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Antibiotics for preventing meningococcal infections (Review)

Zalmanovici Trestioreanu A, Fraser A, Gafter-Gvili A, Paul M, Leibovici L

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Antibiotics for preventing meningococcal infections (Review)

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[Intervention Review]

Antibiotics for preventing meningococcal infections

Anca Zalmanovici Trestioreanu¹, Abigail Fraser², Anat Gafter-Gvili³, Mical Paul⁴, Leonard Leibovici³

¹Clalit Health Services, Tel Aviv District, Tel Aviv, Israel. ²MRC Integrative Epidemiology Unit at the University of Bristol, University of Bristol, Oakfield House, Bristol, UK. ³Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel. ⁴Division of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel

Contact address: Anca Zalmanovici Trestioreanu, Clalit Health Services, Tel Aviv District, Amsterdam 9, Tel Aviv, 6936181, Israel.
anca_z@hotmail.com, anka2@012.net.il.

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ABSTRACT

Background

Meningococcal disease is a contagious bacterial infection caused by *Neisseria meningitidis* (*N meningitidis*). Household contacts have the highest risk of contracting the disease during the first week of a case being detected. Prophylaxis is considered for close contacts of people with a meningococcal infection and populations with known high carriage rates.

Objectives

To study the effectiveness, adverse events and development of drug resistance of different antibiotics as prophylactic treatment regimens for meningococcal infection.

Search methods

We searched CENTRAL 2013, Issue 6, MEDLINE (January 1966 to June week 1, 2013), Embase (1980 to June 2013) and LILACS (1982 to June 2013).

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs addressing the effectiveness of different antibiotics for: (a) prophylaxis against meningococcal disease; (b) eradication of *N meningitidis*.

Data collection and analysis

Two review authors independently appraised the quality and extracted data from the included trials. We analysed dichotomous data by calculating the risk ratio (RR) and 95% confidence interval (CI) for each trial.

Main results

No new trials were found for inclusion in this update. We included 24 studies; 19 including 2531 randomised participants and five including 4354 cluster-randomised participants. There were no cases of meningococcal disease during follow-up in the trials, thus effectiveness regarding prevention of future disease cannot be directly assessed.

Mortality that was reported in one study was not related to meningococcal disease or treatment. Ciprofloxacin (RR 0.04; 95% CI 0.01 to 0.12), rifampin (rifampicin) (RR 0.17; 95% CI 0.13 to 0.24), minocycline (RR 0.28; 95% CI 0.21 to 0.37) and penicillin (RR 0.47; 95% CI 0.24 to 0.94) proved effective at eradicating *N meningitidis* one week after treatment when compared with placebo. Rifampin (RR 0.20; 95% CI 0.14 to 0.29), ciprofloxacin (RR 0.03; 95% CI 0.00 to 0.42) and penicillin (RR 0.63; 95% CI 0.51 to 0.79) still proved effective at one to two weeks. Rifampin was effective compared to placebo up to four weeks after treatment but resistant isolates were seen following prophylactic

treatment. No trials evaluated ceftriaxone against placebo but rifampin was less effective than ceftriaxone after one to two weeks of follow-up (RR 5.93; 95% CI 1.22 to 28.68). Mild adverse events associated with treatment were observed.

Authors' conclusions

Using rifampin during an outbreak may lead to the circulation of resistant isolates. Use of ciprofloxacin, ceftriaxone or penicillin should be considered. All four agents were effective for up to two weeks follow-up, though more trials comparing the effectiveness of these agents for eradicating *N. meningitidis* would provide important insights.

PLAIN LANGUAGE SUMMARY

Antibiotics for preventing meningococcal infections

Meningococcal disease is a contagious bacterial disease caused by the bacteria *Neisseria meningitidis* (*N meningitidis*) with high fatality rates: up to 15% for infection of the central nervous system (meningitis) and up to 50% to 60% among patients with blood stream infection and shock; up to 15% of survivors are left with severe neurological deficits. People who have had close contact with someone who has a meningococcal infection and populations with known high carriage rates are offered antibiotics in order to eradicate the bacteria and thus prevent disease.

Data from 24 studies, most of high quality, including 6885 participants found that rifampin (also known as rifampicin), ciprofloxacin, ceftriaxone and penicillin are effective agents for eradicating carriage of *N meningitidis*. However, the use of rifampin may have a disadvantage as development of resistance to the antibiotic has been noted following treatment. Mild adverse events are associated with the different antibiotics used. Disease prevention could not be evaluated directly in this review as only data for eradication of the bacteria were available. Different follow-up periods were reported in the studies. Evidence in this review is current as of June 2013.

BACKGROUND

Description of the condition

Meningococcal disease is a contagious bacterial disease caused by *Neisseria meningitidis* (*N. meningitidis*). It is spread by person-to-person contact through respiratory droplets. *N. meningitidis* inhabits the mucosal membrane of the nose and throat where it usually causes no harm. Carriage rates vary from 10% among randomly sampled populations to 95% during epidemics. These carriers are crucial to the spread of the disease as most cases are acquired through exposure to asymptomatic carriers (WHO 2003a). The onset of symptoms of meningococcal disease is sudden and death can follow within hours. Case-fatality rates from invasive meningococcal disease are 10% to 15%, rising as high as 50% to 60% among patients with meningococcaemia (blood stream infection) and shock. For survivors, there are persistent neurological defects including hearing loss, speech disorders, loss of limbs, mental retardation and paralysis in as many as 10% to 15% (Ferguson 2002).

Meningococcal disease occurs sporadically and in small clusters throughout the world. It accounts for a variable proportion of endemic bacterial meningitis with seasonal variations. In temperate regions the number of cases increases in winter and spring. Serogroups B and C together account for the large majority of cases in Europe, the Americas and Australasia (WHO 2003b).

Serogroup B meningococcal disease caused 68% of cases reported in Europe between 1993 and 1996 and has also caused outbreaks in other developed countries, with attack rates of 5 to 50 cases per 100,000 persons (Rosenstein 2001). Several local outbreaks due to serogroup C *N. meningitidis* have also been reported in Canada and the USA (1992 to 1993) and in Spain (1995 to 1997). In New Zealand, meningococcal disease activity has increased in the past 10 years and an average of 500 cases occur every year. Most of these cases are due to serogroup B, while serogroup A is usually the cause of meningococcal disease in Asia (WHO 2003b).

In the African 'meningitis belt' that extends from Ethiopia in the east to Senegal in the west, serogroup A meningococcal disease poses a recurrent threat to public health and rates of meningococcal disease are several times higher than in industrialised countries. The reported mortality is usually around 10%, a rate similar to that in industrialised countries, but true mortality is probably much higher. Attack rates can be as high as 100 to 800 cases per 100,000 and individual communities have reported rates as high as 1000 per 100,000. In 1996, the largest outbreak ever reported occurred in the meningitis belt. The total number of cases was over 250,000 with 25,000 reported deaths. Between 1996 and 2002, 223,000 new cases of meningococcal disease were reported to the World Health Organization. The countries most affected were Burkina Faso, Chad, Ethiopia and Niger. In 2002, the outbreaks occurring in Burkina Faso, Ethiopia and Niger accounted for about 65% of the total cases reported in the African continent. In Burkina Faso alone, 13,000 cases caused by serogroup W135 were reported and 1500 deaths recorded. Furthermore, the meningitis belt appears to be extending further south. In 2002 the Great Lakes region was affected by outbreaks in villages and refugee camps, which caused more than 2200 cases and 200 deaths.

In addition, there is increasing evidence of serogroup W135 being associated with other outbreaks of considerable size. In 2000

and 2001 several hundred pilgrims attending the Hajj in Saudi Arabia were infected with *N. meningitidis* W135. Outside Africa only Mongolia has reported a large epidemic in recent years (1994 to 1995) (WHO 2003b).

The relative frequency of disease caused by *N. meningitidis* has increased in recent years due to the widespread use of an effective vaccine for *Haemophilus influenzae* (*H. influenzae*) B and a vaccine for *Streptococcus pneumoniae* (*S. pneumoniae*). The successful use of these vaccines has left *N. meningitidis* as the most common cause of bacterial meningitis (Conterno 2006).

Description of the intervention

The aim of chemoprophylaxis is to reduce the risk of invasive disease by eradicating carriage. Individuals in close contact with cases of meningococcal disease are at increased risk of developing disease. The highest documented relative and absolute risk is for people living in the same household as a case of meningococcal disease, during the first seven days. If prophylaxis is not given, the absolute risk is about 1 in 300 (PHLS 2002), with the risk of contracting the disease increased by a factor of 400 to 800 (Rosenstein 2001). Prophylaxis is also considered in populations with known high carriage rates, such as military personnel. The carriers are at increased risk of contracting the disease themselves and may pose a risk of infection to others.

Post-exposure immunisation with meningococcal polysaccharide vaccine can effectively decrease secondary cases of disease. However, given that the vaccine is not protective for at least 10 days after administration and no effective vaccine is currently available against serogroup B, *N. meningitidis* chemoprophylaxis remains an important component in limiting disease spread (Girgis 1998).

Rifampin (rifampicin) given orally twice daily for two days in a 10 mg/kg dose (600 mg maximum) remains the drug of choice for meningococcal prophylaxis of high-risk groups. Frequent side effects, contraindications during pregnancy and unavailability of a convenient suspension for paediatric usage limit the overall utility of rifampin. Rapid development of rifampin resistance by meningococcal isolates has also been indicated. Thus other systemic antibiotics that effectively eliminate nasopharyngeal carriage of *N. meningitidis*, including ciprofloxacin and ceftriaxone, are also used as prophylactic agents. However, quinolones are not approved for routine paediatric usage and ceftriaxone requires parenteral administration (Girgis 1998).

How the intervention might work

People who had close contact with someone who has a meningococcal infection and populations with high carriage rates are offered antibiotics in order to eradicate the bacteria and thus prevent disease.

Why it is important to do this review

A systematic review comparing the effectiveness and adverse events of different antibiotics for preventing meningococcal infection should establish the best options for preventing further spread of this disease.

OBJECTIVES

To study the effectiveness, adverse events and development of drug resistance of different antibiotics as prophylactic treatment regimens for meningococcal infection, specifically:

1. preventing secondary cases of meningococcal disease after contact with a person with a meningococcal disease, both within and outside the household;
2. preventing cases of meningococcal disease in populations with a high rate of *N meningitidis* carriage; and
3. eradicating *N meningitidis* from the pharynx in healthy carriers of *N meningitidis*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs addressing the effectiveness of different antibiotic treatments for:

1. prophylaxis against meningococcal disease;
2. eradication of *N meningitidis*.

Types of participants

Healthy individuals:

1. exposed to someone with meningococcal disease, whether in the household or elsewhere;
2. exposed to *N meningitidis* carriers;
3. belonging to a population with a high rate of *N meningitidis* carriage, regardless of their carrier status.

Types of interventions

1. Antibiotic treatment versus placebo.
2. One antibiotic drug versus another.
3. Antibiotic treatment versus no intervention.

Types of outcome measures

Primary outcomes

1. Mortality.
2. Occurrence of meningococcal infection.

Secondary outcomes

1. Occurrence of any clinical adverse effects.
2. Proportion of meningococcal carriers and high-risk persons who were culture-negative at end of follow-up.
3. Occurrence of relapse and re-colonisation.
4. Occurrence of resistant strains subsequent to treatment.

Search methods for identification of studies

Electronic searches

For this 2013 review update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 6, part of the Cochrane Library, www.thecochranelibrary.com (accessed 13 June 2013), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (April 2011 to June week 1,

2013), Embase (May 2011 to June 2013) and LILACS (May 2011 to June 2013). Details of previous searches are in [Appendix 1](#).

We searched CENTRAL and MEDLINE using the following search strategy. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format ([Lefebvre 2011](#)). We adapted the search strategy to search Embase (see [Appendix 2](#)) and LILACS (see [Appendix 3](#)). There were no language or publication restrictions.

MEDLINE (Ovid)

```

1 exp Meningitis, Meningococcal/
2 Meningitis, Bacterial/
3 exp Neisseria meningitidis/
4 "N. meningitidis".tw.
5 ((neisseria or epidemic or meningococ*) adj2 mening*).tw.
6 meningococ*.tw.
7 or/1-6
8 exp Chemoprevention/
9 chemoprevent*.tw.
10 chemoprophyl*.tw.
11 Post-Exposure Prophylaxis/
12 (prophyla* or carri* or phary* or colon* or eradic* or prevent* or
nasopharynx* or tonsillopharynx* or elimin*).tw.
13 or/8-12
14 exp Anti-Bacterial Agents/
15 antibiotic*.tw,nm.
16 antibacterial*.tw,nm.
17 (oxytetracycl* or tetracycl* or penicilli* or erythromyci* or
ampicilli* or sulfa* or ciprofloxacin* or norfloxaci* or ofloxaci*
or quinol* or fluoroquinol* or fluoro-quinolon* or ceftriaxon*
or rifampi* or azithromyci* or coumermyci* or minocyclin* or
macrolid* or cephalospori*).tw,nm.
18 or/14-17
19 13 and 18
20 Antibiotic Prophylaxis/
21 19 or 20
22 7 and 21

```

Searching other resources

We searched WHO ICTRP <http://apps.who.int/trialsearch/Default.aspx> and ClinicalTrials.gov <http://clinicaltrials.gov/ct2/search/index> for completed and ongoing trials (13 June 2013). We also searched references of all identified studies as well as major reviews for additional studies.

Data collection and analysis

Selection of studies

Two review authors (AF, AGG) independently inspected each reference identified by the search and applied the inclusion criteria. We obtained the full article for possibly relevant trials or in cases of disagreement and the two review authors inspected this independently. A third, independent review author (LL) was consulted where there was disagreement.

Data extraction and management

Two review authors (AF, AGG) independently extracted the data from included trials. In case of any disagreement, a third review

author (MP) extracted the data. We discussed the data extraction, documented decisions and, where necessary, contacted the trial authors for clarification. We identified trials by the name of the first author and year in which the trial was first published and ordered these chronologically. We extracted, checked and recorded the following data.

Characteristics of trials

1. Date, location and setting of trial.
2. Publication status.
3. Concealment, randomisation method, blinding, drop-outs.
4. Sponsor of trial (specified, known or unknown).
5. Duration of follow-up.

Characteristics of participants

1. Contact status (household contact, outside household contact, no known contact).
2. Number of participants in each group, age, gender and nationality.

Characteristics of interventions

Type of antibiotic, dose, mode of administration, schedule, length of treatment and follow-up.

Characteristics of outcome measures

We recorded the number of events previously listed under [Types of outcome measures](#) in each arm of the randomised trials whenever possible.

Assessment of risk of bias in included studies

Two review authors (AF, AGG) independently assessed trials fulfilling the review inclusion criteria for methodological quality. A third review author (MP) was consulted in case of disagreements. We extracted information about random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, sample size, exclusions after randomisation and different lengths of follow-up. We did this using the criteria described in [Higgins 2011](#).

Measures of treatment effect

We analysed dichotomous data by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed using 95% confidence intervals (CIs). We pooled trial results according to the type of antibiotic assessed and the duration of follow-up at the time outcomes were assessed.

Unit of analysis issues

Five studies including 4354 participants used cluster-randomisation. It should be noted that four studies that used cluster-randomisation but reported data for individuals are included in the meta-analysis ([Cuevas 1995](#); [Guttler 1971](#); [Munford 1974](#); [Schwartz 1988](#)).

Dealing with missing data

We analysed the drop-out rates between the antibiotic and placebo arms across the studies; no significant differences were observed ([Analysis 7.1](#)). For the cluster-randomised trials, due to the lack of data, the intra-cluster correlation coefficient could not

be calculated or estimated from other sources. Thus we could not account for the cluster-randomisation in the meta-analysis. Despite this limitation these studies were included in the analysis as removing them did not substantially alter the results. Four of the six trials conducted on household contacts used cluster-randomisation (see the [Characteristics of included studies](#) table). We performed intention-to-treat (ITT) analyses; for the ITT analysis we used the number of persons randomised as the denominator. Any persons lost to follow-up, or persons who did not complete the treatment and thus were not included in the original analysis for any reason, were assumed to be eradication failures.

Assessment of heterogeneity

We initially assessed heterogeneity in the results of the trials by inspection of graphical presentations and then by calculating a test of heterogeneity (Chi² test, I² statistic). We performed sensitivity analyses in order to assess the impact of these possible sources of heterogeneity on the main results.

Assessment of reporting biases

We did not identify reporting bias across the studies; a small number of studies was available for each of the antibiotic regimens compared and funnel plots could not be performed to assess possible publication bias.

Data synthesis

We pooled trial results according to the type of antibiotic assessed. We anticipated between-trial variation in the estimation of morbidity and mortality for trials comparing individuals at different risk levels (that is contact status). We used a fixed-effect model throughout the review except in the event of significant heterogeneity between the trials ($P < 0.10$), when we chose the random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to extract data separately for *N. meningitidis* carriers, different contact strata, *N. meningitidis* serogroups and vaccination status.

Sensitivity analysis

We performed sensitivity analyses in order to assess the robustness of the findings to different aspects of the trials' methodology:

1. allocation concealment (adequate or unclear);
2. exclusions after randomisation (reported or not reported);
3. sample size; and
4. length of follow-up.

RESULTS

Description of studies

Results of the search

The computerised search strategies identified a large number of studies; not all were relevant for this present review. We screened these for randomised controlled trials (RCTs) and quasi-RCTs, *N. meningitidis* and prophylaxis or eradication. According to protocol, we searched their references in order to identify additional references. We considered 49 studies for this review.

Included studies

Study population

We included 24 trials, performed between the years 1966 to 2000, in the review (see [Characteristics of included studies](#) table). Six trials included household contacts of *N meningitidis* cases. Sixteen studies were eradication trials conducted on healthy individuals. Of these studies one included children exclusively, four included students, seven included army recruits, three included volunteers and in one study the population was unspecified. An additional eradication trial of *N meningitidis* included patients with extragenital gonorrhoea and another included patients with culture or smear-positive tests for anogenital gonorrhoea or confirmed recent exposure to gonorrhoea. Children were included in five trials. In all, only six trials explicitly reported the trial population age (range or mean).

Carrier rates ranged from 6.7% to 72% (see [Table 1](#)) with a median of 22%.

In 10 trials, allocation generation was performed before carrier status was determined (see [Characteristics of included studies](#) table). In five of these trials data were presented for proven carriers only ([Blakebrough 1980](#); [Cuevas 1995](#); [Kaiser 1974](#); [Munford 1974](#); [Simmons 2000](#)).

In 19 studies, 2531 persons were randomised. Five studies used cluster-randomisation (households and military units). These studies included 4354 persons.

Antibiotic regimens

Fifteen studies compared an antibiotic drug given orally or intramuscularly to placebo or no intervention. The antibiotics compared to placebo were: rifampin, cephalexin, minocycline,

ciprofloxacin, coumermycin A1, ampicillin, penicillin G and an investigational compound Sch 29,482. Eleven studies compared different antibiotic drugs and two studies included more than two study arms, one of which was given placebo.

Pre-treatment susceptibility of meningococci to antibiotics was reported in 21 trials. All isolates were susceptible to the antibiotics tested in these trials except for a single study comparing sulphadimidine to placebo, in which nine of 93 strains were resistant to sulphadimidine ([Blakebrough 1980](#)). Susceptibility to sulphur drugs was variable when tested in the other trials.

Excluded studies

We excluded 22 studies (see [Characteristics of excluded studies](#) table). The design of 20 studies was incompatible with the inclusion criteria, one study included only patients with homozygous deficiency of the sixth component of complement (C6) and recurrent meningococcal disease ([Potter 1990](#)) and another was a trial of post-exposure prophylaxis to *H influenzae* and not *N meningitidis* ([Band 1984](#)). We identified three reports as duplicate publications and considered these under their primary reference ([Cuevas 1995](#); [Schwartz 1988](#); [Simmons 2000](#)).

Risk of bias in included studies

We performed an intention-to-treat (ITT) analysis on three trials ([Deal 1969a](#); [Dworzack 1988](#); [Judson 1984](#)). In two trials the number evaluated was the same as the number randomised, with no mention of loss to follow-up ([Blakebrough 1980](#); [Cuevas 1995](#)). In the remaining studies ITT analysis was not performed. The length of follow-up ranged from five days to 130 days. Both the mode and the median length of follow-up were two weeks.

The overall risk of bias is presented graphically in [Figure 1](#) and summarised in [Figure 2](#).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Blakebrough 1980	+	+	+	+	+	+	+
Borgono 1981		?	+		?	+	+
Cuevas 1995		?	+	+	+	+	+
Deal 1969a	+	+	+		+	+	+
Deal 1969b	+	+	+		?	+	+
Deviatkina 1978	?	?	+	+	?	+	+
Devine 1970a	+	?	+		?	+	+
Devine 1970b	+	?	+		?	+	+
Devine 1971a	+	?	+		?	+	+
Devine 1971b	+	?	+	+	?	+	+

Figure 2. (Continued)

Devine 1971b	+	?	-	-	?	+	+
Dowd 1966		?	+		?	+	+
Dworzack 1988		?	+		+	+	+
Edwards 1984	+	?	-	-	?	+	+
Girgis 1998	+	?	-	-	?	+	+
Guttler 1971	+	?	-	-	?	+	+
Judson 1984		?	-	+	+	+	+
Kaiser 1974	+	?	-	-	+	+	+
Kaya 1997		-	-	-	?	+	+
Munford 1974	-	-	-	-	?	+	+
Pugsley 1984	+	-	+		?	+	+
Pugsley 1987	+	?	+		?	+	+
Renkonen 1987	+	+	+		?	+	+
Schwartz 1988		?	-	-	?	+	+
Simmons 2000		?	-	-	?	+	+

Allocation

Adequate allocation concealment, using central randomisation or numbered packages of antibiotic and identical-looking placebo, was described in three trials (Deal 1969a; Deal 1969b; Renkonen 1987). These trials did not involve the same comparisons and when included in their respective analyses did not seem to differ from the other included studies. In the remaining trials allocation concealment was not described.

Adequate allocation generation was described in 13 trials (Deal 1969a; Deal 1969b; Devine 1970a; Devine 1970b; Devine 1971a; Devine 1971b; Edwards 1984; Girgis 1998; Guttler 1971; Kaiser 1974; Pugsley 1984; Pugsley 1987; Renkonen 1987). Two trials used quasi-randomisation methods: one trial assigned households to their respective study arms 'alternately', following the order the index cases were admitted into hospital (Blakebrough 1980); another trial

assigned households to their respective study arms 'serially', in the order they arrived at the study centre and with no knowledge of the index case's age, race or family size (Munford 1974). In one trial (Cuevas 1995) the study arm receiving ceftriaxone was not randomised, thus the data for this group were not included in the analysis.

Blinding

Eleven trials were conducted in a double-blinded fashion (Borgono 1981; Deal 1969a; Deal 1969b; Devine 1970a; Devine 1970b; Devine 1971a; Dowd 1966; Dworzack 1988; Pugsley 1984; Pugsley 1987; Renkonen 1987); 12 others were open (see the Characteristics of included studies table) and in one the outcome assessor was blinded (Judson 1984).

Incomplete outcome data

We looked at the rate of drop-outs after randomisation in the different study arms (see [Data collection and analysis](#) section). In one of the trials ([Kaiser 1974](#)) randomisation was performed before carrier status was determined, while data were presented for carriers only. There was no difference between the number of randomised carriers and the number evaluated. We thus entered this study as no drop-outs. In another study ([Guttler 1971](#)) no information was provided regarding the number of individuals randomised as part of the cluster-randomisation. Thus this trial was excluded from this analysis. No difference in loss to follow-up was found between study arms.

Selective reporting

There was no evidence of selective reporting in the included studies.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

Primary outcomes

1. Mortality

Only one trial comparing rifampicin to ceftriaxone and to ciprofloxacin reported deaths during the study period ([Cuevas 1995](#)). These deaths (one in the rifampin group and two in the ceftriaxone group) were unrelated to meningococcal disease or the treatment.

2. Occurrence of meningococcal infection

Five studies provided information regarding meningococcal disease (see the [Characteristics of included studies](#) table). One trial reported a secondary case among study participants but the case was diagnosed before prophylaxis had begun ([Blakebrough 1980](#)). One case of meningococcal disease was reported in another trial but occurred 12 weeks after treatment with rifampin. This individual did not carry *N meningitidis* at any stage of the trial ([Guttler 1971](#)). No cases of meningococcal disease occurred in the other three trials thus the clinical effectiveness of chemoprophylaxis in disease prevention of meningococcal disease could not be assessed.

Secondary outcomes

1. Occurrence of any clinical adverse effects

Eighteen trials provided quantitative data regarding the occurrence of adverse effects. These were all mild in nature and included nausea, diarrhoea, abdominal pain, headaches, dizziness, skin rash and pain at injection site.

One study comparing rifampin to ceftriaxone yielded an overall risk ratio (RR) for any clinical adverse effects of 1.39 (95% confidence interval (CI) 1.10 to 1.75) ([Analysis 1.1](#)). Two studies comparing rifampin to ciprofloxacin yielded an overall non-significant RR of 0.75 (95% CI 0.36 to 1.56) ([Analysis 1.2](#)).

2. Proportion of meningococcal carriers and high-risk persons who were culture-negative at end of follow-up

Up to one week of follow-up

Failure to eradicate *N meningitidis* from the nasopharynx was the main outcome for all trials. Ciprofloxacin (RR 0.04; 95% CI 0.01 to 0.12), rifampin (RR 0.17; 95% CI 0.13 to 0.24), minocycline (RR 0.28; 95% CI 0.21 to 0.37) and penicillin (RR 0.47; 95% CI 0.24 to 0.94) all proved effective at eradicating *N meningitidis* one week after treatment when compared to placebo ([Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#); [Analysis 2.4](#)).

Rifampin was more effective at eradicating *N meningitidis* when compared to ciprofloxacin but the difference did not reach statistical significance at the 95% confidence level (RR 0.34; 95% CI 0.11 to 1.02) ([Analysis 2.6](#)). No significant difference was found when rifampin was compared to ceftriaxone (RR 3.71; 95% CI 0.73 to 18.86) ([Analysis 2.7](#)).

Between one to two weeks of follow-up

Ciprofloxacin (based on a single study: RR 0.03; 95% CI 0.00 to 0.42) ([Pugsley 1987](#)), rifampin (RR 0.20; 95% CI 0.14 to 0.29) and penicillin (RR 0.63; 95% CI 0.51 to 0.79) proved effective at eradicating *N meningitidis* between one and two weeks after treatment when compared to placebo ([Analysis 3.1](#); [Analysis 3.2](#); [Analysis 3.4](#)). Minocycline (RR 0.37; 95% CI 0.10 to 1.31) was not significantly effective compared to placebo ([Analysis 3.3](#)).

When rifampin was compared with ciprofloxacin again, according to the point estimate, rifampin was more effective but not significantly (RR 0.31; 95% CI 0.09 to 1.11) ([Analysis 3.6](#)). Based on the point estimate of a single study ([Schwartz 1988](#)) rifampin proved less effective when compared to ceftriaxone (RR 5.93; 95% CI 1.22 to 28.68) ([Analysis 3.7](#)). No difference was found when rifampin was compared to minocycline (RR 1.01; 95% CI 0.57 to 1.77) ([Analysis 3.8](#)).

Follow-up longer than two weeks

Six studies presented data for follow-up periods of over two weeks (see [Characteristics of included studies](#) table). Of these studies three compared rifampin with placebo ([Deal 1969a](#); [Guttler 1971](#); [Kaiser 1974](#)). Rifampin proved effective when compared to placebo both at between two to three weeks (RR 0.25; 95% CI 0.16 to 0.37) and three to four weeks (RR 0.24; 95% CI 0.16 to 0.38) after treatment ([Analysis 4.1](#); [Analysis 5.1](#)). In the study with the longest follow-up ([Kaiser 1974](#)), at day 130 there were no positive cultures in the rifampin group (n = 7) while in the control group two of four individuals had a positive culture for *N meningitidis*. Two studies ([Dowd 1966](#); [Guttler 1971](#)) compared penicillin to placebo after three to four weeks of follow-up. Penicillin was found to be ineffective (RR 0.95; 95% CI 0.53 to 1.68) ([Analysis 5.2](#)).

In a single study ([Guttler 1971](#)) comparing minocycline and rifampin after five weeks, no significant difference was seen between the two drugs' effectiveness for eradicating nasopharyngeal carriage of *N meningitidis* (RR 0.97; 95% CI 0.48 to 1.97) ([Analysis 6.1](#)).

Four trials were included in this review but not in the meta-analysis. [Blakebrough 1980](#) found that rifampin was more effective at eradicating carriage of *N meningitidis* than sulphadimidine at both two (RR 0.45; 95% CI 0.25 to 0.80) and seven weeks after treatment (RR 0.26; 95% CI 0.12 to 0.59). In [Girgis 1998](#) no significant

difference was found between the effectiveness of azythromycin and rifampin at one and two weeks post-treatment (RR 0.30; 95% CI 0.30 to 5.54 and RR 0.81; 95% CI 0.23 to 2.88, respectively). [Judson 1984](#) found that at day seven, spectinomycin eradicated carriage of only one out of nine initial *N meningitidis* carriers, while ceftriaxone eradicated carriage from 29 of 29 initial carriers. [Edwards 1984](#) found no difference between amoxycillin and bacampicillin for eradicating *N meningitidis* (RR 1.4; 95% CI 0.16 to 12.60, favours bacampicillin).

3. Occurrence of relapse and re-colonisation

Data on acquisition and re-colonisation were too sparse to allow analysis.

4. Occurrence of resistant strains subsequent to treatment

Eleven trials reported the susceptibility of persistent isolates to at least one of the studied antibiotics ([Blakebrough 1980](#); [Deal 1969a](#); [Deal 1969b](#); [Devine 1971b](#); [Dworzack 1988](#); [Guttler 1971](#); [Kaiser 1974](#); [Munford 1974](#); [Pugsley 1987](#); [Renkonen 1987](#); [Simmons 2000](#)). No development of resistance was detected for any antibiotic drug other than rifampin.

Six trials assessed resistance development to rifampin ([Blakebrough 1980](#); [Deal 1969a](#); [Guttler 1971](#); [Kaiser 1974](#); [Munford 1974](#); [Simmons 2000](#)). In [Guttler 1971](#) rifampin-resistant isolates requiring minimal inhibitory concentrations (MICs) of 100 to 200 µg/ml of rifampin were seen in 20 of 75 post-treatment isolates, while MICs increased from pre-treatment values of less than 0.25 µg/ml to 2 to 6 µg/ml in 37 additional isolates. All resistant isolates were detected among patients treated with rifampin. In [Munford 1974](#), seven resistant isolates were detected out of 37 isolates among 67 patients treated with rifampin (MICs of 16 to 256 µg/ml). All pre-treatment isolates were susceptible to rifampin and no resistance to rifampin developed among patients randomised to rifampin in addition to minocycline in this study. The meningococci identified in these two studies were serogroup B or C and all resistant isolates were identified as group C. One additional study assessing group A meningococci ([Blakebrough 1980](#)) found an increase in rifampin MICs from less than 0.1 µg/ml to 3.2 µg/ml (three isolates) and 6.4 µg/ml (one isolate) post-treatment. In all trials seven eradication failures were assessed for resistance development, which was not found.

Subgroup analysis

Subgroup analysis could not be performed due to lack of data. For information regarding the main *N. meningitidis* serogroups for each trial see the [Characteristics of included studies](#) table.

DISCUSSION

Summary of main results

No direct evidence was available in this review for meningococcal disease prevention. The results obtained for the eradication of bacteria outcome suggest ciprofloxacin, ceftriaxone and rifampin are the most effective immediate prevention measures with only minor adverse events reported. These options should be considered individually.

Overall completeness and applicability of evidence

Ciprofloxacin, rifampin, minocycline and penicillin proved effective at eradicating *N. meningitidis* one week after treatment, compared to placebo. However, after a longer follow-up period of one to two weeks only rifampin, ciprofloxacin and penicillin still proved significantly effective when compared to placebo. No trials evaluated ceftriaxone against placebo but when compared to rifampin after one to two weeks of follow-up, ceftriaxone was more effective in a single study. Rifampin continued to be effective, compared to placebo, for up to four weeks of post-treatment follow-up. However, a disadvantage may exist as isolates resistant to rifampin were identified following prophylactic treatment.

When minocycline was compared with placebo, it proved ineffective after one to two weeks of follow-up; but when compared to rifampin after the same length of follow-up ([Guttler 1971](#); [Munford 1974](#)) and after five weeks ([Guttler 1971](#)) no significant difference was found between the two antibiotics. It should be noted that the comparison between rifampin and minocycline after five weeks of follow-up is based on one study only ([Guttler 1971](#)).

Chemoprophylactic treatment to eradicate nasopharyngeal carriage of *N meningitidis* has been a key approach in the control of meningococcal disease for many decades ([Samuelsson 2002](#)), despite the fact that its effectiveness for disease prevention has never been demonstrated in experimental research.

In 1937, sulphonamide therapy radically altered the outcome of meningococcal infection and replaced serum in its treatment. Prophylaxis with sulphonamides eradicated the carrier state and provided a simple and safe method for the prevention of epidemics, particularly in the crowded environments of military barracks. Increasing sulphonamide resistance among meningococci was recognised by Schoenback and Phair in 1941 to 1943 but did not become a clinically significant problem until meningococcal epidemics occurred in 1963, in two military bases in California. Since then, many agents have been evaluated as agents of eradication under the assumption that eradicating carriage would prevent meningococcal disease ([Mandell 2000](#)).

Rifampin penetrates well into body tissues, achieving therapeutic concentrations in the mucosa. Resistance to rifampin among meningococci, as for other bacteria, has been attributed to mutations in the *rpoB* gene that encodes the beta unit of the RNA polymerase enzyme, which is rifampin's target ([Carter 1994](#)). Increased minimal inhibitory concentrations (MICs) for rifampin were described in three of six studies assessing pre- and post-treatment rifampin susceptibilities, with frank resistance developing in 10% to 27% of isolates in these studies. Thus, despite rifampin's eradication efficacy, a note of caution is required. Induction of resistance may complicate further attempts at eradication.

A recent review that included non-randomised studies, comparing treated and untreated groups, demonstrated that chemoprophylaxis (according to local guidelines) of household contacts reduced the risk of developing meningococcal disease (RR 0.11; 95% CI 0.02 to 0.58). No studies of non-household contacts met the inclusion criteria. Based on four studies, the pooled meningococcal disease attack rate among non-treated family contacts was estimated at five cases per 1000 household contacts ([Purcell 2004](#)).

Based on the median prevalence of carriers among household contacts of 230 per 1000 (see [Table 1](#), 'Carrier rates') and the pooled RR obtained from the comparison of rifampin to placebo, the absolute risk reduction in such a population after a period of one week is 190 per 1000 (95% CI 177 per 1000 to 203 per 1000). Thus the number needed to treat (NNT) in order to eradicate carriage from one carrier is six (95% CI 5 to 20). As the risk of invasive disease following acquisition varies with environmental and host factors and strain characteristics we cannot estimate the NNT in order to prevent a case of meningococcal disease.

Quality of the evidence

Twenty-four studies, most of high quality, were included in this review (see [Characteristics of included studies](#) table). There were similar results across the individual studies despite the different follow-up periods.

Potential biases in the review process

No potential biases were identified in the review process.

Agreements and disagreements with other studies or reviews

The 24 studies included in this review and comparing different antibiotic regimens found similar effects in terms of efficacy for eradicating meningococcal infection and supported each others' findings. The use of the same antibiotics that were found effective in our review is supported by other existing evidence ([Kimmel 2005](#); [Manchanda 2006](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Under the assumption that eradication of *N meningitidis* does reduce the risk of meningococcal infection, the most effective antibiotics to achieve eradication are ceftriaxone, rifampin and ciprofloxacin. Rifampin is usually the drug of choice in clinical practice ([Hart 1993](#)). However, given the facts that rifampin is contraindicated in pregnancy, liver disease and alcoholism, and long-term therapy causes orange discolouration of urine, staining

of contact lenses and induction of hepatic microsomal enzymes which might render contraceptive pills ineffective, the use of ciprofloxacin and ceftriaxone is recommended ([Rosenstein 2001](#)). In addition, despite rifampin's eradication efficacy a note of caution is required. Induction of resistance, seen as circulation of isolates with reduced sensitivity to rifampin, could complicate further attempts at prophylaxis, especially in an outbreak setting.

Although ceftriaxone is administered in a single intramuscular dose, resulting in more frequent adverse effects when compared to rifampin, intramuscular administration ensures adherence to prophylaxis (as opposed to oral administration) and the adverse effects recorded are mild. In addition, it can be given to young children and pregnant women. Ciprofloxacin is given in a single dose thus ensuring compliance and has minimal side effects but is contraindicated in pregnancy and is not recommended for use in children. Finally, trials evaluating ciprofloxacin and ceftriaxone reported no development of resistance following treatment ([Dworzack 1988](#); [Pugsley 1987](#); [Renkonen 1987](#); [Simmons 2000](#)).

Implications for research

Although direct data on the effectiveness of eradication of the carrier state on disease prevention are missing, placebo-controlled trials do not seem ethical.

Trials comparing the effectiveness of ceftriaxone, ciprofloxacin and rifampin for eradicating *N meningitidis* could provide important insights as may trials evaluating oral third-generation cephalosporins (cefixime, cefdinir, cefditoren-pivoxil, cefpodoxime-proxetil and ceftibuten). Trials should evaluate short (after one to two weeks) and long-term (more than two weeks) eradication rates, separating cases of persistent infection from cases of re-infection. Minimal inhibitory concentrations of isolates before and after treatment should be reported to allow for the assessment of the ecological impact of prophylactic treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Blakebrough 1980

Methods	Cluster-randomisation by households, quasi-randomisation by order of admission to hospital, open, no loss to f/u
Participants	Household contacts, Nigeria
Interventions	Rifampin: 0 to 2 years: 4 x 75 mg; 2 to 4 years 4 x 150 mg; 5 to 14 years 4 x 300 mg; 15+ years 4 x 600 mg versus sulphadimidine: 0 to 4 years 4 x 250 mg; 5 to 14 years 4 x 500 mg; 15+ years 4 x 1 G
Outcomes	Morbidity, eradication, resistance developed Follow-up: 6 to 7 weeks
Notes	Data presented for carriers. Main serogroup: A

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomisation
Allocation concealment (selection bias)	High risk	Inadequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open

Blakebrough 1980 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to f/u
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Borgono 1981

Methods	Double-blind, no ITT
Participants	Kindergarten and school children, Chile
Interventions	Rifampin: 2 x 10 mg/kg versus placebo
Outcomes	Eradication, adverse effects Follow-up: 10 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Cuevas 1995

Methods	Cluster-randomisation by households, open, no loss to f/u
Participants	Household contacts, Malawi
Interventions	Rifampicin: 2 to 18 years 4 x 20 mg/kg; > 18 years 4 x 600 mg versus single-dose ciprofloxacin: 2 to 18 years 1 x 15 mg/kg for 2 to 18 years; > 18 years 1 x 750 mg versus

Cuevas 1995 (Continued)

IM ceftriaxone: pregnant women 2 g; < 2 years 50 mg/kg

Outcomes	Morbidity, eradication, re-acquisition, adverse effects Follow-up: 2 weeks
Notes	Data presented for carriers. Main serogroups: A W135. Ceftriaxone group not randomised and not included in analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to f/u
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Deal 1969a

Methods	Adequate allocation generation, double-blind, ITT
Participants	Students, USA
Interventions	Rifampin: 4 x 600 mg versus placebo
Outcomes	Eradication, failure serogroup, adverse effects Follow-up: 30 days
Notes	Main serogroup: B

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Low risk	Adequate

Deal 1969a (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Deal 1969b

Methods	Adequate allocation generation, double-blind, no ITT
Participants	Students, USA
Interventions	Cephalexin: 12 x 500 mg versus placebo
Outcomes	Eradication, adverse effects, re-acquisition Follow-up: 2 weeks
Notes	Main serogroup: B

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Deviatkina 1978

Methods	Open, no ITT
Participants	USSR
Interventions	Rifampin: 4 x 300 mg versus none
Outcomes	Eradication, adverse effects Follow-up: 10 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Devine 1970a

Methods	Adequate allocation generation, double-blind, no ITT
Participants	Army recruits, USA
Interventions	Coumermycin A1: 14 x 50 mg versus placebo
Outcomes	Eradication, acquisition, failure serogroup Follow-up: 10 days
Notes	Data extracted for 1) all (regardless of carrier status), 2) carriers only, 3) non-carriers only

Risk of bias

Bias	Authors' judgement	Support for judgement
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Antibiotics for preventing meningococcal infections (Review)

Devine 1970a (Continued)

Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Devine 1970b

Methods	Adequate allocation generation, double-blind, no ITT
Participants	Army recruits, USA
Interventions	Rifampin: 4 x 600 mg versus placebo
Outcomes	Eradication, failure serogroup of eradication failure Follow-up: 11 days
Notes	Data extracted for 1) all (regardless of carrier status), 2) for carriers only, 3) for non-carriers only. Main serogroup: Y

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence

Antibiotics for preventing meningococcal infections (Review)

Devine 1970b (Continued)

Other bias	Low risk	No evidence
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Devine 1971a

Methods	Adequate allocation generation, double-blind, no ITT
Participants	Army recruits, USA
Interventions	Minocycline 14 x 500 mg versus placebo
Outcomes	Eradication
Notes	Main serogroup: Y

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Devine 1971b

Methods	Adequate allocation generation, open, no ITT
Participants	Army recruits, USA
Interventions	Minocycline: 14 x 500 mg versus none
Outcomes	Eradication, adverse effects, resistance developed Follow-up: 5 days
Notes	Data extracted for 1) all (regardless of carrier status) and 2) carriers only

Risk of bias

Devine 1971b (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Dowd 1966

Methods	Double-blind, no ITT
Participants	Army recruits, USA
Interventions	Ampicillin: 30 x 500 mg versus oral penicillin G: 30 x 462 mg versus placebo
Outcomes	Eradication, serogroup of eradication failure, resistance developed Follow-up: 26 days
Notes	Main serogroup: B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT

Dowd 1966 (Continued)

Selective reporting (re-reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Dworzack 1988

Methods	Double-blind, ITT
Participants	Volunteers
Interventions	Ciprofloxacin 1 x 750 mg versus placebo
Outcomes	Eradication, resistance developed, adverse effects Follow-up: 21 days
Notes	Main serogroups: B, Z

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT
Selective reporting (re-reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Edwards 1984

Methods	Adequate allocation generation, open, no ITT
Participants	Patients with extragenital gonorrhoea, USA
Interventions	Bacampicillin: 12 x 400 mg versus amoxycillin: 6 x 500 mg
Outcomes	Eradication, adverse effects Follow-up: 5 to 9 days
Notes	

Edwards 1984 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Girgis 1998

Methods	Adequate allocation generation, open, no ITT
Participants	Nursing students, Cairo
Interventions	Azythromycin: 1 x 500 mg versus rifampin: 4 x 600 mg
Outcomes	Eradication, reacquisition, resistance developed, adverse effects Follow-up: 2 weeks
Notes	Main serogroups: A, B

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open

Antibiotics for preventing meningococcal infections (Review)

Girgis 1998 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Guttler 1971

Methods	Cluster-randomisation by companies, adequate generation of allocation, open, no ITT
Participants	Army recruits, USA
Interventions	Rifampin: 1 x 600 mg versus minocycline: 10 x 100 mg versus ampicillin: 10 x 500 mg versus placebo
Outcomes	Morbidity, eradication, resistance developed Follow-up: 26 days
Notes	Separate data provided for rifampin and minocycline treatment arms Main serogroups: B, C

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Judson 1984

Methods	Outcome assessor blinded, ITT
Participants	Patients with culture or smear positive for anogenital gonorrhoea or confirmed recent exposure to gonorrhoea
Interventions	IM ceftriaxone 1 x 125 mg versus IM spectinomycin 1 x 2 g
Outcomes	Eradication, adverse effects Follow-up: 7 days

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	No
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Kaiser 1974

Methods	Adequate allocation generation, open, no ITT, no drop-outs
Participants	Household contacts, USA
Interventions	Rifampin: > 66 lb weight 4 x 600 mg/day; < 66 lb 4 x 300 mg/day versus none
Outcomes	Morbidity, eradication, failure serogroup Follow-up: 130 days
Notes	Data presented for carriers. Main serogroups: C, N

Risk of bias

Bias	Authors' judgement	Support for judgement
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Kaiser 1974 (Continued)

Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Kaya 1997

Methods	Open, no ITT
Participants	Volunteers, Turkey
Interventions	Ciprofloxacin: 1 x 750 mg versus rifampin: 4 x 600 mg
Outcomes	Eradication, adverse effects Follow-up: 2 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias)	Unclear risk	No ITT

Kaya 1997 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Munford 1974

Methods	Cluster-randomisation by households, quasi-randomisation assigned by order of arrival at study centre, open, no ITT
Participants	Household contacts, Brazil
Interventions	Sulphadiazine: 4 x 1 g versus minocycline: 1 x 200 mg + 5 x 100 mg versus rifampin: 4 x 600 mg versus minocycline/rifampin: as above
Outcomes	Eradication, serogroup of eradication failure, resistance developed, adverse effects Follow-up: 2 weeks
Notes	Data presented for carriers. Main serogroup: C

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomisation
Allocation concealment (selection bias)	High risk	Inadequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Pugsley 1984

Methods	Adequate allocation generation, double-blind, no ITT
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Antibiotics for preventing meningococcal infections (Review)

Pugsley 1984 (Continued)

Participants	College students
Interventions	Sch 29,482: 4 x 250 mg versus placebo
Outcomes	Eradication
Notes	Main serogroups: B, Z

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Pugsley 1987

Methods	Adequate allocation generation, double-blind, no ITT
Participants	Volunteers
Interventions	Ciprofloxacin: 10 x 500 mg versus placebo
Outcomes	Eradication, resistance developed, failure serogroup adverse effects Follow-up: 2 weeks
Notes	Main serogroup: B

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Unclear risk	Unclear

Pugsley 1987 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Renkonen 1987

Methods	Adequate allocation generation, double-blind, no ITT
Participants	Army recruits
Interventions	Ciprofloxacin: 4 x 250 mg versus placebo
Outcomes	Eradication, serogroup of eradication failure, resistance developed, adverse effects Follow-up: 6 days
Notes	Main serogroup: B

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Schwartz 1988

Methods	Cluster-randomisation by households, open, no ITT
Participants	Household contacts, Saudi Arabia
Interventions	IM ceftriaxone 1 x 250 mg or 125 mg for children versus rifampin: 4 x 600 mg or 10 mg/kg versus none
Outcomes	Eradication, acquisition in non-carriers Follow-up: 2 weeks
Notes	Data presented for carriers. Serogroup A

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Simmons 2000

Methods	Open, no ITT
Participants	Household contacts, New Zealand
Interventions	Rifampicin: 600 mg, children > 1 month, 10 mg/kg versus IM ceftriaxone: 250 mg < 12 years, 125 mg
Outcomes	Morbidity, eradication, eradication of serogroup B, adverse effects Follow-up: 6 days
Notes	Data presented for carriers. Main serogroup: B

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Simmons 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

f/u: follow-up

IM: intramuscular

ITT: intention-to-treat

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Artenstein 1967	No control group
Band 1984	Trial of post-exposure prophylaxis for <i>H. influenzae</i> and not <i>N. meningitidis</i>
Beam 1971	No randomisation
Beaty 1983	Includes previously published data (Guttler 1971) included in this review. New data from a non-randomised study also excluded
Cardenas 1995	No control group
Chapalain 1992	No randomisation
Cheever 1943	No randomisation
Devine 1972	No randomisation
Devine 1973	No randomisation
Fairbrother 1940	Not a controlled trial
Gaunt 1988	Not a RCT. The type of publication was a letter to the editor and did not contain any relevant data
Gilja 1993	Not a controlled trial
Gonzalez 2000	No randomisation
Gray 1941	No randomisation

Study	Reason for exclusion
Halstensen 1995	No control group
Kuhns 1943	No randomisation
Potter 1990	Patients with homozygous deficiency of the sixth component of complement (C6) with recurrent meningococcal meningitis
Sanders 1967	No control group
Sheehab 1991	No control group
Sivonen 1978	No randomisation
Wall 1982	Not a RCT. The type of publication was a letter to the editor and did not contain any relevant data
Weidmer 1971	No randomisation

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rifampin versus ceftriaxone	1	856	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.10, 1.75]
2 Rifampin versus ciprofloxacin	2	1598	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.36, 1.56]

Analysis 1.1. Comparison 1 Adverse effects, Outcome 1 Rifampin versus ceftriaxone.

Study or subgroup	Rifampin n/N	Ceftriaxone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Simmons 2000	129/440	88/416		100%	1.39[1.1,1.75]
Total (95% CI)	440	416		100%	1.39[1.1,1.75]
Total events: 129 (Rifampin), 88 (Ceftriaxone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.72(P=0.01)					
<div style="display: flex; justify-content: space-between;"> Favours rifampin 0.001 0.1 1 10 1000 Favours ceftriaxone </div>					

Analysis 1.2. Comparison 1 Adverse effects, Outcome 2 Rifampin versus ciprofloxacin.

Comparison 2. Failure to eradicate (follow-up: up to one week)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ciprofloxacin versus placebo	3	197	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.12]
2 Rifampin versus placebo	6	725	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.13, 0.24]
3 Minocycline versus placebo	3	464	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.21, 0.37]
4 Penicillin versus placebo	2	386	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.94]
5 Other antibiotics versus placebo	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Rifampin versus ciprofloxacin	2	218	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.11, 1.02]
7 Rifampin versus ceftriaxone	2	286	Risk Ratio (M-H, Random, 95% CI)	3.71 [0.73, 18.86]

Analysis 2.1. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 1 Ciprofloxacin versus placebo.

Analysis 2.2. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 2 Rifampin versus placebo.

Analysis 2.3. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 3 Minocycline versus placebo.

Analysis 2.4. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 4 Penicillin versus placebo.

Analysis 2.5. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 5 Other antibiotics versus placebo.

Analysis 2.6. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 6 Rifampin versus ciprofloxacin.

Analysis 2.7. Comparison 2 Failure to eradicate (follow-up: up to one week), Outcome 7 Rifampin versus ceftriaxone.

Comparison 3. Failure to eradicate (follow-up: one to two weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ciprofloxacin versus placebo	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.42]
2 Rifampin versus placebo	5	495	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.14, 0.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Minocycline versus placebo	2	382	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.10, 1.31]
4 Penicillin versus placebo	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.51, 0.79]
5 Other antibiotics versus placebo	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Rifampin versus ciprofloxacin	2	218	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.09, 1.11]
7 Rifampin versus ceftriaxone	1	91	Risk Ratio (M-H, Fixed, 95% CI)	5.93 [1.22, 28.68]
8 Rifampin versus minocycline	2	419	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.57, 1.77]

Analysis 3.1. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 1 Ciprofloxacin versus placebo.

Analysis 3.2. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 2 Rifampin versus placebo.

Analysis 3.3. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 3 Minocycline versus placebo.

Analysis 3.4. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 4 Penicillin versus placebo.

Analysis 3.5. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 5 Other antibiotics versus placebo.

Analysis 3.6. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 6 Rifampin versus ciprofloxacin.

Analysis 3.7. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 7 Rifampin versus ceftriaxone.

Analysis 3.8. Comparison 3 Failure to eradicate (follow-up: one to two weeks), Outcome 8 Rifampin versus minocycline.

Comparison 4. Failure to eradicate (follow-up: between two to three weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rifampin versus placebo	3	326	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.16, 0.37]

Analysis 4.1. Comparison 4 Failure to eradicate (follow-up: between two to three weeks), Outcome 1 Rifampin versus placebo.

Comparison 5. Failure to eradicate (follow-up between three to four weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rifampin versus placebo	2	311	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.16, 0.38]
2 Penicillin versus placebo	2	386	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.68]

Analysis 5.1. Comparison 5 Failure to eradicate (follow-up between three to four weeks), Outcome 1 Rifampin versus placebo.

Analysis 5.2. Comparison 5 Failure to eradicate (follow-up between three to four weeks), Outcome 2 Penicillin versus placebo.

Comparison 6. Failure to eradicate (follow-up: five weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rifampin versus minocycline	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.48, 1.97]

Analysis 6.1. Comparison 6 Failure to eradicate (follow-up: five weeks), Outcome 1 Rifampin versus minocycline.

Comparison 7. Exclusion after randomisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Drop-outs	13	1260	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.89, 1.15]
1.1 Drop-outs at around one week of follow-up	13	1260	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.89, 1.15]

Analysis 7.1. Comparison 7 Exclusion after randomisation, Outcome 1 Drop-outs.

ADDITIONAL TABLES

Table 1. Carrier rates

Study ID	Comparison	Study population	% carriers (N)
Blakebrough 1980	Rifampin versus sulphadimidine	Household contacts	17 (479)
Borgono 1981	Rifampin versus placebo	Children	12 (2132)
Cuevas 1995	Rifampin versus ciprofloxacin versus ceftriaxone	Household contacts	11 (1875)
Deal 1969b	Rifampin versus placebo	Students	14.4 (270)
Deal 1969a	Cephalexin versus placebo	Students	9.4 (352)
Devine 1970b	Rifampin versus placebo	Military recruits	64 (103)
Devine 1971a	Minocycline versus placebo	Military recruits	72 (121)
Devine 1970a	Coumermycin A1 versus placebo	Military recruits	55 (129)
Dworzack 1988	Ciprofloxacin versus placebo	Volunteers	6.7 (620)
Girgis 1998	Azithromycin versus placebo	Students	24 (500)
Guttler 1971	Rifampin versus minocycline	Military recruits	21 (587)
Kaiser 1974	Rifampin versus placebo	Household contacts	35 (54)

Table 1. Carrier rates (Continued)

Kaya 1997	Ciprofloxacin versus rifampin	Hospital staff	18 (300)
Munford 1974	Rifampin versus minocycline versus minocycline/rifampin versus sulphadiazine	Household contacts	25 (1187)
Pugsley 1984	Sch 29,482 versus placebo	Volunteers	25 (555)
Pugsley 1987	Ciprofloxacin versus placebo	Students	7 (461)
Renkonen 1987	Ciprofloxacin versus placebo	Military recruits	38.6 (552)
Schwartz 1988	Rifampin versus ceftriaxone	Household contacts	33 (347)
Simmons 2000	Rifampin versus ceftriaxone	Household contacts	21 (864)

APPENDICES

Appendix 1. Details of previous search

For the 2011 review update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 2, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 31 May 2011), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (from November 2008 to May Week 3, 2011), EMBASE (from November 2008 to May 2011) and LILACS (from November 2008 to May 2011). Details of the previous search are in [Appendix 1](#).

In the 2008 review update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 4), which contains the Acute Respiratory Infections Group Specialised Register, MEDLINE (1950 to November week 3 2008), EMBASE (1980 to November 2008) and LILACS (1982 to November 2008). We also searched the references of all identified studies.

We searched CENTRAL and MEDLINE using the following strategy combined with the highly sensitive search strategy used by The Cochrane Collaboration ([Lefebvre 2011](#)).

MEDLINE (Ovid)

```

1 exp MENINGITIS, MENINGOCOCCAL/
2 exp Neisseria meningitidis/
3 (neisseria adj mening$).mp.
4 meningococ$.mp.
5 or/1-4
6 exp CHEMOPREVENTION/
7 exp Antibiotic Prophylaxis/
8 chemoprophylaxis.mp.
9 (prophyla$ or carri$ or phary$ or colon$ or eradic$ or prevent$ or nasopharyn$ or tonsillopharyng$ or elimin$).mp.
10 or/6-9
11 exp Anti-Bacterial Agents/
12 (antibiotic$ or oxytetracyc$ or tetracyc$ or penicilli$ or erythromyci$ or ampicilli$ or sulfa$ or ciprofloxacin$ or norfloxaci$ or ofloxaci$ or quinol$ or fluoroquinol$ or fluoro- quinolon$ or ceftriaxon$ or rifampi$ or azithromyci$ or coumermyci$ or minocyclin$ or macrolid$ or cephalospori$).mp
13 or/11-12
14 5 and 10 and 13

```

We searched EMBASE and LILACS using adapted terms from the above search strategy. There were no language or publication restrictions.

Appendix 2. Embase.com search strategy

```

#24 #20 AND #239914 Dec 2010
#23 #21 OR #2282590714 Dec 2010
#22 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR volunteer*:ab,ti OR allocat*:ab,ti OR assign*:ab,ti OR ((singl* OR doubl*) NEAR/2 (mask* OR blind*)):ab,ti AND [embase]/lim78719414 Dec 2010

```

#21 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim23351014 Dec 2010
 #20 #7 AND #19187714 Dec 2010
 #19 #17 OR #1816006514 Dec 2010
 #18 'antibiotic prophylaxis'/de AND [embase]/lim1370014 Dec 2010
 #17 #12 AND #1615403614 Dec 2010
 #16 #13 OR #14 OR #1588484414 Dec 2010
 #15 oxytetracyc*:ab,ti OR tetracyc*:ab,ti OR penicilli*:ab,ti OR erythromyci*:ab,ti OR ampicilli*:ab,ti OR sulfa*:ab,ti OR ciprofloxacin*:ab,ti OR norfloxaci*:ab,ti OR ofloxaci*:ab,ti OR quinol*:ab,ti OR fluoroquinol*:ab,ti OR ceftriaxon*:ab,ti OR rifampi*:ab,ti OR azithromyci*:ab,ti OR coumermyci*:ab,ti OR minocyclin*:ab,ti OR macrolid*:ab,ti OR cephalospori*:ab,ti AND [embase]/lim25683414 Dec 2010
 #14 antibiotic*:ab,ti OR antibacterial*:ab,ti AND [embase]/lim19486614 Dec 2010
 #13 'antibiotic agent'/exp AND [embase]/lim68511614 Dec 2010
 #12 #8 OR #9 OR #10 OR #11157193614 Dec 2010
 #11 prophyla*:ab,ti OR carri*:ab,ti OR phary*:ab,ti OR colon*:ab,ti OR eradic*:ab,ti OR prevent*:ab,ti OR nasopharyng*:ab,ti OR tonsillopharyng*:ab,ti OR elimin*:ab,ti AND [embase]/lim154702314 Dec 2010
 #10 'prophylaxis'/de AND [embase]/lim4950814 Dec 2010
 #9 chemoprevent*:ab,ti OR chemoprophyla*:ab,ti AND [embase]/lim1539014 Dec 2010
 #8 'chemoprophylaxis'/de AND [embase]/lim1256514 Dec 2010
 #7 #1 OR #2 OR #3 OR #4 OR #5 OR #62008214 Dec 2010
 #6 meningococ*:ab,ti AND [embase]/lim742814 Dec 2010
 #5 ((neisseria OR epidemic OR meningococ*) NEAR/2 mening*):ab,ti AND [embase]/lim999614 Dec 2010
 #4 'n. meningitidis':ab,ti AND [embase]/lim171514 Dec 2010
 #3 'neisseria meningitidis'/de AND [embase]/lim866614 Dec 2010
 #2 'bacterial meningitis'/de AND [embase]/lim925614 Dec 2010
 #1 'epidemic meningitis'/de AND [embase]/lim127514 Dec 2010

Appendix 3. LILACS search strategy

mh:"Meningitis, Meningococcal" OR mh:"Meningitis Meningocócica" OR "Meningitis Meningocóccica" OR "Meningite por Meningococos" OR mh:"Meningitis, Bacterial" OR mh:"Meningitis Bacterianas" OR mh:"Meningites Bacterianas" OR "bacterial meningitis" OR "Meningitis Bacteriana" OR "Meningitis por Bacterias" OR "Meningite Bacteriana" OR "Meningite por Bactéria" OR "Meningite por Bactérias" OR "Meningites por Bactérias" OR mh:"Neisseria meningitidis" OR mh:b03.440.400.425.550.550.641* OR mh:b03.660.075.525.520.500* OR meningococcus OR "N. meningitidis" OR meningococ* AND db:("LILACS") AND type_of_study:("clinical_trials")

WHAT'S NEW

Date	Event	Description
19 August 2019	Amended	Lead author's contact details have been updated.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 1, 2005

Date	Event	Description
13 June 2013	New citation required but conclusions have not changed	Our conclusions remain unchanged.
13 June 2013	New search has been performed	Searches updated. No new studies were identified for inclusion or exclusion.
5 August 2010	Amended	Contact details updated.
12 November 2008	New search has been performed	Searches conducted. No new trials identified.

Date	Event	Description
27 July 2008	Amended	Converted to new review format.
5 June 2006	New search has been performed	Searches conducted. No new trials identified.
9 July 2004	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Abigail Fraser (AF): responsible for the reference searches, article retrieval, study inclusion and exclusion, data extraction, analysis, interpretation of results and writing of the review.

Mical Paul (MP): responsible for data extraction, study inclusion and exclusion, analysis, interpretation of results and writing of the review.

Anat Gafer-Gvili (AGG): responsible for data extraction, study inclusion and exclusion, interpretation of results and writing of the review.

Leonard Leibovici: responsible for study inclusion and exclusion, analysis, interpretation of results and writing of the review.

AF updated the electronic searches in June 2006.

Anca Zalmanovici Trestioreanu (AZT) updated the review in April 2011.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- No sources of support supplied

External sources

- Israel National Institute for Health Policy and Health Services Research, Israel.

INDEX TERMS

Medical Subject Headings (MeSH)

Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Ceftriaxone [therapeutic use]; Ciprofloxacin [therapeutic use]; Meningococcal Infections [*prevention & control]; Minocycline [therapeutic use]; Neisseria meningitidis; Randomized Controlled Trials as Topic; Rifampin [therapeutic use]

MeSH check words

Humans