 3.99]
Kanra 1995 5 29 4 27 2.2% 1.16 [0.35, 3.89]
Kilpi 1995 4 50 3 51 1.6% 1.36 [0.32, 5.77]
Lebel 1988a 31 51 23 49 12.4% 1.29 [0.89, 1.88]
Lebel 1988b 32 51 11 49 5.9% 2.80 [1.59, 4.90]
Lebel 1989 14 31 14 29 7.6% 0.94 [0.54, 1.61]
Odio 1991 10 52 9 48 4.9% 1.03 [0.46, 2.31]
Peltola 2007 65 166 66 163 35.2% 0.97 [0.74, 1.26]
Qazi 1996 20 48 14 41 8.0% 1.22 [0.71, 2.10]
Schaad 1993 19 60 11 50 6.3% 1.44 [0.76, 2.73]
Wald 1995 31 69 25 74 12.7% 1.33 [0.88, 2.01]
Subtotal (95% CI) 641 617 100.0% 1.24 [1.07, 1.45]
Total events 240 186
Heterogeneity: Chi² = 13.35, df = 10 (P = 0.20); I² = 25%
Test for overall effect: Z = 2.80 (P = 0.005)
Test for subgroup differences: Chi² = 12.57, df = 2 (P = 0.002), I² = 84.1%
0.01
0.1
1
10
100
Favours Corticosteroids
Favours Placebo

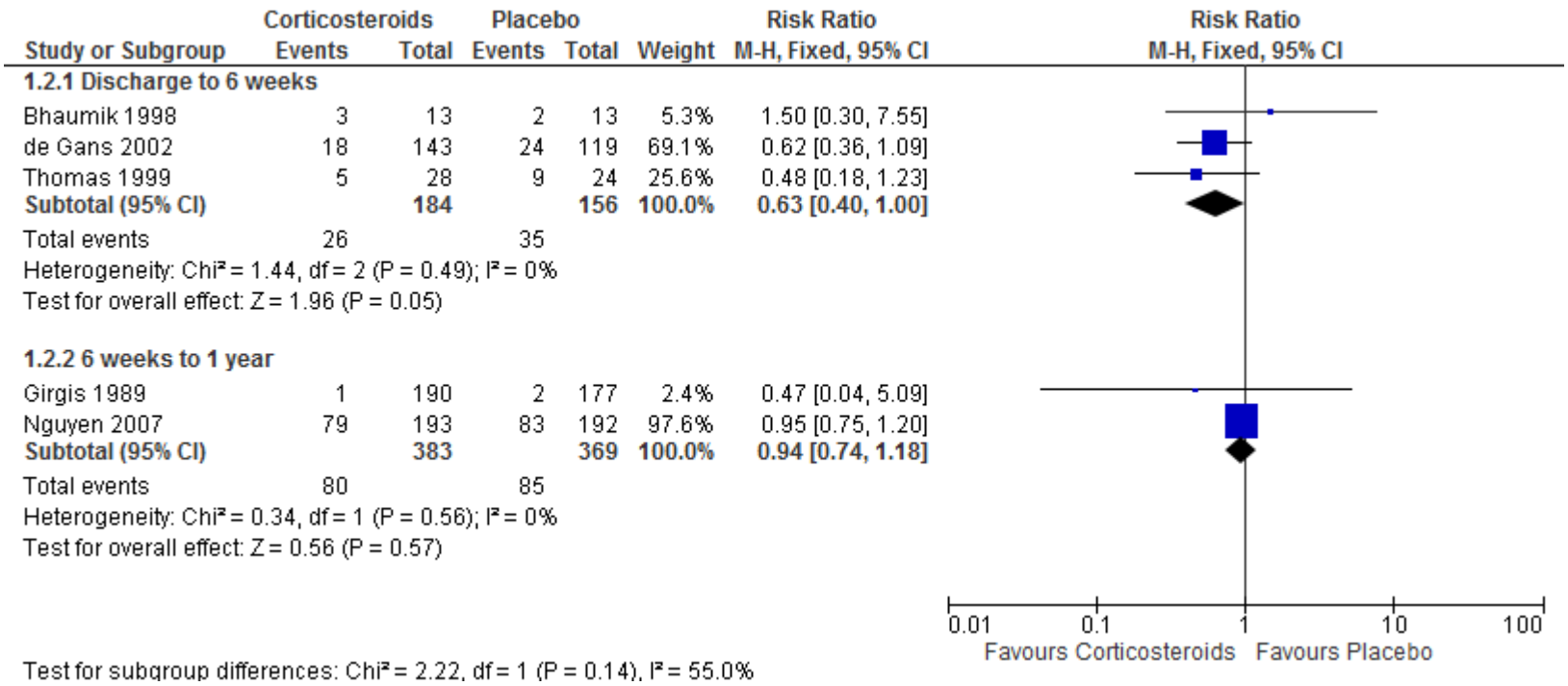
All RCTs extracted from Cochrane SR (Brouwer 2015)
CI: confidence interval; M-H: Mantel-Haenszel

Figure 7: Corticosteroids versus placebo: Mortality in adults*



6 RCTs (Bennett 1963; Bhaumik 1998; De Gans 2002; Girgis 1989; Nguyen 2007; Thomas 1999) extracted from Cochrane SR (Brouwer 2015) and 1 RCT (Khan 2016) extracted from original paper
CI: confidence interval; M-H: Mantel-Haenszel

Figure 8: Corticosteroid versus placebo: Long-term neurological impairment in adults*

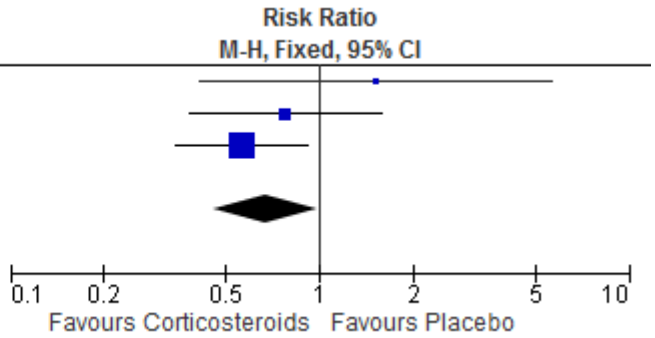


**All RCTs extracted from Cochrane SR (Brouwer 2015)*
CI: confidence interval; M-H: Mantel-Haenszel

Figure 9: Corticosteroid versus placebo: Any hearing impairment in adults*

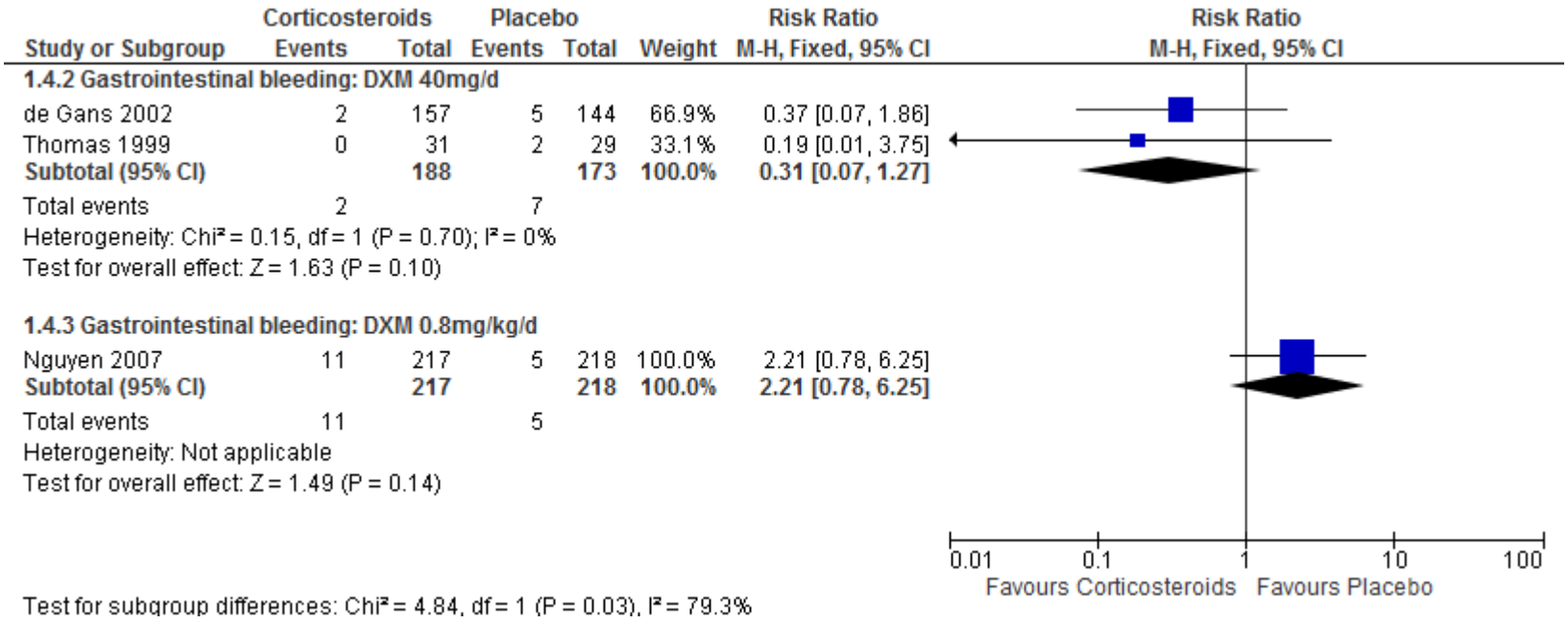
Study or Subgroup	Corticosteroids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhaumik 1998	4	14	3	16	5.1%	1.52 [0.41, 5.67]
de Gans 2002	13	143	14	119	27.6%	0.77 [0.38, 1.58]
Nguyen 2007	21	180	37	177	67.4%	0.56 [0.34, 0.91]
Total (95% CI)		**337**		**312**	**100.0%**	**0.67 [0.45, 0.98]**
Total events	38		54			

Heterogeneity: Chi² = 2.18, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 2.07 (P = 0.04)



**All RCTs extracted from Cochrane SR (Brouwer 2015)*
CI: confidence interval; M-H: Mantel-Haenszel

Figure 10: Corticosteroid versus placebo: Serious intervention related adverse events - Gastrointestinal bleeding during hospitalisation in adults



**All RCTs extracted from Cochrane SR (Brouwer 2015)*
CI: confidence interval; M-H: Mantel-Haenszel

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

Table 6: Clinical evidence profile for comparison: Corticosteroid versus placebo in neonates (<28 days of age) with bacterial meningitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid	Control	Relative (95% CI)	Absolute		
Mortality - neonates (<28 days of age)												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/67 (16.4%)	23/65 (35.4%)	) RR 0.49 (0.20 to 1.24	180 fewer per 1000 (from 283 fewer to 85 more)	VERY LOW	CRITICAL
Developmental delay assessed at approximately 2 years using "optimality score" - neonates (<28 days of age)**												
1 (Daoud 1999 extracted from SR Ogunlesi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/20 (30%)	7/18 (38.9%)	RR 0.77 (0.32 to 1.87)	89 fewer per 1000 (from 264 fewer to 338 more)	VERY LOW	CRITICAL
Seizures persisting after 5 days of treatment - neonates (<28days of age)												
1 (Daoud 1999 extracted from SR Ogunlesi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/27 (7.4%)	1/25 (4%)	RR 1.85 (0.18 to 19.19)	34 more per 1000 (from 33 fewer to 728 more)	VERY LOW	IMPORTANT
Hearing loss at 4-10 weeks after discharge - neonates (<28days of age)												
1 (Marthur 2013 extracted from SR Ogunlesi 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	6/35 (17.1%)	10/24 (41.7%)	RR 0.41 (0.17 to 0.98)	246 fewer per 1000 (from 8 fewer to 346 fewer)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio; SR: systematic review
** See corresponding forest plot*
***See definition of "optimality score" in evidence table*

[1] SR assessed as unclear risk of bias using ROBIS; serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Ogunlesi 2015)
[2] <150 events
[3] 95% CI crosses 2 MIDs
[4] 95% CI crosses 1 MID

Table 7: Clinical evidence profile for comparison: Corticosteroid versus placebo in babies and children with bacterial meningitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo	Relative (95% CI)	Absolute		
Mortality - babies and children												
18*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	167/1269 (13.2%)	182/1242 (14.7%)	RR 0.89 (0.74 to 1.07)	16 fewer per 1000 (from 38 fewer to 10 more)	MODERATE	CRITICAL
Long-term neurological impairment (discharge to 6 weeks) - babies and children												
9*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	114/618 (18.4%)	124/596 (20.8%)	RR 0.88 (0.7 to 1.1)	25 fewer per 1000 (from 62 fewer to 21 more)	LOW	CRITICAL
Long-term neurological impairment (6 weeks to 1 year) - babies and children												
11*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/481 (10.2%)	56/473 (11.8%)	RR 0.85 (0.59 to 1.21)	18 fewer per 1000 (from 49 fewer to 25 more)	LOW	CRITICAL
Any hearing impairment - babies and children												
16*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	158/1001 (15.8%)	196/960 (20.4%)	RR 0.73 (0.61 to 0.86)	55 fewer per 1000 (from 29 fewer to 80 fewer)	LOW	IMPORTANT
Serious intervention related adverse events - Gastrointestinal bleeding (during hospitalisation) – babies and children												
12*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/662 (2.9%)	8/637 (1.3%)	RR 2.25 (1.02 to 4.95)	16 more per 1000 (from 0 more to 50 more)	VERY LOW	IMPORTANT
Serious intervention related adverse events - Persistent fever (during hospitalisation) – babies and children												
3*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/162 (3.7%)	20/154 (13%)	RR 0.29 (0.12 to 0.7)	92 fewer per 1000 (from 39 fewer to 114 fewer)	VERY LOW	IMPORTANT

Serious intervention related adverse events - Recurrent fever (during hospitalisation) – babies and children												
11*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	240/641 (37.4%)	186/617 (30.1%)	RR 1.24 (1.07 to 1.45)	72 more per 1000 (from 21 more to 136 more)	MODERATE	IMPORTANT

CI: confidence interval; RR: risk ratio; SR: systematic review
***** See corresponding forest plot
[1] SR assessed as low risk of bias using ROBIS; serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Brouwer 2015)
[2] 95% CI crossed 1 MID
[3] <150 events

Table 8: Clinical evidence profile for comparison: Corticosteroid versus placebo in adults with bacterial meningitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Corticosteroids**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Mortality - adults												
7*	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/765 (9.3%)	137/773 (17.7%)	RR 0.54 (0.42 to 0.7)	82 fewer per 1000 (from 53 fewer to 103 fewer)	VERY LOW	CRITICAL
Long-term neurological impairment (Discharge to 6 weeks) - adults												
3*	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	26/184 (14.1%)	35/156 (22.4%)	RR 0.63 (0.4 to 1)	83 fewer per 1000 (from 135 fewer to 0 more)	LOW	CRITICAL
Long-term neurological impairment (6 weeks to 1 year) - adults												
2*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	80/383 (20.9%)	85/369 (23%)	RR 0.94 (0.74 to 1.18)	14 fewer per 1000 (from 60 fewer to 41 more)	MODERATE	CRITICAL
Any hearing impairment - adults												
3*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	38/337 (11.3%)	54/312 (17.3%)	RR 0.67 (0.45 to 0.98)	57 fewer per 1000 (from 3 fewer to 95 fewer)	MODERATE	IMPORTANT

Serious intervention related adverse events - Gastrointestinal bleeding (during hospitalisation) – adults: DXM 40mg/day												
2*	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	2/188 (1.1%)	7/173 (4%)	RR 0.31 (0.07 to 1.27)	28 fewer per 1000 (from 38 fewer to 11 more)	LOW	IMPORTANT
Serious intervention related adverse events - Gastrointestinal bleeding (during hospitalisation) – adults: DXM 0.8mg/kg/day												
1 (Nguyen 2007 extracted from SR Brouwer 2015)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	11/217 (5.1%)	5/218 (2.3%)	RR 2.21 (0.78 to 6.25)	28 more per 1000 (from 5 fewer to 120 more)	LOW	IMPORTANT

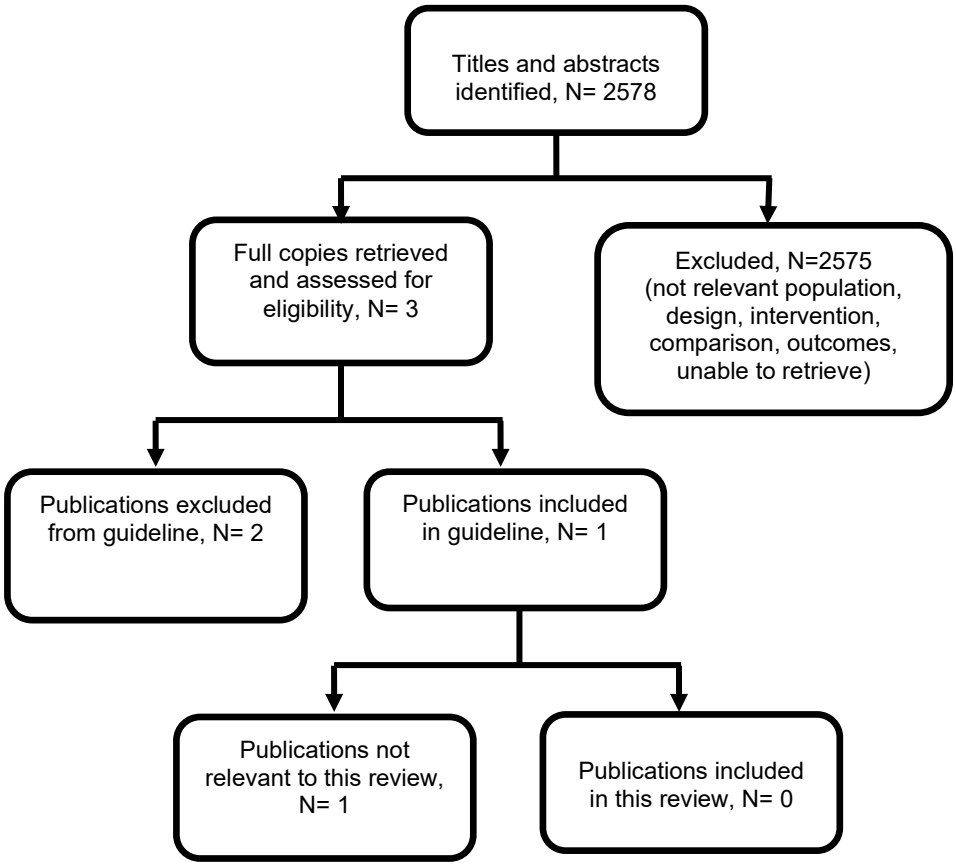
CI: confidence interval; DXM: dexamethasone; RR: risk ratio; SR: systematic review
**** See corresponding forest plot***
[1] SR assessed as low risk of bias using ROBIS; very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Brouwer 2015)
[2] <300 events
[3] SR assessed as low risk of bias using ROBIS; serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR
[4] 95% CI crossed 1 MID
[5] <150 events

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

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

Figure 11: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

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

Appendix I Economic model

Economic model for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of corticosteroid treatment in bacterial meningitis?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Ahsan,T., Shahid,M., Mahmood,T., Jabeen,R., Jehangir,U., Saleem,M., Ahmed,N., Shaheer,A., Role of dexamethasone in acute bacterial meningitis in adults, JPMA - Journal of the Pakistan Medical Association, 52, 233-239, 2002	Study design does not meet the inclusion criteria: non-randomised study
Anonymous (1989) Dexamethasone for bacterial meningitis in children. Medical Letter on Drugs & TherapeuticsMed Lett Drugs Ther 31(784): 06-Jul	Study design does not meet the inclusion criteria: editorial letter
Anonymous (1989) Dexamethasone for bacterial meningitis in children. Medical Letter on Drugs & TherapeuticsMed Lett Drugs Ther 31(784): 06-Jul	Study design does not meet the inclusion criteria: editorial letter
Anonymous (1970) Steroids and acute pyogenic meningitis. British Medical Journal 1(5687): 6	Study design does not meet the inclusion criteria: a short discussion pape; Pyogenic meningitis = bacterial meningitis
Ashwal, S, Perkin, R. M, Thompson, J. R et al. (1994) Bacterial meningitis in children: current concepts of neurologic management. Current problems in pediatrics 24(8): 267-284	Study design does not meet the inclusion criteria: Narrative review about various aspects of bacterial meningitis in children
Arditi,M., Mason,E.O.,Jr., Bradley,J.S., Tan,T.Q., Barson,W.J., Schutze,G.E., Wald,E.R., Givner,L.B., Kim,K.S., Yogev,R., Kaplan,S.L., Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics, and outcome related to penicillin susceptibility and dexamethasone use, Pediatrics, 102, 1087-1097, 1998	Study design does not meet the inclusion criteria: non-randomised study
Assiri, A. M., Alasmari, F. A., Zimmerman, V. A., Baddour, L. M., Erwin, P. J., Tleyjeh, I. M., Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis, Mayo Clinic ProceedingsMayo Clin Proc, 84, 403-9, 2009	Reports on the same studies as Brouwer 2015
Ayaz, C., Celen, M. K., Geyik, M. F., Ulug, M., The efficacy of dexamethasone treatment in adult patients with acute bacterial meningitis, NeurosciencesNeurosciences, 13, 146-50, 2008	Excluded from Brouwer 2015 as trial did not adequately generate a randomisation sequence and alternate allocation regime used
Bernardo, W. M., Aires, F. T., Sa, F. P., Effectiveness of the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis, Revista Da Associacao Medica BrasileiraRev Assoc Med Bras, 58, 319-22, 2012	Systematic review - all included studies are already included in Brouwer 2015

Study	Reason for Exclusion
Bociaga-Jasik, M., Kalinowska-Nowak, A., Garlicki, A., Mach, T., The effect of antiinflammatory therapy with dexamethasone and dexamethasone with pentoxifylline on the course of bacterial meningitis, Przeglad lekarski, 60 (11), 710-715, 2003	Article in Polish
Boisson, C, Arnaud, S, Vialet, R et al. (1999) Severe community-acquired meningitis. Critical Care 3(4): R55-R65	Study type does not meet the inclusion criteria: narrative review about various types of meningitis
Borchorst, S., Moller, K., The role of dexamethasone in the treatment of bacterial meningitis - a systematic review, Acta Anaesthesiologica ScandinavicaActa Anaesthesiol Scand, 56, 1210-21, 2012	Review - included studies were either already included or failed to meet inclusion criteria
Bortolussi, R, Moore, D. L, Robinson, J. L et al. (2008) Therapy of suspected bacterial meningitis in Canadian children six weeks of age and older - Summary. Paediatrics and Child Health 13(4): 309-310	Study design does not meet the inclusion criteria: recommendations
Bradley, J. S., Farhat, C., Stamboulian, D., Branchini, O. G., Debbag, R., Compogiannis, L. S., Ceftriaxone therapy of bacterial meningitis: cerebrospinal fluid concentrations and bactericidal activity after intramuscular injection in children treated with dexamethasone, Pediatric infectious disease journal, 13, 724-8, 1994	Systematic review including studies that are already in Brouwer 2015 and those which do not meet eligibility criteria of the review
Brouwer, M. C., Heckenberg, S. G., de Gans, J., Spanjaard, L., Reitsma, J. B., van de Beek, D., Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis, Neurology, 75, 1533-9, 2010	Study design does not meet the inclusion criteria: non-randomised study
Buke, A. C., Cavusoglu, C., Karasulu, E., Karakartal, G., Does dexamethasone affect ceftriaxone [corrected] penetration into cerebrospinal fluid in adult bacterial meningitis, International Journal of Antimicrobial AgentsInt J Antimicrob Agents, 21, 452-6, 2003	Outcome of interest not reported
Cabellos, C, Verdaguer, R, Olmo, M et al. (2009) Community-acquired bacterial meningitis in elderly patients: Experience over 30 years. Medicine 88(2): 115-119	Intervention not of interest for review: no relevant interventions reported; study describes characteristics and prognostic factors of bacterial meningitis in elderly patients
Casella, E. B., Cypel, S., Osmo, A. A., Okay, Y., Lefevre, B. H., Lichtig, I., Marques-Dias, M. J., Sequelae from meningococcal meningitis in children: a critical analysis of dexamethasone therapy, Arquivos de Neuro-PsiquiatriaArq Neuropsiquiatr, 62, 421-8, 2004	Study design not of interest for review: critical analysis
Christie, A. B. (1974) The treatment of pyogenic bacterial meningitis. Prescribers' Journal 14(6): 110-117	Study design not of interest for review: narrative review
Cooper, D. D and Seupaul, R. A. (2012) Is adjunctive dexamethasone beneficial in patients with bacterial meningitis?. Annals of Emergency Medicine 59(3): 225-6	Study design does not meet the inclusion criteria: editorial comment
Damodaran, A, Aneja, S, Malhotra, V. L et al.	Intervention not of interest for review and wrong

Study	Reason for Exclusion
(1996) Sensorineural hearing loss following acute bacterial meningitis - A prospective evaluation. Indian Pediatrics 33(9): 763-766	intervention: no mention of steroids. Wrong study design: descriptive non comparative study
Daoud,A.S., Batieha,A., Al-Sheyyab,M., Abuekteish,F., Obeidat,A., Mahafza,T., Lack of effectiveness of dexamethasone in neonatal bacterial meningitis, European Journal of Pediatrics, 158, 230-233, 1999	The study was included in a systematic review (Ogunlesi 2015) which has been selected for inclusion.
Davey, M. (2010) Theme: Acute bacterial meningitis. Emergency Medicine Journal 27(3): 178	Study design does not meet the inclusion criteria: Emergency Medicine Questions
Davies, E. G, Gibb, D, Kroll, S et al. (1992) Should we use dexamethasone in meningitis?. Archives of Disease in Childhood 67(11): 1398-1401	Study design does not meet the inclusion criteria: discussion paper
De Gans, J., Van De Beek, D., Dexamethasone in adults with bacterial meningitis; a randomised placebo-controlled trial, Nederlands tijdschrift voor geneeskunde, 146, 2235-2240, 2002	Study reported in Brouwer 2015
de Gans, J., van de Beek, D., European Dexamethasone in Adulthood Bacterial Meningitis Study, Investigators, Dexamethasone in adults with bacterial meningitis, New England Journal of MedicineN Engl J Med, 347, 1549-56, 2002	Duplicate of De Gans 2002
de Gans, J and van de Beek, D. (2003) Dexamethasone improved disability in acute bacterial meningitis. Evidence-Based Medicine 8(3): 86	Study design does not meet the inclusion criteria: commentary
Dele Davies, H and Tan, B. (2001) Therapy of suspected bacterial meningitis in Canadian children six weeks of age and older. Paediatrics and Child Health 6(3): 147-160	Study design does not meet the inclusion criteria: Canadian Paediatric Society Statement
DeLemos, R. A., Haggerty, R. J., Corticosteroids as an adjunct to treatment in bacterial meningitis. A controlled clinical trial, PediatricsPediatrics, 44, 30-4, 1969	Study conducted prior to 1980
Dias, S., Brouwer, M. C., Van De Beek, D., Differences between sexes in the response to corticosteroids in adults with community-acquired bacterial meningitis, European journal of neurology, 26 (Supplement 1), 59, 2019	Study design does not meet the inclusion criteria: conference abstract
El Bashir, H., Laundy, M., Booy, R., Diagnosis and treatment of bacterial meningitis, Archives of Disease in Childhood, 88, 615-620, 2003	Study type does not meet the inclusion criteria: discussion paper
Ellis, Jayne, Harvey, David, Defres, Sylviane et al. (2022) Clinical management of community-acquired meningitis in adults in the UK and Ireland in 2017: a retrospective cohort study on behalf of the National Infection Trainees Collaborative for Audit and Research (NITCAR). BMJ open 12(7): e062698	Outcome not of interest for review
Ellison, G. W., Corticosteroids in neurologic disease, Hospital Practice (Office Edition)Hosp Pract (Off Ed), 19, 105-9, 113-5, 1984	Study type does not meet the inclusion criteria: discussion paper
Farina, J. L. S., Alencastro, R., Dalligna, C.,	Study type does not meet the inclusion criteria:

Study	Reason for Exclusion
Rotta, N. T., Dexamethasone and bacterial meningitis: a randomised controlled trial in Brazilian children and a meta-analysis study, Neurology, 45, A349, 1995	conference abstract
Faust, S. N; Pathan, N; Levin, M. (2007) Bacterial meningitis and brain abscess. Foundation Years 3(2): 70-75	Study design does not meet the inclusion criteria: discussion paper
Feigin, R. D; McCracken Jr, G. H; Klein, J. O. (1992) Diagnosis and management of meningitis. Pediatric Infectious Disease Journal 11(9): 785-814	Study design does not meet the inclusion criteria: report
Feldman, C., Anderson, R., Bacteraemic pneumococcal pneumonia: current therapeutic options, Drugs, 71, 131-53, 2011	Study type does not meet the inclusion criteria: Discussion paper
Fischer, M., Hilinski, J., Stephens, D. S., Adjuvant therapy for meningococcal sepsis, Pediatric infectious disease journal, 24, 177-178, 2005	Study type does not meet the inclusion criteria: Discussion paper
Fox, J. L. (2006) In children with bacterial meningitis, does the addition of dexamethasone to an antibiotic treatment regimen result in a better clinical outcome than the antibiotic regimen alone?: Part A: Evidence-based answer and summary. Paediatrics & Child HealthPaediatr child health 11(1): 33-4	Study design does not meet the inclusion criteria: discussion paper
Fritz, D., Brouwer, M. C., van de Beek, D., Dexamethasone and long-term survival in bacterial meningitis, NeurologyNeurology, 79, 2177-9, 2012	Follow-up data from de Gans 2002
Geiman, B. J., Smith, A. L., Dexamethasone and bacterial meningitis. A meta-analysis of randomized controlled trials, Western Journal of MedicineWest J Med, 157, 27-31, 1992	Reports on the same studies as Brouwer 2015
Gijwani, D., Kumhar, M. R., Singh, V. B., Chadda, V. S., Soni, P. K., Nayak, K. C., Gupta, B. K., Dexamethasone therapy for bacterial meningitis in adults: a double blind placebo control study, Neurology IndiaNeurol India, 50, 63-7, 2002	Excluded from Brouwer 2015 as trial did not adequately generate a randomisation sequence and alternate allocation regime used
Ginsberg, L. (2004) Difficult and recurrent meningitis. Journal of Neurology, Neurosurgery and Psychiatry 75(suppl1)	Study design does not meet the inclusion criteria: discussion paper
Glimaker, M, Brink, M, Naucler, P et al. (2016) Betamethasone and dexamethasone in adult community-acquired bacterial meningitis: a quality registry study from 1995 to 2014. Clinical Microbiology and Infection 22(9): 814	Population does not match inclusion criteria: bacterial meningitis
Grimwood, K and Dawson, K. P. (1982) Management of acute bacterial meningitis in childhood. New Zealand Medical Journal 95(713): 545-548	Study design does not meet the inclusion criteria: discussion paper
Gupta, A., Singh, N. K., Dexamethasone in adults with bacterial meningitis, Journal of the Association of Physicians of IndiaJ Assoc Physicians India, 44, 90-2, 1996	Study design: non-randomised study
Gupta, S., Tuladhar, A. B., Does early	Narrative review

Study	Reason for Exclusion
administration of dexamethasone improve neurological outcome in children with meningococcal meningitis?, Archives of disease in childhood, 89, 82-83, 2004	
Havens, P. L., Wendelberger, K. J., Hoffman, G. M., Lee, M. B., Chusid, M. J., Corticosteroids as adjunctive therapy in bacterial meningitis. A meta-analysis of clinical trials, American Journal of Diseases of ChildrenAm J Dis Child, 143, 1051-5, 1989	Meta-analysis including studies already included in Brouwer 2015 and those which are not eligible for inclusion
Heyderman, R. S and Klein, N. J. (2000) Emergency management of meningitis. Journal of the Royal Society of Medicine 93(5): 225-229	Study design does not meet the inclusion criteria: discussion paper
Heyderman, R. S, Lambert, H. P, O'Sullivan, I et al. (2003) Early management of suspected bacterial meningitis and meningococcal septicaemia in adults. Journal of infection 46(2): 75-77	Study design does not meet the inclusion criteria: discussion paper
Heckenberg, S. G., Brouwer, M. C., van der Ende, A., van de Beek, D., Adjunctive dexamethasone in adults with meningococcal meningitis, Neurology, 79, 1563-9, 2012	Comparator of interest does not meet the inclusion criteria: results do not distinguish between dexamethasone and non-dexamethasone groups
Hoen, B, Varon, E, Debroucker, T et al. (2019) Management of acute community-acquired bacterial meningitis (excluding newborns). Short text. Medecine et Maladies Infectieuses 49(6): 367-404	Study design does not meet the inclusion criteria: summary of a consensus conference on anti-infective agents
Hsieh, Dong-Yi, Lai, Yun-Ru, Lien, Chia-Yi et al. (2021) Nationwide Population-Based Epidemiological Study for Outcomes of Adjunctive Steroid Therapy in Pediatric Patients with Bacterial Meningitis in Taiwan. International journal of environmental research and public health 18(12)	Study design does not meet the inclusion criteria: non-RCT studies - there are sufficient RCTs included in the review
Isaacs, D. (2000) The management of neonatal meningitis. Current Paediatrics 10(2): 96-103	Study design does not meet the inclusion criteria: discussion paper
Jafari, H. S and McCracken Jr, G. H. (1993) Update on steroids for bacterial meningitis. Report on Pediatric Infectious Diseases 3(2): 05-Jun	Study design does not meet the inclusion criteria: discussion paper
Johnson, R., Ho, J., Fowler, P., Heidari, A., Coccidioidal Meningitis: A Review on Diagnosis, Treatment, and Management of Complications, Current Neurology & Neuroscience ReportsCurr Neurol Neurosci Rep, 18, 19, 2018	Study type does not meet the inclusion criteria: discussion paper
Kanra, G. Y., Ozen, H., Secmeer, G., Ceyhan, M., Ecevit, Z., Belgin, E., Beneficial effects of dexamethasone in children with pneumococcal meningitis, Pediatric Infectious Disease JournalPediatr Infect Dis J, 14, 490-4, 1995	Included in Brouwer 2015
Kaplan, S. L. (1990) Corticosteroids and bacterial meningitis. Scandinavian Journal of Infectious Diseases SupplementScand J Infect Dis Suppl 73: 43-54	Study design not of interest for review: narrative review of bacterial meningitis
Kaplan, S. L. (1997) Adjunctive therapy in children with bacterial meningitis. Annals of	Study design does not meet the inclusion criteria: Narrative review about the current

Study	Reason for Exclusion
Saudi Medicine 17(2): 204-208	concepts regarding the pathophysiology of bacterial meningitis
Kaplan, S.L. (1992) New aspects of prevention and therapy of meningitis. Infectious Disease Clinics of North America 6(1): 197-214	Study design not of interest for review: narrative review of bacterial meningitis
Kellner, J. D. (2005) Corticosteroids for suspected bacterial meningitis in children - Status in 2005. Paediatrics & Child HealthPaediatr child health 10(2): 107-8	Study design does not meet the inclusion criteria: discussion paper
Kennedy,W.A., Hoyt,M.J., McCracken,G.H.,Jr., The role of corticosteroid therapy in children with pneumococcal meningitis, American Journal of Diseases of Children, 145, 1374-1378, 1991	Subset of Lebel 1988
Kilpi, T., Peltola, H., Jauhiainen, T., Kallio, M. J., Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. The Finnish Study Group, Pediatric Infectious Disease JournalPediatr Infect Dis J, 14, 270-8, 1995	Included in Brouwer 2015
King, S. M., Law, B., Langley, J. M., Heurter, H., Bremner, D., Wang, E. E., Gold, R., Dexamethasone therapy for bacterial meningitis: Better never than late?, Canadian Journal of Infectious DiseasesCan, 5, 210-5, 1994	Included in Brouwer 2015
Klastersky, J. (1971) Effectiveness of adrenal corticosteroids in the management of severe bacterial infections. Revue europeenne d'etudes cliniques et biologiques. European journal of clinical and biological research 16(5): 413-417	Study design does not meet the inclusion criteria: discussion paper
Klein, J. O. (1989) Bacterial meningitis in infants and children. Current Opinion in Infectious Diseases 2(2): 206-209	Study design does not meet the inclusion criteria: discussion paper
Klugman, K. P., Dagan, R., Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. Meropenem Meningitis Study Group, Antimicrobial Agents & ChemotherapyAntimicrob Agents Chemother, 39, 1140-6, 1995	Intervention does not meet the inclusion criteria: no corticosteroid treatment
Koelman, Diederik L H, Brouwer, Matthijs C, Ter Horst, Liora et al. (2022) Pneumococcal Meningitis in Adults: A Prospective Nationwide Cohort Study Over a 20-year Period. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 74(4): 657-667	Study design does not meet the inclusion criteria: non-RCT studies - here are sufficient RCTs included in the review
Lambert, H. P. (1994) Meningitis. Journal of Neurology Neurosurgery and Psychiatry 57(4): 405-415	Study design does not meet the inclusion criteria: discussion paper
Lebel, M. H., Freij, B. J., Syrogiannopoulos, G. A., Chrane, D. F., Hoyt, M. J., Stewart, S. M., Kennard, B. D., Olsen, K. D., McCracken, G. H., Jr., Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials, New England Journal of MedicineN Engl J Med, 319, 964-71, 1988	Included in Brouwer 2015
Lebel, M. H., Hoyt, M. J., Waagner, D. C.,	Included in Brouwer 2015

Study	Reason for Exclusion
Rollins, N. K., Finitzo, T., McCracken, G. H., Jr., Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis, American Journal of Diseases of ChildrenAm J Dis Child, 143, 301-6, 1989	
Lipton, J.D and Schafermeyer, R.W. (1993) Evolving concepts in pediatric bacterial meningitis - Part II: Current management and therapeutic research. Annals of Emergency Medicine 22(10): 1616-1629	Study design does not meet the inclusion criteria: narrative review
Lorber, J. (1976) Treatment of neonatal meningitis. Prescribers' Journal 16(4): 82-90	Population not of interest for review: neonates. Study design not of interest for review: narrative review of current treatment recommendations, complications, prognosis
Low, P. S. (1991) An update on bacterial meningitis. Journal of the Singapore Paediatric SocietyJ Singapore Paediatr Soc 33(01feb): 11-May	Study design not of interest for review: narrative review of bacterial meningitis: diagnosis, progression of the illness, pathophysiology, prevention, and current treatment
Mathur, N. B., Garg, A., Mishra, T. K., Role of dexamethasone in neonatal meningitis: a randomized controlled trial, Indian Journal of PediatricsIndian J Pediatr, 80, 102-7, 2013	Included in Brouwer 2015
McCracken Jr, G. H. (2004) Current management of bacterial meningitis. Advances in Experimental Medicine and Biology 549: 31-33	Study design not of interest for review: narrative overview of bacterial meningitis, including diagnosis, vaccine development, and treatment
McCracken, G. H and Jr. (1992) Current management of bacterial meningitis in infants and children. Pediatric Infectious Disease Journal 11(2): 169-74	Study design does not meet the inclusion criteria: editorial
McCracken, G. H., Jr., Lebel, M. H., Dexamethasone therapy for bacterial meningitis in infants and children, American Journal of Diseases of ChildrenAm J Dis Child, 143, 287-9, 1989	Study type does not meet the inclusion criteria: editorial
McGee, S., Hirschmann, J., Use of corticosteroids in treating infectious diseases, Archives of Internal MedicineArch Intern Med, 168, 1034-46, 2008	Mixed population. 15 studies identified which investigated corticosteroid therapy in bacterial meningitis. Limited information provided on these studies.
McIntyre,P.B., Berkey,C.S., King,S.M., Schaad,U.B., Kilpi,T., Kanra,G.Y., Perez,C.M., Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988, JAMA, 278, 925-931, 1997	All studies were included in Brouwer 2015
McIntyre,P.B., Macintyre,C.R., Gilmour,R., Wang,H., A population based study of the impact of corticosteroid therapy and delayed diagnosis on the outcome of childhood pneumococcal meningitis, Archives of Disease in Childhood, 90, 391-396, 2005	Study design does not meet the inclusion criteria: non-randomised study
Molyneux, E and Njiram'madzi, J. (2015) Prevention and treatment of bacterial meningitis in resource poor settings. Pediatric Infectious Disease Journal 34(4): 441-443	Study design does not meet the inclusion criteria: review
Morley, S. L and Levin, M. (1998) Bacterial	Study design not of interest for review: narrative

Study	Reason for Exclusion
meningitis. Prescribers' Journal 38(3): 129-141	review of the clinical picture, diagnosis, management, antibiotic treatment and resistance, and steroid use
Mulhem, Elie, In adults with acute bacterial meningitis, is adding corticosteroids to standard treatment with antibacterial agents helpful?, Cochrane Clinical Answers, 2016	Already included in Brouwer 2015
Mulhem, Elie, In children with acute bacterial meningitis, is there randomized controlled trial evidence to support adding corticosteroids to standard treatment with antibacterial agents?, Cochrane Clinical Answers, 2016	Already included in Brouwer 2015
Murray, J. D, Fleming, P. C, Anglin, C. S et al. (1972) Acute bacterial meningitis in childhood: an outline of management. Clinical Pediatrics 11(8): 455-64	Intervention not of interest for review: no relevant interventions reported
Namani, S; Milenkovic, Z; Koci, B. (2013) A prospective study of risk factors for neurological complications in childhood bacterial meningitis. Jornal de Pediatria 89(3): 256-62	Population and study design combination does not match inclusion criteria
Nguyen, T. H., Tran, T. H., Thwaites, G., Ly, V. C., Dinh, X. S., Ho Dang, T. N., Dang, Q. T., Nguyen, D. P., Nguyen, H. P., To, S. D., Nguyen v, V., Nguyen, M. D., Campbell, J., Schultsz, C., Parry, C., Torok, M. E., White, N., Nguyen, T. C., Tran, T. H., Stepniewska, K., Farrar, J. J., Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis, New England Journal of MedicineN Engl J Med, 357, 2431-40, 2007	Included in Brouwer 2015
Nichols, D and Jordan, V. (2003) Dexamethasone in acute bacterial meningitis. CJEM Canadian Journal of Emergency Medical CareCJEM, Can 5(6): 412-5	Study design does not meet the inclusion criteria: commentary paper, review of de Gans 2002
Odio, C. M., Faingezicht, I., Paris, M., Nassar, M., Baltodano, A., Rogers, J., Saez-Llorens, X., Olsen, K. D., McCracken, G. H., Jr., The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis, New England Journal of MedicineN Engl J Med, 324, 1525-31, 1991	Included in Brouwer 2015
Peltola, H., Roine, I., Improving the outcomes in children with bacterial meningitis, Current Opinion in Infectious DiseasesCurr Opin Infect Dis, 22, 250-5, 2009	Narrative review
Peltola, H., Roine, I., Fernandez, J., Gonzalez Mata, A., Zavala, I., Gonzalez Ayala, S., Arbo, A., Bologna, R., Goyo, J., Lopez, E., Mino, G., Dourado de Andrade, S., Sarna, S., Jauhiainen, T., Hearing impairment in childhood bacterial meningitis is little relieved by dexamethasone or glycerol, PediatricsPediatrics, 125, e1-8, 2010	Analysis not of interest for review: secondary analysis of Peltola 2007 examining the effect of interventions and presenting status on different thresholds of hearing loss
Peltola,H., Roine,I., Fernandez,J., Zavala,I., Ayala,S.G., Mata,A.G., Arbo,A., Bologna,R., Mino,G., Goyo,J., Lopez,E., de Andrade,S.D., Sarna,S., Adjuvant glycerol and/or dexamethasone to improve the outcomes of	Included in Brouwer 2015

Study	Reason for Exclusion
childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial, Clinical Infectious Diseases, 45, 1277-1286, 2007	
Peterkovic, V, Trkulja, V, Kutlesa, M et al. (2011) Dexamethasone for adult community-acquired bacterial meningitis: 20 years of experience in daily practice. Journal of neurology: 01-Dec	Population and study design combination does not match inclusion criteria
Plotkin, S. A, Halsey, N. A, Lepow, M. L et al. (1990) Dexamethasone therapy for bacterial meningitis in infants and children. Pediatrics 86(1): 130-133	Study type does not meet the inclusion criteria: discussion paper
Pomeroy, S. L. (1990) Neurologic sequelae of bacterial meningitis in children. Current Opinion in Pediatrics 2(6): 1071-1074	Intervention not of interest for review: no relevant interventions reported
Prasad, K., Karlupia, N., Kumar, A., Treatment of bacterial meningitis: an overview of Cochrane systematic reviews, Respiratory MedicineRespir Med, 103, 945-50, 2009	Overview of systematic reviews
Prats, J. A. G. G., Gaspar, A. J., Ribeiro, A. B. G., de Paula, G. D., de Boas, L. V. S. P. V., de Sa, F. P., Systematic review of dexamethasone as an adjuvant therapy for bacterial meningitis in children, Revista Paulista de Pediatria, 30, 586-593, 2012	All studies included in Brouwer 2015
Qazi, S. A., Khan, M. A., Mughal, N., Ahmad, M., Joomro, B., Sakata, Y., Kuriya, N., Matsuishi, T., Abbas, K. A., Yamashita, F., Dexamethasone and bacterial meningitis in Pakistan, Archives of Disease in ChildhoodArch Dis Child, 75, 482-8, 1996	Included in Brouwer 2015
Quagliarello, V. J and Scheld, W. M. (1997) Treatment of bacterial meningitis. New England journal of medicine 336(10): 708-16	Study design does not meet the inclusion criteria: discussion paper
Quagliarello, V and Scheld, W. M. (2010) Do steroids benefit patients with bacterial meningitis?. Nature Reviews Neurology 6(10): 529-530	Study type does not meet the inclusion criteria: commentary
Rayanakorn, A., Ser, H. L., Pusparajah, P., Chan, K. G., Goh, B. H., Khan, T. M., Saokaew, S., Lee, S. W. H., Lee, L. H., Comparative efficacy of antibiotic(s) alone or in combination of corticosteroids in adults with acute bacterial meningitis: A systematic review and network meta-analysis, 15, e0232947, 2020	All the relevant studies are included in Brouwer 2015 and Gijwani 2002
Rosdahl, N; Jensen, K; Ranek, L. (1970) Steroids and acute pyogenic meningitis. British Medical Journal 2(5701): 113	Study design not of interest for review: short report on pneumococcal meningitis (wrong population); Pyogenic m = bacterial m: Pneumococcal Meningitis. letter to the Editor
Saez-Llorens, X, Ramilo, O, Mustafa, M. M et al. (1990) Molecular pathophysiology of bacterial meningitis: Current concepts and therapeutic implications. Journal of Pediatrics 116(5): 671-684	Study type does not meet the inclusion criteria: review

Study	Reason for Exclusion
Sankar,J., Singhi,P., Bansal,A., Ray,P., Singhi,S., Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis, Indian Pediatrics, 44, 649-656, 2007	Included in Brouwer 2015
Scarborough, M., Gordon, S. B., Whitty, C. J., French, N., Njalale, Y., Chitani, A., Peto, T. E., Lalloo, D. G., Zijlstra, E. E., Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa, New England Journal of MedicineN Engl J Med, 357, 2441-50, 2007	Population not of interest for review: 89% of population HIV positive
Schaad, U. B., Lips, U., Gnehm, H. E., Blumberg, A., Heinzer, I., Wedgwood, J., Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group, LancetLancet, 342, 457-61, 1993	Included in Brouwer 2015
Scheifele, D. W. (1994) Dissenting views on dexamethasone therapy for bacterial meningitis. Canadian Journal of Infectious DiseasesCan 5(5): 201-2	Study design does not meet the inclusion criteria: editorial
Shao, M., Xu, P., Liu, J., Liu, W., Wu, X., The role of adjunctive dexamethasone in the treatment of bacterial meningitis: an updated systematic meta-analysis, Patient preference & adherencePatient Prefer Adherence, 10, 1243-9, 2016	Eight of the ten studies in meta-analysis included in Brouwer 2015. 2 studies not included were published in Chinese (Fu 2009 and He 2013) and insufficient study details in meta-analysis to complete risk of bias assessment.
Shembesh, N. M., Elbargathy, S. M., Kashbur, I. M., Rao, B. N., Mahmoud, K. S., Dexamethasone as an adjunctive treatment of bacterial meningitis, Indian Journal of PediatricsIndian J Pediatr, 64, 517-22, 1997	Excluded from Brouwer 2015 as trial did not adequately generate a randomisation sequence and alternate allocation regime used
Singhi, P.D. (1994) Recent trends in the management of acute bacterial meningitis. Indian Pediatrics 31(11): 1321-1327	Study design does not meet the inclusion criteria: editorial
in childhood bacterial meningitis in Malawi: a randomized controlled trial. Current Infectious Disease ReportsCurr Infect Dis Rep 4(5): 375-376	Study design does not meet the inclusion criteria: editorial comment
Suh, K. N., Dexamethasone in adults with bacterial meningitis, Canadian medical association journal, 168, 740, 2003	Study type does not meet the inclusion criteria: editorial
Svendsen, M. B, Ring Kofoed, I, Nielsen, H et al. (2020) Neurological sequelae remain frequent after bacterial meningitis in children. Acta Paediatrica 109(2): 361-367	Population not of interest for review: no relevant data reported; only 9% of the study population received dexamethasone
Tan, B; Davies, H; members of the Paediatric Investigators' Collaborative Network on Infections in, Canada (2002) Dexamethasone and antibiotics for the empirical treatment of bacterial meningitis in Canadian children: A survey of paediatric infectious diseases specialists. Paediatrics & Child HealthPaediatr child health 7(6): 390-7	Study design does not meet the inclusion criteria: survey of a group of paediatric infectious diseases specialists and microbiologists in Canada
Thomas, R., Le Tulzo, Y., Bellissant, E., The role of corticosteroid therapy on bacterial meningitis in adults, Medecine ET maladies	Article in French

Study	Reason for Exclusion
infectieuses, 26, 1119-1124, 1996	
Thomas, R., Le Tulzo, Y., Bouget, J., Camus, C., Michelet, C., Le Corre, P., Bellissant, E., Trial of dexamethasone treatment for severe bacterial meningitis in adults. Adult Meningitis Steroid Group, Intensive Care MedicineIntensive Care Med, 25, 475-80, 1999	Study reported on in Brouwer 2015
Tian, C., Jin, S., Zhao, Z. et al. (2022) Association of Corticosteroid Treatment With Outcomes in Pediatric Patients With Bacterial Meningitis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Clinical Therapeutics 44(4): 551-564	Systematic review - included studies failed to meet inclusion criteria
Tolaj, I., Dreshaj, S., Qehaja, E., Tolaj, J., Doda-Ejupi, T., Mehmeti, M., Dexamethasone as adjuvant therapy in the treatment of invasive meningococcal diseases, Medicinski ArhivMed Arh, 64, 228-30, 2010	Meningococcal disease (population incorrect for this question)
Tolaj, I., Ramadani, H., Mehmeti, M., Gashi, H., Kasumi, A., Gashi, V., Jashari, H., Does Dexamethasone Helps in Meningococcal Sepsis?, Medical archives (Sarajevo, Bosnia and Herzegovina), 71, 173-177, 2017	Population not of interest for review: all population had meningococcal disease
Townsend, G.C and Scheld, W.M. (1996) Anti-inflammatory therapy for bacterial meningitis. Rationale and practice. Clinical Immunotherapeutics 5(3): 223-229	Study design does not meet the inclusion criteria: discussion paper about the pathophysiology and management of bacterial meningitis
Tubiana, S, Varon, E, Biron, C et al. (2020) Community-acquired bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort. Clinical Microbiology and Infection 26(9): 1192-1200	Outcome not of interest for review: data not presented by corticosteroid treatment group; cannot extract relevant data (no comparative data). Supplementary tables also checked: not sure if it is relevant
Tunkel, A. R. (2003) Adjunctive Dexamethasone in Bacterial Meningitis in Children. Current Infectious Disease Reports 5(4): 319	Study design does not meet the inclusion criteria: A short clinical trial report
Tunkel, A. R. (2003) Adjunctive Dexamethasone in Bacterial Meningitis in Adults. Current Infectious Disease Reports 5(4): 320-321	Study design does not meet the inclusion criteria: editor's comment
Tunkel, A. R and Scheld, W. M. (1989) Therapy of bacterial meningitis: principles and practice. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America 10(12): 565-569	Study design not of interest for review: narrative review of antibiotic therapy and use of corticosteroids
Tunkel, A. R and Scheld, W. M. (1991) Therapy of bacterial meningitis in children. International Journal of Antimicrobial Agents 1(02mar): 109-115	Study design not of interest for review: narrative review of antimicrobial therapy and other adjunct therapies
Tuomanen, E. (1990) Advances in the diagnosis and management of bacterial meningitis. Current Opinion in Infectious Diseases 3(5): 596-602	Study type does not meet the inclusion criteria: discussion paper
van de Beek, D, Brouwer, M, Hasbun, R et al. (2016) Community-acquired bacterial meningitis. Nature Reviews. Disease PrimersNat Rev Dis Prim 2: 16074	Study design does not meet the inclusion criteria: an overview of various aspects of bacterial meningitis

Study	Reason for Exclusion
Van De Beek, D., De Gans, J., Dexamethasone and pneumococcal meningitis, Annals of internal medicine, 141, 327, 2004	Study type does not meet the inclusion criteria: editorial letter
van de Beek, D, de Gans, J, McIntyre, P et al. (2004) Review: Adjuvant corticosteroid therapy reduces death, hearing loss, and neurological sequelae in bacterial meningitis. Evidence-Based Medicine 9(2): 48	Study design not of interest for review: short report on Cochrane SR; superseded by more recent publication (Brouwer 2015)
van de Beek, D., de Gans, J., McIntyre, P., Prasad, K., Steroids in adults with acute bacterial meningitis: a systematic review, The Lancet Infectious DiseasesLancet Infect Dis, 4, 139-43, 2004	Study type does not meet the inclusion criteria: Editorial letter
van de Beek, D., Farrar, J. J., de Gans, J., Mai, N. T., Molyneux, E. M., Peltola, H., Peto, T. E., Roine, I., Scarborough, M., Schultsz, C., Thwaites, G. E., Tuan, P. Q., Zwinderman, A. H., Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data, Lancet NeurologyLancet neurol, 9, 254-63, 2010	All relevant studies included in Brouwer 2015
Van Der Heide, R. M., De Gans, J., Van De Beek, D., Favorable effect of dexamethasone in adults with acute bacterial meningitis; a randomized placebo-controlled study, Nederlands tijdschrift voor geneeskunde, 147, 223-224, 2003	Article in Dutch
Vardakas, K. Z., Matthaiou, D. K., Falagas, M. E., Adjunctive dexamethasone therapy for bacterial meningitis in adults: a meta-analysis of randomized controlled trials, European Journal of NeurologyEur J Neurol, 16, 662-73, 2009	All relevant studies included in Brouwer 2015
Wald, E. R., Kaplan, S. L., Mason, E. O., Jr., Sabo, D., Ross, L., Arditi, M., Wiedermann, B. L., Barson, W., Kim, K. S., Yogov, R., et al.,, Dexamethasone therapy for children with bacterial meningitis. Meningitis Study Group, PediatricsPediatrics, 95, 21-8, 1995	Included in Brouwer 2015
Wang, Y., Liu, X., Wang, Y., Liu, Q., Kong, C., Xu, G., Meta-analysis of adjunctive dexamethasone to improve clinical outcome of bacterial meningitis in children [Correction: Childs Nervous System 2018; 34(2): 225], Childs Nervous SystemChilds Nerv Syst, 34, 217-223, 2018	Systematic review - eligible studies in the review have been included
Weisfelt, M., van de Beek, D., de Gans, J., Dexamethasone treatment in adults with pneumococcal meningitis: risk factors for death, European Journal of Clinical Microbiology & Infectious DiseasesEur J Clin Microbiol Infect Dis, 25, 73-8, 2006	Study design does not meet the inclusion criteria: non-randomised study

HIV: human immunodeficiency virus.

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 is the effectiveness of corticosteroid treatment in bacterial meningitis?

Research question

What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in newborn babies with suspected or confirmed bacterial meningitis?

Why this is important

Neonatal bacterial meningitis is associated with high morbidity, despite the availability of antibiotics that are highly effective against the leading causes of bacterial meningitis in this age group. New approaches to management are needed because there are currently no vaccines to protect against infection from the causative organisms. Corticosteroids are effective as an adjunct to antibiotic treatment in older children with meningitis caused by Hib, and in adults with bacterial meningitis. However, there is insufficient evidence for adjunctive corticosteroid treatment in neonates. Extrapolation from older age groups would be inappropriate because the spectrum of organisms causing infection in neonates is different, and the impact on the developing brain of the causative organisms during inflammation may not be the same.

Table 4: Research recommendation rationale

Research question	**What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in newborn babies with suspected or confirmed bacterial meningitis?**
Why is this needed	
Importance to 'patients' or the population	Neonatal bacterial meningitis is associated with high morbidity. New approaches to management are needed because there are currently no vaccines to protect against infection from the causative organisms.
Relevance to NICE guidance	The committee agreed to not write recommendations on the use of corticosteroids in neonates due to insufficient evidence
Relevance to the NHS	New approaches to management are needed. Bacterial meningitis is accompanied by marked inflammation in the subarachnoid space and corticosteroids given with antibiotics can reduce this inflammation.
National priorities	This does not align with any specific NHS priority but new approaches to the clinical management of bacterial meningitis in neonates are required
Current evidence base	There is evidence showing corticosteroids (as an adjunct to antibiotics) are effective in older children with meningitis caused by Hib and in adults with bacterial meningitis, but there is insufficient evidence for adjunctive corticosteroid treatment in neonates. Extrapolation from older age groups would be inappropriate because the

Research question	What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in newborn babies with suspected or confirmed bacterial meningitis?
	spectrum of organisms causing infection in neonates is different, and the impact on the developing brain of the causative organisms during inflammation may not be the same.
Equality	No equality issues identified
Feasibility	Given that adjunctive corticosteroid treatment is in line with current NHS practice, the use of adjunctive corticosteroids in neonates was considered feasible
Other comments	None

Table 5: Research recommendation modified PICO table

Criterion	Explanation
Population	Neonates (aged 28 days old and younger) with confirmed bacterial meningitis
Intervention	Corticosteroids (dexamethasone, hydrocortisone, prednisolone, or methylprednisolone; administered via any route) as an adjunct to antibiotic treatment
Comparator	Antibiotic treatment alone (no corticosteroid treatment)
Outcomes	All-cause mortality Long-term neurological deficits Developmental delay Diagnosis of epilepsy or occurrence of seizures during hospitalisation Hearing impairment Serious intervention-related adverse effects
Study design	RCT
Timeframe	2-year post-intervention follow-up
Additional information	None

RCT: randomised controlled trial