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[Intervention Review]

Pre-admission antibiotics for suspected cases of meningococcal disease

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ABSTRACT

Background

Meningococcal disease can lead to death or disability within hours after onset. Pre-admission antibiotics aim to reduce the risk of serious disease and death by preventing delays in starting therapy before confirmation of the diagnosis.

Objectives

To study the effectiveness and safety of pre-admission antibiotics versus no pre-admission antibiotics or placebo, and different pre-admission antibiotic regimens in decreasing mortality, clinical failure, and morbidity in people suspected of meningococcal disease.

Search methods

We searched CENTRAL (6 January 2017), MEDLINE (1966 to 6 January 2017), Embase (1980 to 6 January 2017), Web of Science (1985 to 6 January 2017), LILACS (1982 to 6 January 2017), and prospective trial registries to January 2017. We previously searched CAB Abstracts from 1985 to June 2015, but did not update this search in January 2017.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing antibiotics versus placebo or no intervention, in people with suspected meningococcal infection, or different antibiotics administered before admission to hospital or confirmation of the diagnosis.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data from the search results. We calculated the risk ratio (RR) and 95% confidence interval (CI) for dichotomous data. We included only one trial and so did not perform data synthesis. We assessed the overall quality of the evidence using the GRADE approach.

Main results

We found no RCTs comparing pre-admission antibiotics versus no pre-admission antibiotics or placebo. We included one open-label, non-inferiority RCT with 510 participants, conducted during an epidemic in Niger, evaluating a single dose of intramuscular ceftriaxone versus a single dose of intramuscular long-acting (oily) chloramphenicol. Ceftriaxone was not inferior to chloramphenicol in reducing mortality (RR 1.21, 95% CI 0.57 to 2.56; N = 503; 308 confirmed meningococcal meningitis; 26 deaths; moderate-quality evidence), clinical failures (RR 0.83, 95% CI 0.32 to 2.15; N = 477; 18 clinical failures; moderate-quality evidence), or neurological sequelae (RR 1.29, 95% CI 0.63 to 2.62; N = 477; 29 with sequelae; low-quality evidence). No adverse effects of treatment were reported. Estimated treatment costs were similar. No data were available on disease burden due to sequelae.

Authors' conclusions

We found no reliable evidence to support the use pre-admission antibiotics for suspected cases of non-severe meningococcal disease. Moderate-quality evidence from one RCT indicated that single intramuscular injections of ceftriaxone and long-acting chloramphenicol were equally effective, safe, and economical in reducing serious outcomes. The choice between these antibiotics should be based on affordability, availability, and patterns of antibiotic resistance.

Further RCTs comparing different pre-admission antibiotics, accompanied by intensive supportive measures, are ethically justified in people with less severe illness, and are needed to provide reliable evidence in different clinical settings.

PLAIN LANGUAGE SUMMARY

Antibiotics to treat suspected cases meningitis due to infection with meningococcus before confirmation of diagnosis

Review question

We wanted to know if people suspected to have inflammation of the membranes covering the brain and spinal cord (meningitis) due to infection with the meningococcal bacteria should be given antibiotics before the diagnosis is confirmed in order to prevent death or disability. We found one relevant study.

Background

Meningococcal disease is a rapidly progressing, contagious bacterial infection that can cause epidemics of severe disease of the brain and blood. If not treated early many will die or have permanent disabilities. Antibiotics are very effective if given early. Waiting for confirmation of the diagnosis with laboratory tests can result in delays in starting antibiotics. Giving antibiotics early based on a clinical suspicion (empiric treatment) could prevent delays in treatment and consequent death and disability. However, doing so could also result in unnecessary treatment.

Study characteristics

We searched for studies comparing giving versus not giving empiric antibiotics or comparing different antibiotics in those with suspected meningococcal disease. We found one randomised trial comparing single intramuscular doses of two different long-acting antibiotics. The evidence is current to January 2017.

The included study was conducted in nine primary care facilities in Niger during an outbreak of meningococcal disease in 2003. Of 510 adults and children studied, 251 received ceftriaxone and 259 received chloramphenicol. The study was funded by Médecins Sans Frontières.

Key results

There was no difference in the number of people who died, did not respond to treatment, or with neurological disabilities with either antibiotic empirically. The results were similar in whom the diagnosis was subsequently confirmed. Neither antibiotic had significant adverse effects.

Quality of the evidence

Although the study was well conducted, the overall quality of the evidence was only moderate for death and treatment failures because the study excluded children less than two months old, pregnant women, and the severely ill. The quality of evidence was lower for neurological disabilities because of the shortness of follow-up.

Since meningococcal disease has serious consequences, not giving antibiotics empirically would be unethical. However, future research comparing different antibiotics in people of all ages and illness severity is required to provide reliable evidence in different clinical settings.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ceftriaxone versus long-acting (oily) chloramphenicol in people suspected to have meningococcal disease

Ceftriaxone versus long-acting (oily) chloramphenicol in people suspected to have meningococcal disease

Patient or population: people suspected to have meningococcal disease (adults and children)

Settings: primary care centres in a low-income country in Africa during an epidemic

Intervention: intramuscular ceftriaxone (100 mg/kg; max 4 g) single dose

Comparison: long-acting (oily) chloramphenicol (100 mg/kg; max 3 g) single dose

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long-acting (oily) chloramphenicol	Intramuscular ceftriaxone				
Death - in all participants - short term Follow-up: 72 hours	47 per 1000 ¹	57 per 1000 (27 to 120)	RR 1.21 (0.57 to 2.56) ²	503 (1 study) ⁸	⊕⊕⊕⊖ moderate 3,4,5,6,7	All outcomes in this table are from 1 trial that randomised 510 participants to either intervention (Nathan 2005)
Death - in confirmed cases of meningococcal meningitis (subgroup) Follow-up: 72 hours	34 per 1000 ¹	38 per 1000 (12 to 121)	RR 1.11 (0.35 to 3.56) ²	308 (1 study) ⁸	⊕⊕⊕⊖ moderate 3,4,6,7	
Clinical failure - in all participants - short term Composite clinical criteria ¹⁰ Follow-up: 24 to 48 hours	41 per 1000 ¹	34 per 1000 (13 to 84)	OR 0.83 (0.32 to 2.15) ²	477 (1 study) ⁸	⊕⊕⊕⊖ moderate 3,4,6,7,9	
Clinical failure - in confirmed cases of meningococcal meningitis (subgroup) Composite clinical criteria ¹⁰ Follow-up: 24 to 48 hours	14 per 1000 ¹	19 per 1000 (3 to 107)	OR 1.39 (0.23 to 8.47) ²	308 (1 study) ⁸	⊕⊕⊕⊖ moderate 3,4,6,7,9	

Neurological sequelae - in all participants- short term Clinical assessment ¹¹ Follow-up: 72 hours	53 per 1000 ¹	68 per 1000 (33 to 139)	RR 1.29 (0.63 to 2.62) ²	477 (1 study) ⁸	⊕⊕○○ low 3,4,7,9,12,13	
Neurological sequelae - in confirmed cases of meningococcal meningitis (subgroup) Clinical assessment ¹¹ Follow-up: 72 hours	63 per 1000 ¹	91 per 1000 (41 to 203)	RR 1.44 (0.65 to 3.23)	297 (1 study) ⁸	⊕○○○ very low 3,4,5,7,9,12	
Adverse events - short term Follow-up: 72 hours	See comment	See comment	Not estimable	0 (1 study) ⁸	See comment	No adverse events were detected with either intervention

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Basis of the assumed risk: control group risk.

²Effect estimate: consistent with non-inferiority of ceftriaxone versus chloramphenicol.

³No serious study limitations: block randomised using off-site computer-generated codes in blocks of 20; allocation concealed in numbered, sealed, opaque envelopes; recruitment was by personnel not involved in generating random sequence; baseline variables matched in intervention arms; open-label trial but outcome was objective; outcomes completely and adequately reported; no other biases.

⁴No serious inconsistency: results for all participants and in subgroups were consistent.

⁵Serious imprecision: sample size was estimated to demonstrate non-inferiority for the primary outcome and not for neurological sequelae (secondary outcome). A sample size of 175 individuals with confirmed meningococcal meningitis per group (350 total) was needed for the primary outcome with a one-sided 5% significance level, 80% power, and assuming 10% dropouts. Only 308 participants were confirmed to have meningococcal meningitis, thus trial may be underpowered to detect non-inferiority for neurological outcomes. Downgraded by one.

⁶No serious imprecision: trial was adequately powered to demonstrate non-inferiority. Not downgraded.

⁷Publication bias unlikely: search for trials was comprehensive. Not downgraded.

⁸Parallel-group, open-label, non-inferiority trial.

⁹Serious indirectness: trial excluded infants, pregnant women, and those with serious illness (in non-reactive coma or with convulsions). Downgraded by one.

¹⁰Clinical failure: composite of: a) state of consciousness remaining severely altered (Glasgow Coma Scale < 11 at 24 hours or < 13 at 48 hours); b) no improvement in the state of consciousness since 0 hour; c) appearance of or worsened neurological symptoms since 0 hour; d) repeated or persistent convulsions; and e) axillary temperature above 38.5°C in the absence of other evident infectious pathological changes.

¹¹Neurological sequelae: judged on gross clinical abnormality.

¹²Serious indirectness: follow-up was too short to detect neurological sequelae adequately. Downgraded by one.

¹³No serious imprecision: sample size of 350 required to demonstrate non-inferiority for primary outcome, but sample size adequately powered to demonstrate non-inferiority for this secondary outcome as well. Not downgraded.

BACKGROUND

This is an update of a Cochrane review first published in the Cochrane Database of Systematic Reviews 2008, Issue 1 and updated in 2011 and 2013 (Sudarsanam 2008; Sudarsanam 2011; Sudarsanam 2013).

Description of the condition

Meningococcal disease is a contagious bacterial disease caused by *Neisseria meningitidis*. *N meningitidis* strains are classified primarily into serogroups based on the type of polysaccharide capsule expressed. While 13 serogroups have been described (A, B, C, D, 29E, H, I, K, L, Y, W-135, X, and Z), most of the disease is caused by strains belonging to serogroups A, B, C, X, Y, and W-135 (Hill 2010). Serogroups B and C account for most of the cases in Europe and the Americas (Al-Tawfiq 2010). Serogroups A and C are responsible for most of the cases in Asia and Africa (Schwartz 1989; Sinclair 2010). In the African 'meningitis belt' that extends from Ethiopia in the east to Senegal in the west, newer strains of serogroup A meningococcal disease have occurred in epidemic form that have posed a recurrent threat to public health, and rates of meningococcal disease in this region are several times higher than in high-income countries (WHO 2007).

In a systematic review of 132 studies published between 1980 to 2008 that reported on the incidence of disabling sequelae of bacterial meningitis in 18,183 adult and child survivors of bacterial meningitis, *Haemophilus influenzae* type b (Hib) was the most common cause of bacterial meningitis (35.5%), with pneumococcus accounting for 19.6%, meningococcus for 16.4% and other pathogens for 12% (Edmond 2010). However, the relative frequency of disease caused by *N meningitidis* has increased in recent years due to the widespread and successful use of an effective vaccine for *H influenzae* B and a conjugate vaccine for *Streptococcus pneumoniae*, leaving *N meningitidis* as the most common cause of bacterial meningitis, particularly in some parts of Africa where surveys indicate that *N meningitidis* was responsible for 60% to 70% of cases of meningitis (Hsu 2009; WHO 2010). Meningococcal disease is most common in children (due to waning maternal antibody levels), adolescents, and young adults (WHO 2010).

Up to 5% to 10% of a population may be asymptomatic carriers of *N meningitidis*, in whom the bacteria are harmless commensals of the nasopharyngeal mucosa (WHO 2010). Meningococcal disease is caused by a combination of bacterial virulence factors (particularly the ability to express capsules) and host susceptibility, including age, prior viral infection, overcrowding, smoking, co-infections, and genetic polymorphisms (Hill 2010; Stephens 2007). Meningococcal disease is spread by person-to-person contact through respiratory droplets from infected people. Meningococcal disease attack rates can be as high as 100 to 800 cases per 100,000 but individual communities have on occasion reported rates as high as 1000 per 100,000 (WHO 2004). In 1996, the largest outbreak ever reported occurred in the meningitis belt, in which the total number of cases was over 250,000 with 25,000 reported deaths (Rosenstein 2001).

Mortality

The onset of symptoms of meningococcal disease is sudden, and death can follow within hours (Borg 2009; Hackett 2002; Perea-Milla 2009). It is estimated that around 50,000 people, mostly children

and young adults, die every year from among the approximately 500,000 cases of meningococcal disease reported annually (Granoff 2009). Case fatality rates from invasive meningococcal disease are usually in the range of 10% to 15%, but mortality rates depend on the type and severity of invasive disease, and are greatest in people with meningococcaemia, fulminant septicaemia and shock (50% to 60%), followed by those with meningitis and associated septicaemia (up to 25%), and are lowest for meningitis without sepsis (less than 5%) (Borg 2009; Ferguson 2002; Hill 2010).

Meningococcal disease differs from other gram-negative bacterial infections by the release of lipopolysaccharide endotoxins and vesicles that cause rapidly progressing skin haemorrhage and necrosis, disseminated intravascular coagulation, and shock (Brandtzaeg 2005). Other meningococcal virulence factors have been identified such as capsular polysaccharides (serogroups A, B, C, W-135, Y, and X) and a number of surface-expressed adhesive proteins, including factor H-binding protein (fHbp), Opa, and Opc, that contribute to the ability to avoid innate immune responses and which aid adherence to mucosal surfaces (Hill 2010; Roupael 2012; Schneider 2006; Stephens 2007). Capsules of *N meningitidis* help with transmission and colonisation, and the ability to express and modify capsule is associated with its epidemic potential (Stephens 2007).

Sequelae

There is significant resultant morbidity in 10% to 15% of survivors (Baraff 1993; Borg 2009); from reports published between 1988 to 2008, the pooled median risk (and interquartile range) of developing at least one major sequela after hospital discharge in people with invasive meningococcal disease was 7.2% (4.3% to 11.2%) (Edmond 2010). The risk of major sequelae is greatest in the African and Southeast Asian regions and in low-income countries (Edmond 2010; Ramakrishnan 2009). Major sequelae are permanent neurological defects caused by pathophysiological inflammatory responses during infections. These involve increased blood-brain barrier permeability; a large compartmentalised inflammatory response in the subarachnoid space, with pronounced increase in concentrations of tumour necrosis factor α (TNF- α), interleukins, chemokines and other mediators; and increased resistance to the outflow of cerebrospinal fluid and oedema of the brain leading to elevated intracranial pressure and alterations in cerebral blood flow (Hill 2010; Stephens 2007; Tunkel 1993). The alteration in the permeability of the blood-brain barrier is caused in part by inflammatory mediators such as matrix metalloproteinases (particularly MMP-8), leading to disassembly of brain microvascular endothelial cell junction components and cell adhesion during meningococcal infection (Schubert-Unkmeir 2010).

The resultant neurological deficits include hearing loss or deafness (most common), vision defects, speech disorders, amputation of limbs or digits and scarring of skin (due to extensive necrosis), hydrocephalus, mental retardation, spasticity, paralysis, and seizures, and present a long-term and serious challenge for families with limited means to care for a disabled child, especially in resource-poor settings (Borg 2009; Edmond 2010; Ramakrishnan 2009; WHO 2004). Prevalence estimates of these sequelae do not account for the increased mortality or social drift further down the socio-economic ladder in those with such disabilities, particularly in low-income families and in resource-poor settings, leading to underestimates of prevalence in surveys of postmeningitis

sequelae (Edmond 2010). Even in high-income countries, impaired cognitive functions and behavioural sequelae result in impairments in many areas of social, educational, occupational functioning and quality of life after bacterial meningitis (Borg 2009).

These estimates of the sequelae of invasive meningococcal disease also do not account for deaths that might have occurred before admission to hospital due to difficulties in establishing a clinical diagnosis, lack of clinical suspicion in areas not prone to epidemics, and delays in instituting effective treatment in areas with health systems unable to respond to these needs. Meningococcal disease has many clinical manifestations and is often difficult to differentiate from common, less serious illnesses. The infectious syndromes associated with meningococcaemia include meningitis, bacteraemia, pneumonia, epiglottitis, otitis, and focal diseases such as urethritis, conjunctivitis, arthritis, and pericarditis (Stephens 2007). Clinical suspicion of meningococcal infection may vary with the geographic locale of the study, the age group of the patients being studied (children or adults), and the criteria used for clinical diagnosis of meningococcal disease. Meningococcal disease is suspected when there is a characteristic skin rash, headache, weakness, fever, vomiting, and depressed sensorium, with or without evidence of sepsis (Hahné 2006; Harnden 2006).

Diagnosis

The definitive diagnosis of meningococcal infection requires isolation of *N meningitidis* (a gram-negative intracellular diplococcus that ferments glucose and maltose) from a sterile body fluid such as blood, cerebrospinal fluid (CSF), or synovial, pleural, or pericardial fluids. In meningococcal meningitis, sterilisation of the CSF occurs rapidly (within two hours) after the instigation of antibiotics (Kanegaye 2001). Culture confirmation occurs in only a third of clinically diagnosed cases, yet meningococcal DNA can be detected in 88% of admission blood samples from the same patients, and molecular techniques using polymerase chain reaction (PCR) on the CSF are informative, even after starting antibiotics (Hackett 2002). Polymerase chain reaction of the blood is highly specific for *N meningitidis*, can be used for subgroup and serotyping, and may even be of prognostic significance; quantitative PCR reveals higher bacterial DNA load to be associated with greater severity of illness and greater risk of mortality (El Bashir 2003; Hackett 2002). Polymerase chain reaction is more sensitive than culture, particularly in the context of pre-admission treatment. The UK National Institute for Health and Care Excellence (NICE) guideline recommends that blood real-time PCR should be done to confirm a diagnosis of meningococcal disease, and that CSF should also be submitted for PCR if the CSF culture is negative (NICE 2010). However, these techniques may not be readily available in resource-poor settings.

Description of the intervention

The use of antibiotics has dramatically reduced mortality due to meningococcal disease. Once diagnosis is confirmed, crystalline penicillin is commonly given intravenously every 4 to 6 hours for 7 to 10 days in individuals not at risk of anaphylaxis. Rates of bacterial penicillin resistance vary. In areas where penicillin resistance predominates, third-generation cephalosporins such as cefotaxime and ceftriaxone are recommended by the Scottish Intercollegiate Guidelines Network (SIGN) guidelines, SIGN 2008, and the NICE guidelines, NICE 2010, respectively. However, quinolones are not

approved for routine paediatric usage and ceftriaxone requires parenteral administration (Girgis 1998). Sulphonamides are now rarely used, as intermediate resistance to these drugs is reported in some areas (Eickhoff 1965). Oral macrolide and beta-lactam antibiotics are also effective in treating invasive meningococcal disease and averting mortality, though their routine use in suspected cases of invasive meningococcal disease may depend on 'indication bias' (bias in initiating oral versus parenteral or no antibiotics due to perceptions of mild to moderate, as opposed to severe, illness severity) (Perea-Milla 2009). A Cochrane review studied osmotic agents for bacterial meningitis and found no benefit (Wall 2013).

The efficacy of short courses of ceftriaxone and oily chloramphenicol has been demonstrated in the treatment of meningococcal meningitis in adults (El Filali 1993). In one epidemic, a single intramuscular injection of an oily suspension of long-acting chloramphenicol proved as effective as a five-day course of crystalline penicillin (WHO 1995). Chloramphenicol is bactericidal for *N meningitidis* and penetrates the blood-brain barrier more effectively than beta-lactam antibiotics (Pecoul 1991). Intravenous cefotaxime plus either ampicillin or amoxacillin is recommended in children under three years of age (NICE 2010). Cefotaxime or ceftriaxone, often combined with vancomycin, are also used in high-income countries until the causative agent has been identified (Stephens 2007). A systematic review did not reveal important differences between third-generation cephalosporins or conventional antibiotics in averting death or deafness in people with bacterial meningitis (Prasad 2011).

A recent Cochrane review found that rifampicin, ciprofloxacin, ceftriaxone, or penicillin are effective for prophylaxis, with rifampicin resistance being an issue, as mentioned above (Zalmanovici 2013).

How the intervention might work

The aim of pre-admission antibiotic therapy is to reduce the risk of serious disease by preventing delays in starting therapy. This delay may occur if confirmation of meningococcus is sought before initiation of therapy. It is believed that if treatment is begun early, the associated severe complications and mortality may be avoided or minimised by preventing or reducing the effects of the systemic inflammatory response of the body, including reduced inflammatory cytokines and chemokines, and endotoxin production; and also lead to a reduction in bacterial proliferation (Brandtzaeg 1989; Kanegaye 2001; Wang 2000). Preventing meningococcal shock is dependent on reducing endotoxin levels and meningococcal bacterial load (Hackett 2002), and given that meningococcaemia is a rapidly progressive disease, with an estimated doubling time of meningococci of 30 to 40 minutes (Stephens 2007), the time available for early administration of antibiotics is limited.

With this in mind, the concept of empiric antibiotic use based on clinical suspicion, before a confirmed bacteriological diagnosis is made, or the 'pre-admission' use of antibiotics prescribed or administered by the doctor in first contact with the patient, has been found to be effective in reducing mortality and complications due to meningococcal disease in observational studies (Hahné 2006; Perea-Milla 2009; Strang 1992; Wang 2000).

Why it is important to do this review

Standard policy in many countries ([Hahné 2006](#)), backed by recommendations from professional associations, mandates the initiation of antibiotics, particularly penicillin, once criteria for bacterial meningitis are met. Some policies contend that initiating antibiotic therapy requires the prior collection of CSF for bacterial confirmation or the use of PCR of the CSF, though there is a lack of consensus on the need for confirmation of the diagnosis before starting antibiotics ([Hahné 2006](#)). The NICE guideline states that children with suspected meningitis and meningococcal disease should have a lumbar puncture unless specifically contraindicated ([NICE 2010](#)).

However, it is not clear whether treating all suspected cases is associated with improved outcomes, since the effects of confounding are difficult to interpret in the observational studies supporting this view ([Hahné 2006](#); [Harnden 2006](#); [Keeley 2006](#); [Sorensen 1998](#)).

In previous versions of this review we identified no trials comparing pre-admission antibiotics to no antibiotic prior to confirmation of meningococcal meningitis ([Sudarsanam 2008](#); [Sudarsanam 2011](#); [Sudarsanam 2013](#)). We identified one trial that demonstrated the non-inferiority of a single dose of intramuscular ceftriaxone versus a single dose of intramuscular long-acting (oily) chloramphenicol in reducing serious outcomes.

This review update sought additional trials assessing the use of antibiotic therapy in suspected cases of meningococcal disease, and those that compared different classes of antibiotics used for this infection before confirmation of the diagnosis.

OBJECTIVES

To study the effectiveness and safety of pre-admission antibiotics versus no pre-admission antibiotics or placebo, and different pre-admission antibiotic regimens in decreasing mortality, clinical failure and morbidity in people suspected of meningococcal disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

People of all ages who were suspected to have meningococcal infection in whom antibiotics were started presumptively before confirmation of the diagnosis, or transfer to hospital.

Participants of trials that looked at treatment of 'meningitis' or 'bacterial meningitis', where it may not have been possible to distinguish the results that applied to meningococcal disease, were treated as having 'suspected meningococcal infection'.

Types of interventions

1. Antibiotic treatment versus placebo or no intervention.

2. Any antibiotic versus another antibiotic from a different class.
3. Combinations of antibiotics versus another antibiotic or combinations of other antibiotics.

Pre-admission antibiotic treatment refers to the use of antibiotic treatment for an initial dose, or doses, by any route before the diagnosis is confirmed.

Types of outcome measures

Primary outcomes

1. Mortality: death before reaching hospital, in hospital, or within a month of discharge or leaving the hospital.
2. Lack of clinical improvement: as defined by individual trials.
3. Morbidity: persistent neurological defects in the form of vision and hearing loss, speech disorders, persistent cognitive or intellectual impairment, and paralysis, or any other recorded persistent neurological defects.

Secondary outcomes

1. Burden of disease: on the family, individual, or caregiver; as reported using a validated scale or measure.
2. Adverse events: antibiotic-related clinical adverse effects.
3. Economic costs of the intervention: if reported as done alongside the conduct of included RCTs.

We grouped the primary outcome of morbidity and all secondary outcomes by time. We defined 'short term' as less than six weeks; 'medium term' as six weeks to six months; and 'long term' as more than six months after the onset of symptoms subsequently confirmed to be due to meningococcal meningitis.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12), part of the Cochrane Library, www.cochranelibrary.com/ (accessed 6 January 2017), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE Ovid (1966 to 6 January 2017), Embase.com (1980 to 6 January 2017), Web of Science (1985 to 6 January 2017), and LILACS (Latin American and Caribbean Health Sciences Literature) (1982 to 6 January 2017). We did not update the previous CAB Abstracts search (1985 to June 2015) in January 2017 due to lack of institutional access to that database. See [Appendix 1](#) for details of previous searches.

We used the search strategy in [Appendix 2](#) to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format ([Lefebvre 2011](#)). We adapted the search strategy for Embase.com ([Appendix 3](#)), Web of Science ([Appendix 4](#)), LILACS ([Appendix 5](#)), and CAB Abstracts ([Appendix 6](#)). We applied no language or publication restrictions.

The PRISMA figure summarises this process ([Figure 1](#)).

Figure 1. Study flow diagram

Searching other resources

We also searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/default.aspx), ClinicalTrials.gov (clinicaltrials.gov), and the ISRCTN register (www.controlled-trials.com/isrctn/search.html) for ongoing and completed clinical trials, using the search terms 'meningococcal' AND 'meningitis' (searched 13 February 2017). We searched the references of all identified studies, as well as major reviews, for additional studies.

Data collection and analysis

Selection of studies

Two review authors (TS, PR) independently inspected each reference identified by the electronic searches and applied the inclusion criteria. We retrieved the full articles of trials that were deemed potentially relevant and in cases of disagreement. Two review authors (TS, PR) independently inspected the full articles to determine if they met the inclusion criteria, consulting a third review author (PT) when disagreements persisted. We discarded reports that were clearly irrelevant. We recorded studies on pre-admission antibiotics that did not fulfil the inclusion criteria along with the reasons for their exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

Two review authors (TS, PR) independently extracted data. We discussed the data extraction, documented decisions and, where necessary, contacted the trial authors for clarification. A third review author (PT) independently checked the extracted data.

We extracted, checked, and recorded the following data.

1. Characteristics of trials: design, date, location, and setting of trial; publication status; sponsor of trial (specified, known or unknown); duration of follow-up.
2. Characteristics of participants: age; number of participants in each group; gender, setting, location.

3. Characteristics of interventions: type of antibiotics; dose, mode of administration, schedule; length of treatment and follow-up.
4. Characteristics of outcome measures: we recorded data for events listed in the [Types of outcome measures](#) section for each intervention arm.
5. For economic analyses, key items of resource use (costs) and outcomes (beneficial and adverse), cost per unit of effort, quality adjusted life years (QALYs), or cost-benefit analyses (resource inputs and effects of alternative interventions expressed in monetary units), if detailed in trial reports. If available, we would have recorded the following: analytic perspective adopted (for example, societal; national/subnational; third-party payer; institution); time horizon for both costs (resource use) and effects (beneficial and adverse effects); and sources of resource use, unit costs, and (if applicable) effects and benefit valuation data ([Campbell Collaboration 2008](#)).

Assessment of risk of bias in included studies

Two review authors (TS, PR) independently assessed the included studies for risk of bias using Cochrane's 'Risk of bias' assessment tool on the following six domains: sequence generation, allocation concealment, blinding or masking, incomplete outcome data, selective outcome reporting, and other biases ([Higgins 2011a](#)). A third review author (PT) checked this assessment.

We judged each of these six domains as low risk of bias, high risk of bias, or unclear risk of bias, the last when due to lack of information in the report or after contacting the trial authors we were unable to make a reliable assessment. We used the criteria summarised in Table 8.5.c of the *Cochrane Handbook for Systematic Reviews of Interventions* to make judgements ([Higgins 2011a](#)), and recorded these assessments in the standard 'Risk of bias' tables in Review Manager 5 ([RevMan 2014](#)). We presented these evaluations in the 'Risk of bias' summary figure ([Figure 2](#)) and discussed them further in the [Risk of bias in included studies](#) section. We incorporated these judgements in assessing limitations in study design for critical and important outcomes in the [Summary of findings for the main comparison](#).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for **Nathan 2005**.

Measures of treatment effect

Only one study fulfilled the inclusion criteria, and we analysed dichotomous data from this trial by calculating the risk ratio (RR) and 95% confidence intervals (CI) for each outcome.

Unit of analysis issues

No non-standard designs were used in the single included trial.

Had more trials been included in this review and had the included trials randomised participants by clusters, such as villages or health centres, and had the results been adjusted for clustering, we would have combined the adjusted measures of effects of these cluster-randomised trials. If results had not been adjusted for clustering, we would have attempted to adjust the results for clustering, by multiplying the standard errors of the estimates by the square root of the design effect (where the design effect is calculated as $D_{\text{Eff}} =$

$1 + (M - 1) ICC$, where M is the average cluster size and ICC is the intracluster coefficient). If this was not possible, we would not have combined the trials in a meta-analysis, but would have presented the results in an Additional table.

If time-to-event outcomes had been reported, we would have extracted the estimates of the log hazard ratio and its standard error. If standard errors were unavailable, we would have extracted alternative statistics such as confidence intervals or P values.

Dealing with missing data

We contacted trial authors for missing data. We planned to exclude any trial with more than 20% unexplained dropouts in any arm. However, the included trial reported reasons for dropouts, and the trial authors provided supplementary information. The data were adequately presented, and the report provided intention-to-treat (ITT) and per-protocol analyses data, as well as a participant flow diagram in a sufficiently detailed manner as to facilitate data retrieval.

We extracted data to allow an ITT analysis in which all randomised participants were analysed in the groups to which they were originally assigned. If there was a discrepancy in the number randomised and the numbers analysed in each treatment group, we calculated the percentage loss to follow-up in each group and reported this information. If unexplained dropouts exceeded 10% in either group, we would have assigned the worst outcome to those lost to follow-up for dichotomous outcomes (except for mortality) and assessed the impact of this in sensitivity analyses with the results of completers.

For continuous outcomes, if provided and where possible, we would have calculated missing standard deviations from other available data such as standard errors (Higgins 2011b). However, we would not have imputed missing values in order to present these in the analyses. We would not have made any assumptions about loss to follow-up for continuous data and would have analysed results for those participants who completed the trial.

Assessment of heterogeneity

Had we included additional trials, we would have supplemented the inspection of the graphical display of results for non-overlapping CIs among individual trials with the Mantel-Haenszel χ^2 test of heterogeneity. Since this test has low power to detect heterogeneity, we would have interpreted a significance level of less than 0.10 as evidence of heterogeneity.

In addition, we would have quantified inconsistency across studies and its impact on the meta-analysis by examining the value of the I^2 statistic to estimate the percentage of variability due to intertrial variability rather than random error. We would have interpreted an I^2 statistic of 50% or greater as indicating substantial levels of heterogeneity (Higgins 2003).

Assessment of reporting biases

Had there been sufficient studies (at least 10), we would have used a funnel plot of treatment effect against its standard error (as a measure of study size) to assess possible publication bias or small-study effects.

Data synthesis

Since only one trial fulfilled the inclusion criteria, we presented the RR and 95% CI for the prespecified outcomes from this trial.

Had there been more included trials, we would have pooled data for dichotomous outcomes using the inverse variance fixed-effect model; if heterogeneity was deemed substantial, we would have used the random-effects model.

For continuous data such as caregiver burden or quality of life assessments measured in similar ways, we had planned to calculate the difference in means weighted by the inverse of the variance. We would have used the standardised mean difference to pool results if continuous outcome data assessing similar outcomes were measured in different ways. If the distribution of the outcome data was significantly skewed and the studies were small, we would have looked for a suitable normalisation method or requested more appropriate summaries of the data from the investigators.

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: death in all participants with a short-term follow-up of 72 hours; death in confirmed cases of meningococcal meningitis; clinical failure in confirmed cases of meningococcal meningitis; neurological sequelae in all participants with a short-term follow-up of 72 hours; neurological sequelae in confirmed cases of meningococcal meningitis; and adverse events with a short-term follow-up of 72 hours. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We would have evaluated the pooled results from additional studies that used comparable participants, interventions, methods, and outcomes for evidence of significant heterogeneity that would have precluded a reliable interpretation of a common 'average' effect of the combined effects of the interventions.

Had the I^2 statistic exceeded 75% with no explanation for this inconsistency (see below) in the effects of interventions across trials, we would have presented the results in a forest plot without pooling data.

We anticipated between-trial variations in the following situations and therefore intended to perform subgroup analyses when:

1. baseline risk levels (severity of infection) differed between trials;
2. trials presented results for people with suspected versus confirmed meningococcal meningitis; analysing the results separately allows for evaluating the effects of differences in these proportions across trials and the effects of different indices of suspicion for bacterial meningitis during and outside of epidemic settings;

3. trials differed by levels of health service delivery (low-income versus moderate- to high-income settings);
4. trials differed by duration of follow-up (short term (< six weeks); medium term (six weeks to six months); long term (> than six months).

If subgroups appeared to differ in the effects of interventions, as evident by non-overlapping CIs, we would have performed formal tests for subgroup differences using the methods described in [Higgins 2011b](#), which are possible in Review Manager 5 when the inverse variance method is used to pool dichotomous data ([RevMan 2014](#)).

Sensitivity analysis

We had also planned to perform sensitivity analyses to assess the robustness of our findings to different aspects of risk of bias among included trials and to evaluate the assumptions made in ITT and completer analyses.

RESULTS

Description of studies

Results of the search

Our original review retrieved 136 reports ([Sudarsanam 2008](#)). Of these, we obtained hard copies of 30 potentially eligible trials. Only [Nathan 2005](#) met the inclusion criteria. The search also retrieved a systematic review on the same topic that was published while the first version of this review was underway ([Hahné 2006](#)). [Hahné 2006](#) included 14 cohort studies but did not include any RCTs. Another review of observational studies looked at seven trials and also did not include any RCTs ([Leclerc 2001](#)).

An updated search in June 2010 retrieved 46 records, only one of which was relevant to this review ([Sudarsanam 2011](#)). It was a retrospective analysis that controlled for the effects of indication bias in prescribing antibiotics by using propensity scores to evaluate the effects of pre-admission antibiotics in preventing deaths due to meningococcal disease during an epidemic in Spain ([Perea-Milla 2009](#)). This is listed in the [Characteristics of excluded studies](#) table.

Our 2013 review update retrieved 125 records ([Sudarsanam 2013](#)). We identified no relevant trials.

This 2017 update retrieved 77 records. We identified no relevant trials ([Figure 1](#)).

Included studies

Our protocol predefined participants as those with suspected cases of meningococcal meningitis awaiting transfer to hospital and randomised to treatment before confirmation of diagnosis. The trial by [Nathan 2005](#), funded by Médecins Sans Frontières, was conducted between March and April 2003 in Niger, during an epidemic of meningococcal infection, and recruited people with suspected meningococcal meningitis from one of eight peripheral health centres, as well from a regional hospital at Zinder, Niger.

Clarifications from the trial authors revealed that anyone presenting with suspected meningitis to any site included in the study, who met the inclusion criteria, was invited to participate. If informed consent was obtained, a lumbar puncture was conducted

(along with a rapid diagnostic test for malaria), and the participant was then randomised to the interventions. Participants remained at the site to which they had initially presented (and had received the intervention) for a minimum of 72 hours of follow-up. If a second treatment dose was required, or if an alternative treatment was necessary, these too were administered at the original site. No transfer of participants between sites occurred. Of the 510 participants originally included in the study, 97 (19%) were recruited at the National Hospital in Zinder and 41 (8%) at a district hospital in Matameye. The trial authors clarified that the hospital in Matameye was a hospital by name, but had no medical facilities beyond those of the other health centres. The remaining 372 (73%) were treated in peripheral health centres.

We felt that as 81% of participants were treated in what were effectively peripheral health centres, and since participants were randomised to the interventions before confirmation of diagnosis, the data from this trial could be used without biasing our review's stated objectives.

The sample size in this trial was chosen to show non-inferiority between the two groups (less than 10% difference in the failure rate between the two groups at 72 hours) for the primary outcome of treatment failure (death at 72 hours or clinical failure). Most participants (~55% to 57%) were in the five-to-14-years age group, with 31% under the age of five years but greater than two months old. The trial evaluated the effects of a single intramuscular dose of ceftriaxone (a third-generation cephalosporin) and a single dose of oily chloramphenicol (long-acting intramuscular chloramphenicol) in people suspected of having meningococcal disease. This trial is further described in the [Characteristics of included studies](#) table.

Excluded studies

Thirty-one studies are described in the [Characteristics of excluded studies](#) table. We excluded nine as they randomised only proven, not suspected, cases of meningitis ([Barson 1985](#); [Congeni 1984](#); [del Rio 1983](#); [Kavaliotis 1989](#); [Martin 1990](#); [Molyneux 2011](#); [Pecoul 1991](#); [Rodriguez 1986](#); [Schaad 1990](#)). The other two were RCTs of the effects of dexamethasone in children with proven bacterial meningitis with both groups receiving antibiotics ([Girgis 1989](#); [Wald 1995](#)). A report of mortality following pre-admission antibiotics in suspected meningococcal meningitis was a retrospective case-control study ([Harnden 2006](#)). [Perea-Milla 2009](#) was also a retrospective case-control study adjusted for indication bias. [Riordan 2001](#) was a prospective cohort where the intervention being studied was the effect of training on 'door to needle time' for giving antibiotics. Most other studies were observational case-control, case series, or review articles.

Risk of bias in included studies

We found no RCTs or quasi-RCTs comparing pre-admission antibiotics for suspected meningococcal infection versus placebo or no intervention. The trial by [Nathan 2005](#), comparing two antibiotics, had the following characteristics.

Allocation

This trial used off-site computer-generated codes in blocks of 20. Sealed, numbered, opaque envelopes containing the description of the allocated intervention were delivered to each intervention site in lots of 50 to be opened sequentially by on-site study physicians who, after obtaining consent and a sample of CSF for

diagnostic confirmation, administered the intervention. The study investigators involved in random sequence generation were not involved in recruitment of the study participants.

Blinding

The study physicians were not blinded to the interventions once participants were allocated. However, the pre-stated outcomes were objective and unlikely to be influenced by assessor bias.

Incomplete outcome data

A total of 510 participants were randomised, 251 to receive ceftriaxone and 259 to receive chloramphenicol. Three participants left the treatment facility in the ceftriaxone arm and four in the chloramphenicol arm within the 72 hours of follow-up. Reasons were not provided, but it would be difficult to assume that they had poor outcomes. Data on these participants were not included in the ITT analysis reported by the trial authors, but the numbers were few and similar in both arms, so we used data provided in the ITT analysis in the report for evaluating outcomes. We also used as presented data provided in the report on those participants in whom bacteriologic confirmation of meningococcal meningitis was done.

Selective reporting

The trial protocol was not available, and the report did not have any identification to suggest that it had been prospectively registered in a publicly accessible database. However, the trial reported all pre-stated and expected outcomes and appeared to be free of selective reporting.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison Ceftriaxone versus long-acting \(oily\) chloramphenicol in people suspected to have meningococcal disease](#)

We found no trials that evaluated the effects of pre-admission antibiotics versus placebo for suspected cases of meningococcal disease.

The one included trial screened 557 participants and randomised 510, of whom 251 were given intramuscular ceftriaxone and 259 long-acting intramuscular (oily) chloramphenicol during an epidemic of meningococcal meningitis ([Nathan 2005](#)).

Primary outcomes

1. Mortality

Data were only available for short-term outcomes, as defined in the [Types of outcome measures](#) section. At 72 hours, deaths occurred in 14 out of 247 (6%) participants in the ceftriaxone arm and 12 out of 256 (5%) participants in the long-acting chloramphenicol arm (ITT values from the report). Mortality did not differ significantly between the two interventions (RR 1.21, 95% CI 0.57 to 2.56; N = 503; moderate-quality evidence) ([Figure 3](#); [Analysis 1.1](#)). A subgroup analysis of the participants who were later confirmed to have meningococcal disease also failed to show any difference in mortality between the two study arms (RR 1.11, 95% CI 0.35 to 3.56; N = 308). Mortality did not differ in the remaining 195 participants in the intervention arms without confirmed meningococcal meningitis (RR 1.42, 95% CI 0.54 to 3.76). We did not undertake formal tests for subgroup differences since the confidence intervals for subgroup effects overlapped considerably.

Figure 3. Forest plot of comparison: 1 Ceftriaxone versus long-acting (oily) chloramphenicol, outcome: 1.1 Death

There were no data on mortality before presentation to the health centres or after discharge from the facilities, though all participants were discharged only when well.

2. Lack of clinical improvement

This composite outcome was defined as a Glasgow Coma Scale of less than 11 at 24 hours or less than 13 at 48 hours; no improvement or worsening in the state of consciousness or neurological status; persistent convulsions; and axillary temperature above 38.5°C. The ITT analysis reported that clinical failure occurred in 8 out of 233 (3%) participants in the ceftriaxone arm and 8 out of 244 (4%)

participants in the long-acting chloramphenicol arm. Again, this difference was not statistically significant (RR 0.83, 95% CI 0.32 to 2.15; N = 477; moderate-quality evidence) (Figure 4; Analysis 1.2). The interventions did not differ in the proportions of those with clinical failure in the 308 confirmed cases of meningococcal meningitis (RR 1.39, 95% CI 0.23 to 8.47), nor in the 169 participants in whom meningococcal meningitis was not confirmed (RR 0.81, 95% CI 0.25 to 2.58). The interventions did not differ significantly in the proportions of participants requiring a second injection between 48 to 72 hours (risk difference -0.9%, 95% CI -4.7% to 3.0%).

Figure 4. Forest plot of comparison: 1 Ceftriaxone versus long-acting (oily) chloramphenicol, outcome: 1.2 Clinical failure

3. Morbidity

Neurological sequelae were recorded in 16 out of 233 (7%) participants in the ceftriaxone arm and 13 out of 244 (5%) participants in the chloramphenicol arm. Sequelae included hearing impairment in 14 participants and motor dysfunction in 15 participants (ataxia, motor deficit, or both), but data for individual sequelae were not separable by intervention arms.

The incidence of sequelae did not differ significantly between interventions among all participants using the ITT analysis in the report (RR 1.29, 95% CI 0.63 to 2.62; N = 477; low-quality evidence) (Figure 5; Analysis 1.3). The incidence in those with confirmed meningococcal meningitis was also not significantly different (RR 1.44, 95% CI 0.65 to 3.23; N = 297), nor did it differ significantly in those without confirmed meningococcal meningitis (RR 0.64, 95% CI 0.12 to 3.40; N = 180).

Figure 5. Forest plot of comparison: 1 Ceftriaxone versus long-acting (oily) chloramphenicol, outcome: 1.3 Neurological sequelae

Secondary outcomes

1. Burden of disease

No data were available on the burden of disease on the family, individual, or caregiver as participants were followed up only until discharge.

2. Adverse effects

Neither intervention was associated with adverse effects.

3. Economic costs of the intervention

The trial reported that the average treatment dose used was 2 g per person for both drugs. The treatment cost per patient was estimated as USD 4 to 6 for chloramphenicol and USD 2 to 3 for ceftriaxone. No details were provided on how these costs were arrived at or of other economic issues such as resource use, etc.

DISCUSSION

Summary of main results

Pre-admission antibiotics versus no antibiotics

Our primary question regarding the efficacy and safety of pre-admission antibiotics in decreasing mortality or morbidity in people with suspected meningococcal disease remains unanswered, since we did not find any RCTs comparing antibiotics versus placebo or no antibiotic in suspected cases of meningococcal meningitis and the initiation of antibiotics in the control group after confirmation of the diagnosis.

Comparison of a third-generation cephalosporin (ceftriaxone) versus long-acting chloramphenicol

The sole eligible RCT included in this review reported that a single dose of ceftriaxone was not inferior to long-acting chloramphenicol in preventing mortality, neurological sequelae, the need for a

second injection, and clinical non-response (in the first 48 hours after admission), in those with suspected, and those subsequently confirmed, to have meningococcal meningitis who were given the antibiotic at presentation to the healthcare facility during an epidemic of meningitis ([Summary of findings for the main comparison](#)) ([Nathan 2005](#)). No adverse events were reported for either drug, and costs were comparable.

The trial excluded very ill participants (people in an unresponsive coma and in shock), thus leaving unanswered the question of the efficacy of the schedule of treatments in such instances and the role of supportive measures, even if antibiotics were to be given early. Even among those with a less severe illness at the start of the trial, treatment failure at 72 hours and death were significantly more likely in those with impaired consciousness prior to admission (univariate odds ratio 5.51, 95% CI 2.90 to 10.45). This suggests that a single dose of antibiotics prior to admission may be insufficient to prevent negative outcomes in some people with moderately severe illness, perhaps due to suboptimal dosage, the toxic effects of rapid bacteriolysis, or the absence of adequate additional interventions to combat or prevent haemodynamic imbalance, respiratory distress, renal insufficiency, dehydration or overhydration, and electrolyte imbalance ([Keeley 2006](#)). These speculations are borne out by experiences with intensive treatment of meningococcal disease elsewhere ([Booy 2001](#)), though the speculation on the toxic effects of rapid bacteriolysis due to antibiotic treatment have not been borne out uniformly by empiric enquiry ([Stephens 2007](#)).

Overall completeness and applicability of evidence

Completeness

We found no reliable evidence on the relative efficacy of giving antibiotics before confirmation of the diagnosis or withholding them until confirmation of the diagnosis.

We believe that we have identified all trials relevant to this review.

Applicability

The trial by [Nathan 2005](#) provided moderate-quality evidence to endorse the use of a single dose of either ceftriaxone or oily chloramphenicol in reducing mortality, though the short follow-up precludes the drawing of valid conclusions regarding neurological sequelae.

The external validity of this trial is less clear. When generalising the results to settings and periods other than during epidemics, as in this trial, it is uncertain whether similar mortality and morbidity estimates would be achieved in the absence of high levels of treatment-seeking and alertness to the possibility of meningococcal meningitis that epidemics engender.

The oily suspension of chloramphenicol is ideal for use in low-income countries, due to the comparable efficacy of a single intramuscular dose, repeated if needed after 48 hours, to 10 days of intravenous ampicillin given four times a day ([Pecoul 1991](#)), achieved at a 10th of the cost. Widespread resistance to chloramphenicol in high-income countries limits its usefulness in these settings. However, long-acting chloramphenicol may be a useful drug of choice in low-income countries where resistance to chloramphenicol is not a major problem and if supply is not compromised ([Pecoul 1999](#)).

Ceftriaxone was initially around six to 10 times more expensive than long-acting chloramphenicol, but patent rights for ceftriaxone have expired in most countries, and the generic drug costs have also fallen ([Nathan 2005](#)). Given the comparative efficacy and costs of both agents evaluated in the included trial, the choice of drug for initial pre-admission antibiotic therapy would depend on the proportion of people with chloramphenicol resistance among the population in question, and the affordability of ceftriaxone at local costs. When antibiotic susceptibility testing is limited in low-income countries with emerging chloramphenicol resistance, oily chloramphenicol as the initial drug followed by ceftriaxone, if symptoms do not improve within 48 hours and bacterial meningitis is confirmed, is a possible strategy ([Duke 2003](#)). Ceftriaxone could be used as the first-line drug in the presence of widespread chloramphenicol resistance, though the emergence of resistance to ceftriaxone could also result if this use was indiscriminate. Ceftriaxone would also be preferable to chloramphenicol in situations where the suspected case of meningococcal meningitis is caused by *H influenzae* or *S pneumoniae*, where chloramphenicol is not as effective.

The other factor that would influence the choice of antibiotic is safety. Both drugs were considered safe in the trial by [Nathan 2005](#).

Additional caveats must be considered before instituting pre-admission antibiotics in areas with and without epidemic meningitis. One is the need to rule out other common infections with similar presentations, such as malaria, and meningitis due to other infective pathogens. The alarm engendered by epidemics or local outbreaks may also result in the indiscriminate use of antibiotics. In the included trial malaria was diagnosed in 44 (9%) of participants, and three cases of meningitis were due to *H influenzae* and three to *S pneumoniae*; moreover 133 (23%) had sterile lumbar punctures ([Nathan 2005](#)).

The other caveat is that unless early initiation of antibiotics in suspected cases of meningococcal disease is accompanied by other measures to improve healthcare delivery (increased recognition and case detection, early transfer to hospital and facilities, and the rapid initiation of supportive measures to manage complications of the more severe forms of the illness), the benefits of antibiotics alone are unlikely to affect mortality rates significantly ([Booy 2001](#); [NICE 2010](#)).

Quality of the evidence

Design and quality of reporting

The included trial was designed to demonstrate non-inferiority of ceftriaxone to chloramphenicol, assuming 15% of those allocated to chloramphenicol would be treatment failures, a difference of less than 10% between the interventions, a one-sided 5% significance level, 80% power, and 10% loss to follow-up. The trial authors stated that they calculated the risk difference and 90% CIs of the primary and secondary outcomes and considered the difference as equivalent if the upper limit of its 90% CI was below 10%.

Non-inferiority trials present particular difficulties in design, conduct, analysis, and interpretation, as do trials assessing equivalence. True equivalence is difficult to prove, but the assumption of equivalence in this instance was based on the demonstration of non-inferiority initially, using one-sided 5% significance and a one-sided 90% CI. Equivalence was then assessed using a pre-stated one-sided 90% CI of less than 10% (a two-sided CI might have been more appropriate) and an ITT analysis. The design, conduct, reporting, and interpretation of this trial conformed to the recommendations in the extension to the CONSORT statement for non-inferiority and equivalence trials ([Piaggio 2006](#)). We considered the study to be adequate in reporting randomisation, allocation concealment, and attrition, and although it was an open-label trial, we considered the risk of detection bias to be low due to the objective outcomes used.

Overall quality of the evidence

We rated the overall quality of the evidence for primary outcomes as moderate, and although there were no limitations in study design, we downgraded the trial for indirectness for all outcomes due to the exclusion of infants, pregnant women, and those with severe disease ([Summary of findings for the main comparison](#)).

We further downgraded the quality of the evidence to low for neurological outcomes since the duration of follow-up was only 72 hours and was deemed too short to adequately detect neurological outcomes. Trials that assess deficits in the longer term would enable the detection of neurological sequelae that are detected only after discharge, particularly hearing deficits and spasticity in young children, and milder cognitive deficits and behavioural changes in adolescents ([Borg 2009](#)). The methods used to detect these outcomes in [Nathan 2005](#) were based on gross clinical evaluation and may also have been insensitive to detect them accurately.

The trial may also have been underpowered to demonstrate non-inferiority for neurological outcomes in confirmed cases of meningococcal meningitis, and the follow-up was too short, therefore we judged the quality of the evidence for this subgroup as very low ([Summary of findings for the main comparison](#)).

Potential biases in the review process

Despite the importance of the issue, the surprising lack of RCTs for our main objective is worrying. While it may suggest that we were unable to locate small trials, particularly those with inconclusive results, and indicate publication or retrieval bias, our search of multiple sources with no language restrictions reassures us that this is unlikely. A more credible explanation is that pre-admission antibiotics have become the standard of care in many countries and hence an RCT, especially a placebo-controlled trial, may be deemed unethical.

At first reading, the sole included trial seemed to not fulfil our inclusion criteria of 'pre-admission' use of antibiotics (Nathan 2005), since participants were those treated in health centres; written communication with trial authors confirmed that the first dose of antibiotic was administered to people suspected as having meningococcal meningitis prior to seeking confirmation of the diagnosis. The trial authors also clarified that the majority of the treatment facilities (8/9) were primary care centres, and the majority of participants were treated at these centres (81%). The results of this trial also showed that 195/503 (39%) randomised participants were not subsequently confirmed to have meningococcal meningitis on culture or by polymerase chain reaction, attesting to the actual use of antibiotics prior to disease confirmation and the suitability of this trial for inclusion in this review. None of the excluded RCTs fulfilled this definition of antibiotic use.

Agreements and disagreements with other studies or reviews

Pre-admission antibiotics versus no antibiotics

The available evidence for this comparison comes from retrospective case series, case-control, and cohort studies. Considering the non-specific nature of symptoms, especially in milder cases and in young children, and the lack of sensitivity of the specific clinical signs of both Kernig and Brudzinski, in adults as well as in children (El Bashir 2003), it is likely that data from these sources are confounded by diagnostic errors and inclusion of the more severely ill (Hahné 2006; Harnden 2006; Keeley 2006; Sorensen 1998). The latter are more likely to seek help in clinic-based studies, be perceived to have meningitis by clinicians in these and in community-based studies, and to be treated with parenteral antibiotics early, leading to 'indication bias' (Perea-Milla 2009). Consequently, the often paradoxical outcomes of these observational studies, both positive and negative, are confounded by disease severity, and the proportions that received pre-admission antibiotics (Hahné 2006; Harnden 2006; Perera 2006). Similarly, observational studies of oral pre-admission antibiotics that report lower mortality and morbidity are also confounded by indication bias, in this case the inclusion of people with less severe or non-meningococcal disease (Harnden 2006; Keeley 2006; Perea-Milla 2009).

A retrospective analysis of 848 people admitted with invasive meningococcal disease, 49 of whom died (6%), from 1995 to 2000 in 31 hospitals in Spain, used the 'propensity score' to assign patients the probability of receiving pre-hospital antibiotics prior to admission, based on clinical symptoms, and matched the 228 who had received oral antibiotics in the 48 hours prior to admission with controls who had not received pre-hospital antibiotics, again based

on their propensity scores for not being thus treated (Perea-Milla 2009). Adjusted multivariate analyses indicated that pre-hospital antibiotics appeared to protect against death (odds ratio 0.37, 95% CI 0.15 to 0.93). The propensity score technique has been equated with randomisation in situations where randomisation is difficult, and this trial attempted to adjust for the indication bias that has confounded interpretation of previous observational studies. The imprecision of the effect estimate (the confidence intervals suggest a protective effect that could be clinically very important to only marginally important) is in concordance with evidence from case-control studies that indicate, on balance, that early diagnosis, early admission to hospital (within three hours), and early initiation of supportive measures are as important as the early commencement of antibiotics (Keeley 2006).

Pre-admission cephalosporins versus chloramphenicol

Previous NICE guidance recommended that children with suspected meningococcal disease be given parenteral antibiotics (benzylpenicillin or a third-generation cephalosporin) at the earliest opportunity (NICE 2007). The SIGN guideline on the management of invasive meningococcal disease in children and young people recommends that parenteral antibiotics (benzylpenicillin or cefotaxime) should be given as soon as invasive meningococcal disease is suspected and even before confirmation of the diagnosis is sought (SIGN 2008). The latest NICE guidance considers transfer to hospital and fluid management of greater priority than administering pre-hospital antibiotics, unless immediate transfer is not possible, or if the clinical suspicion of meningococcal meningitis is accompanied by a non-blanching rash or meningococcal septicaemia (NICE 2010). In contrast to earlier guidance, NICE 2010 recommends using ceftriaxone as first-line treatment for bacterial meningitis and meningococcal disease in children and young people older than three months of age.

An economic analysis, done from the perspective of the National Health Service (NHS) and a socialised medicine approach, strongly suggests that ceftriaxone is the most cost-effective antibiotic for the treatment of suspected meningococcal disease or suspected meningitis in a majority of children (NICE 2010). This concurs with the cruder estimates in Nathan 2005. The NICE analyses did not take into account variations in drug prices or any effects on health or costs arising from antibiotic resistance, both of which may vary widely in different settings. These estimates also assumed that survival is the only health-related quality of life outcome of importance with antibiotic use and did not consider other outcomes such as prevention of neurological disability and its (more difficult to estimate) consequences and associated costs, and quality adjusted life years (QALYs) lost or gained.

AUTHORS' CONCLUSIONS

Implications for practice

This review update again found no trials to provide reliable evidence to support or refute the routine use of pre-admission antibiotics for suspected cases of meningococcal disease.

The decision to start antibiotics before admission or confirmation of the diagnosis will therefore depend on local health policy. Considering the potential for serious outcomes and rapid evolution of the disease, the routine use of antibiotics when meningococcus meningitis is suspected appears to be supported by the balance of

evidence from available observational studies, which suggest that early intervention, coupled with intensive support measures, are beneficial in reducing mortality and morbidity in people suspected to have meningococcal meningitis, and particularly meningococcal septicaemia.

When symptoms are milder, false-positive diagnoses are more likely and close monitoring and investigations to confirm suspicions, and investigations to rule out other infections, are especially warranted.

If antibiotics are given before confirmation of the diagnosis, the benefits may outweigh the risks inherent in their use, though this needs to be reviewed on an individual basis. Limited data from the one randomised controlled trial reviewed here, which excluded infants, pregnant women, and those with severe illness, suggest that pre-admission antibiotics in people suspected to have meningococcal meningitis are more likely to prevent unfavourable outcomes if initiated before the onset of frequent seizures or impaired consciousness, or in the absence of concurrent infections. Early antibiotic treatment should be accompanied by better healthcare delivery that facilitates more rapid and accurate diagnosis, rapid transfer to hospital, and the immediate initiation of intensive supportive measures.

While penicillin is commonly recommended as a pre-admission antibiotic, we found no trials of penicillin for this indication. In the sole trial of pre-admission antibiotics for meningococcal meningitis identified in this review, single intramuscular injections of ceftriaxone and long-acting chloramphenicol (with an additional dose in 24 to 48 hours, if clinical recovery was poor) were equally effective and safe in reducing mortality and morbidity in suspected and confirmed cases. Ceftriaxone may also be the cheaper alternative to penicillin (NICE 2010).

Implications for research

Meningococcal disease has serious consequences and progresses rapidly in a sizeable proportion of patients. Standard policy in many countries (Hahné 2006), backed by recommendations from professional associations (NICE 2010; SIGN 2008), mandates the early initiation of antibiotics, particularly penicillin or a third-generation cephalosporin, once criteria for bacterial meningitis are met.

Under these circumstances, it is unlikely that randomised, placebo-controlled trials will be conducted to answer the primary question on the efficacy and safety of initiating early antibiotic treatment versus delaying antibiotics until confirmation of the diagnosis in suspected cases of meningococcal meningitis, to prevent deaths and neurological or other disabling or disfiguring sequelae.

More accurate and early diagnosis would aid the early and appropriate use of antibiotics. Dot enzyme-linked immunosorbent assay (Dot-ELISA) using outer membrane complexes from *Neisseria meningitidis* B as a target was found to be specific for serologic verification of clinically suspected meningococcal disease in patients; determination of antibody titres produced during different phases of natural infection was also possible (Belo 2010). The increased use of dip-stick rapid diagnostic tests (RDTs), which can be easily and accurately used by non-specialist healthcare personnel in basic healthcare facilities and which are comparable in diagnostic accuracy to polymerase chain reaction diagnosis, will

obviate the need to wait until samples are confirmed in reference laboratories, and will aid the decision to institute life-saving measures early for those diagnosed with meningococcal meningitis (Chanteau 2007). The use of RDTs would also facilitate attempts to use scarce stocks of emergency vaccines more appropriately (Boisier 2009). However, the sensitivity of RDTs would need to improve and large-scale production be stabilised to ensure less batch-to-batch variation than is currently observed (Rose 2010). Molecular testing of nasopharyngeal specimens using loop-mediated isothermal amplification (LAMP) to detect the *ctrA* gene involved in *N meningitidis* capsular transport is a non-invasive near-patient diagnostic test that is being evaluated (Bourke 2010).

The need for placebo-controlled trials to guide decisions pertaining to the pre-hospital use of antibiotics will then have less urgency, due to the shorter times to confirmation of diagnoses.

However, randomised controlled trials comparing the efficacy and safety of different pre-admission antibiotics, particularly in comparison with penicillin, are ethically justifiable and are needed to widen the evidence-base for antibiotics available to clinicians in settings of differing resistance patterns, drug costs, availability, and preferences.

Given that the majority of treatment failures and fatalities in many observational studies (Edmond 2010; Perea-Milla 2009), and in the sole randomised controlled trial included in this review (Nathan 2005), occurred in those with more severe manifestations of the disease at presentation, the efficacy of immediate antibiotic use needs to be evaluated alongside other immediate measures to prevent death or clinical deterioration. Nathan 2005 excluded people with established evidence of serious illness pre-randomisation, severely ill people, and those in coma or shock. Including people with such characteristics in future trials may be ethically justified if coupled with measures for rapid confirmation of the diagnosis, and if other intensive supportive measures were also given to all participants, or were the focus of specific enquiry, when given along with pre-admission antibiotics.

Trials in those with less severe forms of illness are also both needed and ethically justified. An important issue is the potential for antibiotic resistance should antibiotics be indiscriminately used for this indication. Evidence for the efficacy of pre-confirmation antibiotic use is particularly important in those with suspected meningitis without indicators of severe disease, as many such cases could eventually be found not to be due to meningitis or due to other aetiologies. Such trials should be adequately powered to detect differences in outcomes between those with and without confirmed meningococcal meningitis, and could stratify participants by levels of severity.

However, uncertainties in the speed of, and variations in, disease evolution, and the problems of identifying an ideal threshold of clinical symptoms and signs for inclusion in such trials, given the problems with sensitivity and specificity of clinical diagnostic criteria (unless replaced or supplemented by molecular or dip-stick rapid diagnostic tests), would pose ethical and logistical problems in the implementation and interpretation of such trials.

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REFERENCES

References to studies included in this review

Nathan 2005 {published and unpublished data}

Nathan N, Borel T, Djibo A, Evans D, Djibo S, Corty JF, et al. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. *Lancet* 2005;**366**:308-13.

References to studies excluded from this review

Barquet 1997 {published data only}

Barquet N, Domingo P, Cayla JA, Gonzalez J, Rodrigo C, Fernandez-Viladrich P, et al. Prognostic factors in meningococcal disease: Development of a bedside predictive model and scoring system. *JAMA* 1997;**278**(6):491-6.

Barquet 1999 {published data only}

Barquet N, Domingo P, Cayla JA, Gonzalez J, Rodrigo C, Fernandez-Viladrich P, et al. Meningococcal disease in a large urban population (Barcelona, 1987-1992): predictors of dismal prognosis. *Archives of Internal Medicine* 1999;**159**(19):2329-40.

Barson 1985 {published data only}

Barson WJ, Miller MA, Brady MT, Powell DA. Prospective comparative trial of ceftriaxone vs. conventional therapy for treatment of bacterial meningitis in children. *Pediatric Infectious Disease* 1985;**4**(4):362-8. [CN-00039069]

Bohr 1983 {published data only}

Bohr V, Rasmussen N, Hansen B, Kjersem H, Jessen O, Johnsen N, et al. 875 cases of bacterial meningitis: diagnostic procedures and the impact of preadmission antibiotic therapy. Part III of a three-part series. *Journal of Infection* 1983;**7**(3):93-202.

BSSI 1995 {published data only}

BSSI Research Committee. Bacterial meningitis: causes for concern. *Journal of Infection* 1995;**30**(2):89-94. [7478351]

Cartwright 1992 {published data only}

Cartwright K, Reilly S, White D, Stuart J. Early treatment with parenteral penicillin in meningococcal disease. *BMJ* 1992;**305**(6846):143-7.

Congeni 1984 {published data only}

Congeni BL. Comparison of ceftriaxone and traditional therapy of bacterial meningitis. *Antimicrobial Agents & Chemotherapy* 1984;**25**(1):40-4. [CN-00033949]

del Rio 1983 {published data only}

del Rio MA, Chrane D, Shelton S, McCracken GH Jr, Nelson JD. Ceftriaxone versus ampicillin and chloramphenicol for treatment of bacterial meningitis in children. *Lancet* 1983;**321**(8336):1241-4. [CN-00031211]

Gedde-Dahl 1990 {published data only}

Gedde-Dahl TW, Hoiby EA, Brandtzaeg P, Eskerud JR, Bovre K. Some arguments on early hospital admission and treatment

of suspected meningococcal disease cases. *NIPH Annals* 1990;**13**(2):45-60.

Girgis 1989 {published data only}

Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatric Infectious Disease Journal* 1989;**8**(12):848-51. [CN-00066058]

Gunn 1996 {published data only}

Gunn A, Hollyoak V. Meningitis: public health issues. *Nursing Times* 1996;**92**(6):27-9.

Harnden 2006 {published data only}

Harnden A, Ninis N, Thompson M, Perera R, Levin M, Mant D, et al. Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study. *BMJ* 2006;**332**(7553):1295-8. [DOI: [10.1136/bmj.38789.723611.55](https://doi.org/10.1136/bmj.38789.723611.55)]

Jolly 2001 {published data only}

Jolly K, Stewart G. Epidemiology and diagnosis of meningitis: results of a five-year prospective, population-based study. *Communicable Disease and Public Health* 2001;**4**(2):124-9.

Kavaliotis 1989 {published data only}

Kavaliotis J, Manios SG, Kansouzidou A, Danielidis V. Treatment of childhood bacterial meningitis with ceftriaxone once daily: open, prospective, randomized, comparative study of short-course versus standard-length therapy. *Chemotherapy* 1989;**35**(4):296-303. [CN-00061937]

Leclerc 2001 {published data only}

Leclerc F, Noizet O, Dorkenoo A, Cremer R, Leteurtre S, Sadik A, et al. Treatment of meningococcal purpura fulminans. *Archives de Pediatrie* 2001;**8**(Suppl 4):667-88. [MEDLINE: 2001324586]

Martin 1990 {published data only}

Martin E, Hohl P, Gugli T, Kayser FH, Fernex M. Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results of a Swiss multicenter study. Part I: clinical results. *Infection* 1990;**18**(2):70-7. [CN-00067277]

Molyneux 2011 {published data only}

* Molyneux E, Nizami SQ, Saha S, Huu KT, Azam M, Bhutta ZA, et al. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. *Lancet* 2011;**377**(9780):1837-45.

Newcombe 1997 {published data only}

Newcombe J, Dyer S, Blackman L, Cartwright K, Palmer WH, McFadden J. PCR-single-stranded confirmational polymorphism analysis for non-culture-based subtyping of meningococcal strains in clinical specimens. *Journal of Clinical Microbiology* 1997;**35**(7):1809-12.

Noorgard 2002 {published data only}

Noorgard B, Soorensen HT, Jensen ES, Faber T, Schoonheyder HC, Nielsen GL. Pre-hospital parenteral antibiotic treatment of meningococcal disease and case fatality:

a Danish population-based cohort study. *Journal of Infection* 2002;**45**(3):144-51.

Pecoul 1991 {published data only}

Pecoul B, Varaine F, Keita M, Soga G, Djibo A, Soula G, et al. Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. *Lancet* 1991;**338**(8771):862-6. [CN-00078644]

Perea-Milla 2009 {published data only}

Perea-Milla E, Olalla J, Sanchez-Cantalejo E, Martos F, Matute-Cruz P, Carmona-Lopez G, et al. Pre-hospital antibiotic treatment and mortality caused by invasive meningococcal disease, adjusting for indication bias. *BMC Public Health* 2009;**9**:95. [Research Support, Non-U.S. Gov't 19344518]

Quagliarello 2003 {published data only}

Quagliarello V. Short-course penicillin therapy for meningococcal disease: accumulating evidence and persistent uncertainty. *Clinical Infectious Diseases* 2003;**37**(5):663-4. [MEDLINE: 2003369547]

Riordan 2001 {published data only}

Riordan FAI. Improving promptness of antibiotic treatment in meningococcal disease. *Emergency Medicine Journal* 2001;**18**(3):162-3. [MEDLINE: 2002028693]

Rodriguez 1986 {published data only}

Rodriguez WJ, Puig JR, Khan WN, Feris J, Gold BG, Sturla C. Ceftazidime vs. standard therapy for pediatric meningitis: therapeutic, pharmacologic and epidemiologic observations. *Pediatric Infectious Disease* 1986;**5**(4):408-15. [CN-00043513]

Roord 2001 {published data only}

Roord JJ, Kaandorp CJ. CBO-guideline 'Bacterial meningitis'. *Nederlands Tijdschrift voor Geneeskunde* 2001;**145**(5):211-4.

Roznovsky 2003 {published data only}

Roznovsky L, Krizova P, Struncova V, Dostal V, Plisek S, Kasal E, et al. Administration of antibiotics before admission in patients with meningococcal disease. *Central European Journal of Public Health* 2003;**11**(1):14-8.

Schaad 1990 {published data only}

Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J, Auckenthaler R, Bernath O, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *New England Journal of Medicine* 1990;**322**(3):141-7. [CN-00064505]

Sorensen 1998 {published data only}

Sorensen HT, Nielsen GL, Schonheyder HC, Steffensen FH, Hansen I, Sabroe S, et al. Outcome of pre-hospital antibiotic treatment of meningococcal disease. *Journal of Clinical Epidemiology* 1998;**51**(9):717-21. [MEDLINE: 1998321631]

Strang 1992 {published data only}

Strang JR, Pugh EJ. Meningococcal infections: reducing the case fatality rate by giving penicillin before admission to hospital. *BMJ* 1992;**305**(6846):141-3.

Wald 1995 {published data only}

Wald ER, Kaplan SL, Mason EOJ, Sabo D, Ross L, Arditi M, et al. Dexamethasone therapy for children with bacterial meningitis. *Pediatrics* 1995;**95**(1):21-31. [CN-00174080]

Wylie 1997 {published data only}

Wylie PAL, Stevens D, Drake W 3rd, Stuart J, Cartwright K. Epidemiology and clinical management of meningococcal disease in west Gloucestershire: retrospective, population based study. *BMJ* 1997;**315**(7111):774-9. [MEDLINE: 1997291389]

Additional references

Al-Tawfiq 2010

Al-Tawfiq JA, Clark TA, Memish ZA. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. *Journal of Travel Medicine* 2010;**17**:3-8.

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Baraff 1993

Baraff LJ. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatric Infectious Disease Journal* 1993;**12**:389-94.

Belo 2010

Belo EFT, Farhat CK, Gaspari END. Comparison of dot-ELISA and standard ELISA for detection of *Neisseria meningitidis* outer membrane complex-specific antibodies. *Brazilian Journal of Infectious Diseases* 2010;**14**(1):35-40.

Boisier 2009

Boisier P, Mahamane AE, Hamidou AA, Sidikou F, Djibo S, Nato F, et al. Field evaluation of rapid diagnostic tests for meningococcal meningitis in Niger. *Tropical Medicine and International Health* 2009;**14**:111-7.

Booy 2001

Booy R, Habibi P, Nadel S, de Munter C, Britto Morrison JA, Levin M, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Archives of Disease in Childhood* 2001;**85**:386-90.

Borg 2009

Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics* 2009;**123**:e502-9. [DOI: [10.1542/peds.2008-0581](https://doi.org/10.1542/peds.2008-0581)]

Bourke 2010

Bourke TW, Fairley DJ, Shileds MD. Rapid diagnosis of meningococcal disease (editorial). *Expert Review of Anti-infective Therapy* 2010;**8**(12):1321-3.

Brandtzaeg 1989

Brandtzaeg P, Kierulf P, Gaustad P, Skulberg A, Bruun JN, Halvorsen S, et al. Plasma endotoxin as a predictor of multiple

organ failure and death in systemic meningococcal disease. *Journal of Infectious Diseases* 1989;**159**(2):195-204.

Brandtzaeg 2005

Brandtzaeg P, van Deuren M. Meningococcal infections at the start of the 21st century. *Advances in Pediatrics* 2005;**52**:129-62.

Campbell Collaboration 2008

The Campbell Collaboration. The Campbell Collaboration Economics Methods Policy Brief Version 1.0 April 2008. www.campbellcollaboration.org/artman2/uploads/1/Economic_Methods_Policy_Brief.pdf 2009 (accessed 21 July 2009).

Chanteau 2007

Chanteau S, Rose AM, Djibo S, Nato F, Boiesier P. Biological diagnosis of meningococcal meningitis in the African meningitis belt: current epidemic strategy and new perspectives. *Vaccine* 2007;**25**(Suppl 1):A30-6.

Duke 2003

Duke T, Michael A, Mokela D, Wal T, Reeder J. Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries?. *Archives of Disease in Childhood* 2003;**88**(6):536-9.

Edmond 2010

Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infectious Diseases* 2010;**10**(5):317-28.

Eickhoff 1965

Eickhoff TC, Finland M. Changing susceptibility of meningococci to antimicrobial agents. *New England Journal of Medicine* 1965;**272**:395-8.

El Bashir 2003

El Bashir H, Laundry M, Booy R. Diagnosis and treatment of bacterial meningitis. *Archives of Disease in Childhood* 2003;**88**:615-20.

El Filali 1993

el Filali M, Noum M, Chakib A, Zahraoui M, Himmich H. Ceftriaxone versus penicillin G in the short term treatment of meningococcal meningitis in adults. *European Journal of Clinical Microbiology & Infectious Diseases* 1993;**12**:766-8.

Ferguson 2002

Ferguson LE, Hormann MD. Neisseria meningitidis: presentation, treatment and prevention. *Journal of Pediatric Health Care* 2002;**16**:119-24.

Girgis 1998

Girgis N, Sultan Y, Frenck RW Jr, El-Gendy A, Farid Z, Mateczun A. Azithromycin compared with rifampin for eradication of nasopharyngeal colonization by Neisseria meningitidis. *Pediatric Infectious Disease Journal* 1998;**17**:816-9.

GRADEpro GDT 2014 [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT [GRADEpro GDT]. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Granoff 2009

Granoff DM, Harrison LH, Borrow R. Meningococcal vaccines. In: Plotkin SA, Orenstein WA, Offit P editor(s). *Vaccines*. 5th Edition. Philadelphia: Saunders Elsevier, 2008:399-434.

Hackett 2002

Hackett SJ, Guiver M, Marsh J, Sills JA, Thomson APJ, Kaczmarek EB, et al. Meningococcal bacterial DNA load at presentation correlates with disease severity. *Archives of Disease in Childhood* 2002;**86**:44-6.

Hahné 2006

Hahné SJM, Charlett A, Purcell B, Samuelsson S, Camaroni I, Ehrhard I, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ* 2006;**332**:1299-303.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011a

Higgins JP, Altman, DG, Sterne JAC on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JP, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hill 2010

Hill DJ, Griffiths NJ, Borodina E, Virji M. Cellular and molecular biology of *Neisseria meningitidis* colonization and invasive disease. *Clinical Science (London)* 2010;**9**(118):547-64.

Hsu 2009

Hsu HE, Shutt KA, Moore MR, Beall BW, Bennett NM, Craig AS, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *New England Journal of Medicine* 2009;**360**(3):244-56.

Kanegaye 2001

Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001;**108**:1169-74.

Keeley 2006

Keeley D. Parenteral penicillin before admission to hospital for meningitis. *BMJ* 2006;**332**:1283-4.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

NICE 2007

National Collaborating Centre for Women's and Children's Health. Feverish illness in children. Assessment and initial management in children younger than 5 years. NICE Clinical Guideline CG47. www.nice.org.uk/nicemedia/pdf/cg47niceguideline.pdf (accessed prior to 2 June 2017).

NICE 2010

National Collaborating Centre for Women's and Children's Health. Bacterial meningitis and meningococcal septicaemia: the management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE Clinical Guideline CG 102. www.nice.org.uk/CG102 (accessed prior to 2 June 2017).

Pecoul 1999

Pecoul B, Chirac P, Trouiller P, Pinel J, Pecoul B, Chirac P, et al. Access to essential drugs in poor countries: a lost battle?. *JAMA* 1999;**281**(4):361-7.

Perera 2006

Perera R. Statistics and death from meningococcal disease in children. *BMJ* 2006;**332**(7553):1297-8.

Piaggio 2006

Piaggio G, Elbourne D, Altman DG, Pocock SJ, Evans SJW, for the CONSORT Group. Reporting of noninferiority and equivalence randomized trials. An extension of the CONSORT statement. *JAMA* 2006;**295**:1152-60.

Prasad 2011

Prasad K, Kumar A, Singhal T, Gupta PK. Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2011, Issue 10. [DOI: [10.1002/14651858.CD001832.pub3](https://doi.org/10.1002/14651858.CD001832.pub3)]

Ramakrishnan 2009

Ramakrishnan M, Ulland AJ, Steinhardt LC, Moisi JC, Were F, Levine OS. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Medicine* 2009;**7**:47. [DOI: [10.1186/1741-7015-7-47](https://doi.org/10.1186/1741-7015-7-47)]

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rose 2010

Rose AMC, Mueller JE, Gerstl S, Njanpop-Lafourcade B-M, Page A-L, Nicolas P, et al. Meningitis dipstick rapid test: evaluating diagnostic performance during an urban *Neisseria meningitidis* serogroup A outbreak, Burkina Faso, 2007. *PLoS ONE* 2010;**5**(6):e11086. [DOI: [10.1371/journal.pone.0011086](https://doi.org/10.1371/journal.pone.0011086)]

Rosenstein 2001

Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *New England Journal of Medicine* 2001;**344**:1378-88.

Rouphael 2012

Rouphael NG, Stephens DS. *Neisseria meningitidis*: biology, microbiology, and epidemiology. *Methods in Molecular Biology* 2012;**799**:1-20.

Schneider 2006

Schneider MC, Exley RM, Chan H, Feavers I, Kang YH, Sim RB, et al. Functional significance of factor H binding to *Neisseria meningitidis*. *Journal of Immunology* 2006;**176**:7566-75.

Schubert-Unkmeir 2010

Schubert-Unkmeir A, Konrad C, Slanina H, Czapek F, Hebling S, Frosch M. *Neisseria meningitidis* induces brain microvascular endothelial cell detachment from the matrix and cleavage of occludin: a role for MMP-8. *PLoS Pathogens* 2010;**6**(4):e1000874. [DOI: [10.1371/journal.ppat.1000874](https://doi.org/10.1371/journal.ppat.1000874)]

Schwartz 1989

Schwartz B, Moore PS, Broome CV. Global epidemiology of meningococcal disease. *Clinical Microbiology Reviews* 1989;**2**(Suppl):118-24.

SIGN 2008

Scottish Intercollegiate Guidelines Network. Management of invasive meningococcal disease in children and young people. A National Clinical Guideline: 102. www.sign.ac.uk/pdf/sign102.pdf (accessed prior to 2 June 2017).

Sinclair 2010

Sinclair D, Preziosi MP, John JT, Greenwood B. The epidemiology of meningococcal disease in India. *Tropical Medicine and International Health* 2010;**15**:1421-35.

Stephens 2007

Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcal sepsis, and *Neisseria meningitidis*. *Lancet* 2007;**369**:2196-201.

Tunkel 1993

Tunkel AR, Scheld WM. Pathogenesis and pathophysiology of bacterial meningitis. *Annual Reviews in Medicine* 1993;**44**:103-20.

Wall 2013

Wall ECB, Ajdukiewicz KMB, Heyderman RS, Garner P. Osmotic therapies added to antibiotics for acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: [10.1002/14651858.CD008806.pub2](https://doi.org/10.1002/14651858.CD008806.pub2)]

Wang 2000

Wang VJ, Malley R, Fleisher GR, Inkelis SH, Kuppermann N. Antibiotic treatment of children with unsuspected meningococcal disease. *Archives of Pediatrics and Adolescent Medicine* 2000;**154**(6):556-60.

WHO 1995

WHO Working Group. Control of Epidemic Meningococcal Diseases: WHO Practical Guidelines. Lyon, France: Edition Foundation Marcel Merieux, 1995.

WHO 2004

World Health Organization. Meningococcal meningitis. www.who.int/csr/disease/meningococcal/en/ 2004 (accessed prior to 2 June 2017).

WHO 2007

World Health Organization. Risk of epidemic meningitis in Africa: a cause for concern. *Weekly Epidemiological Record* 2007;**82**:77-88.

WHO 2010

World Health Organization. Bacterial infections: meningococcal disease. www.who.int/vaccine_research/diseases/soa_bacterial/en/print.html 2010 (accessed prior to 2 June 2017).

Zalmanovici 2013

Zalmanovici Trestioreanu A, Fraser A, Gafer-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections.

Cochrane Database of Systematic Reviews 2013, Issue 10. [DOI: [10.1002/14651858.CD004785.pub5](https://doi.org/10.1002/14651858.CD004785.pub5)]

References to other published versions of this review

Sudarsanam 2005

Sudarsanam T, Thomas K, Rupalli P, Abraham OC, Tharyan P. Pre-admission antibiotics for suspected cases of meningococcal disease. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: [10.1002/14651858.CD005437](https://doi.org/10.1002/14651858.CD005437)]

Sudarsanam 2008

Sudarsanam T, Rupali P, Tharyan P, Abraham OC, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: [10.1002/14651858.CD005437.pub2](https://doi.org/10.1002/14651858.CD005437.pub2)]

Sudarsanam 2011

Sudarsanam T, Rupali P, Tharyan P, Abraham OC, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: [10.1002/14651858.CD005437.pub2](https://doi.org/10.1002/14651858.CD005437.pub2)]

Sudarsanam 2013

Sudarsanam T, Rupali P, Tharyan P, Abraham OC, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: [10.1002/14651858.CD005437.pub3](https://doi.org/10.1002/14651858.CD005437.pub3)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Nathan 2005

Methods	Randomised, open-label, parallel-group, non-inferiority trial
	Period of study: March to April 2003
Participants	Number randomised: 510 Age: children and adults > 2 months of age (< 5 years 33%; 5 to 14 years 57%; > 15 years 12%) Gender: 54% male Included: sudden onset of fever or history of fever in the previous 24 hours associated with at least 1 of the following symptoms: neck stiffness, impaired consciousness, or petechial rash for patients older than 1 year; or bulging fontanel, axial hypotonia, upwardly turned gaze, or petechial rash for patients younger than 1 year Excluded: < 2 months of age; allergy to study drug; coma; shock; pregnant women; recurrent meningitis; severely ill patients Diagnosis meningococcal meningitis confirmed by: CSF white blood cell count of more than 50 cells/mL and a biological confirmation of <i>Neisseria meningitidis</i> meningitis by: - pathogen identification in the CSF by Gram staining; - presence of soluble antigens in the CSF detected by direct agglutination test (Pastorex, Bio-Rad Laboratories, Hercules, CA, USA);

Nathan 2005 (Continued)

- pathogen identification in CSF culture; or
- detection of bacterial DNA of pathogen by PCR.

Interventions	Intervention Ceftriaxone 100 mg/kg (max 4 g) IM at 0 hour, 1 dose (N = 251) Control LA chloramphenicol 100 mg/kg (max 3 g) IM at 0 hour, 1 dose (N = 259) No concomitant steroids were used.
Outcomes	Outcomes used: 1. Death at 72 hours in all participants and in those with confirmed diagnosis 2. Death within 72 hours 3. Clinical failure at 72 hours in all participants and in those with confirmed diagnosis (see notes for definition of clinical failure) 4. Clinical failure between 24 hours and 48 hours needing a second injection 5. Neurological sequelae (short term - 72 hours) 6. Drug-related adverse effects 7. Treatment costs per person for chloramphenicol and ceftriaxone in USD Outcomes not used: 1. Treatment failure, defined by: death or clinical failure at 72 hours 2. Risk of treatment failure at 72 hours analysed for baseline characteristics Outcomes not available: 1. Burden of disease on the family and the caregiver
Notes	Setting: Niger during an epidemic; 8 primary healthcare centres and Zinder regional hospital. Individuals with suspected disease represented more than 90% of those attending health facilities during the study. Clinical failure: GCS < 11 at 24 hours/< 13 at 48 hours; no change in GCS from baseline; worsening of neurological deficits/new deficits; increase in convulsions; fever > 38.5° C after 24 to 48 hours Exact treatment protocol: 1. Ceftriaxone: 100 mg/kg (max 4 g) IM at 0 hour 1 dose; if clinical failure at 24 to 48 hours then repeat dose at 75 mg/kg 2. LA chloramphenicol: 100 mg/kg (max 3 g) IM at 0 hour 1 dose; if clinical failure at 24 to 48 hours then repeat dose at 100 mg/kg (19/259 of in the LA chloramphenicol group and 16/251 in the ceftriaxone group were given a second injection.) If clinical failure at 72 hours then ceftriaxone 100 mg/kg/day IV for a minimum of 4 days as rescue therapy Sample size estimation for non-inferiority: based on estimated proportion of treatment failure in the chloramphenicol group of 15% and a difference of less than 10% between the 2 groups (beyond which non-inferiority could not be proven) The difference in risk between interventions for primary and secondary outcomes was regarded as equivalent if the upper limit of its 90% confidence interval was below 10%. Analyses: primary and secondary endpoints were analysed according to:

Nathan 2005 (Continued)

1. intention-to-treat principle (all individuals with suspected disease included); 251 in ceftriaxone arm and 259 in chloramphenicol arm (4 and 3 in the respective arms left the facility before 72 hours);
2. per-protocol principle (restricted to individuals with confirmed meningococcal meningitis without any additional infection or concomitant antibiotic therapy); 148/256 (58%) in the chloramphenicol arm and 160/247 (65%) in the ceftriaxone arm.

Data were not provided for proportions with antibiotic resistance in intervention arms.

Sponsor: Médecins Sans Frontières (MSF), Paris

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Block randomisation was done with a computer-generated list" Comment: Communication with trial authors clarified that randomisation was done in blocks of 20.
Allocation concealment (selection bias)	Low risk	Quote: "At inclusion (0 h), medical doctors who were assigned to the study obtained CSF samples by lumbar puncture, undertook a rapid test for malaria diagnosis (Optimal, Diamed, Switzerland), and randomly assigned patients" Quote: "the treatment group was allocated with individually sealed envelopes" Quote: "Principal investigators undertook the randomisation in Paris before the trial began. They did not assign patients to treatment groups in the field" Comment: Additional information from the trial authors clarified that serially numbered, opaque envelopes were distributed in blocks to inclusion sites (e.g. 1 to 50 to one site, 51 to 100 to a second site). The study physicians opened the envelopes sequentially and allocated the interventions. Comment: Although interventions were not given blind, allocation appears to have been concealed until the administration of the interventions.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Because of field conditions, our trial was not masked; the vials had different appearances and the treating doctors were not masked to which treatment was given." Comment: The trial was open label, but the outcomes evaluated were objective; allocation was concealed, and therefore the review authors do not believe this introduced selection or detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 557 patients screened, 510 were randomly assigned to receive ceftriaxone or chloramphenicol. Of these individuals, 47 (9%) were excluded because they were ineligible and another seven (1%) were lost to follow-up after treatment allocation" Comment: 4/251 in the ceftriaxone arm and 3/259 in the chloramphenicol arm who left the facility before 72 hours were not included in the intention-to-treat analysis by the trial authors. The review authors feel this is a reasonable way to explain these dropouts for the primary outcomes of this review. The original version of this review used a revised intention-to-treat analysis of these dropouts considering them to have had the worst outcome for primary and secondary outcomes; the results of the 2 analyses did not significantly differ. Comment: 160/247 in the ceftriaxone arm and 148/256 in the chloramphenicol arm who were included in the intention-to-treat analyses were confirmed to have meningococcal meningitis and were included in the per-protocol analysis. The remaining 87 and 108 participants in the respective arms did not have

Nathan 2005 (Continued)

the suspected diagnosis confirmed. The differences in confirmed cases for primary and secondary outcomes excluded clinically and statistically important differences between interventions.

Quote: "Patients in clinical failure at 72 h were followed through to complete recovery. Although the risk of relapse after discharge was regarded as low and all patients were advised to return to the clinic in the event of clinical deterioration, no patients returned during the study period."

Comment: Unlikely to introduce bias as both drugs were associated with very low relapse rates in other observational studies done in the region with longer follow-up periods

Selective reporting (reporting bias)	Low risk	Comment: All prespecified outcomes were reported
Other bias	Low risk	Comment: No other sources of bias were apparent

CSF: cerebrospinal fluid
GCS: Glasgow Coma Scale
IM: intramuscular
IV: intravenous
LA: long-acting
PCR: polymerase chain reaction
RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Barquet 1997	Design: prospective population-based study
Barquet 1999	Design: population-based cohort study
Barson 1985	Design: RCT Participants: confirmed cases of meningitis based in a hospital. 10% participants in each group (ceftriaxone versus ampicillin and chloramphenicol) had pre-admission antibiotics and data regarding outcomes were not available separately.
Bohr 1983	Design: retrospective chart review
BSSI 1995	Design: retrospective case series
Cartwright 1992	Design: retrospective case review
Cogeni 1984	Design: RCT Participants: only those with CSF-confirmed meningitis; those not confirmed by CSF culture were excluded
del Rio 1983	Design: mentioned as randomised but methods not described Participants: only confirmed cases of meningitis; excluded as not 'pre-admission' antibiotics
Gedde-Dahl 1990	Review article
Girgis 1989	Design: RCT Participants: people with meningitis randomised to receive dexamethasone or no dexamethasone - both groups received ampicillin and chloramphenicol

Study	Reason for exclusion
Gunn 1996	Design: review of cases in a district programme
Harnden 2006	Design: case-control study
Jolly 2001	Design: prospective, non-controlled study in a health district
Kavaliotis 1989	Design: RCT Participants: proven cases with meningitis
Leclerc 2001	Design: a meta-analysis of observational studies
Martin 1990	Design: RCT Participants: children with proven bacterial meningitis
Molyneux 2011	Design: RCT Participants: proven meningitis Intervention: 5 days of ceftriaxone Control: 10 days of ceftriaxone
Newcombe 1997	Design: laboratory-based PCR study
Noorgard 2002	Design: cohort study
Pecoul 1991	Design: RCT Participants: children with proven meningitis; clinical suspicion with CSF microbiology suggestive of meningitis or CSF cell counts > 5000/cu mm
Perea-Milla 2009	Design: retrospective analysis adjusted for indication bias by using propensity scores of risk factors to predict mortality
Quagliarello 2003	Review article
Riordan 2001	Design: not an RCT; cohort of the effect of training on "door to needle time"
Rodriguez 1986	Design: ? RCT Participants: only confirmed cases of meningitis included
Roord 2001	Review article
Roznovsky 2003	Design: description of confirmed cases only
Schaad 1990	Design: RCT Participants: only confirmed cases were included
Sorensen 1998	Design: 16-year historical follow-up
Strang 1992	Design: retrospective case-control study
Wald 1995	Design: RCT Participants: children with proven bacterial meningitis Intervention: dexamethasone versus placebo. Both groups received antibiotics
Wylie 1997	Design: description of cases

CSF: cerebrospinal fluid
PCR: polymerase chain reaction
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Ceftriaxone versus long-acting (oily) chloramphenicol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1 In all participants - short-term	1	503	Risk Ratio (IV, Fixed, 95% CI)	1.21 [0.57, 2.56]
1.2 In confirmed cases of meningococcal meningitis - short-term	1	308	Risk Ratio (IV, Fixed, 95% CI)	1.11 [0.35, 3.56]
1.3 In cases due to other causes - short-term	1	195	Risk Ratio (IV, Fixed, 95% CI)	1.42 [0.54, 3.76]
2 Clinical failure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 In all participants - short-term	1	477	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.32, 2.15]
2.2 In confirmed cases of meningococcal meningitis - short-term	1	308	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.23, 8.47]
2.3 In cases due to other causes - short-term	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.25, 2.58]
3 Neurological sequelae	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 In all participants - short-term	1	477	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.63, 2.62]
3.2 In confirmed cases of meningococcal meningitis - short-term	1	297	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.65, 3.23]
3.3 In cases due to other causes - short-term	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.12, 3.40]

Analysis 1.1. Comparison 1 Ceftriaxone versus long-acting (oily) chloramphenicol, Outcome 1 Death.

Study or subgroup	Ceftriaxone n/N	Chloramphenicol n/N	Risk Ratio IV, Fixed, 95% CI	Weight	Risk Ratio IV, Fixed, 95% CI
1.1.1 In all participants - short-term					
Nathan 2005	14/247	12/256		100%	1.21[0.57,2.56]

Analysis 1.2. Comparison 1 Ceftriaxone versus long-acting (oily) chloramphenicol, Outcome 2 Clinical failure.

Analysis 1.3. Comparison 1 Ceftriaxone versus long-acting (oily) chloramphenicol, Outcome 3 Neurological sequelae.

APPENDICES

Appendix 1. Details of previous searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library) (2007, Issue 1 and 2013, Issue 5), MEDLINE (1966 to February 2007 and to May 2013) and EMBASE (1980 to February 2007 and to May 2013), and handsearched the references of all identified studies.

The following search terms were run over MEDLINE and CENTRAL. The MEDLINE search was combined with the search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials. See [Appendix 3](#) for the EMBASE search strategy.

MEDLINE (Ovid)

```

1 exp MENINGOCOCCAL INFECTIONS/
2 exp Neisseria meningitides/
3 (neisseria adj mening$).mp.
4 meningococ$.mp
5 or/1-4
6 exp Anti-bacterial Agents/
7 (antibiotic$ or penicillin$ or cefotaxime$ or ampicillin$ or sulfa$ or ciprofloxacin$ or norfloxaci$ or ofloxaci$ or quinol$ or fluoroquinol$ or fluoro-quinolon$ or ceftriaxon$ or rifampi$ or azithromyci$ or minocyclin$ or macrolid$ or cephalospori$).mp.
8 or/6-7
9 exp Patient Admission/
10 (preadmission or pre-admission).mp.
11 empiric.mp.
12 or/9-11
13 5 and 8 and 12
  
```

Embase.com

```
#16 #6 and #10 and #15
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Pre-admission antibiotics for suspected cases of meningococcal disease (Review)

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#15 #11 or #12 or #13 or #14
 #14 (empiric in ti) or (empiric in ab)
 #13 (preadmission or pre-admission)in ab
 #12 (preadmission or pre-admission)in ti
 #11 explode 'hospital-admission' / all subheadings in DEM,DER,DRM,DRR
 #10 #7 or #8 or #9
 #9 (antibiotic* or penicillin or cefotaxime or ampicilli* or sulfa* or ciprofloxacin* or norfloxacin* or ofloxaci* or quinol* or fluoroquinol* or fluoro-quinolon* or ceftriaxon* or rifampi* or azithromyci* or minocyclin* or macrolid* or cephalospori*) in ab
 #8 (antibiotic* or penicillin or cefotaxime or ampicilli* or sulfa* or ciprofloxacin* or norfloxacin* or ofloxaci* or quinol* or fluoroquinol* or fluoro-quinolon* or ceftriaxon* or rifampi* or azithromyci* or minocyclin* or macrolid* or cephalospori*) in ti
 #7 'antibiotic-agent' / all subheadings in DEM,DER,DRM,DRR
 #6 #1 or #2 or #3 or #4 or #5
 #5 (neisseria adj mening*) in ab
 #4 (neisseria adj mening*) in ti
 #3 explode 'Neisseria-meningitidis' / all subheadings in DEM,DER,DRM,DRR
 #2 (meningococcal infection* in ti) or (meningococcal infection* in ab)
 #1 explode 'meningococcosis-' / all subheadings in DEM,DER,DRM,DRR

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Meningococcal Infections/
 2 exp Neisseria meningitidis/
 3 (neisseria adj2 mening*).tw.
 4 meningococc*.tw.
 5 Meningitis/
 6 meningit*.tw.
 7 or/1-6
 8 exp Anti-Bacterial Agents/
 9 antibiotic*.tw,nm.
 10 (penicillin* or cefotaxim* or ampicillin* or sulfa* or ciprofloxacin* or norfloxacin* or ofloxacin* or quinol* or fluoroquinol* or fluoro-quinol* or ceftriaxon* or rifampi* or azithromyci* or minocyclin* or macrolid* or cephalosporin*).tw,nm.
 11 or/8-10
 12 Patient Admission/
 13 (patient* adj2 (admis* or admit*)).tw.
 14 ((pre or before or prior or previous) adj2 hospital*).tw.
 15 ((previous or prior or before) adj2 (admit* or admiss*)).tw.
 16 (preadmit* or pre admit* or pre-admit* or preadmiss* or pre admiss* or pre-admiss*).tw.
 17 empiric.tw.
 18 or/12-17
 19 7 and 11 and 18

Appendix 3. Embase.com search strategy

#31 #22 AND #30
 #30 #25 NOT #29
 #29 #26 NOT #28
 #28 #26 AND #27
 #27 'human'/de
 #26 'nonhuman'/de OR 'animal'/de OR 'animal experiment'/de
 #25 #23 OR #24
 #24 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
 #23 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
 #22 #7 AND #21
 #21 #11 AND #20
 #20 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
 #19 (emergenc* NEAR/3 treat*):ab,ti OR triage:ab,ti
 #18 'emergency health service'/de
 #17 empiric*:ab,ti
 #16 preadmit*:ab,ti OR preadmis*:ab,ti OR (pre NEXT/1 (admit* OR admis*)):ab,ti
 #15 ((previous OR prior OR before) NEAR/3 (admit* OR admis*)):ab,ti
 #14 ((pre OR before OR prior OR previous) NEAR/5 hospital*):ab,ti
 #13 ((hospital* OR patient*) NEAR/3 (admis* OR admit*)):ab,ti
 #12 'hospital admission'/de

```
#11 #8 OR #9 OR #10
#10 penicillin*:ab,ti OR cefotaxim*:ab,ti OR ampicillin*:ab,ti OR sulfa*:ab,ti OR ciprofloxacin*:ab,ti OR norfloxacin*:ab,ti OR ofloxacin*:ab,ti
OR quinol*:ab,ti OR fluoroquinol*:ab,ti OR fluoro-quinol*:ab,ti OR ceftriaxon*:ab,ti OR rifampi*:ab,ti OR azithromyci*:ab,ti OR
minocyclin*:ab,ti OR macrolid*:ab,ti OR cephalosporin*:ab,ti
#9 antibiotic*:ab,ti
#8 'antibiotic agent'/exp
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#6 meningococc*:ab,ti OR meningit*:ab,ti OR (neisseria NEAR/2 mening*):ab,ti OR 'n. meningitidis':ab,ti
#5 'neisseria meningitidis'/de
#4 'meningitis'/de
#3 'bacterial meningitis'/de
#2 'epidemic meningitis'/de
#1 'meningococcosis'/exp
```

Appendix 4. Web of Science (Thomson Reuters) search strategy

# 3	#2 AND #1 <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=1985-2012</i> <i>Lemmatization=Off</i>
# 2	Title=(trial) OR Topic=(random* or placebo* or ((singl* or doubl*) NEAR/1 blind*)) <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=1985-2012</i> <i>Lemmatization=Off</i>

Appendix 5. LILACS (BIREME) search strategy

Search > (MH:"Meningococcal Infections" OR "Infecciones Meningocólicas" OR "Infecções Meningocólicas" OR MH:C01.252.400.625.549\$ OR MH:"Neisseria meningitidis" OR MH:B03.440.400.425.550.550.641\$ OR MH:B03.660.075.525.520.500\$ OR "Neisseria meningitidis" OR "N. meningitidis" OR meningit\$ OR meningococ\$ OR MH:Meningitis OR MH:"Meningitis, Bacterial" OR "Meningitis Bacteriana" OR "Meningite Bacteriana" OR "Bacterial Meningitis" OR MH:"Meningitis, Meningococcal" OR "Meningitis Meningocócica" OR "Meningite Meningocócica" OR "Meningitis Meningocóccica" OR "Meningite Meningocóccica") AND (MH:"Anti-Bacterial Agents" OR antibacter\$ OR antibiotic\$ OR Antibióticos OR Antibacterianos OR MH:D27.505.954.122.085\$ OR penicillin\$ OR cefotaxim\$ OR ampicillin\$ OR sulfa\$ OR ciprofloxacin\$ OR norfloxacin\$ OR ofloxacin\$ OR quinol\$ OR fluoroquinol\$ OR fluoro-quinol\$ OR ceftriaxon\$ OR rifampi\$ OR azithromycin\$ OR minocyclin\$ OR macrolid\$ OR cephalosporin\$) > clinical_trials

Appendix 6. CAB Abstracts (Thomson Reuters) search strategy

# 3	#2 AND #1 <i>Databases=CAB Abstracts Timespan=1985-2012</i> <i>Lemmatization=Off</i>
# 2	Title=(trial) AND Topic=((random* or placebo* or ((singl* or doubl*) NEXT/1 blind*))) <i>Databases=CAB Abstracts Timespan=1985-2012</i> <i>Lemmatization=Off</i>
# 1	Topic=((meningococcal OR "Neisseria meningitidis" OR "N. meningitidis" OR meningitis)) AND Topic=(antibiotic* OR penicillin* OR cefotaxim* OR ampicillin* OR sulfa* OR ciprofloxacin* OR norfloxacin* OR ofloxacin* OR quinol* OR fluoroquinol* OR fluoro-quinol* OR ceftriaxon* OR rifampi* OR azithromycin* OR minocyclin* OR macrolid* OR cephalosporin*)

(Continued)

Databases=CAB Abstracts Timespan=1985-2012

Lemmatization=Off

WHAT'S NEW

Date	Event	Description
6 January 2017	New citation required but conclusions have not changed	Our conclusions remain unchanged.
6 January 2017	New search has been performed	We identified no new trials for inclusion or exclusion in this 2017 update.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 1, 2008

Date	Event	Description
3 May 2013	New citation required but conclusions have not changed	The conclusions remain unchanged.
3 May 2013	New search has been performed	We updated our searches and identified 45 records. We excluded one new trial (Molyneux 2011).
4 June 2010	New search has been performed	Search updated; no new trials found.
22 February 2007	New search has been performed	Searches conducted. Review published Issue 1, 2008.

CONTRIBUTIONS OF AUTHORS

Thambu Sudarsanam (TS) and Priscilla Rupali (PR) wrote the initial draft of the protocol, selected trials, assessed quality, entered data for the review, and screened studies for the review updates.

TS wrote the draft of the earlier version of the review and the updates.

Prathap Tharyan (PT) modified the draft of the protocol, checked extracted data, checked study quality, wrote the final version of the initial review, updated the Background, Methods, and Discussion sections, completed the 'Risk of bias' tables, created the 'Summary of findings' table and wrote the final version of the 2007 review update, and checked study selection and the 2017 update.

Ooriapadickal Cherian Abraham (OCA) and Kurien Thomas (KT) helped modify the protocol.

All authors approved the final version of the review and the review updates.

DECLARATIONS OF INTEREST

Thambu D Sudarsanam: None known.

Priscilla Rupali: None known.

Prathap Tharyan: Prathap Tharyan is a program partner of the Effective Health Care Research Consortium (funded by the UK Department for International Development) and a recipient of a grant under this project. He was also contracted by Cochrane to help build capacity in authors from India and the region to undertake systematic reviews.

Ooriapadickal Cherian Abraham: None known.
Kurien Thomas: None known.

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- Effective Health Care Research Consortium, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2010 update

Since the first publication of this review, newer methods were introduced with the release of RevMan 5.3 and were incorporated with this update ([RevMan 2014](#)). These include a more detailed description of methods, such as the 'Risk of bias' assessment and the 'Summary of findings' tables. These also encouraged the implementation of other changes during this update to better evaluate the outcomes in the context of potential biases and confounders and other contextual factors that were not immediately apparent nor considered in the original review.

1. Outcomes

For this update of the review, we also included the proportion of people with confirmed diagnosis of meningococcal meningitis among those randomised as subgroups in the analyses of primary and secondary outcomes. This omission was an oversight in the initial review, as such an analysis enables an exploration of the efficacy of pre-admission antibiotics in confirmed meningococcal meningitis versus that due to other organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae*, or in those participants without a bacterial aetiology for their presenting symptoms. Since overall mortality is also of importance from a public health perspective in recommending particular antibiotics, and not just that due to meningococcal disease, we introduced this exploration to inform our conclusions better of their relative efficacy in the two subgroups.

In addition, comparisons of trials with short follow-up durations, as in the trial included in this review, and those that assess deficits in the longer term, if identified by future updates, would enable comparison of the development of neurological sequelae that are detected only after discharge, particularly hearing deficits and spasticity in young children and milder cognitive deficits and behavioural changes in adolescents ([Borg 2009](#)), which may differ in those with meningitis due to meningococcus and those without.

We included the outcome of lack of clinical improvement as a subgroup for the same purpose in this update. We presented the results for this outcome in the previous version of this review, although this outcome had not been explicitly pre-stated in the protocol. Additional subgroups introduced were levels of severity and low-income versus moderate- to high-income settings, however no data were available for this review; both are factors that can impact the outcomes independent of the kind of antibiotic used prior to confirmation of the diagnosis.

In this updated review, we used the intention-to-treat data provided in the trial report and did not attribute a poor outcome to the seven dropouts in the first 72 hours after randomisation, as we had done in the first version, since it did not seem reasonable to do so. The results were only marginally different between the two approaches.

We also included the economic costs provided in the report for this update, which had not be used in the original review.

2. Methods

We expanded on the sections describing methods for dealing with missing data and unit of analysis issues and, as stated above, subgroup analyses and explorations of heterogeneity. We added a section on summarising findings.

While these were done after knowledge of the results of [Nathan 2005](#), they were necessitated by the newer methods incorporated with RevMan 5.3 and will better inform interpretation of results and conclusions, should future updates include additional trials ([RevMan 2014](#)).

We also note that many of the subgroup analyses we had planned in the methods section could not be carried out due to lack of data.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Anti-Bacterial Agents [therapeutic use]; Ceftriaxone [therapeutic use]; Chloramphenicol [therapeutic use]; Injections, Intramuscular; Meningitis, Meningococcal [complications] [drug therapy] [mortality]; Meningococcal Infections [complications] [*drug therapy] [mortality]; Patient Admission

MeSH check words

Humans