National Institute for Health and Care Excellence

Final

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

[H] Evidence review for corticosteroids in meningococcal disease

NICE guideline NG240

Evidence review underpinning recommendations 1.8.6 and 1.8.7 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

Disclaimer

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

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

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Corticosteroids in meningococcal disease

Review question

What is the effectiveness of corticosteroid treatment in meningococcal disease?

Introduction

Meningococcal disease (meningococcal sepsis with or without an associated meningitis) is a rare but serious infection, which can occur in any age group. Meningococcal disease is a life-threatening medical emergency, which may progress with devastating speed. Prompt recognition and early treatment are the most important aspects of early management. Adjunctive treatment with corticosteroids in the management of meningococcal disease is controversial.

The aim of this review is to determine the effectiveness of supplemental corticosteroids in the management of meningococcal disease.

Summary of the protocol

See Table1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis).
Intervention	Corticosteroids (any or the below administered via any route, alone or in combination with fludrocortisone): • Dexamethasone • Hydrocortisone • Prednisolone • Methylprednisolone
Comparison	• Head-to-head comparisons between the above corticosteroids • Placebo • No corticosteroid treatment
Outcome	**Critical** 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. **Important** Population: adults • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • 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 • Length of hospitalisation Population: infants and children • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • 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

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

For further details see the review protocol in appendix A.

Methods and process

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

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

Effectiveness evidence

Included studies

Two studies were included for this review, 1 randomised controlled trial (RCT; Tolaj 2010), and 1 retrospective cohort study (Madhi 2013).

The included studies are summarised in Table 2.

Both studies compared corticosteroid to no corticosteroid treatment (Madhi 2013, Tolaj 2010).

One study included babies and children (Madhi 2013). One study included babies, children, and adults, however, as only 10% of the population was aged over 12 years suggesting very little data on adults, the population was categorised as babies and children (Tolaj 2010). The retrospective cohort study did not provide analyses adjusted for confounding factors (Madhi 2013).

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

Excluded studies

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

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Madhi 2013 Retrospective cohort study France	N=805 Children 1 day to 18 years old with meningococcal meningitis or meningococcal septic shock Age in years (mean; SD): Corticosteroids: 4.4; 4.9 No corticosteroid treatment 4.3; 4.4 Mortality: Corticosteroids: 12.6% No corticosteroid treatment: 4.5%	Corticosteroids (n = 270) No further details reported	No corticosteroid treatment (n = 535) No further details reported	• All-cause mortality	Corticosteroids were used in 41.7% of severe cases as compared with 25.8% of other cases.
Tolaj 2010 RCT Kosovo	N=147 Meningococcal bacteraemia (all ages) with or without meningitis, isolated by blood and/or CSF culture, or clinical presentation consistent with sepsis with skin petechial haemorrhages. Age in years (median; range): 4.76; 0-33 Mortality: Dexamethasone:	Dexamethasone (n = 92) Treated with dexamethasone, 0.15 mg/kg, every 6 h, for 4(four) days, as adjuvant therapy. The first dose of dexamethasone was given up to 30 minutes before the initiation of the antibiotic treatment.	No dexamethasone (n = 55) No further details reported	• All-cause mortality	

Study	Population	Intervention	Comparison	Outcomes	Comments
	10.9% No dexamethasone: 3.6%				

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

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

Summary of the evidence

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

The evidence was assessed as being very low quality due to risk of bias (arising from failure to adjust for confounding, missing data, and inadequate information about randomisation) and very serious imprecision.

Evidence showed a higher rate of all-cause mortality was associated with corticosteroid treatment compared with no corticosteroid treatment in babies and children with meningococcal disease. No other outcomes in the protocol were reported.

No evidence was available for head-to-head comparisons between different types of corticosteroids or comparing corticosteroids to placebo.

See appendix F for full GRADE tables.

Economic evidence

Included studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. This was because intervention is not expensive, and the committee did not expect their recommendations would change current NHS practice.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Meningococcal disease is associated with high rates of mortality and morbidity, 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 meningococcal disease on the ability to carry out certain activities of daily life.

In addition to functional impairment (in children and babies), skin, soft tissue or orthopaedic complications requiring surgical intervention, hearing impairment and serious intervention-related adverse effects were selected as important outcomes as these are relatively common after meningococcal disease 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. Evidence for all-cause mortality was rated as very low quality due to risk of bias (arising from failure to adjust for confounding, missing data, and inadequate information about randomisation) and imprecision (due to the small number of events).

No evidence was identified for long-term neurological impairment, functional impairment, severe developmental delay, skin, soft tissue or orthopaedic complications requiring surgical intervention, hearing impairment, serious intervention-related adverse effects, or length of hospitalisation.

Benefits and harms

The committee considered the evidence comparing corticosteroids to no corticosteroid treatment in babies and children with meningococcal disease, that showed a higher rate of all-cause mortality associated with corticosteroid treatment. The committee were aware that the previous NICE guideline on meningitis (NICE 2010) recommended that meningococcal disease should not be treated with high-dose corticosteroids (defined as dexamethasone 0.6 mg/kg/day or an equivalent dose of another corticosteroid) and noted that the current evidence was in line with this recommendation. Based on the evidence, and their clinical knowledge and experience, the committee recommended that corticosteroids should not be routinely used for the treatment of meningococcal disease. Although the current evidence, and previous NICE guideline recommendation, was limited to babies and children, the committee were aware that there was also evidence of a lack of benefit of high-dose corticosteroids in adults with sepsis (Annane 2019). Therefore, the committee agreed to extend the recommendation to include adults.

No evidence was identified for the use of low-dose replacement corticosteroids in people with meningococcal septic shock who are not responding to high-dose vasoactive agents. However, based on their clinical knowledge and experience, and a wider evidence base (Annane 2019) including those with sepsis (not restricted to meningococcal disease), the committee noted that there may be benefits associated with low-dose replacement corticosteroids in this population. The evidence for people with septic shock and adrenal insufficiency was not reviewed as part of this guideline. However, the committee agreed it was important to include a recommendation promoting the consideration of low-dose replacement corticosteroids in this population as without this the above recommendation may be misinterpreted as precluding this option.

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. Although the data was limited the committee agreed that it was not cost-effective to recommend corticosteroids to people with meningococcal disease because the evidence suggested some harms and an absence of benefits. The committee's recommendations do not change current NHS practice and therefore no significant cost savings are expected.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.6 and 1.8.7 in the NICE guideline.

References – included studies

Effectiveness

Madhi 2013

Madhi, F., Levy, C., Deghmane, A. E., Bechet, S., Cohen, R., Taha, M. K., Corticosteroid therapy in genotype ST-11 meningococcal infections, Pediatric Infectious Disease Journal, 32, 291-293, 2013

Tolaj 2010

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

Economic

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

Other

Annane 2019

Annane, D., Bellisant, E., Bollaert, P. E., Briegel, J., Keh, D., Kupfer, Y., Pirracchio, R., Rochwerg, B., Corticosteroids for treating sepsis in children and adults, Cochrane Database of Systematic Reviews 2019, Issue 12, Art. No.: CD002243

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 26/09/2022]

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of corticosteroids in meningococcal disease?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021232489
Review title	Corticosteroids in meningococcal disease
Review question	What is the effectiveness of corticosteroid treatment in meningococcal disease?
Objective	To determine the effectiveness of corticosteroid treatment in meningococcal disease.
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: 1950 • 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	Meningococcal disease
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with confirmed meningococcal disease (excluding meningococcal

Field	Content
	meningitis alone, as this is included in the reviews on bacterial meningitis). Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis.
Intervention/Exposure/Test	Corticosteroids (any or the below administered via any route, alone or in combination with fludrocortisone): • 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 1950 as this is approximately when the first RCT was published. Studies published not in English-language Studies where corticosteroids are used for adrenal insufficiency

Field	Content
	Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: • 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** • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge)

Field	Content
	• Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Length of hospitalisation **Population: infants and children** • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • 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. 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.

Field	Content
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 I^2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • 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: • 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,

Field	Content	
	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: 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 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)

Field	Content		
Language	English		
Country	England		
Anticipated or actual start date	21/01/2021		
Anticipated completion date	07/12/2023		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

Field	Content	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=232489	
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	Meningococcal disease, 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; 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 meningococcal disease?

Clinical Search

This was a combined search to cover both this review (evidence review H) and also evidence review G4.

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

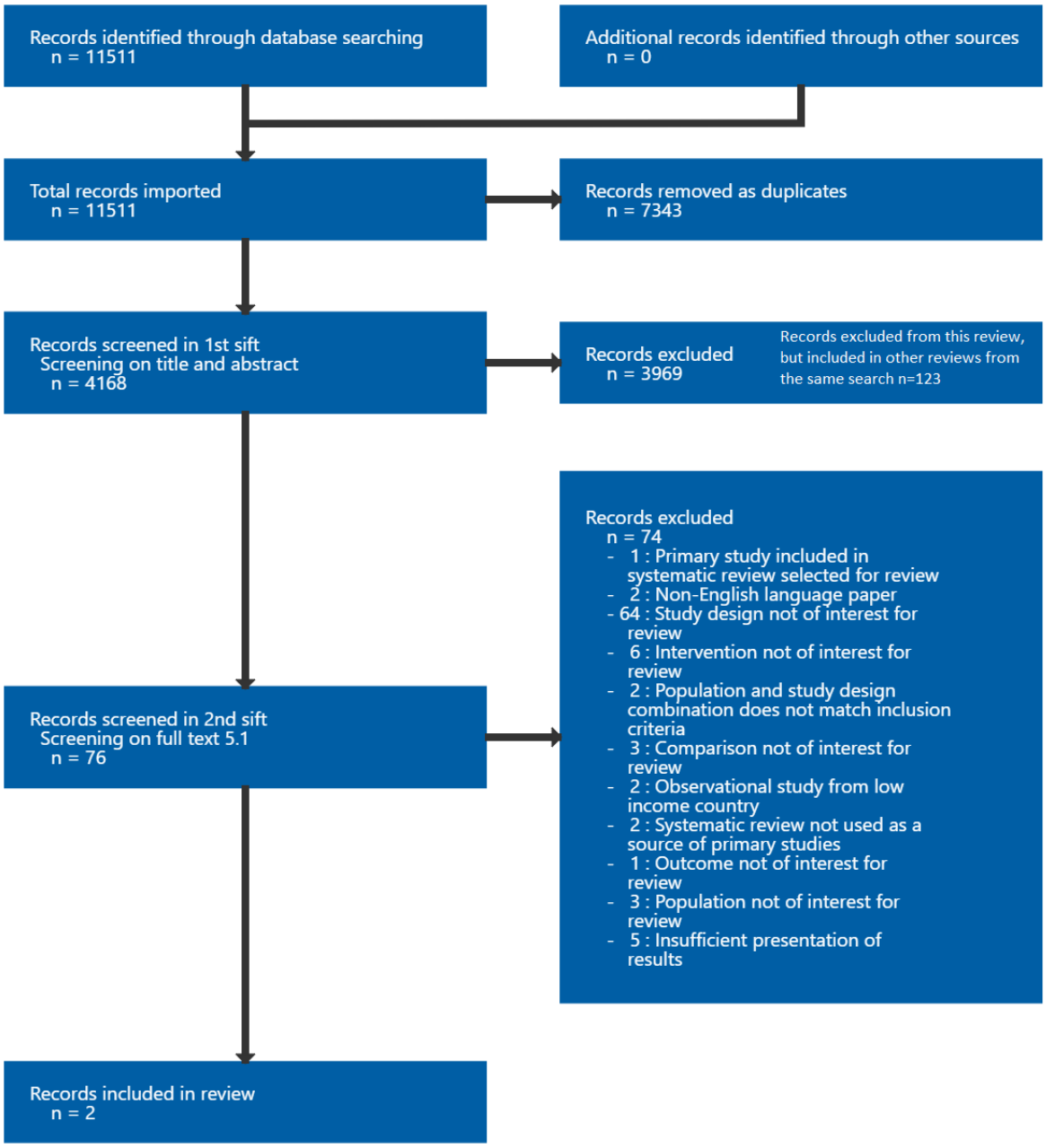
#	Searches
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic 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 meningococcal disease?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of corticosteroid treatment in meningococcal disease?

Table 4: Evidence tables – effectiveness evidence

Study details	Results and risk of bias assessment
Full citation Madhi, F., Levy, C., Deghmane, A. E., Bechet, S., Cohen, R., Taha, M. K., Corticosteroid therapy in genotype ST-11 meningococcal infections, Pediatric Infectious Disease Journal, 32, 291-293, 2013 **Ref Id** 1302787 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Study dates** January 2001 to December 2009 **Inclusion criteria** Children and neonates under the age of 18 years old with clinical meningeal syndrome, cerebrospinal fluid (CSF) pleocytosis (>10 cells/µL) and at least 1 positive microbiological test result consisting of direct detection or culture of Gram-negative cocci in CSF, CSF capsular antigen detection, CSF polymerase chain reaction and/or blood culture. **Exclusion criteria** No additional criteria reported **Patient characteristics**	**Results** All-cause mortality (follow-up time not reported) Corticosteroids: 34/269 No corticosteroid treatment: 24/531 **1. Bias due to confounding (Low/Moderate/Serious/Critical/No information)** Critical: analysis not adjusted for confounding factors for example, corticosteroids were prescribed for more severe cases with significant differences in shock/purpura fulminans and mechanical ventilation between groups. **2. Bias in selection of participants into the study (Low/Moderate/Serious/Critical/No information)** Low: all eligible cases with complete information were included. **3. Bias in classification of interventions (Low/Moderate/Serious/Critical/No information)** Serious: No details reported on how the intervention was defined. **4. Bias due to deviations from intended interventions (Low/Moderate/Serious/Critical/No information)** Low: No evidence of deviation from intended interventions. **5. Bias due to missing data (Low/Moderate/Serious/Critical/No information)** Critical: 1885 cases of meningococcal infections identified, however complete data and information on treatment only available for 805 cases.

Study details	Results and risk of bias assessment
N = 805 Age in years (mean; SD) 4.4; 4.6 Sex M/F: Corticosteroids 1.15; No corticosteroids 1.27 Meningitis[1]: Corticosteroids 220 (81.5%); No corticosteroids 492 (92.0%) Purpura fulminans[1]: Corticosteroids 50 (18.5%); No corticosteroids 43 (8.0%) Shock/purpura fulminans*: Corticosteroids 152 (57.8%); No corticosteroids 189 (36.7%) [1]Cases of meningococcal meningitis were enrolled from January 2001, whereas cases of meningococcal septic shock (purpura fulminans) were reported from 2003. However, the authors report those with meningococcal infection, split into meningitis and purpura fulminans and also those with shock/purpura fulminans. These categories may be explained by the differences in inclusion criteria based on the dates above, but this is not clear. Mortality: Corticosteroids: 12.6% No corticosteroid treatment: 4.5% **Interventions** Corticosteroids: No further information reported **Follow-up** Not reported	**6. Bias in measurement of outcomes (Low/Moderate/Serious/Critical/No information)** Low: Objective outcome of mortality. **7. Bias in selection of the reported result (Low/Moderate/Serious/Critical/No information)** Moderate: No indication of selection of the reported analysis from among multiple analyses **Overall risk of bias (Low/Moderate/Serious/Critical/No information)** Critical **Source of funding** Not industry funded **Other information** Corticosteroids were used in 41.7% of severe cases as compared with 25.8% of other cases. The authors note that this difference may possibly be explained by the trend of corticosteroids being prescribed for severe cases.
Full citation 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 **Ref Id** 1136643 **Country/ies where the study was carried out** Kosovo	**Results** All-cause mortality (reported 24 hours after the hospitalization) Dexamethasone: 10/92 No Dexamethasone: 2/55 **1. Bias arising from the randomisation process (Low/High/Some concerns)** High: No information reported about randomisation process. **2. Bias arising due to deviations from intended interventions**

Study details	Results and risk of bias assessment
Study type RCT **Study dates** Not reported **Inclusion criteria** Individuals with meningococcal sepsis. Cases with no etiological confirmation but with clinical picture of sepsis with skin petechial haemorrhages were also included. **Exclusion criteria** No additional criteria reported **Patient characteristics** N = 147 Sex: Male 87 (59.2%); Female 60 (40.8%) Age in years (median; range): 4.76; 0-33 Sepsis with meningitis:130 (88%) Sepsis without meningitis: 17 (12%) Mortality: Dexamethasone: 10.9% No dexamethasone: 3.6% **Interventions** Dexamethasone**:**, 0.15 mg/kg, every 6 hours, for 4 days, as adjuvant therapy. The first dose of dexamethasone was given up to 30 minutes before the initiation of the antibiotic treatment. No dexamethasone: No further details reported. **Follow-up**	**(Low/High/Some concerns)** Some concerns: No deviations reported, however no information provided whether participants or those administering the intervention were aware of the assigned interventions. **3. Bias due to missing outcome data (Low/High/Some concerns)** High: 23.1% of cases data are missing, no explanation given. **4. Bias in measurement of the outcome (Low/High/Some concerns)** Low: The outcome is an objective outcome and is unlikely to have been influenced by knowledge of the intervention received. **5. Bias in selection of the reported result (Low/High/Some concerns)** Moderate: No indication of selection of the reported analysis from among multiple analyses. **Overall risk of bias (Low/High/Some concerns)** High **Source of funding** No sources of funding reported.

Study details	Results and risk of bias assessment
All mortality cases reported within the first 24 hours after the hospitalization.	

CNS: central nervous system; CSF: cerebrospinal fluid; RCT: randomized controlled trials; SD: standard deviation

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of corticosteroid treatment in meningococcal disease?

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

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of corticosteroid treatment in meningococcal disease?

Table 5: Evidence profile for comparison between corticosteroids and no corticosteroid treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroid treatment	Control	Relative (95% CI)	Absolute		
All-cause mortality: babies and children[1] (follow-up time not reported - Madhi, 2013; reported 24 hours after the hospitalization - Tolaj, 2010)												
2 (Madhi, 2013 and Tolaj, 2010)	randomised trial & observational study	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	44/361 (12.2%)	26/586 (4.4%)	RR 2.82 (1.75 to 4.55)	81 more per 1000 (from 33 more to 158 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio

[1] *1.6% of data from the combined studies was from people aged over 12*

[2] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2; Critical risk of bias in the evidence contributing to the outcomes as per ROBIS-I.*

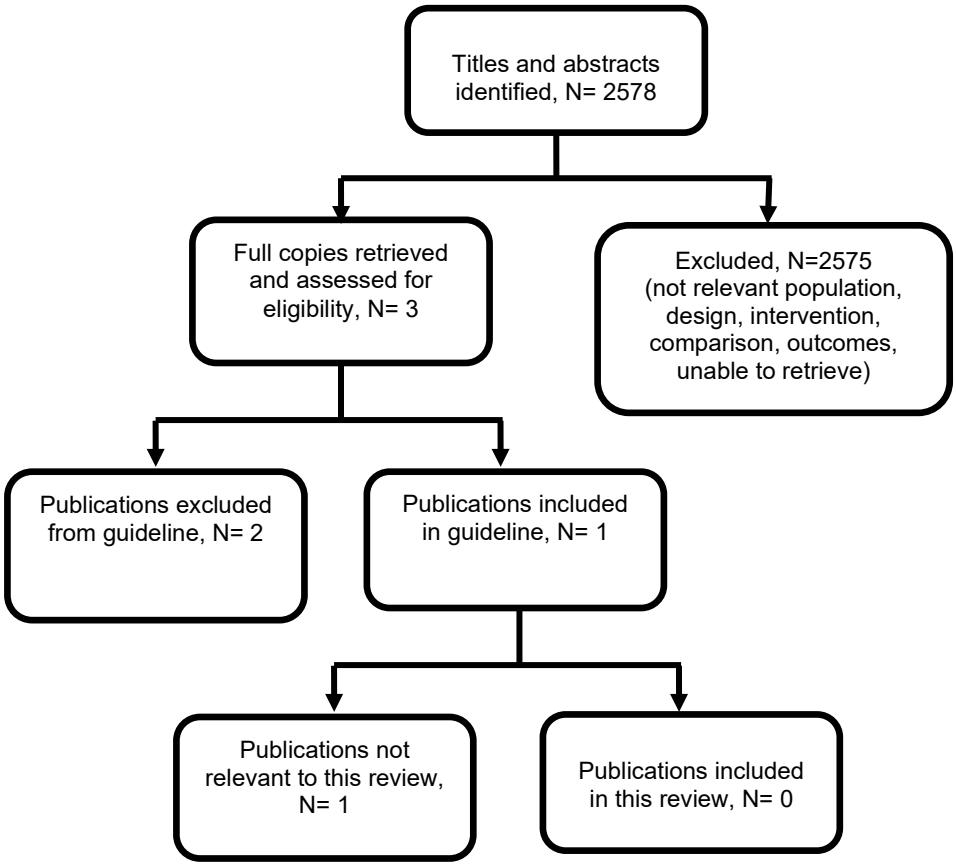
[3] *<150 events*

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of corticosteroid treatment in meningococcal disease?

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

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

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

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

Appendix I Economic model

Economic model for review question: What is the effectiveness of corticosteroid treatment in meningococcal disease?

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 meningococcal disease?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Anonymous (2011) Which antibiotics and vaccines should be used for meningococcal disease?. Pharmaceutical Journal 287(7675): 471-472	Study design does not meet the inclusion criteria: case study
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
Barbante Casella, E, Cypel, S, Osmo, A. A et al. (2004) Sequelae from meningococcal meningitis in children: A critical analysis of dexamethasone therapy. Arquivos de Neuro-Psiquiatria 62(2b): 421-428	Population and study design combination does not meet the inclusion criteria
Baumann, F; Pearson, D. E; Levin, M. (1953) Adrenal cortical steroids in the management of a case of meningococcemia. Journal of Pediatrics 43(5): 575-7	Study design does not meet the inclusion criteria: case report
Bhat, B. V. (1992) Treatment of pyogenic meningitis in children. Journal of the Indian Medical Association 90(9): 249-250	Study design does not meet the inclusion criteria: narrative review
Booe, J., Solberg, C. O., Saeter, T., Corticosteroid treatment for acute meningoencephalitis: A retrospective study of 346 cases, British medical Journal (1857), 1, 1094-1095, 1965	Population does not meet the inclusion criteria: cause of infection - morbilli, varicella, rubeola, parotitis, uncertain/unknown, and not "post-infectious"
Breen, G. E., Corticosteroid Treatment for Acute Meningoencephalitis, British Medical Journal, 1, 1375-6, 1965	Study design does not meet the inclusion criteria: letter to the Editor
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
Cabellos, C., Pelegrin, I., Benavent, E., Gudiol, F., Tubau, F., Garcia-Somoza, D., Verdaguer, R., Ariza, J., Fernandez Viladrich, P., Invasive Meningococcal Disease: What We Should Know, Before It Comes Back, Open Forum Infectious Diseases, 6, ofz059, 2019	Insufficient presentation of results: cannot extract data for those with meningococcal disease that did and did not receive dexamethasone
Campsall, P. A., Laupland, K. B., Niven, D. J., Severe Meningococcal Infection. A Review of Epidemiology, Diagnosis, and Management, Critical Care Clinics, 29, 33-409, 2013	Study design does not meet the inclusion criteria: narrative review about the epidemiology, diagnostic and therapeutic interventions for severe meningococcal infections

Study	Reason for Exclusion
Carmel, P. W and Greif, L. K. (1993) The aseptic meningitis syndrome: A complication of posterior fossa surgery. Pediatric Neurosurgery 19(5): 276-280	Study design not of interest for review: descriptive observational study. Aseptic meningitis syndrome: neurological procedure: exclude for wrong population
Cathie, K., Levin, M., Faust, S. N., Drug use in acute meningococcal disease, Archives of Disease in Childhood: Education and Practice Edition, 93, 151-158, 2008	Study design does not meet the inclusion criteria: discussion about the conventional and experimental therapies used in meningococcal disease
Chang, L. C and Tung, H. Y. (1959) Cortisone or corticotropin in treatment of fulminating meningococcal meningitis: clinical report of 20 cases. Chin. J. Pediat. 10(2): 111-112	Non-English language (Chinese)
Correia, J. B., Hart, C. A., Meningococcal disease, Clinical EvidenceClin Evid, 1164-81, 2004	Systematic review not used as a source of primary studies: SR with no meta-analysis. References checked for relevance
Costello, J., McConachie, I., Steroids in sepsis - From past to present, CPD Anaesthesia, 5, 26-28, 2003	Study design not of interest for review: narrative review
Daher, E. F., Maia, R. C. L., Ciarlini, B. S., Da Silva, S. L. A., Da Silva, E. C., Silva Junior, G. B., Clinical and laboratory aspects of adults and children admitted with meningococcal meningitis to a tertiary hospital in Fortaleza, Ceara, Brazil, Annals of Tropical Medicine and Public Health, 5, 483-488, 2012	Intervention not of interest for review: no relevant interventions reported
Darnell, R., Shephard, R. H., Taylor, J. C., Firth, J. L., Management of central nervous system sepsis, Drugs under Experimental and Clinical Research, 9, 383-386, 1983	Intervention does not meet the inclusion criteria: examining the mechanisms of the illness and possible treatments
de Louvois, J., Blackbourn, J., Hurley, R., Harvey, D., Infantile meningitis in England and Wales: a two year study, Archives of Disease in Childhood, 66, 603-7, 1991	Study type does not meet the inclusion criteria: descriptive study exploring the incidence of meningitis among children under 1 year of age
De Silva, D. D. S., De Silva, D. G. H., Soysa, P. E., Lamabadusuriya, S. P., Meningococcal septicaemia, Ceylon Medical Journal, 21, 132-136, 1976	Study design not of interest for review: case reports
Deorari, A. K., Verma, I. C., Maheshwari, M. C., Bhujwala, R. A., Paul, V. K., Prognostic factors related to mortality in meningococcal disease, Indian Journal of Medical Research, 86, 212-217, 1987	Comparisons does not meet inclusion criteria: no comparisons based on corticosteroid treatment
Dhar, R., Badawi, M., Al Haque, E., Mubasher, L., Qabazard, Z., Sadek, S., Zaki, M., Outcome of treatment of Haemophilus influenzae meningitis in children complicated by febrile episodes, Medical Principles and Practice, 9, 198-204, 2000	Population not of interest for review: Haemophilus influenzae meningitis, not m caused by Neisseria meningitidis
Drake, R., Dravitski, J., Voss, L., Hearing in children after meningococcal meningitis, Journal of Paediatrics & Child HealthJ Paediatr Child Health, 36, 240-3, 2000	Insufficient presentation of results: data not presented by corticosteroid treatment group; cannot extract relevant data (no comparative data)
Duramaz, B. B., Kihtir, H. S., Petmezci, M. T., Yesilbas, O., Ankay, N., Hatipoglu, N., Sevketoglu, E., Analysis of meningitis cases in pediatric intensive care unit: 8-year single center experience, Medical Journal of Bakirkoy, 16, 26-32, 2020	Population does not meet inclusion criteria: retrospective review of 2 groups - Bacterial meningitis and aseptic meningitis. Wrong intervention: need for steroids is an outcome, not intervention
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

Study	Reason for Exclusion
Emonts, M., De Groot, R., Sepsis syndrome in children: Can we do better?, Advances in Experimental Medicine and Biology, 549, 63-70, 2004	Study design not of interest for review: narrative review of physiological mechanisms of the illness
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
Forbes, J. A., Purulent meningitis: Principles and results of revised standardized treatment in 281 cases, Aust. Ann. Med., 2, 92-101, 1962	Study design not of interest for review: case series describing antibiotic treatments used as standard care
Freij, L., Hebelka, M., Seeberg, S., Meningitis developing during cephalothin therapy of septicaemia, Scandinavian Journal of Infectious Diseases, 7, 153-155, 1975	Study design not of interest for review: case report of a 63 years old woman
Geppert, T., Meningitis, South Dakota Journal of MedicineS D J Med, 18, 17-8, 1965	Study type does not meet the inclusion criteria: commentary
Gill, D., Treatment of meningitis and encephalitis, British Medical Journal, 1, 95, 1976	Study design not of interest for review: letter to the Editor
Grilli, A., What the 483s tell us, Contract Pharma, 2013	Study design not of interest for review: narrative description of lab testing processes
Gupta, P. S and Sharma, M. L., Corticosteroids in pyogenic meningtis. Journal of the Indian Medical Association 34: 126-8, 1960	Study design not of interest for review: retrospective review of 50 cases of pyogenic (bacterial) meningitis. Corticosteroids were used in 27/50 cases
Gupta, S., Tuladhar, A. B., Does early administration of dexamethasone improve neurological outcome in children with meningococcal meningitis?, Archives of disease in childhood, 89, 82-83, 2004	Study design not of interest for review: narrative review
Hasbun, R., Rosenthal, N., Balada-Llasat, J. M., Chung, J., Duff, S., Bozzette, S., Zimmer, L., Ginocchio, C. C., Epidemiology of Meningitis and Encephalitis in the United States, 2011-2014, Clinical Infectious Diseases, 65, 359-363, 2017	Outcome not of interest for review: no relevant data reported
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	Systematic review not used as a source of primary studies. References checked for relevance.
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
Heckenberg, S. G. B., De Gans, J., Brouwer, M. C., Weisfelt, M., Piet, J. R., Spanjaard, L., Van Der Ende, A., Van De Beek, D., Clinical features, outcome, and meningococcal genotype in 258 adults with meningococcal meningitis: A prospective cohort study, Medicine, 87, 185-192, 2008	Intervention not of interest for review: no relevant interventions reported
Heycock, J. B., Noble, T. C., Pyogenic Meningitis in Infancy and Childhood, British Medical Journal, 1, 658-62, 1964	Study design and intervention combination not of interest for review: retrospective review of 337 cases over 13 years period and only 14 cases received

Study	Reason for Exclusion
	steroids.
Hildreth, C. J., Lynm, C., Glass, R. M., Sepsis, JAMA - Journal of the American Medical Association, 301, 2516, 2009	Study design not of interest for review: patient information booklet
Hopkins, P., Sriskandan, S., Gram-positive bacterial infection in severe sepsis, Clinical Intensive Care, 13, 147-160, 2002	Study design not of interest for review: narrative review of different bacterial strains present in sepsis
Joachim, C., Nadel, S., Management of meningococcal disease, Paediatrics and Child Health, 21, 153-158, 2011	Study design does not meet the inclusion criteria: narrative review about various aspects of meningitis
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	Study population not of interest for review: participants with bacteriologically proven pneumococcal meningitis
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	Population does not meet the inclusion criteria: participants with pneumococcal meningitis
Lanman, J. T., Adrenal steroids in meningococcemia, Journal of Pediatrics, 46, 724-8, 1955	Study design does not meet inclusion criteria: narrative review
Levin, M., Infections of the central nervous system in children, Current Opinion in Neurology and Neurosurgery, 3, 390-393, 1990	Study type does not meet the inclusion criteria: discussion paper
Liu, Shuiqu, Septicemia due to gram-negative bacilli. A clinical analysis of 60 cases, Chinese Medical Journal, 93, 562-564, 1980	Study design not of interest for review: descriptive observational study of 60 cases of septicaemia
Maat, M., Buysse, C. M., Emonts, M., Spanjaard, L., Joosten, K. F., de Groot, R., Hazelzet, J. A., Improved survival of children with sepsis and purpura: effects of age, gender, and era, Critical Care (London, England)Crit Care, 11, R112, 2007	Intervention not of interest for review: no relevant intervention reported
Makwana, N., Nye, K., Riordan, F. A., Meningitis without a petechial rash in children in the Hib vaccine era, Journal of Infection, 49, 297-301, 2004	Insufficient presentation of results: impossible extract data by treatment group (only 16 children had steroids, but data not presented separately for comparative analysis)
Manginello, F. P., Pascale, J. A., Wolfsdorf, J., Klein, G. M., Neonatal meningococcal meningitis and meningococcemia, American Journal of Diseases of Children, 133, 651-652, 1979	Study type does not meet the inclusion criteria: case report
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
Nadel, S., Kroll, J. S., Diagnosis and management of meningococcal disease: The need for centralized care, FEMS Microbiology Reviews, 31, 71-83, 2007	Study type does not meet the inclusion criteria: narrative review about various aspects related to meningococcal disease
Osterud, B., Meningococcal septicemia: the use of	Study design not of interest for review:

Study	Reason for Exclusion
plasmapheresis or blood exchange and how to detect severe endotoxin induced white cell activation, Scandinavian Journal of Clinical and Laboratory Investigation SupplementScand J Clin Lab Invest Suppl, 178, 47-51, 1985	narrative review of the use of blood and plasma exchange as an intervention for Meningococcal septicaemia and the use of corticosteroids for septic shock
Raman, G. V., Meningococcal septicaemia and meningitis: A rising tide, British Medical Journal, 296, 1141-1142, 1988	Study type does not meet the inclusion criteria: discussion paper
Riedo, F. X., Plikaytis, B. D., Broome, C. V., Epidemiology and prevention of meningococcal disease, Pediatric Infectious Disease Journal, 14, 643-657, 1995	Study design not of interest for review: epidemiological and narrative review of meningitis worldwide, and development of vaccines and further treatment
Roznovsky, L., Gutvirth, J., Benes, J., Dostal, V., Kasal, E., Hobstova, J., Kumpel, P., Krizova, P., Tichacek, M., Plisek, S., Struncova, V., Proposal of standard effective clinical care in pre-hospitalization emergency care: Invasive meningococcal infection, Klinicka Mikrobiologie a Infekcni Lekarstvi, 8, 57-59, 2002	Non-English language paper
Ryan, J. M., The meningitis problem in children, Journal of the Indiana State Medical Association, 68, 255-260, 1975	Study design not of interest for review: narrative review of meningitis: signs and symptoms, diagnosis, therapy, antibiotics, steroids for septic shock, and complications
Salluh, J. I. F., Bozza, F. A., Japiassu, A. M., Neto, H. C. C. F., Bozza, P. T., Povoa, P., Corticosteroids in sepsis: Pathophysiological rationale and the selection of patients, Endocrine, Metabolic and Immune Disorders - Drug Targets, 10, 266-273, 2010	Study design not of interest for review: narrative review of the pathophysiology of the illness, and mechanisms of possible treatment
Santhanakrishnan, B. R., Varadarajan, V. V., Surendran, D., Raju, V. B., Pyogenic meningitis in children, Antiseptic, 74, 443-450, 1977	Study design not of interest for review: descriptive observational study of symptoms of the illness, and discussion of treatment options. No primary research
Saxe, T. G., Finch, R. G., Meningococcal infections: sixteen years' experience, West Virginia Medical Journal, 74, 99-102, 1978	Study design not of interest for review: case report and summary/description of a case series (descriptive observational study)
Shneerson, J. M., Fawcett, I. W., The complications and management of meningococcal meningitis, Intensive Care Medicine, 5, 5-9, 1979	Study type does not meet the inclusion criteria: case reports
Singh, S., Singhal, P. K., Kumar, H., Sen, S., Dutta, A. K., Sharma, D., Clinical profile of meningococcal infection in Delhi, Indian Pediatrics, 24, 985-990, 1987	Cohort study from low-income country: non-OECD country: India
Stephens, D. S., Hajjeh, R. A., Baughman, W. S., Harvey, R. C., Wenger, J. D., Farley, M. M., Sporadic meningococcal disease in adults: results of a 5-year population-based study, Annals of Internal Medicine, 123, 937-40, 1995	No relevant data reported
Tan, K. H., Chen, T. M., The treatment of purulent meningitis with adrenal cortico-steroids, Singapore Medical Journal, 3, 73-77, 1962	Population and study design combination does not match inclusion criteria: bacterial meningitis; non-RCT and sufficient RCTs identified
Thomson, A. P. J., Riordan, F. A. I., The management of meningococcal disease, Current Paediatrics, 10, 104-109, 2000	Study type does not meet the inclusion criteria: discussion paper
Tolaj, I., Ramadani, H., Mehmeti, M., Gashi, H.,	Insufficient presentation of results

Study	Reason for Exclusion
Kasumi, A., Gashi, V., Jashari, H., Does Dexamethasone Helps in Meningococcal Sepsis?, Medical archives (Sarajevo, Bosnia and Herzegovina), 71, 173-177, 2017	(mortality outcome) and population not of interest for review: as defined in the protocol length of hospitalisation outcome applies only for adult population - majority of the population in the paper are babies and children
Wall, R. A., Meningococcal disease - Some issues in treatment, Journal of Infection, 42, 87-99, 2001	Study type does not meet the inclusion criteria: discussion paper
Wall, R. A., Meningococcal disease: treatment and prevention, Annals of MedicineAnn Med, 34, 624-34, 2002	Study type does not meet the inclusion criteria: discussion paper about various aspects regarding meningococcal disease
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 population does not meet the inclusion criteria: participants with pneumococcal meningitis
Whittle, H. C., Greenwood, B. M., Meningococcal meningitis in the northern savanna of Africa, Tropical Doctor, 6, 99-104, 1976	Study design and country do not meet inclusion criteria: non-OECD country: Nigeria; Epidemiological and narrative review from low-income country (Nigeria)
Wilson, M. R., Roos, K. L., Infectious Diseases and Impaired Consciousness, Neurologic Clinics, 29, 927-942, 2011	Study type does not meet the inclusion criteria: discussion paper
Word,B.M., Klein,J.O., Therapy of bacterial sepsis and meningitis in infants and children: 1989 poll of directors of programs in pediatric infectious diseases, Pediatric Infectious Disease Journal, 8, 635-637, 1989	Study design not of interest for review: questionnaire/survey study
Yu, J., Neonatal Meningitis: Pathogenesis, Diagnosis, Management, Sequelae, Clinical Pediatrics, 4, 387-90, 1965	Study type does not meet the inclusion criteria: discussion paper

RCT: randomised control trial

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 meningococcal disease?

No research recommendation was made for this review.