Antibiotics for whooping cough (pertussis) (Review)

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[Intervention Review]

Antibiotics for whooping cough (pertussis)

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ABSTRACT

Background

Whooping cough is a highly contagious disease. Infants are at highest risk of severe disease and death. Erythromycin for 14 days is currently recommended for treatment and contact prophylaxis, but is of uncertain benefit.

Objectives

To study the benefits and risks of antibiotic treatment of and contact prophylaxis against whooping cough.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library,* 2007, issue 1) which contains the Acute Respiratory Infections Group's specialized register; MEDLINE (January 1966 to March 2007); EMBASE (January 1974 to March 2007).

Selection criteria

All randomised and quasi-randomised controlled trials of antibiotics for treatment of, and contact prophylaxis against, whooping cough.

Data collection and analysis

Three to four review authors independently extracted data and assessed the quality of each trial.

Main results

Thirteen trials with 2197 participants met the inclusion criteria: 11 trials investigated treatment regimens; 2 investigated prophylaxis regimens. The quality of the trials was variable. Short-term antibiotics (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) were as effective as long-term (erythromycin for 10 to 14 days) in eradicating *Bordetella pertussis (B. pertussis)* from the nasopharynx (relative risk (RR) 1.02, 95% confidence interval (CI) 0.98 to 1.05), but had fewer side effects (RR 0.66, 95% CI 0.52 to 0.83). Trimethoprim/sulfamethoxazole for seven days was also effective. Nor were there differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. Contact prophylaxis of contacts older than six months of age with antibiotics did not significantly improve clinical symptoms or the number of cases developing culture-positive *B. pertussis*.

Authors' conclusions

Although antibiotics were effective in eliminating *B. pertussis*, they did not alter the subsequent clinical course of the illness. There is insufficient evidence to determine the benefit of prophylactic treatment of pertussis contacts.

PLAIN LANGUAGE SUMMARY

Antibiotics for whooping cough (pertussis)

Whooping cough is a highly contagious disease caused by pertussis bacteria and may lead to death, particularly in infants less than 12 months of age. Although it can be prevented by routine vaccination, it still affects many people. Thirteen trials involving 2197 participants were included. We found that several antibiotic treatments were equally effective in eliminating the bacteria infecting patients, but they did not alter the clinical outcome. There was insufficient evidence to decide whether there is benefit for treating healthy contacts.

BACKGROUND

Description of the condition

Whooping cough is an acute respiratory tract infection, first described in the 1500s and endemic in Europe by the 1600s. *Bordetella pertussis (B. pertussis)* is the sole cause of epidemic whooping cough and the usual cause of sporadic pertussis. *Bordetella parapertussis (B. parapertussis)* accounts for five per cent of isolates of *Bordetella* species in the United States, and characteristically causes a less protracted illness (Heininger 1994; Long 1997).

Whooping cough epidemics in the pre vaccine era (that is, before the mid 1940s) occurred at two to five years intervals, and these cycles have continued in the vaccine era. Although immunisation has controlled the disease, it has not reduced the transmission of the organism in the population (Cherry 1984). *B. pertussis* can be prevented by vaccination and since the introduction of routine childhood immunisation whooping cough morbidity and mortality have declined markedly (Cherry 1984). However, despite widespread vaccination the disease has not been eradicated, and an increased incidence rate has been reported in the last two decades (Isacson 1993). There are 20 to 40 million cases of whooping cough annually worldwide (WHO 1999). Ninety percent of cases occur in low income countries and result in an estimated 200,000 to 300,000 fatalities annually (WHO 1999).

Although adults and older children usually have mild or moderate symptoms, infants younger than six months of age, who are not old enough to have received three doses of diphtheria-tetanus-pertussis (DTP) vaccine, and incompletely vaccinated preschool children are at high risk of severe disease and complications including death (CDC 1995; Cherry 1988).

Whooping cough is highly contagious. Between 70 and 100% of susceptible household members and between 50 and 80% of susceptible school contacts become infected following exposure to an acute case (Atkinson 1996). Data from the Centers for Disease Control and Prevention (CDC) for the years 1997 to 2000 showed that among 29,048 persons with whooping cough, 8390 (29%) were aged less than one year; 3359 (12%) were aged one to four years; 2835 (10%) were aged five to nine years; 8529 (29%) were aged 10 to 19 years; and 5935 (20%) were aged over 20 years old. The average annual incidence rates were highest among infants aged less than one year (55.5 cases per 100,000 population). They were lower in children aged one to four years (5.5 cases/100,000), children aged five to nine years (3.6 cases/100,000), individuals aged 10 to 19 years (5.5 cases/100,000), and individuals aged over 20 years old (0.8 cases/100,000) (CDC 2002). The incubation period is thought to be 7 to 10 days (range 4 to 21 days) and, rarely, may be as long as 42 days (Heininger 1998).

Since 1976, reported cases of pertussis in the United States have increased, with a substantial rise among persons aged 10 to 19 years old (CDC 2005). PCR-confirmed cases make up a substantial proportion of the total number of reported cases in this age group. Exactly how the increase in reported pertussis cases in adolescents reflects a true change in the burden of disease, remains unclear (CDC 2005).

Whooping cough is characterised by spasms of severe coughing (paroxysms). The paroxysms are continuous without inspiration until the end and are often followed by the characteristic inspiratory whoop or post-tussive vomiting or both. The illness onset is insidious, with symptoms similar to those of a minor upper respiratory infection (that is, a catarrhal period). During the first one to two weeks of the illness, coryza (a head cold) with an intermittent non-productive cough is common. This phase is followed by episodes of paroxysmal coughing which frequently last for several weeks (that is, paroxysmal phase). The disease peaks in severity after one or more weeks of paroxysmal coughing and begins to taper off with an extensive convalescent period of two to six weeks; convalescence may last up to three months in some cases.

Description of the intervention

Whooping cough may cause severe illness in young infants and result in complications such as apnoea, cyanosis, feeding difficulties, pneumonia, and encephalopathy. Infants and other patients with severe whooping cough may require hospitalisation for supportive care; for very severe cases, intensive care facilities may be required. Corticosteroids and albuterol (a B2-adrenergic stimulant) may be effective in reducing paroxysms of coughing but further evaluation is required before their use can be recommended (Broomhall 1984; Pillay 2003).

Clinical studies have used erythromycin estolate, erythromycin ethylsuccinate, or erythromycin stearate for treatment in patients with whooping cough or for prophylaxis. The studies using erythromycin estolate 40 to 50 mg/kg/day in divided doses have reported elimination of *B. pertussis* from the nasopharynx within seven days and no clinical relapses (Bass 1969; Islur 1975). In contrast, studies with erythromycin ethylsuccinate 50 to 55 mg/kg/day (Halsey 1980) or erythromycin stearate 40 to 50 mg/kg/day (Henry 1981) have reported delay or failure of bacterial eradication, or apparent failure of prophylaxis, in 10 to 30% of cases. This has been explained in part by a higher serum and tissue concentration of the drug achieved following administration of the estolate preparation compared with other esters (Bass 1985).

How the intervention might work

The CDC recommends erythromycin for treatment of whooping cough and contact prophylaxis (CDC 2000). The recommended dose of erythromycin for use in treatment of whooping cough in children is 40 to 50 mg/kg per day (maximum 2 g/day) and in adults 1 to 2 g/day orally in four divided doses for 14 days. Some experts recommend the use of erythromycin estolate because it achieves higher serum levels compared to erythromycin ethylsuccinate or stearate when equal doses are given (CDC 2000; Ginsburg 1986). The antimicrobial agents and dosages used for

chemoprophylaxis of contacts are the same as that recommended for treatment of clinical cases (CDC 2000).

The gastrointestinal side effects of erythromycin limit its usefulness in some patients. The erythromycin estolate preparation Ilosone is no longer available in Australia (Thomas 2002), and possibly in other parts of the world, due to discontinuation of manufacture of the drug.

The newly developed macrolides clarithromycin, and azithromycin may be superior to erythromycin because of improved absorption, a longer half-life, good in vitro activity against *B. pertussis* and a better side effect profile (Aoyama 1996; Lebel 2001). Roxithromycin has not been well studied in the treatment of whooping cough. Based on a few studies, Trimethoprim-sulfamethoxazole (TMP-SMZ) also appears to be effective in eradicating *B. pertussis* and it is currently recommended as an alternative antibiotic treatment for patients who cannot tolerate erythromycin (CDC 1991).

Why it is important to do this review

The recommended therapy for treatment of and prophylaxis against whooping cough infection is inconvenient and prolonged and it is likely that compliance is often poor (CDI 1997). The optimal duration of treatment is uncertain (Halperin 1997; Hoppe 1988). There is also some controversy as to whether prophylaxis of contacts is effective and, therefore, worthwhile (De Serres 1995). To date, there has not been a systematic review of the literature regarding the antibiotic treatment of and contact prophylaxis against whooping cough.

OBJECTIVES

To study the benefits and risks of antibiotic treatment of, and contact prophylaxis against, whooping cough.

Treatment

- Do antibiotics achieve microbiological eradication of *B. pertussis*?
- Do antibiotics improve the clinical illness of whooping cough?
- The appropriate dose and duration of therapy.
- The side effects profile of antibiotics used to treat whooping cough.

Contact prophylaxis

- Do antibiotics achieve microbiological eradication of *B. pertussis*?
- Do antibiotics prevent the clinical illness of whooping cough?
- The appropriate dose and duration of therapy.
- The side effects profile of antibiotics used for prophylaxis of whooping cough.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised clinical trials and quasi-randomised controlled trials comparing two or more antibiotics or antibiotics versus placebo/no treatment for the treatment or prophylaxis (prevention) of whooping cough. Quasi-randomised studies are those studies which are intended to be randomised by using methods of allocation such as alternation, date of birth, or case record number (Higgins 2005a).

Types of participants

- Patients: children and adults with whooping cough, diagnosed clinically or by laboratory means (therapeutic regimen).
- Contacts: children and adults who had contact with individual(s) with proven whooping cough but have not developed clinical whooping cough (prophylactic regimen).

Types of interventions

This review will address the following comparisons in both treatment and prophylaxis groups:

- antibiotic versus placebo or no intervention;
- one type of antibiotic versus another type of antibiotic; and
- one antibiotic regimen (dose or duration or both) versus another regimen of the same antibiotic.

Types of outcome measures

- Mortality from any cause.
- Clinical assessment of whooping cough: assessment of severity including a decrease in frequency of paroxysmal coughing, frequency of whoop, severity of the cough, mean duration of symptoms, and development of complications for example, otitis media and respiratory complications.
- Complete remission (clinical cure).
- Number of contacts that develop clinical whooping cough (in prophylactic studies).
- Laboratory outcome measures for example, microbiological eradication and microbiological relapse of *B. pertussis* organisms.
- Antibiotic side effects/adverse events.

- Patient compliance and tolerance to antibiotics.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library*, 2007, issue 1) which contains the Acute Respiratory Infections Group's specialized register; MEDLINE (January 1966 to March 2007); EMBASE (January 1974 to March 2007). (See Appendix 1 for the CENTRAL search strategy). (See Appendix 2 for the EMBASE search strategy).

MEDLINE (OVID)

1 exp Whooping Cough/
2 whoop$.mp.
3 exp Bordetella pertussis/
4 pertus$.mp.
5 or/1-4
6 exp Anti-Bacterial Agents/
7 antibiotic$.mp.
8 antimicrob$.mp.
9 or/6-8
10 RANDOMIZED CONTROLLED TRIAL.pt.
11 CONTROLLED CLINICAL TRIAL.pt.
12 RANDOMIZED CONTROLLED TRIALS.sh.
13 RANDOM ALLOCATION.sh.
14 DOUBLE BLIND METHOD.sh.
15 SINGLE-BLIND METHOD.sh.
16 or/10-15
17 Animals/
18 Humans/
19 17 not 18
20 16 not 19
21 CLINICAL TRIAL.pt.
22 exp Clinical Trials/
23 (clin$ adj25 trial$).ti,ab.
24 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
25 PLACEBOS.sh.
26 placebo$.ti,ab.
27 random$.ti,ab.
28 or/21-27
29 28 not 19
30 20 or 29
31 and/5,9,30

Searching other resources

We scanned reference lists of medical journal articles and reviews relevant to the use of antibiotics in pertussis. We also searched conference abstracts and reference lists of articles. Study investigators and pharmaceutical companies were approached for additional information (published or unpublished studies). There were no language restrictions.

Data collection and analysis

The criteria used to assess the quality of the study were randomisation of participants; allocation concealment; blinding of participants, investigators and outcome assessors; intention-to-treat analysis; and completeness of follow up. Criteria were assessed separately and not combined to give a quality score.

RevMan was used to analyse data. Statistical analysis was performed for dichotomous outcomes and results were expressed as a relative risk (RR) with 95% confidence interval (CI). Fixed-effect models were used for outcomes without statistically significant heterogeneity and random-effects models for outcomes with significant heterogeneity ($P < 0.10$). Where continuous scales of measurement were used to assess the effect of treatment the mean difference (MD) between groups and 95% CI were used. The standardised mean difference (SMD) and 95% CI were used to compare different measurement scales.

Selection of studies

Three review authors (SA, RK and JM) independently screened the titles and abstracts resulting from the literature search. If it was felt that the trial could possibly meet the criteria, the full paper was obtained for further screening. Four review authors (SA, RK, JM and NC) independently assessed study eligibility using defined criteria.

Dealing with missing data

Authors of primary studies were contacted when necessary, to clarify data and to provide missing information. Disagreements among review authors were resolved by discussion and consensus.

Subgroup analysis and investigation of heterogeneity

A subgroup analysis comparing short-term (three to seven days) to long-term (14 days) treatment was conducted with antibiotics. Other subgroup analyses to determine potential causes of variability amongst treatment effects were not possible because of the difficulties of obtaining enough detailed data from studies of those various subgroups.

Sensitivity analysis

When studies differed considerably in quality, a sensitivity analysis was performed in which poorer quality studies (unknown or inadequate allocation concealment) were excluded.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Thirteen randomised controlled trials (RCTs) were identified for inclusion in this review, published between 1953 and 2004. Eight

of the RCTs were found by a MEDLINE search, two studies in EMBASE (Henry 1981; Lebel 2001), one in CENTRAL (Cruickshank 1953), one by screening reference lists (Adcock 1972), one by searching conference abstracts on a medical web site (http://www.icmask.org) and then contacting the authors (Bace 2002). No unpublished RCTs were identified by contacting drug companies (Table 1).

Table 1. Sources of included studies

Trials	MEDLINE	EMBASE	The Cochrane Library	Reference lists	Conference abstracts	Personal contacts	Drugs company
Adcock 1972				+			
Bace 2002					+	+	
Bass 1969	+		+				
Cruickshank 1953			+				
Degn 1981	+	+	+				
Grob 1981	+	+					
Halperin 1997	+	+	+				
Halperin 1999	+		+				
Henry 1981		+				+	
Hoppe 1992	+		+				
Langley 2004	+		+				
Lebel 2001		+					
Strangert 1969	+						

Included studies

There were eleven studies on the treatment of whooping cough that met the inclusion criteria (Adcock 1972; Bace 2002; Bass 1969; Cruickshank 1953; Degn 1981; Halperin 1997; Henry 1981; Hoppe 1992; Langley 2004; Lebel 2001; Strangert 1969). Of these, ten were RCTs and one was a quasi-RCT (Strangert 1969).

There were two studies on prophylaxis against whooping cough infection (Grob 1981; Halperin 1999) that met the inclusion criteria. The two studies were conducted in household contacts of children who were culture positive for *B. pertussis*.

Ten studies of treatment of whooping cough compared one antibiotic with another antibiotic (Adcock 1972; Bace 2002; Cruickshank 1953; Degn 1981; Halperin 1997; Henry 1981; Hoppe 1992; Langley 2004; Lebel 2001; Strangert 1969) and one study compared antibiotics versus no treatment (Bass 1969). The two studies of contact prophylaxis were placebo controlled (Grob

1981; Halperin 1999).

Immunisation status was reported in five of the studies on the treatment of whooping cough (Bass 1969; Halperin 1997; Hoppe 1992; Langley 2004; Lebel 2001) and in one study of contact prophylaxis (Grob 1981). Bass (Bass 1969) reported that only 9/50 (18%) children studied had received any previous pertussis vaccine injection and only 2/50 (4%) children had previously received three DTP injections; their illness appeared milder than in non-immunised children. Grob (Grob 1981) found that 60/91 (66%) children were vaccinated, with 32 vaccinated children in the erythromycin group and 28 in the placebo group. Halperin (Halperin 1997) reported that 65/74 (88%) of the seven days of erythromycin estolate group and 88% (83/94) of the 14 days of erythromycin estolate group had received three or more doses of the vaccine. Hoppe (Hoppe 1992) found that pertussis vaccination status was similar in both study groups: 115/190 (60.5%) of patients had not been vaccinated at all - 56/93 (60.2%) in the erythromycin estolate group and 59/97 (60.8%) in the erythromycin ethylsuccinate group). Langley (Langley 2004) reported previous number of pertussis vaccine doses received by children who were assigned to erythromycin or azithromycin (mean 4.4 versus 4.1). Lebel (Lebel 2001) reported that 68/76 (89%) of children had received whooping cough vaccination in the clarithromycin treatment group and 69/77 (90%) in the erythromycin control group.

Outcome measures used to assess efficacy of antibiotic treatment or prophylaxis varied between trials. Most trials considered clinical improvement (for example, decreased frequency of cough, whoop, and complete remission) or microbiological eradication or both. Mortality was reported in two trials (Bass 1969; Cruickshank 1953).

Clinical assessment was reported in almost all the included randomised trials but sufficient data for analysis were available for six trials only. However, in these trials (Adcock 1972; Grob 1981; Halperin 1997; Halperin 1999; Hoppe 1992; Lebel 2001) the clinical assessment was reported differently; for example, in some trials complete remission was assessed and in other trials frequency of whoop, paroxysmal cough were assessed. Complications due to whooping cough were reported in two trials (Cruickshank 1953; Lebel 2001). The number of cases that resulted in clinical whooping cough in contacts (attack rate) was evaluated in one study (Halperin 1999).

Microbiological eradication (defined as *B. pertussis* negative culture at the end of treatment) was reported in ten trials (Adcock 1972; Bace 2002; Bass 1969; Degn 1981; Halperin 1997; Henry 1981; Hoppe 1992; Langley 2004; Lebel 2001; Strangert 1969).

Microbiological relapse (defined as a positive culture one week post-completion of therapy after a negative end-of-therapy culture) was reported in two trials (Halperin 1997; Langley 2004).

Drug side effects (such as abdominal pain and diarrhoea) were stated in nine trials (Bace 2002; Cruickshank 1953; Halperin 1997; Halperin 1999; Henry 1981; Hoppe 1992; Langley 2004; Lebel 2001; Strangert 1969). Patient compliance (measured as the mean percent of drug taken or in other ways such as measurement of antimicrobial activity in the urine) was reported in five trials (Halperin 1997; Halperin 1999; Hoppe 1992; Langley 2004; Lebel 2001). Analysis of compliance in Halperin 1997 was not possible because data were presented as a mean percent of drugs taken without the standard deviation.

For further details, please *see* the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Risk of bias in included studies

Allocation

In only four trials (Halperin 1999; Henry 1981; Langley 2004; Lebel 2001) was the treatment assignment adequately concealed prior to allocation. Allocation concealment was unclear in eight studies (Adcock 1972; Bace 2002; Bass 1969; Cruickshank 1953; Degn 1981; Grob 1981; Halperin 1997; Hoppe 1992) and in one quasi-RCT the allocation concealment was inadequate (Strangert 1969).

Blinding

There were three double blinded trials (Cruickshank 1953; Degn 1981; Halperin 1999), four single blinded trials (patients or investigators) (Adcock 1972; Grob 1981; Henry 1981; Lebel 2001), three open (unblinded) trials (Halperin 1997; Hoppe 1992; Langley 2004), and in three trials neither intervention nor outcome assessments were blinded to treatment (Bace 2002; Bass 1969; Strangert 1969). Intention to treat analysis was reported in two trials (Langley 2004; Lebel 2001).

Other potential sources of bias

The method of randomisation was described in eight of thirteen trials (computer generated random lists, random number book, or random sequence) (Cruickshank 1953; Degn 1981; Halperin 1997; Halperin 1999; Henry 1981; Hoppe 1992; Langley 2004; Lebel 2001). In four trials the method of randomisation was not stated (Adcock 1972; Bace 2002; Bass 1969; Grob 1981) and in one quasi-randomised trial (Strangert 1969) alternation of patients (each second child admitted with whooping cough was treated with ampicillin) was used.

Follow up was complete for children admitted to hospital. Follow up was incomplete for children who were not admitted to hospital. The duration of follow up varied from one study to another (up to 40 days after discharge from hospital). In four of thirteen trials patients were considered to have completed their follow up (Bass 1969; Halperin 1999; Hoppe 1992; Lebel 2001).

Effects of interventions

Antibiotics for treatment of whooping cough

Mortality

Mortality was reported in two trials (Bass 1969; Cruickshank 1953). Neither trial showed a statistically significant difference in mortality.

In the trial by Cruickshank (Cruickshank 1953) one child died in the aureomycin group (1/96), and one died in the chloramphenicol group (1/98). In detail, in the aureomycin group a male aged seven months developed convulsions on the fourteenth day of observation and died the following day; in the chloramphenicol group a female aged one year developed widespread atelectasis of the lungs on the seventh day of observation and died on the eleventh day of observation. Authors of the trial reported that none of the complicated or fatal cases occurred in patients treated within eight days of the onset of symptoms.
In the trial by Bass (Bass 1969) one child died in the ampicillin group (1/10) compared to none in the untreated group (0/10), oxytetracycline (0/10), chloramphenicol (0/10), or erythromycin (0/10) groups. The child who died was two months old and with *B. pertussis* proven on a nasopharyngeal (NP) specimen. He was on penicillin V for seven days in the catarrhal stage before admission; during admission he was on ampicillin (100 mg/kg/day) for about 20 days. He was also given three doses of whooping cough hyperimmune globulin but remained *B. pertussis* culture positive and died in the paroxysmal stage. No further details were reported regarding his death.

Clinical cure (complete remission) / improvement

Clinical cure/improvement was worded and defined differently between studies, therefore, results were analysed separately for each study and according to the definition used by the trial authors. In the trial by Hoppe (Hoppe 1992) clinical cure (according to parents' judgement after the completion of antimicrobial treatment and as compared with the onset) was 4/97 (4%) in the erythromycin ethylsuccinate (14 days) group and 13/92 (14%) in the erythromycin estolate (14 days) group. The results showed that erythromycin estolate was superior to erythromycin ethylsuccinate (RR 3.43; 95% CI 1.16 to 10.13). Clinical improvement after one week of treatment was not statistically different when tetracycline was compared to trimethoprim/sulfamethoxazole (Adcock 1972). Decreased frequency of cough at 14 days of treatment was reported by Hoppe (Hoppe 1992) and was 72/97 (74%) in the erythromycin ethylsuccinate (14 days) and 72/92 (78%) in erythromycin estolate (14 days) with no statistically significant difference between these esters.
The presence of any signs or symptoms of whooping cough at the completion of treatment was similar whether participants were treated with erythromycin estolate for 7 or 14 days (Halperin 1997). Clinical outcomes in the study by Degn (Degn 1981) were not possible to analyse since tables were reported as medians, however, the clinical course of the disease as estimated by the number of bouts of coughing per day was identical in the two groups. The clinical course of illness in the study by Bass (Bass 1969) was presented per individual patients and it was not possible to analyse these data accurately, however, the author reported that there was no significant difference in the subsequent course of illness in those groups receiving antimicrobial therapy when compared with the untreated control group.

Microbiological eradication

Microbiological eradication was reported in ten trials involving 811 participants and varied from 0% to 100%. Meta-analysis of microbiological eradication as an outcome in these trials was not possible because of the difference in type of antibiotics used. For this reason, results were analysed separately for each study.
In the study by Bass (Bass 1969) there was microbiological eradication on day seven of treatment in the oxytetracycline (8/10) and erythromycin (9/10) treatment groups over the untreated group (RR 17; 95% CI 1.11 to 259.89 and RR 19; 95% CI 1.25 to 287.93 respectively). Microbiological eradication was not statistically significant in the chloramphenicol treatment group (7/10) compared with the untreated group (0/10); and microbiological eradication was not achieved in the ampicillin treatment group (0/10) compared with the untreated group (0/10). No statistically significant benefit was found with one antibiotic compared with another antibiotic, with regard to microbiological eradication, in nine trials (Adcock 1972; Bace 2002; Degn 1981; Halperin 1997; Henry 1981; Hoppe 1992; Langley 2004; Lebel 2001; Strangert 1969).

Microbiological relapse

In a study by Halperin (Halperin 1997) microbiological relapse (defined as a positive culture one week post-completion of therapy after a negative end-of-therapy culture) was reported in 1/72 (1.4%) with erythromycin estolate (seven days) compared to 0/83 (0%) with erythromycin estolate (14 days) (RR 3.45; 95% CI 0.14 to 83.45). In the study by Langley (Langley 2004) no bacterial recurrence was demonstrated in the 51 patients in the azithromycin group or the 53 patients in the erythromycin group with one week post-treatment cultures available.

Complications

Respiratory complications (defined as development of bronchopneumonia, lobar pneumonia, or bronchitis complications) of whooping cough were reported in one trial (Cruickshank 1953): 7/96 (7%) in the aureomycin group compared to 5/98 (5%) in the chloramphenicol group. Otitis media as a complication of whooping cough was reported in the (Lebel 2001) trial with 0/76 (0%) developing otitis media in the clarithromycin (7 days) group and 6/77 (8%) in the erythromycin estolate (14 days) group. There was no significant difference in complications in either trial.

Side effects

Side effects were reported in six trials involving 975 participants. Meta-analysis of side effects in these trials was not possible because of the difference in the types of antibiotics used. Results were, therefore, analysed separately for each study. Fewer side effects were noted with azithromycin (3 days) compared with erythromycin (14 days) (RR 0.38; 95% CI 0.19 to 0.75) in (Bace 2002); and with clarithromycin (7 days) compared with erythromycin estolate (14 days) (RR 0.72; 95% CI 0.53 to 0.97) (Lebel 2001). No significant difference in side effects of one antibiotic over another was found in four trials (Cruickshank 1953; Halperin 1997; Hoppe 1992; Strangert 1969). In the study by Langley (Langley 2004) fewer gastro-intestinal adverse effects were noted with azithromycin (5 days) compared with erythromycin estolate (10 days) (RR 0.46, 95% CI 0.34 to 0.62). In the study by Lebel (Lebel 2001) 24/76 (32%) had gastro-intestinal adverse effects with clarithromycin (7 days) and in 34/77 (44%) with erythromycin estolate (14 days) but this was not statistically different. Diarrhoea as a drug related side effect was reported by Henry (Henry 1981): in 2/10 (20%) with erythromycin stearate (7 days) compared to 1/12 (10%) with co-trimoxazole (7 days) but this was not statistically different.

Compliance

The study participant compliance with medication was reported in three trials (Hoppe 1992; Langley 2004; Lebel 2001). In the study by Hoppe (Hoppe 1992) better compliance was achieved in those receiving erythromycin ethylsuccinate compared to those receiving erythromycin estolate (RR 0.80; 95% CI 0.69 to 0.94). Compliance was better in those children who received azithromycin compared to those who received erythromycin estolate (RR 1.63, 95% CI 1.45 to 1.85) (Langley 2004). In the study by Lebel (Lebel 2001) those receiving clarithromycin had better compliance than those receiving erythromycin estolate (WMD 9.90; 95% CI 5.34 to 14.46).

Antibiotics for short-term (three to seven days) versus long-term (10 to 14 days) in treatment of whooping cough (subgroup analysis)

This section is a subgroup analysis comparing short-term to long-term treatment with antibiotics.

Clinical improvement

In the study by Halperin (Halperin 1997) the presence of any sign or symptom of whooping cough was reported in 73/74 (99%) with erythromycin estolate (7 days) compared to 93/94 (99%) with erythromycin estolate (14 days). There was no difference in clinical improvement with 14 day treatment duration compared to the seven day duration with erythromycin estolate (RR 1.00; 95% CI 0.96 to 1.03).

Microbiological eradication

Four trials involving 358 participants compared the efficacy of antibiotics in the microbiological eradication of *B. pertussis* (Halperin 1997; Langley 2004; Lebel 2001; Bace 2002). Meta-analysis showed that there was no significant benefit of long-term antibiotic treatment (10 to 14 days with erythromycin estolate or unspecified salt of erythromycin) compared to short-term antibiotic treatment (azithromycin for three to five days, erythromycin estolate for seven days, or clarithromycin for seven days) in microbiological eradication of *B. pertussis* (RR 1.02; 95% CI 0.98 to 1.05).

Sensitivity analysis was performed by excluding the Bace (Bace 2002) study, which to date has only been published as an abstract. This again showed that there was no significant benefit of long-term antibiotic treatment over short-term antibiotic treatment in the microbiological eradication of B. pertussis (RR 1.01; 95% CI 0.97 to 1.05) (Halperin 1997; Langley 2004; Lebel 2001).

Microbiological relapse

Microbiological relapse was reported in two trials involving 259 participants (Langley 2004; Halperin 1997). In the study by Langley (Langley 2004) no bacterial relapse was demonstrated in the 51 patients in the azithromycin group or the 53 patients in the erythromycin group with one week post-treatment cultures available. In the study by Halperin (Halperin 1997) microbiological relapse was reported in 1/72 (1.4%) of patients receiving erythromycin estolate for seven days compared to 0/83 (0%) in the group receiving erythromycin estolate for 14 days. However, there was no significant difference in microbiological relapse between seven days treatment with erythromycin estolate and 14 days treatment of the same antibiotic (RR 3.45; 95% CI 0.14 to 83.45).

Side effects

Three trials involving 443 participants reported side effects (Bace 2002; Halperin 1997; Lebel 2001). Meta-analysis showed that fewer side effects were reported in those receiving short-term antibiotic treatment compared to those receiving long-term antibiotic treatment (14 days of erythromycin) (RR 0.66; 95% CI 0.52 to 0.83). Sensitivity analysis excluding the Bace (Bace 2002) study was performed. Meta-analysis again showed significantly fewer side effects reported in those receiving short-term antibiotic treatment compared to those receiving long-term antibiotic treatment (RR 0.73; 95% CI 0.57 to 0.93) (Halperin 1997; Lebel 2001). Other subgroup analyses to determine potential causes of variability amongst treatment effects were not possible because it was not possible to obtain enough detailed data from studies of various patient subgroups.

Antibiotics for prophylaxis against whooping cough

Mortality

No mortality was reported in any of the included prophylaxis trials in this review.

Clinical improvement

In the prophylaxis trials, clinical symptoms, frequency of whooping cough, and frequency of paroxysmal cough in the household contacts were slightly less in the treatment group compared to placebo (not statistically significant) (Grob 1981; Halperin 1999). Frequency of whooping cough in the vaccinated contacts was reported by Grob (Grob 1981). No vaccinated child had whooping cough: in the erythromycin ethylsuccinate group (0/32) or in the placebo group (0/28) (RR not estimable). The frequency of whooping cough in the unvaccinated contacts in the same trial was 4/20 (20%) in the treatment group and 2/11 (18%) in the placebo group with no benefit of antibiotic over the placebo (RR 1.10; CI 0.24 to 5.08).

Number of contacts that became culture positive or developed clinical pertussis (attack rate)

In the study by (Halperin 1999) the number of cases that became culture positive for *B. pertussis* after prophylaxis was slightly less in the erythromycin group 3/142 (2.1%) compared to placebo 8/158 (5.1%) group but the difference was not statistically significant (RR 0.42; 95% CI 0.11 to 1.54). Culture positivity or development of two weeks of paroxysmal cough after prophylaxis occurred in 6/124 (4.8%) contacts in the erythromycin estolate group and 8/132 (6.1%) contacts in the placebo group. There was no significant benefit of erythromycin estolate over placebo in contacts (RR 0.80; 95% CI 0.29 to 2.24) (Halperin 1999).

Side effects

Any side effects which were reported by the participants (including nausea, vomiting, diarrhoea, abdominal pain) were more frequently reported by participants in the erythromycin estolate group 49/144 (34%) than in the placebo group 26/166 (16%) (RR 2.17; 95% CI 1.43 to 3.31) (Halperin 1999).

Compliance

Compliance (greater than 90% of doses taken by the participants) was assessed in one study by Halperin (Halperin 1999). It was better in the placebo group 78/144 (54.2%) than in the erythromycin estolate group 108/166 (65.1%) although this difference was borderline for statistical significance (RR 0.83; 95% CI 0.69 to 1.00).

DISCUSSION

Summary of main results

Only 13 studies met our inclusion criteria in our literature search between 1953 and 2006. Eleven of these addressing treatment included 1796 (1628 children and 168 adults) patients or household contacts; and two addressing contact prophylaxis of 401 household contacts with children culture positive for *B. pertussis*.
Not only was the number of RCTs small, but those included were undertaken over 20 years ago, and of poor methodological quality. All but one was undertaken in high income countries.

Heterogeneity of studies

Included studies were too heterogeneous with regard to intervention and outcomes to allow pooling of results. In only three trials was meta-analysis possible, comparing short-term versus long-term antibiotic treatment of whooping cough (subgroup analysis). The studies varied greatly in timing of *B. pertussis* cultures for participants (for example, catarrhal stage versus paroxysmal stage), types of antibiotic used, dose regimes and duration of treatment with antibiotics. In general, nasopharyngeal aspirates were taken at the beginning of the study and repeated after the completion of treatment. The end of treatment cultures varied according to the planned duration of therapy. For example, in the study by Strangert (Strangert 1969) the duration of treatment in both treatment groups was six days while in a study by Lebel (Lebel 2001) the duration of treatment was seven days with clarithromycin compared to fourteen days with erythromycin estolate. Nasopharyngeal cultures were taken at seven days (for clarithromycin group) and at fourteen days (for the erythromycin group) but not at seven and fourteen days for both. Furthermore, cultures taken one or two weeks post-completion of therapy, that might indicate microbiological relapses, were missing in many studies.
Interestingly, many studies initially enrolled larger number of patients based on the clinical diagnosis of pertussis (for example, Bace 2002; Hoppe 1992) but subsequently only 30 to 40% were found to be *B. pertussis* culture positive. This can be attributed to many factors:
(i) the organism can usually be recovered during the catarrhal stage but not two or three weeks after the onset of paroxysms (Krugman 1992);
(ii) isolation of *B. pertussis* depends on correct collection of samples, careful transport, and efficient processing of the samples obtained for culture; isolation is enhanced if the clinical microbiologist is experienced with the organism (Krugman 1992);
(iii) although *B. pertussis* is the sole cause of epidemic pertussis, other organisms such as *B. parapertussis*, *Bordetella bronchiseptica (B. bronchiseptica)* are occasional cause of pertussis (Long 1997).
Clinical diagnosis varied from one study to another. In the study by Adcock (Adcock 1972) the clinical diagnosis of whooping cough was based on presence of typical 'whoop' and relative or absolute lymphocytosis; while in the study by Hoppe (Hoppe 1992) clinical pertussis meant non-specific cough at a time when pertussis was prevalent in the community, or early paroxysmal stage. Other studies provided no clear definition of clinical pertussis.

Types of antibiotics used in trials for treatment or contact prophylaxis were different. Antibiotic choice varied in every aspect: (i) type of antibiotic used, (ii) dose, (iii) salt preparation, and (iv) duration of treatment (that is, from 3 to 14 days or more). It was difficult to find even two studies that used similar antibiotic regimens. These differences made it difficult to undertake quantitative meta-analysis for most aspects of the study and recommendations, therefore, were finally made on the basis of individual studies.

It is noticeable that there was only one study included in the treatment regimen that compared antibiotics with no treatment (Bass 1969). Hoppe 1992 reported that in Germany it would be considered unethical by most physicians to withhold appropriate antimicrobial treatment from a child with proven or strongly suspected pertussis. This view might also be applicable in many other parts of the world. However, from a purely scientific perspective the lack of such knowledge makes it hard to know the true effect of antibiotic therapy.

The age of participants enrolled in the studies was not mentioned in most of the included studies, the one exception being the study by Bass (Bass 1969) where findings were stratified according to individual patient age. It is known that almost 90% of the reported deaths caused by whooping cough occur in non-immunized infants younger than one year of age (Hoppe 2000).

Further difficulties were encountered in the contact prophylaxis studies. The unit of randomisation in the two contact prophylactic studies (Grob 1981; Halperin 1999) was the household rather than individuals. All household members were allocated to the same treatment group (either antibiotic or placebo). Halperin 1999 reported that households were used as the unit of randomisation and in analysis because of concern that the risk of second cases of pertussis within a household were dependent not only on the index case but potentially on the other household contacts. Grob 1981 reported that individual household member randomisation was not achievable and it was simpler to use the household as the unit of randomisation. Household randomisation is not equivalent to individual randomisation. Although it might be easier for the investigator to use the household as a unit for randomisation, such a method of randomisation made it difficult to know the 'real' effect of the antibiotic on individuals because all household members received either erythromycin or placebo. As a result of household randomisation it was not possible to determine the age of participants; assess the effectiveness of antibiotics in different age subgroups; or assess the effectiveness of antibiotics on immunised, partially immunized, or non-immunised children.

The prophylaxis studies were only relevant to children older than six months of age. In the study by Halperin (Halperin 1999) children younger than six months of age were excluded from the study and in the study by Grob (Grob 1981) there was no clear data about the inclusion of younger infants. Children below six months of age (who are incompletely immunised) have a higher rate of whooping cough and are at considerable risk of morbidity and mortality. A low incidence of culture-positive pertussis was found in the study by Halperin (Halperin 1999) in both erythromycin and placebo groups, perhaps due to the high rate of immunisation, and this led to the study being insufficiently powered to detect any significant difference.

Unfortunately, information on immunisation status was deficient in 6/10 (60%) of trials in the treatment of whooping cough and in 1/2 (50%) trials of contact prophylaxis. Immunisation status and type of immunisation (that is, passive or active) of individuals is valuable data because it may influence the apparent efficacy of antibiotics, particularly in contact prophylaxis. The proportion of individuals protected against clinical pertussis by full immunisation with the whole-cell vaccine is high but not as high as the proportion protected by natural disease (Krugman 1992). Vaccine failure occurs in approximately 10% of individuals with some variation perhaps caused by the intensity of exposure to wild pertussis (Krugman 1992). Comparative efficacy trials of acellular versus whole cell vaccine for primary immunisation have been conducted in several countries. Products containing multiple pertussis components were superior to simple vaccines and compared favourably with whole cell diphtheria-tetanus-pertussis (DTP) vaccines. Reactogenicity of acellular DTP was significantly less (Long 1997).

Immunity to whooping cough has been shown to wane 5 to 10 years after vaccination with whole-cell pertussis vaccines. Waning immunity following vaccination with acellular pertussis vaccines may also occur but data are currently limited (CDC 2000). This apparent loss of immunity has become particularly evident in recent years because of an increase in the incidence of reported cases of whooping cough in adolescents and young adults (Krugman 1992).

There was a lack of uniformity in the monitoring of side effects and compliance of patients. The studies varied in types and clear definitions of the side effects, microbiological relapse and recurrence. Compliance was also poorly estimated in most of the studies. It was reported in only three studies and these varied in their measures of compliance. In the study by Hoppe (Hoppe 1992) compliance was measured by the detection of antimicrobial activity in the urine whereas in the studies by Lebel (Lebel 2001) and Halperin (Halperin 1999) compliance was measured by the amount of the drug taken by patients.

A cost-benefit analysis was not part of this review but it is an important factor for healthcare services when considering choice of treatment. Unfortunately cost information was not provided in any of the included studies. In general, the cost of treatment with antibiotics varies from one country to another and many drugs are no longer patented. Calculation of the exact cost for each drug was not, therefore, undertaken in this review. In addition, modest benefits of antibiotics must be weighed up against the cost and inconvenience of therapy and the risk of side effects.

Methodological quality of included studies

This review identified thirteen randomised controlled trials investigating antibiotics for treatment and contact prophylaxis of

whooping cough. The methodological quality of these trials was variable. Four RCTs reported adequate randomisation; in eight RCTs the method of allocation was unclear. Only in one trial (Strangert 1969) was the method of allocation concealment considered inadequate. Blinding was reported in 7 of the 12 trials. Most trials compared one antibiotic with another antibiotic. The two prophylactic trials were placebo controlled (Grob 1981; Halperin 1999).

Seven trials were excluded from this review. These trials might have provided some useful information if they were included (for example, efficacy of antibiotics used and occurrence of side effects). On the other hand, these studies had many methodological errors including the use of historical control patients, large numbers of dropout participants, poor quality methods or analysis, and non-interpretable results. Inclusion of such studies might lead to several forms of bias (for example, performance bias, attrition bias) and hence misleading conclusions. Management of secondary respiratory infections in patients with whooping cough was not part of the inclusion criteria of this systematic review. Intervention with symptomatic drugs such as steroids, bronchodilators, and cough syrups for whooping cough was also not part of the inclusion criteria as another Cochrane review on symptomatic treatment in whooping cough is has been published (Pillay 2003).

Methodological process of the review

Four independent review authors (SA, RK, JM & NC) assessed study eligibility using defined criteria. The defined criteria to assess the quality of the study were participant randomisation; allocation concealment; blinding of participants, investigators and outcome assessors; intention to treat analysis, and completeness of follow up. Criteria were assessed separately and not combined to give a quality score. The Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005a) highlights that involvement of at least two review authors to conduct a systematic review has an important effect on reducing the possibility that relevant reports will be discarded and may also limit bias, minimise errors, and improve reliability of findings.

The inclusion of studies in this systematic review was influenced mainly by the method of allocation concealment. Empirical research has shown that lack of adequate allocation concealment is associated with bias (Chalmers 1983; Schulz 1995). Indeed, concealment has been found to be more important in preventing bias than other components of allocation such as the generation of the allocation sequence (for example, computer, random number table, alternation). Thus studies can be judged on the method of allocation concealment (Higgins 2005b).

Data analysis

A subgroup analysis was done comparing short-term (3 to 7 days) with long-term (14 days) treatment with antibiotics. Other subgroup analyses, to determine potential causes of variability amongst treatment effects, were not possible because obtaining enough detailed data from studies of various subgroups was not possible. Important subgroups that should be addressed are adults versus children, early antibiotic treatment (that is, catarrhal stage) versus late antibiotic treatment (that is, paroxysmal or convalescent stage), antibiotics versus placebo, and immunised versus non-immunised children. It is hoped that further data may become available to permit such analyses.

Although sensitivity analysis was performed by excluding one (Bace 2002) study, which to date has been published as an abstract only, this did not alter the conclusions significantly. Some of the planned analyses were constrained owing to heterogeneity of the included studies and the inability to perform a quantitative meta-analysis. Important sensitivity analyses may include method of randomisation (excluding studies with inadequate allocation concealment), chronology of RCTs (to distinguish between RCTs by their place in time), and size of RCTs (to distinguish between RCTs by the number of participants). It was not possible to undertake a funnel plot graph for publication bias again because of the heterogeneity of the included studies and inability to perform a meta-analysis.

Limitations of the systematic review

All eleven of the included RCTs of treatment involved children only and no trials were found specifically in adults. The two prophylaxis trials, which were done in household contacts, did not report separate data for adults and, therefore, subgroup analysis for adults was not possible. The results should be interpreted with caution because of the heterogeneity between studies. Furthermore, this review may be subject to bias because the summary results are based on a limited number of trials and some of these trials involved small numbers of patients. There were some differences between the studies regarding definition of whooping cough, patient diagnosis, inclusion criteria, interventions (that is, various types of antibiotics, doses used, duration), and outcome measures (that is, clinical cure, clinical improvement, microbiological eradication); which did not allow quantitative meta-analysis for most of the outcome measures.

In addition, there was minimal information on immunisation status of participants, microbiological relapse, definition of clinical cure or improvement, and timing of intervention (for example, catarrhal stage, paroxysmal stage). There was a lack of blinding in some studies (for example, Bass 1969; Halperin 1997; Hoppe 1992). There is a possibility of publication and selection bias in this systematic review. However, a comprehensive literature search was conducted using a systematic strategy to avoid bias. Attempts to find unpublished trials were carried out by consulting experts in the field, searching abstracts from recent conferences, and corresponding with the authors of the included studies.

Recommendation for treatment of and contact

prophylaxis against whooping cough

This systematic review of RCTs examining the treatment of whooping cough has found that antibiotic treatment is effective in eliminating *B. pertussis* from the nasopharynx and thus rendering participants non-infectious, but does not alter the clinical course of the illness. Prophylaxis with antibiotic was significantly associated with side effects; it did not significantly improve clinical symptoms, prevent the development of culture positive *B. pertussis*, nor paroxysmal cough for more than two weeks, in contacts older than six months of age.

Information from other sources

Special precaution is needed when treating or providing prophylaxis for newborns because infantile hypertrophic pyloric stenosis (IHPS) in neonates has been reported following the use of erythromycin. In one case, pyloric stenosis developed in a breast fed infant whose mother took erythromycin (CDC 2000; Honein 1999; Stang 1986).

Although short-term treatment of azithromycin successfully eradicated *B. pertussis* from the nasopharynx (Bace 2002), it may affect carriage of *Streptococcus pneumoniae (S. pneumoniae)* in the nasopharynx. Leach (Leach 1997) reported in a prospective study that community based treatment with azithromycin may result in the appearance of azithromycin resistant strains of *S. pneumoniae* in the nasopharynx. No data is available regarding the effect of clarithromycin on *S. pneumoniae* nasopharyngeal carriage.

The results of this review suggest that tetracycline and chloramphenicol are also effective antibiotics for the clearance of *B. pertussis* from the nasopharynx but these drugs have a number of serious side effects. The American Academy of Pediatrics (AAP) does not recommend the use of tetracycline in children less than eight years old (Ray 1977), based on the fact that administration of tetracycline during tooth development (last half of pregnancy, infancy, and childhood to the age of eight years) may cause permanent discolouration of the teeth (AAP 1975). Tetracycline may also result in photosensitivity, hepatotoxicity, and is contraindicated in pregnancy and breast-feeding (Smilack 1999). The most serious side effect of chloramphenicol is aplastic anaemia; it increases the relative risk of this disorder by 13-fold (Wallerstein 1969). Gray baby syndrome is another potentially fatal adverse reaction to chloramphenicol, occurring mainly in neonates (Weiss 1960). Dose-related association between the use of chloramphenicol and the development of acute lymphocytic and non-lymphocytic leukaemias has also been reported (Shu 1987). With the availability of other effective antibiotics it seems unnecessary to use these antibiotics for treatment of whooping cough.

Roxithromycin is a very popular antibiotic in Australia and is frequently used as an alternative to erythromycin but this macrolide antibiotic has not been studied in whooping cough. In vitro studies show that roxithromycin is generally two- to four-fold less active than erythromycin against *B. pertussis* organisms (Kucers 1997). However, there are no clinical studies of the efficacy of this antibiotic in the treatment or prophylaxis of whooping cough.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotics for treatment of pertussis

The findings of this review suggest that administration of antibiotics for the treatment of whooping cough is effective in eliminating *B. pertussis* from patients with the disease to render them non-infectious but does not alter the subsequent clinical course of the illness. The effective regimens include:

three days of azithromycin (10 mg/kg as a single dose);

five days of azithromycin (10 mg/kg on the first day of treatment and 5 mg/kg once daily on the second day to fifth days of treatment);

seven days of clarithromycin (7.5 mg/kg/dose twice daily);

seven to 14 days of erythromycin (40 mg/kg/day in three divided doses);

fourteen days of erythromycin (60 mg/kg/day in three divided doses);

seven days of oxytetracycline (50 mg/kg/day in four divided doses); or

seven days of chloramphenicol (50 mg/kg/day in four divided doses).

The best regimens for microbiological clearance, with fewer side effects, are:

three days of azithromycin (10 mg/kg as a single dose);

five days of azithromycin (10 mg/kg on the first day of treatment and 5 mg/kg once daily on the second day to fifth days of treatment); or

seven days of clarithromycin (7.5 mg/kg/dose twice daily).

Seven days of trimethoprim/sulfamethoxazole (20 mg trimethoprim with 100 mg sulfamethoxazole per dose, twice daily, for children under six months of age; double this dose for older children) appears to be effective in eradicating *B. pertussis* from the nasopharynx and may serve as an alternative antibiotic treatment for patients who can not tolerate a macrolide. The use of oxytetracycline or chloramphenicol is not recommended in the treatment of whooping cough because of their potential side effects, especially in children, and because of the availability of other effective and safer antibiotics.

Antibiotics for prophylaxis against whooping cough

There is insufficient evidence to determine the benefit of prophylactic treatment of pertussis contacts. Prophylaxis with antibiotic was significantly associated with side effects and did not significantly improve clinical symptoms, whoop, paroxysmal cough, number of cases who develop culture positive *B. pertussis* or paroxysmal cough for more than two weeks in contacts older than six months of age. Due to the high risk of morbidity and mortality in infants less than six months of age who are incompletely immunised, contact prophylaxis is recommended for families who have an infant less than six months of age. The recommended antibiotics and dosages for contact prophylaxis are the same as those recommended in the treatment of whooping cough.

Implications for research

General

We would encourage authors of future papers to follow the revised CONSORT guidelines (Consolidated Standards of Reporting Trials), which have been adopted by several leading journals and can be found on the Internet (www.consort-statement.org). CONSORT comprises a checklist and flow diagram to help improve the quality of reports of randomised controlled trials. It offers a standard way for researchers to report trials. The checklist includes descriptions of the randomisation procedure (allocation concealment), the mechanisms of blinding, number of people lost during the follow up, and some details about the analysis made.

Specific

Given the growing importance of pertussis in infants and adolescents, there seems to be an urgent need for larger randomised controlled trials for treatment of and prophylaxis against whooping cough. Future trials should incorporate simple and clear indices for clinical outcomes (such as clinical cure, duration of symptoms, severity and improvement), microbiological eradication, microbiological relapse, side effects, compliance, and attack rate (in prophylaxis trials). Further therapeutic studies of appropriate size are needed based on age, immunological status, duration of disease and cost/benefit ratios from both patients and contacts. Special emphasis on the effectiveness of antibiotics, compared to placebo, for treatment of or prophylaxis against whooping cough in vaccinated and unvaccinated participants is needed. Short-duration trials with newer macrolides such as azithromycin, clarithromycin and perhaps roxithromycin are desirable.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adcock 1972

Methods	Randomised single blinded controlled trial Method of randomisation: not stated Allocation concealment: Unclear Blinding of intervention: Unclear Blinding of outcome measure: Yes Complete follow up: no
Participants	88 children with isolated B. pertussis from nasopharynx or with a typical 'whooping' cough and a relative and absolute lymphocytosis No account was taken of previous vaccination history Exclusion criteria: not stated Tetracycline group N = 44 (55% male); 0 to 4 years: 22 males, 19 females; 5 to 10 years: 2 males, 1 female Trimethoprim/sulphamethoxasole group N = 44 (36% male); 0 to 4 years: 15 males, 24 females; 5 to 10 years: 1 male, 4 females
Interventions	Treatment group: received tetracycline: children under 2 years old were given 62.5 mg tetracycline 6 hourly and older children 125 mg 6 hourly for one week Control group: received trimethoprim/sulphamethoxazole: children under 6 months old were given 20 mg trimethoprim with 100 mg sulphamethoxazole twice daily for one week; older children received double this dose All children received phenobarbitone 15 mg t.d.s until vomiting and spasmodic cough had ceased, and were also given a simple linctus for use as required
Outcomes	Primary outcome: microbiological eradication of B. pertussis Secondary outcome: clinical improvement after one week of treatment
Notes	Children were treated at home by their carers who were asked to bring the children back after one week for assessment to the same doctor who saw the children at first attendance. This assessment was based on a full clinical examination, detailed history concerning cough, sleep pattern, vomiting, feeding and general behaviour. Pernasal swabs were taken on first and second attendance Out of 88 patients only 66 returned for follow up. Missed (drop out) patients = 22 (25%). Immunisation status: not stated
Risk of bias	

Adcock 1972 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bace 2002

Methods	Randomised controlled trial Method of randomisation: not stated Allocation concealment: Unclear Blinding of intervention: no Blinding of outcome measure: no Complete follow up: no
Participants	Inclusion criteria: hospitalised children aged 0 to 18 months with symptoms and signs of pertussis were enrolled in the study 122 children; 84 (69%) had pertussis confirmed by bacteriological or serological findings or both, and 38 (31%) had pertussis syndrome caused by other pathogens
Interventions	Treatment group received single dose of 10 mg/kg azithromycin for 3 days Controlled group received 50 mg/kg of erythromycin three times daily for 14 days
Outcomes	Microbiological eradication Clinical scores and adverse reactions were also recorded
Notes	This is a conference abstract. Full article is not yet available. We tried to contact the authors but did not receive a reply Clinical examination were scheduled at baseline and 72 hours, 7, 14, and 21 days after the start of the therapy. Immunisation status: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bass 1969

Methods	Randomised controlled trial Method of randomisation: not stated Allocation concealment: unclear Blinding of Intervention: no Blinding of outcome measure: no Complete follow up: yes
Participants	Inclusion criteria: hospitalised children with clinical pertussis and initial nasopharyngeal swap positive for B. pertussis both by culture and by fluorescent microscopy. Patients who had received previous antimicrobial therapy or those who had previous immunisation against pertussis were not excluded Exclusion criteria: those whose cultures subsequently were negative were withdrawn
Interventions	Children were assigned to 1 of 5 study groups, each group consist of 10 patients. Group 1 received no antimicrobial agents (control group). Group 2 received ampicillin 100 mg/kg/day. Group 3 received oxytetracyclin 50 mg/kg/day . Group 4 received chloramphenicol 50 mg/kg/day. Group 5 received erythromycin (estolate) 50 mg/kg/day. All antimicrobial drugs were administered in 4 divided doses at 6 hourly interval for at least 7 days, by oral route except in those who were comatose or with severe vomiting in which parenteral route were used Pertussis hyperimmune globulin was administered to some of the patients according to physician's preference
Outcomes	Microbiological eradication, clinical improvement, duration of the illness
Notes	The second part of the study regarding antimicrobial prophylaxis against pertussis was excluded since it was not a randomised controlled trial Immunisation status: only 9 (19%) of the 50 children studied had received any previous injection of pertussis vaccine. Only 2 children out of 50 studies had previously received 3 DTP injections and their illness appeared milder than non-immunised children

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cruickshank 1953

Methods	Randomised double blinded controlled trial Method of randomisation: randomly determined sequence. Allocation concealment: unclear Blinding of intervention: yes Blinding of outcome measure: yes. Double blinded trial Complete follow up: no

Cruickshank 1953 (*Continued*)

Participants	Inclusion criteria: children 0 to 5 years of age admitted to the 8 hospitals with uncomplicated clinical pertussis within 21 days after the onset of the earliest symptoms were included in the study Exclusion criteria: children with complicated pertussis
Interventions	Treatment group: Group 1: Aureomycin (Chlortetracycline) 0 to 11 months: 1 g daily, 12 to 35 months: 1.5 g and children aged 36 to 59 months 2 g daily in 2 divided doses daily for 7 days Second group: Chloramphenicol doses are given in similar doses as in Aureomycin for 7 days Control group: children were given a mixture of lactose and quinine
Outcomes	1. Mortality rate 2. Respiratory complications 3. All side effects 4. Bacteriological eradication: can not be assessed for each group 5. Clinical assessment can not be assessment for each group
Notes	On admission the patients were divided by sex and placed in one of 3 age groups 0 to 11 months, 12 to 35 months, and 36 to 59 months, then they were allocated to one of the 3 treatment groups by a randomly determined sequence. Immunisation status: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Degn 1981

Methods	Randomised double blinded controlled trial Method of randomisation: sequence of random numbers Allocation concealment: unclear Blinding of intervention: yes Blinding of outcome measure: yes Complete follow up: no
Participants	Inclusion criteria: Children 1 to 12 months old with a body weight above 4 kg, and with clinical pertussis or B. pertussis culture positive or both Exclusion criteria: children with another infectious disease, with bronchial asthma, cerebrally injured patients, with radiologically proven lung infiltration and patients previously exhibiting allergic manifestations to treatment of sulpha-preparations or chloramphenicol
Interventions	Treatment group: sulfadiazine/trimethoprim 30 mg/6 mg per kg per day in 4 divided dose for 6 days followed by observational period of further 6 days Control group: Chloramphenicol 50 mg/kg /day in 4 divided doses for 6 days

Degn 1981 (*Continued*)

Outcomes	Microbiological eradication Median number of paroxsymal coughs per day
Notes	The article was in Danish language and was translated by The Cochrane Library. Immunisation status: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Grob 1981

Methods	Randomised single blinded placebo controlled study Method of randomisation: not stated Allocation concealment: unclear Blinding of intervention: yes Blinding of outcome measure: unclear Complete follow up: no
Participants	Inclusion criteria: symptoms-free family contacts containing a child with B. pertussis culture positive Exclusion criteria: If none of the swabs taken from the children (including the index case) grew B. pertussis the contacts were not included Any contact showing early signs of whooping cough was excluded This study was in general practice, and children were living in good social circumstances in South-West Thames region in the UK The children were visited frequently by a nurse who recorded progress and took swabs
Interventions	Treatment group: erythromycin (ethylsuccinate) 50 mg/kg/day in 4 divided doses. The dosage schedule was: 125 mg before meals 4 times a day for contacts under 2 years. 250 mg before meals 4 times a day for those aged 2 to 8 years both for 14 days. Controlled group: identical placebo syrup
Outcomes	Frequency of whooping-cough in vaccinated and non-vaccinated contacts. Microbiological eradication result is unclear
Notes	This is a prophylactic erythromycin placebo controlled study in whooping cough contacts. Immunisation status: 60 (66%) children were vaccinated out of 91 children included in the trial. No vaccinated child had whooping cough

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Halperin 1997

Methods	Open randomised controlled trial Method of randomisation: table of random numbers Allocation concealment: unclear Blinding of intervention: no Blinding of outcome measure: no Complete follow up: no
Participants	Inclusion criteria: children and their households contacts with culture-positive pertussis Exclusion criteria: allergy to erythromycin, pre-existing liver disease, or pregnancy Immunization status: % >= 3 doses in treatment group = 88.1%, control group = 87.8
Interventions	Treatment group: erythromycin estolate 40 mg/kg/day in 3 divided doses with a maximum of 1000 mg /day for 7 days Control group: erythromycin estolate 40 mg/kg/day in 3 divided doses with a maximum of 1000 mg/day for 14 days
Outcomes	Microbiological eradication, clinical assessments, adverse reactions and compliance
Notes	Immunization status: % >= 3 doses in treatment group = 88.1%, control group = 87.8%

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Halperin 1999

Methods	Randomised double blinded placebo controlled study Method of randomisation: Eligible households members were allocated by the pharmacy department by using a table of random numbers Allocation concealment: adequate Blinding of intervention: yes Blinding of outcome measure: yes Complete follow up: yes
Participants	Inclusion criteria: All household contacts of 152 children with culture positive pertussis who provided consent Exclusion criteria: pregnancy, age < 6 months, had history of culture positive pertussis, already receiving erythromycin-containing antibiotics, erythromycin allergy or liver disease
Interventions	Treatment group: erythromycin estolate 40 mg/kg/day in 3 divided doses, maximum dose 1 g/day for 10 days Controlled group: identical placebo for 10 days

Halperin 1999 (*Continued*)

Outcomes	Microbiological eradication, clinical assessments, adverse reactions and compliance. Immunisation status: Not stated
Notes	This is prophylactic erythromycin placebo controlled study in whooping cough households contacts The unit of randomisation was the household, therefore all household members were allocated to the same treatment group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Henry 1981

Methods	Randomised single blinded (patient) controlled trial Method of randomisation: pharmacy randomly allocated patients according to random number book Allocation concealment: adequate Blinding of intervention: no Blinding of outcome measure: yes Complete follow up: no
Participants	Children with whooping cough and B. pertussis culture positive Children who had received antibiotics other than erythromycin or co-trimoxazole for their illness before their admission and children who had been immunised were included Exclusion criteria: Those who received antibiotics by the parenteral route or fluids by the intravenous route
Interventions	Treatment group: co-trimoxazole 6 mg/kg/day of trimethoprim in 2 divided doses orally for 7 days Controlled group: erythromycin stearate 40 mg/kg/day in 4 divided doses orally for 7 days
Outcomes	Microbiological eradication, diarrhoea
Notes	Author supplied us with information regarding the article's methodology through personal contact. Immunisation status: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hoppe 1992

Methods	Open randomised multicentre controlled trial Method of randomisation: computer generated list of numbers Allocation concealment : unclear Blinding of intervention: no Blinding of outcome measure: no Complete follow up: yes
Participants	Inclusion criteria: Ambulatory children with whooping cough and B. pertussis culture positive Exclusion criteria: antimicrobial treatment during the 3 days before enrolment of patients, hypersensitivity to macrolide antibiotics, preexisting liver or renal disease, simultaneous treatment of theophyllin or ergotamin, or body weight > 27.5 kg The pertussis vaccination status was similar in both study groups. 115 patients (60.5%) had not been vaccinated at all (EST, 56 patients (60.2%); ETH, 59 patients (60.8))
Interventions	Treatment group: erythromycin estolate (EST) 40 mg/kg/day in 2 divided doses orally taken during meal for 14 days Controlled group: erythromycin ethylsuccinate (ETH) 60 mg/kg/day in 3 divided doses orally taken during meals for 14 days
Outcomes	Microbiological eradication, clinical assessment, decrease frequency and severity of cough, improved or cured general condition, adverse reactions, and patients' compliance measured by antimicrobial activity in the urine
Notes	Immunisation status: the pertussis vaccination status was similar in both study groups. 115 patients (60.5%) had not been vaccinated at all (EST, 56 patient (60.2%); ETH, 59 patients (60.8))

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Langley 2004

Methods	Randomised controlled trial Method of randomisation: computer generated randomisation list Allocation sequence: concealed Group assignment was not blinded after randomisation
Participants	Inclusion criteria: children aged 6 months to 16 years and had either culture proven B. pertussis infection or cough illness suspected by a physician to be pertussis. Exclusion criteria: children with known allergy to any macrolide, immunodeficiency, had hepatic, renal, cardiovascular, hematologic disease or chronic lung disease, had concomitant use of theophylline, phenytion, digitalis ... etc.

Langley 2004 (*Continued*)

Interventions	Treatment group: azithromycin 10 mg/kg (maximum: 500 mg) by mouth on first day of treatment and 5 mg/kg (maximum daily dose: 250 mg) once daily on the second to fifth days of treatment. Controlled group: 3 doses of erythromycin estolate (40 mg/kg/day: maximum 1 g) by mouth for 10 days
Outcomes	Microbiological eradication, bacteriological relapse, compliance, presence of clinical symptoms, treatment-associated adverse events
Notes	Immunisation status: mean previous number of pertussis vaccine doses received was 4.4 and 4.1 for erythromycin and azithromycin treatment group respectively

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Lebel 2001

Methods	Randomised single blinded (investigator) controlled trial Method of randomisation: computer generated random list Allocation concealment: adequate Blinding of intervention: yes Blinding of outcome measure: yes Complete follow up: yes
Participants	Inclusion criteria: children aged 1 month to 16 years with clinical pertussis Exclusion criteria: the presence of a cough for 21 days or longer, treatment with any antibiotic with known activity against B. pertussis, concomitant therapy with terfenadine, astemizole, or zidovudine, concomitant therapy with theophylline, digitalis glycoside, ergotamine, carbamazepine, phenytoin, warfarin therapy, known allergy to macrolide antibiotics, presence of a disease requiring the use of steroid medications, presence of underlying cardiac, hepatic, bronchopulmonary, renal, immunodeficiency, malabsorption disorder, or pregnancy Immunisation status: pertussis vaccination: (%) in treatment group = 89, control group = 90
Interventions	Treatment group: clarithromycin granules for suspension 7.5 mg/kg/dose twice daily (maximum dose 500 mg twice daily) orally for 7 days Controlled group: erythromycin estolate 13.3 mg/kg/dose (maximum dose, 333 mg three times a day) orally for 14 days
Outcomes	Microbiological eradication, clinical cure, adverse reactions, complications (otitis media), and compliance to medications

Lebel 2001 (*Continued*)

Notes	The study populations considered in the analysis: 1. The per protocol population included those patients who had a positive culture for B. pertussis at baseline and a. received study drug for a minimum 3 days b. had a post-treatment culture and clinical assessment c. did not take any interfering concomitant antimicrobial therapy, and d. did not violate the study protocol Immunisation status: pertussis vaccination treatment group = 89%, control group = 90%

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Strangert 1969

Methods	Quasi-randomised controlled trial Method of randomisation: alternation of patients (each second child admitted with whooping-cough was treated with ampicillin) Allocation concealment: inadequate Blinding of intervention: no Blinding of outcome measure: no Complete follow up: no
Participants	Inclusion criteria: children admitted with clinical pertussis Exclusion criteria: children who received chloramphenicol or ampicillin prior to their stay in hospital or were discharged before the course of therapy had been completed
Interventions	Treatment group: ampicillin 75 to 100 mg/kg/day divided in 4 doses for 6 days Controlled group: chloramphenicol 75 -100 mg/kg/day divided in 4 doses for 6 days Children under 6 months of age were also given immunoglobulin against whooping-cough each other day on altogether 3 occasions
Outcomes	Microbiological eradication, adverse reactions, complications (secondary infections)
Notes	This is quasi-randomised study for treatment of pertussis. Immunisation status: not stated

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

DTP: diphtheria-tetanus-pertussis
EST: erythromycin estolate
ETH: erythromycin ethylsuccinate
t.d.s: three times a day

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

Aoyama 1996	Non-randomised controlled trial with historical control patients
Bergquist 1987	Excluded as used salbutamol in the control group. Results showed fewer whoops and eradication of B. pertussis in erythromycin treated group (n = 17) compared to the salbutamol control group (n = 21)
Di Nola 1974	RCT excluded as used antibiotics in secondary respiratory infection in childhood pertussis
LaBoccetta 1952	Quasi-RCT with non-interpretable results for control group some of them received antibiotics and others received no antibiotics and results can not be separated
Spencely 1981	RCT excluded because of insufficient data
Torre 1984	RCT with non-interpretable results; large numbers of patients were missed for follow up (i.e. on day 15: only 5 out of 16 patients showed up in Josamycin group, and 6 out of 19 showed up in Erythromycin group for microbiological investigation
Trollfors 1978	Quasi-RCT. Poor quality study. Randomisation is inadequate. Randomised participants are combined with non randomised participants and can not be analysed separately. Results suggest amoxycillin is poorly effective

DATA AND ANALYSES

Comparison 1. Antibiotics for treatment of whooping cough

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Ampicillin (treatment) versus untreated control group, oxytetracycline, chloramphenicol or erythromycin	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.14, 65.90]
1.2 Aureomycin (treatment) versus chloramphenicol (control)	1	194	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
2 Complete remission (clinical cure)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)	1	189	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [1.16, 10.13]
3 Clinical improvement (better condition) after one week	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Trimethoprim/ sulfamethoxazole (treatment) versus tetracycline (control)	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.70, 1.83]
4 Decreased frequency of cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.90, 1.24]
5 Presence of any sign or symptoms of whooping cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
6 Microbiological eradication	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Ampicillin (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Oxytetracycline (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	17.01 [1.11, 259.87]
6.3 Chloramphenicol (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	15.01 [0.97, 231.84]

6.4 Erythromycin (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	19.01 [1.25, 287.92]
6.5 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.95, 1.03]
6.6 Erythromycin esterate for 7 days (treatment) versus co-trimoxazole for 7 days (control)	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.65, 1.90]
6.7 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	153	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
6.8 Azithromycin (treatment) for 3 days versus erythromycin for 14 days (control)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.16]
6.9 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)	1	106	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.10 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.17]
6.11 Trimethoprim/ sulphamethoxazole for 7 days (treatment) versus tetracycline (control) for 7 days	1	66	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.12 Sulfadiazine/ trimethoprim for 6 days (treatment) versus chloramphenicol for 6 days (control)	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.67, 1.26]
6.13 Ampicillin (treatment) versus chloramphenicol (control)	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.03]
7 Bacteriological relapse	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Ampicillin (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.26, 3.81]
7.2 Oxytetracycline (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.69]
7.3 Chloramphenicol (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.26, 3.81]
7.4 Erythromycin (treatment) versus untreated group (control)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.69]

7.5 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	155	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.14, 83.44]
7.6 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Respiratory complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Aureomycin (treatment) versus chloramphenicol (control)	1	194	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.47, 4.35]
9 Complications (otitis media)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	153	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.36]
10 All side effects	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.12]
10.2 Azithromycin (treatment) for 3 days versus erythromycin for 14 days (control)	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.19, 0.75]
10.3 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	153	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.53, 0.97]
10.4 Ampicillin for 6 days (treatment) versus chloramphenicol for 6 days (control)	1	148	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.94, 3.48]
10.5 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.35, 1.46]
10.6 Aureomycin (chlortetracycline) (treatment) versus chloramphenicol (control)	1	194	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.63, 2.58]
11 Gastro-intestinal system side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	153	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.47, 1.08]
11.2 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)	1	477	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.34, 0.62]
12 Side effects (diarrhoea)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

12.1 Erythromycin sterate for 7 days (treatment) versus co-trimoxazole for 7 days (control)	1	22	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.25, 22.75]
13 Compliance (detected by antimicrobial activity in urine)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.69, 0.94]
14 Compliance (presented as number of children who took 100% of prescribed doses)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)	1	477	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.45, 1.85]
15 Compliance (presented as percentage of drugs taken)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	200	Mean Difference (IV, Fixed, 95% CI)	9.90 [5.34, 14.46]

Comparison 2. Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Presence of any sign or symptoms of whooping cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	168	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
2 Microbiological eradication	4	358	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]
3 Microbiological eradication	3	313	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.97, 1.05]
4 Bacteriological relapse	2	259	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.14, 83.44]
4.1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)	1	155	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.14, 83.44]
4.2 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)	1	104	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 All side effects	3	443	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.52, 0.83]
6 All side effects	2	321	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.93]

Comparison 3. Antibiotic for prophylaxis of whooping cough

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All (any) clinical symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.02]
2 Presence of all (any) cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.09]
3 Paroxysmal cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.31]
4 Frequency of whoop in contacts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.07]
5 Frequency of whooping cough in contacts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Erythromycin ethyl succinate (treatment) versus identical placebo (control)	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.29, 7.78]
6 Frequency of whooping cough in vaccinated contacts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Erythromycin ethyl succinate (treatment) versus identical placebo (control)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Frequency of whooping cough in unvaccinated contacts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Erythromycin ethyl succinate (treatment) versus identical placebo (control)	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.24, 5.08]
8 Culture positive after prophylaxis in contacts (attack rate post-prophylaxis)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.11, 1.54]
9 Culture positive or paroxysmal cough > 2 weeks after prophylaxis in contacts (attack rate post-prophylaxis)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	256	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.29, 2.24]
10 All (any) side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

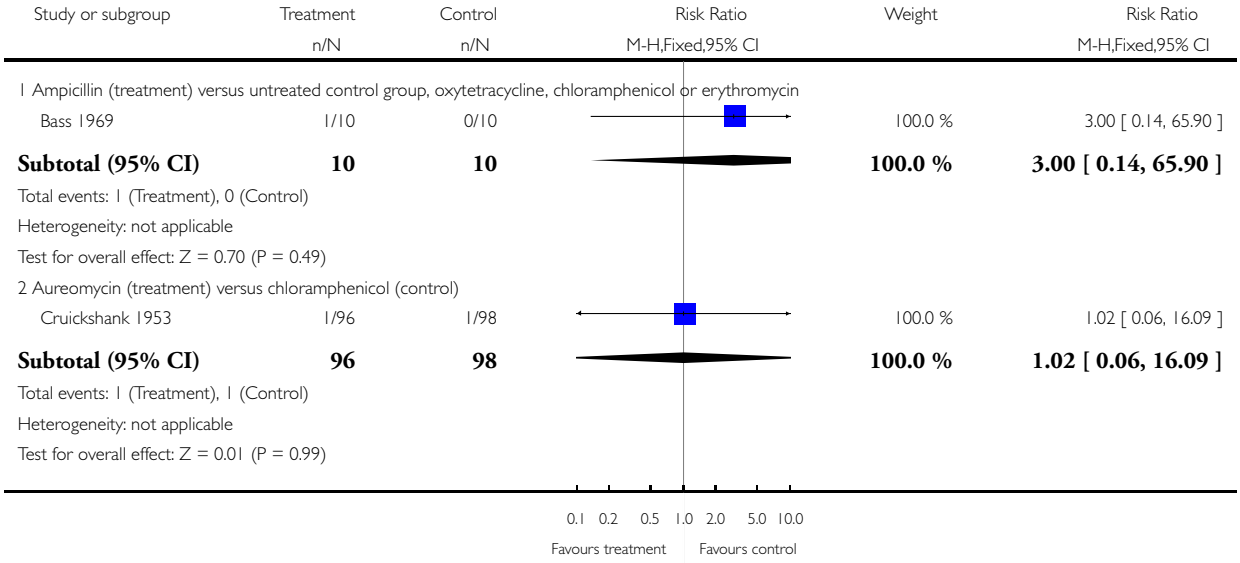
10.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	310	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.43, 3.31]
11 Compliance (> 90% of doses)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Erythromycin estolate (treatment) versus identical placebo (control)	1	310	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 1.00]

Analysis 1.1. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 1 Mortality.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

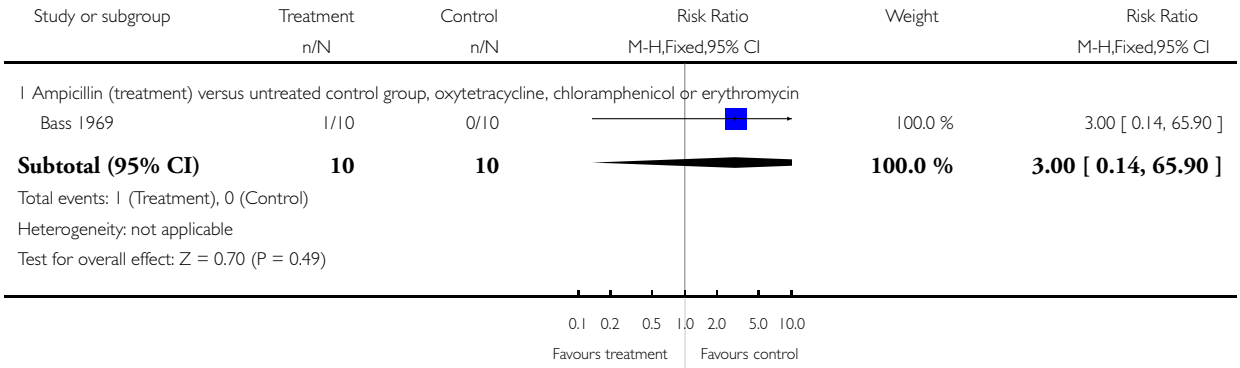
Outcome: 1 Mortality



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

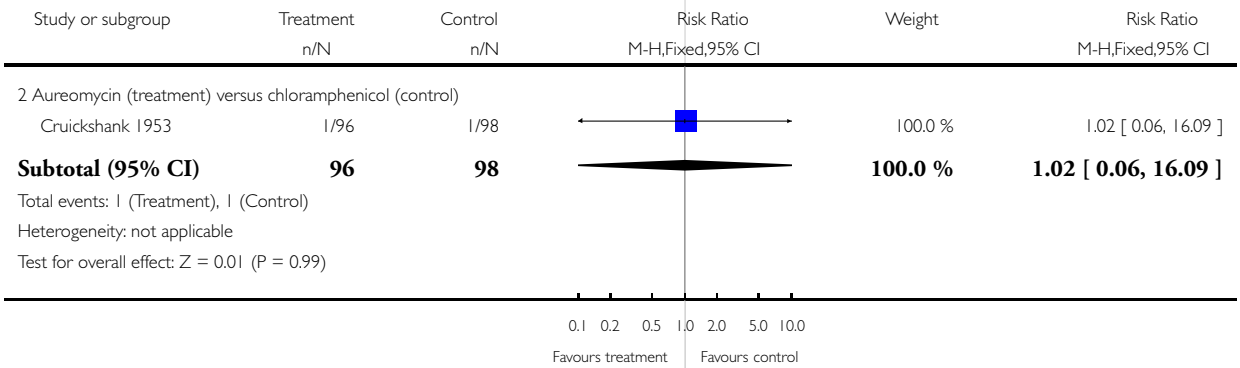
Outcome: 1 Mortality



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 1 Mortality

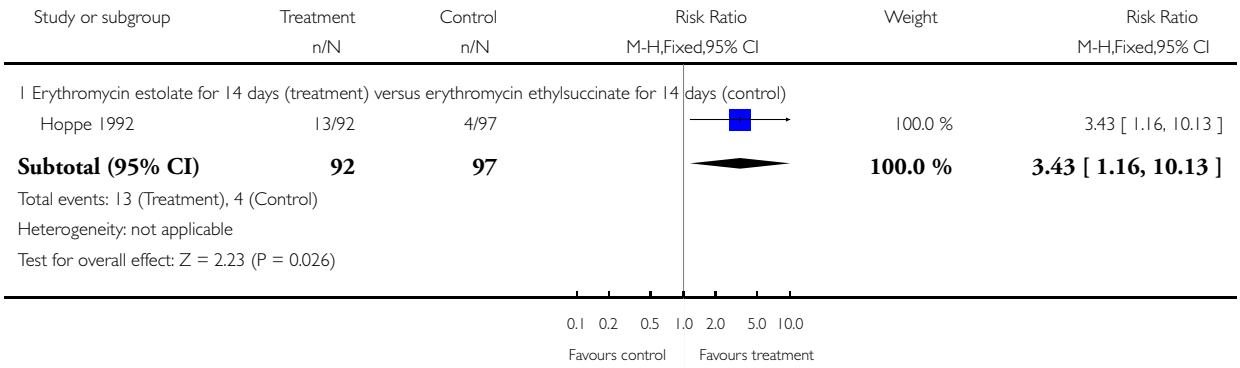


Analysis 1.2. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 2 Complete remission (clinical cure).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

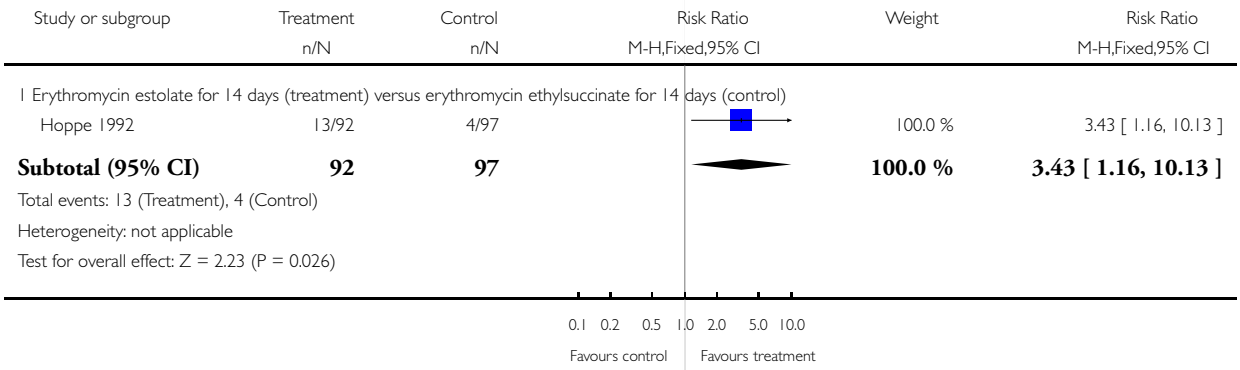
Outcome: 2 Complete remission (clinical cure)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 2 Complete remission (clinical cure)

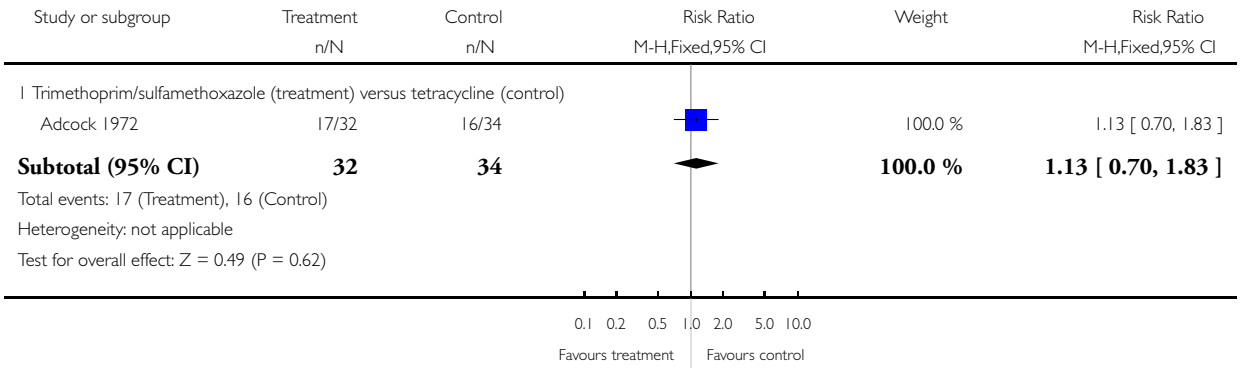


Analysis 1.3. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 3 Clinical improvement (better condition) after one week.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

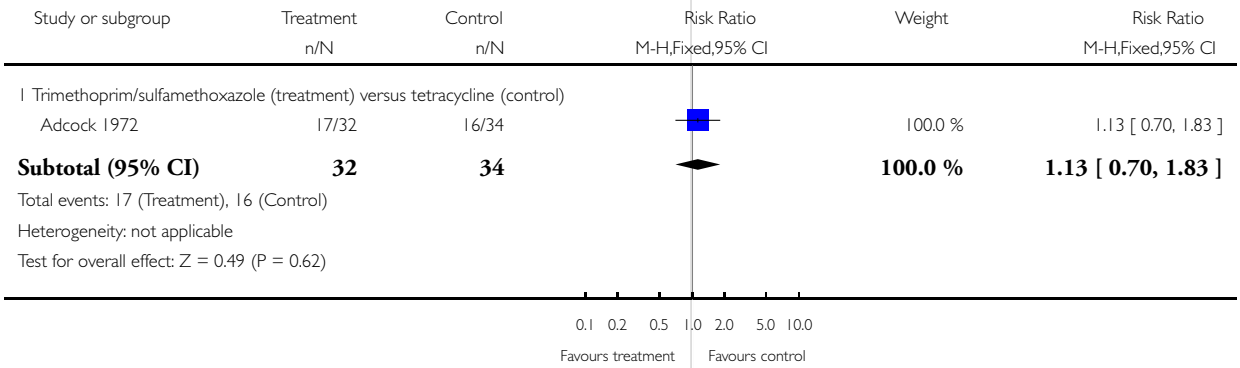
Outcome: 3 Clinical improvement (better condition) after one week



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 3 Clinical improvement (better condition) after one week

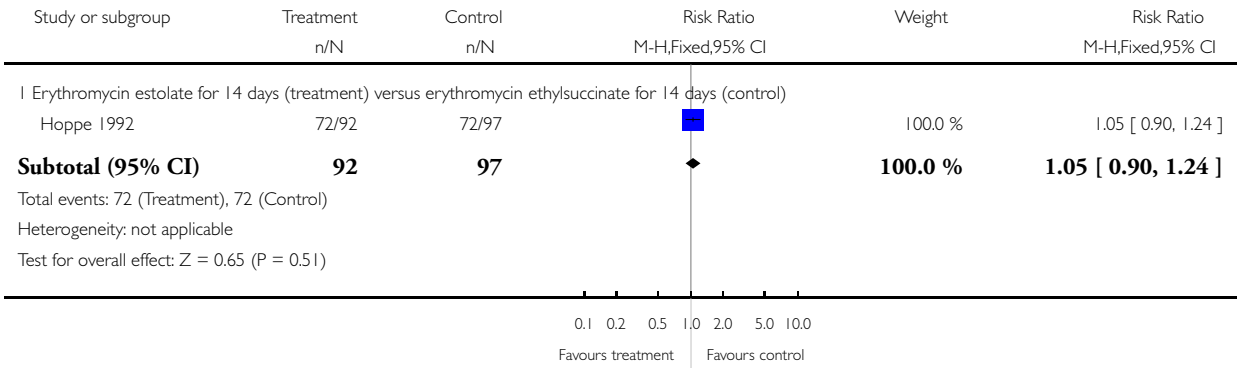


Analysis 1.4. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 4 Decreased frequency of cough.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

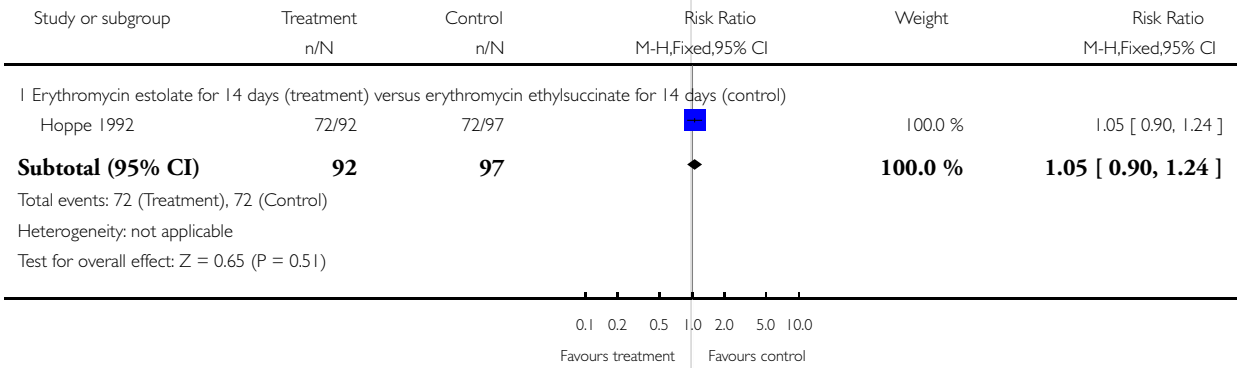
Outcome: 4 Decreased frequency of cough



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 4 Decreased frequency of cough

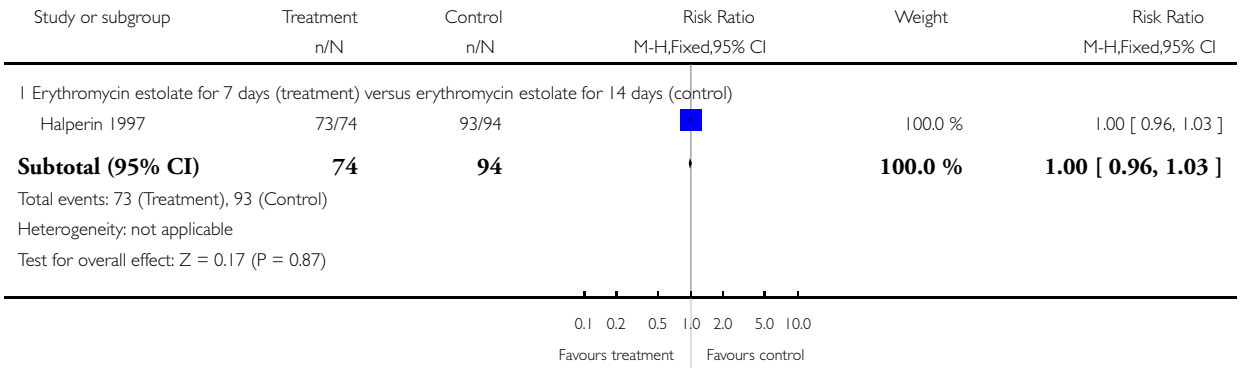


Analysis 1.5. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 5 Presence of any sign or symptoms of whooping cough.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

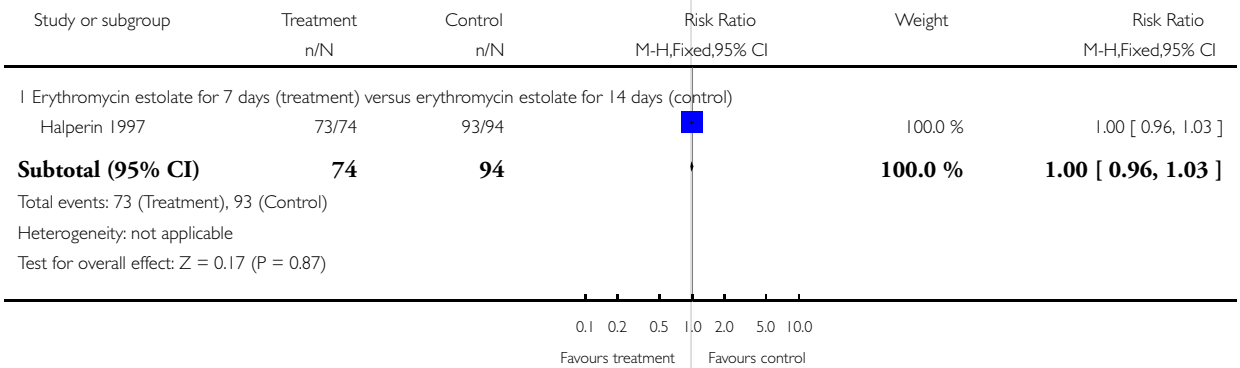
Outcome: 5 Presence of any sign or symptoms of whooping cough



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 5 Presence of any sign or symptoms of whooping cough



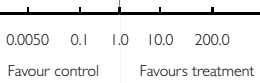
Analysis 1.6. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 6 Microbiological eradication.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Ampicillin (treatment) versus untreated group (control)					
Bass 1969	0/10	0/10		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**10**	**10**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
2 Oxytetracycline (treatment) versus untreated group (control)					
Bass 1969	8/10	0/10		100.0 %	17.00 [1.11, 259.87]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**17.00 [1.11, 259.87]**
Total events: 8 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.042)					
3 Chloramphenicol (treatment) versus untreated group (control)					
Bass 1969	7/10	0/10		100.0 %	15.00 [0.97, 231.84]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**15.00 [0.97, 231.84]**
Total events: 7 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.053)					
4 Erythromycin (treatment) versus untreated group (control)					
Bass 1969	9/10	0/10		100.0 %	19.00 [1.25, 287.92]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**19.00 [1.25, 287.92]**
Total events: 9 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.12 (P = 0.034)					
5 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)					
Hoppe 1992	91/93	96/97		100.0 %	0.99 [0.95, 1.03]
Subtotal (95% CI)	**93**	**97**		**100.0 %**	**0.99 [0.95, 1.03]**
Total events: 91 (Treatment), 96 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
6 Erythromycin esterate for 7 days (treatment) versus co-trimoxazole for 7 days (control)					
Henry 1981	7/9	7/10		100.0 %	1.11 [0.65, 1.90]
Subtotal (95% CI)	**9**	**10**		**100.0 %**	**1.11 [0.65, 1.90]**



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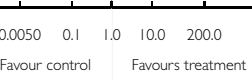
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 7 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					
7 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	68/69	83/84		100.0 %	1.00 [0.96, 1.03]
Subtotal (95% CI)	**69**	**84**		**100.0 %**	**1.00 [0.96, 1.03]**
Total events: 68 (Treatment), 83 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
8 Azithromycin (treatment) for 3 days versus erythromycin for 14 days (control)					
Bace 2002	20/20	24/25		100.0 %	1.04 [0.92, 1.16]
Subtotal (95% CI)	**20**	**25**		**100.0 %**	**1.04 [0.92, 1.16]**
Total events: 20 (Treatment), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
9 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	53/53	53/53		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**53**	**53**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 53 (Treatment), 53 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
10 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Lebel 2001	31/31	22/23		100.0 %	1.05 [0.94, 1.17]
Subtotal (95% CI)	**31**	**23**		**100.0 %**	**1.05 [0.94, 1.17]**
Total events: 31 (Treatment), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
11 Trimethoprim/sulphamethoxazole for 7 days (treatment) versus tetracycline (control) for 7 days					
Adcock 1972	32/32	34/34		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**32**	**34**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 32 (Treatment), 34 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
12 Sulfadiazine/trimethoprim for 6 days (treatment) versus chloramphenicol for 6 days (control)					
Degn 1981	15/19	12/14		100.0 %	0.92 [0.67, 1.26]
Subtotal (95% CI)	**19**	**14**		**100.0 %**	**0.92 [0.67, 1.26]**
Total events: 15 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					
13 Ampicillin (treatment) versus chloramphenicol (control)					
Strangert 1969	32/47	40/48		100.0 %	0.82 [0.65, 1.03]



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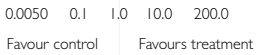
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**47**	**48**		**100.0 %**	**0.82 [0.65, 1.03]**
Total events: 32 (Treatment), 40 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.70 (P = 0.089)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

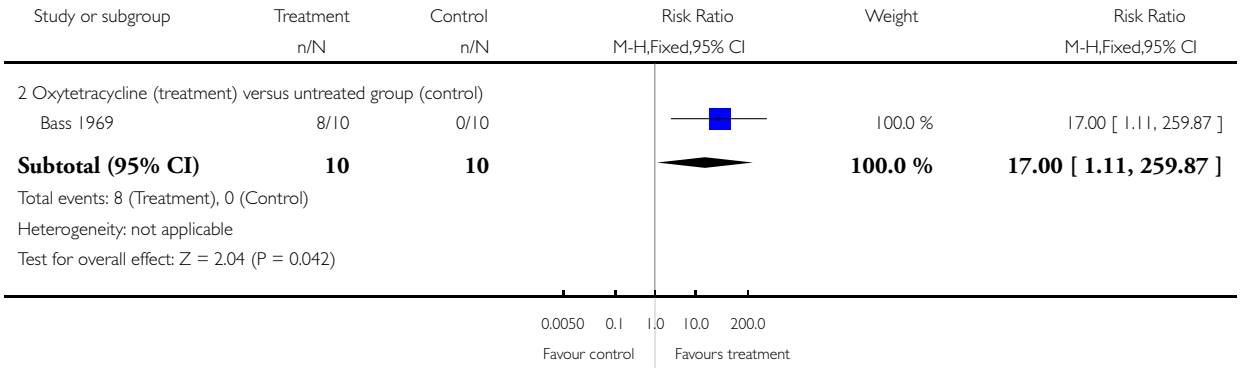
Outcome: 6 Microbiological eradication

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Ampicillin (treatment) versus untreated group (control)					
Bass 1969	0/10	0/10		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**10**	**10**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

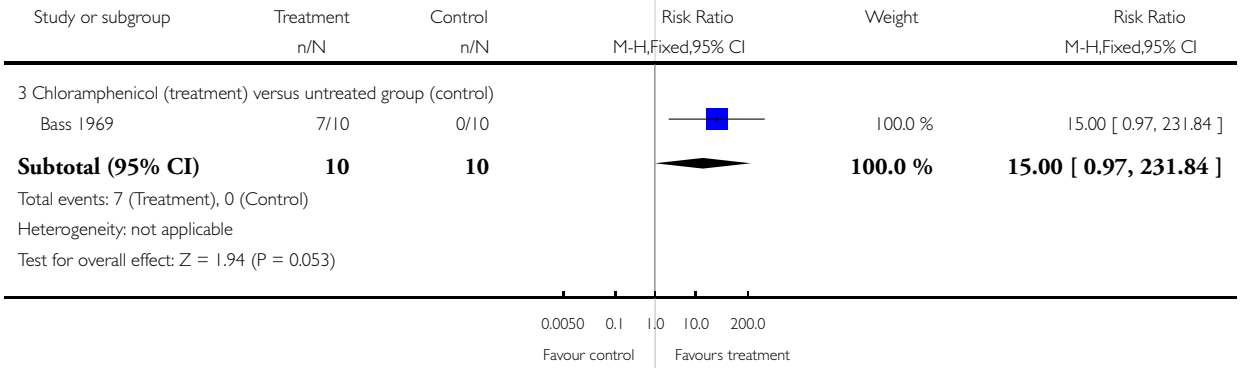
Outcome: 6 Microbiological eradication



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

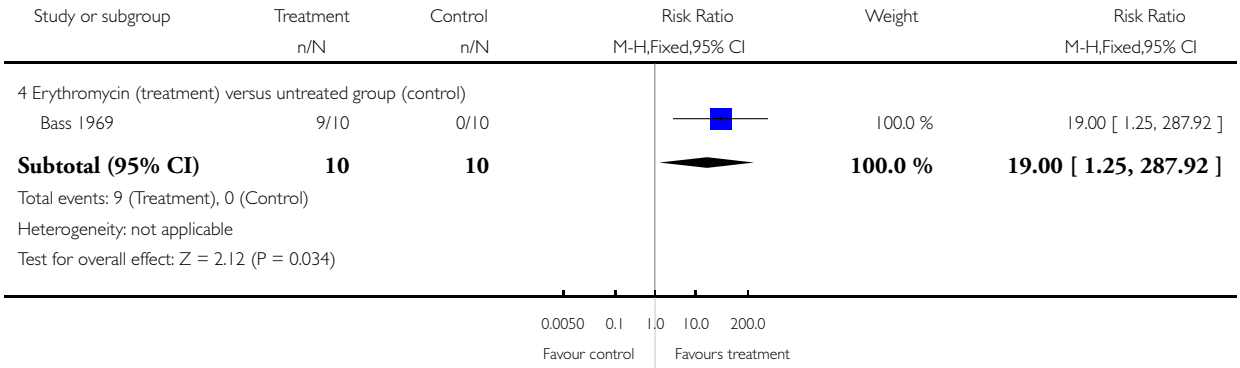
Outcome: 6 Microbiological eradication



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

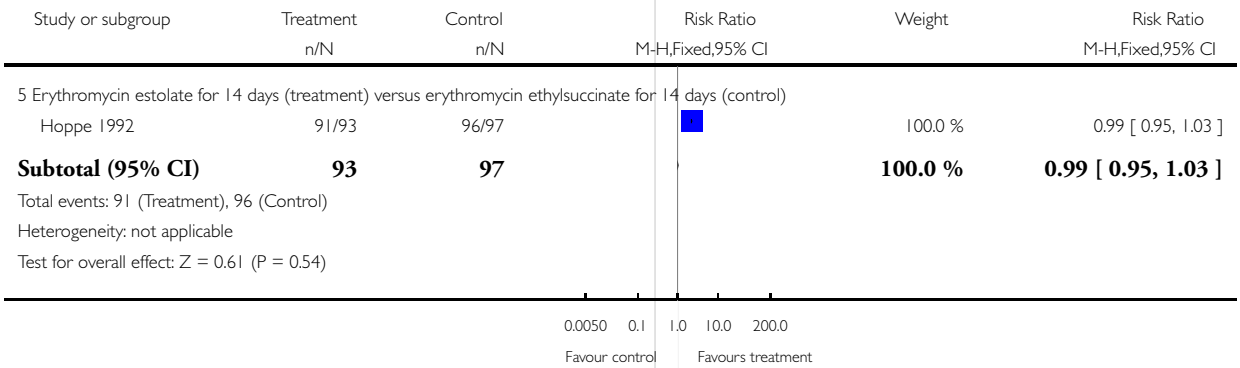
Outcome: 6 Microbiological eradication



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

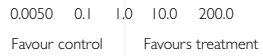


Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
6 Erythromycin esterate for 7 days (treatment) versus co-trimoxazole for 7 days (control)					
Henry 1981	7/9	7/10		100.0 %	1.11 [0.65, 1.90]
Subtotal (95% CI)	**9**	**10**		**100.0 %**	**1.11 [0.65, 1.90]**
Total events: 7 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.70)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

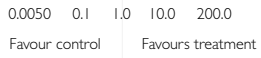
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
7 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	68/69	83/84		100.0 %	1.00 [0.96, 1.03]
Subtotal (95% CI)	**69**	**84**		**100.0 %**	**1.00 [0.96, 1.03]**
Total events: 68 (Treatment), 83 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
8 Azithromycin (treatment) for 3 days versus erythromycin for 14 days (control)					
Bace 2002	20/20	24/25		100.0 %	1.04 [0.92, 1.16]
Subtotal (95% CI)	**20**	**25**		**100.0 %**	**1.04 [0.92, 1.16]**
Total events: 20 (Treatment), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					

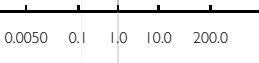


Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

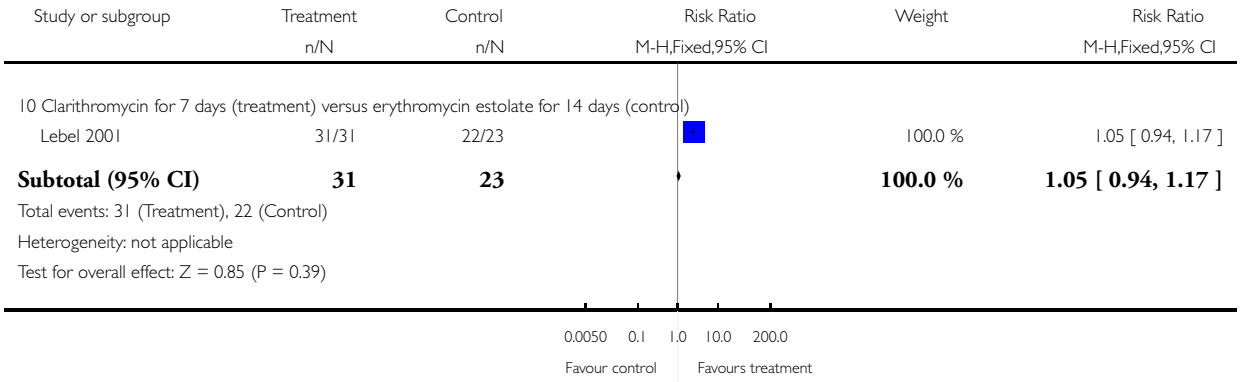
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
9 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	53/53	53/53		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**53**	**53**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 53 (Treatment), 53 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

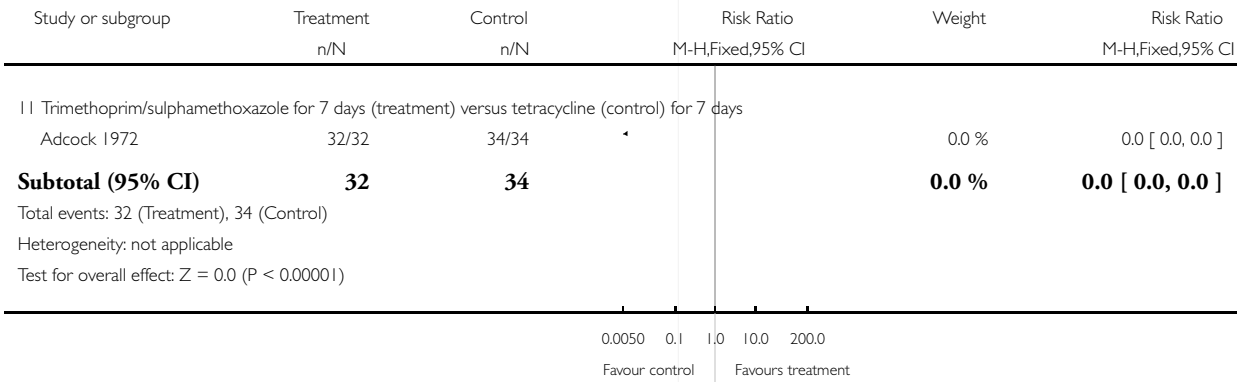
Outcome: 6 Microbiological eradication



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

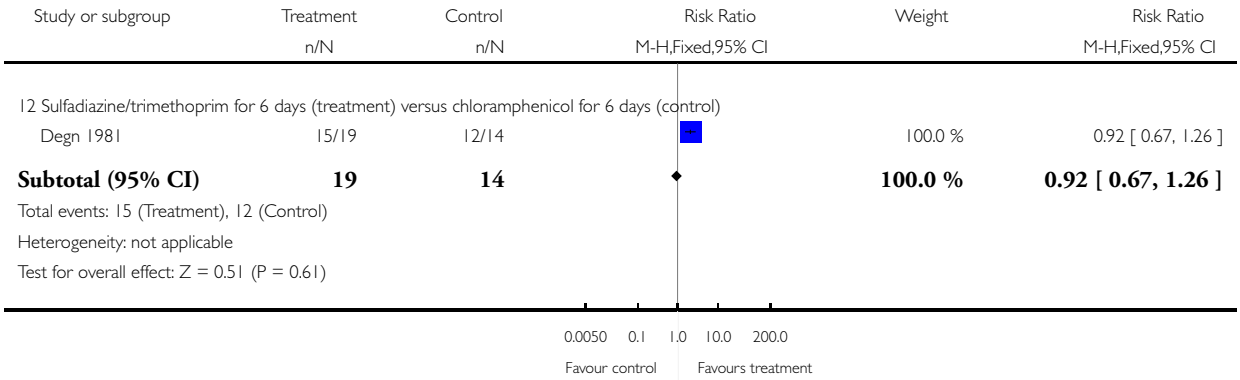
Outcome: 6 Microbiological eradication



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

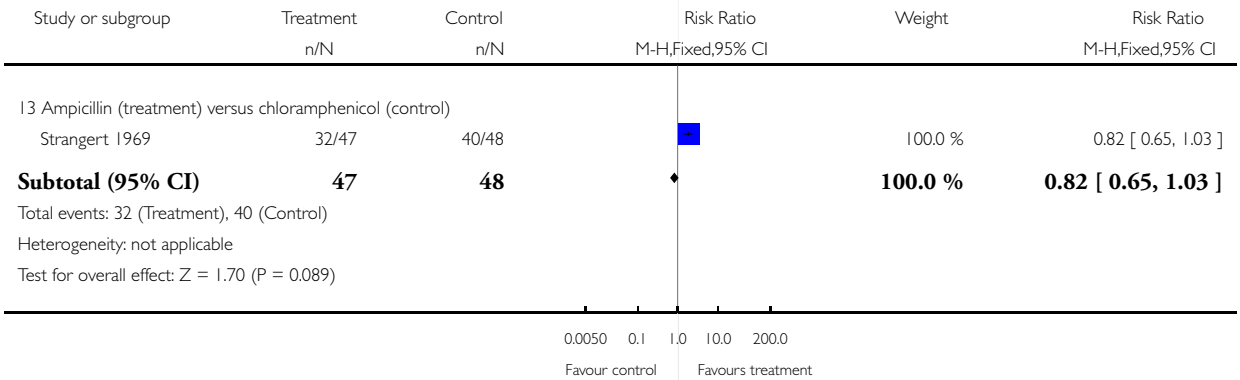
Outcome: 6 Microbiological eradication



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 6 Microbiological eradication

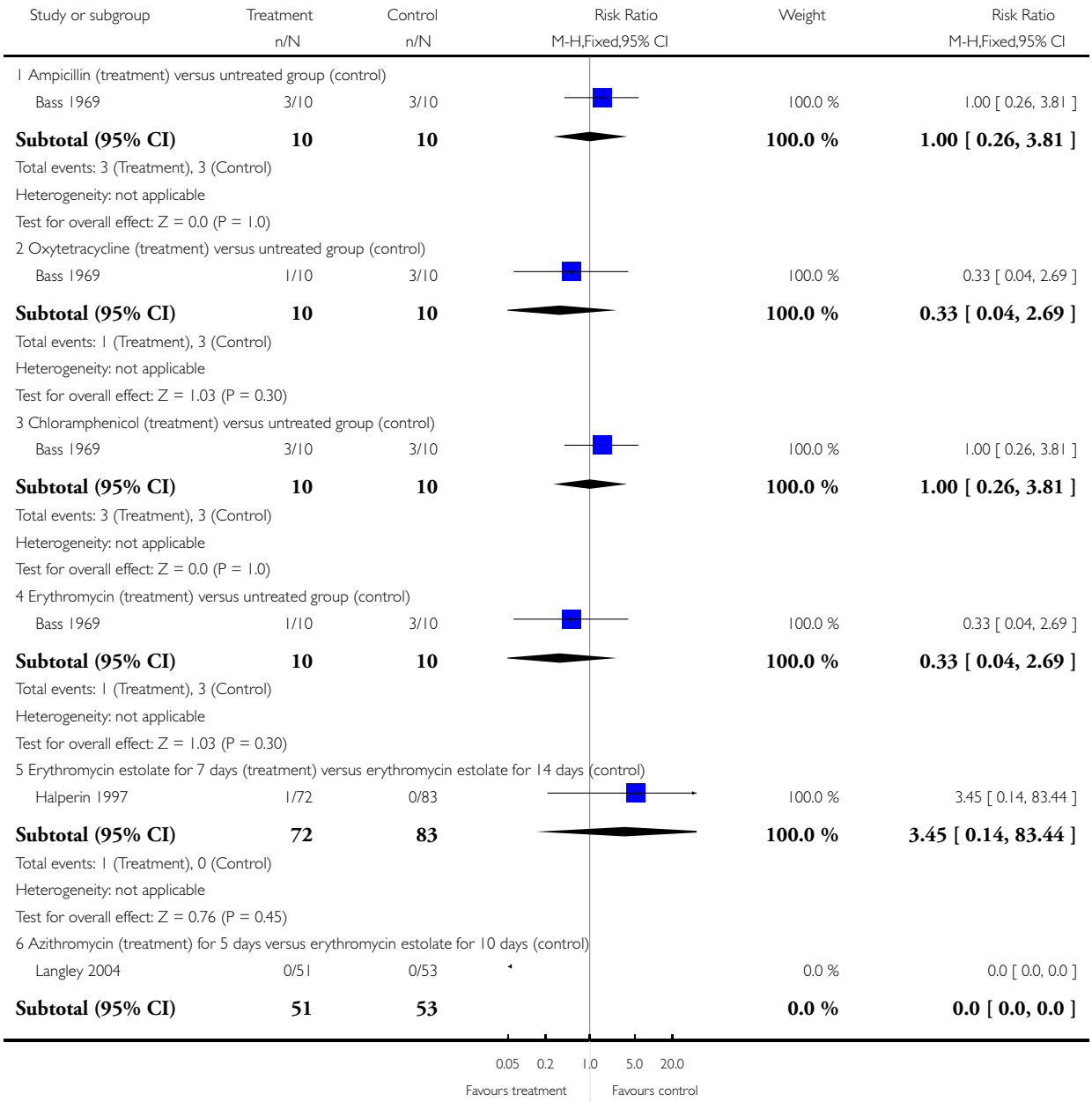


Analysis 1.7. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 7 Bacteriological relapse.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 7 Bacteriological relapse



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

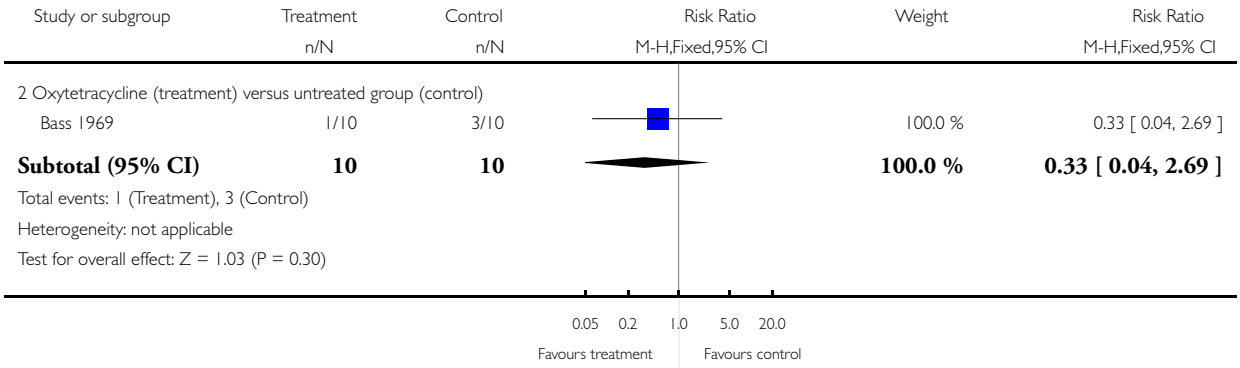
Outcome: 7 Bacteriological relapse

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Ampicillin (treatment) versus untreated group (control)					
Bass 1969	3/10	3/10		100.0 %	1.00 [0.26, 3.81]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**1.00 [0.26, 3.81]**
Total events: 3 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

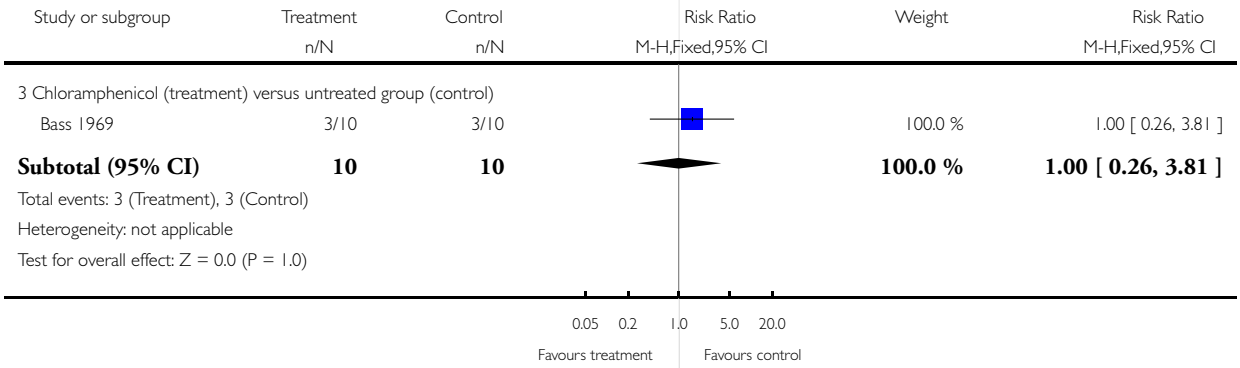
Outcome: 7 Bacteriological relapse



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

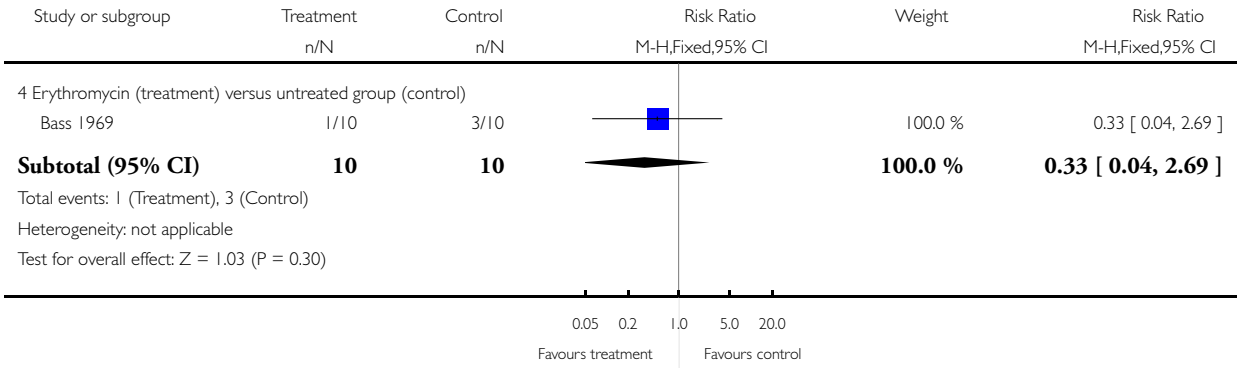
Outcome: 7 Bacteriological relapse



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

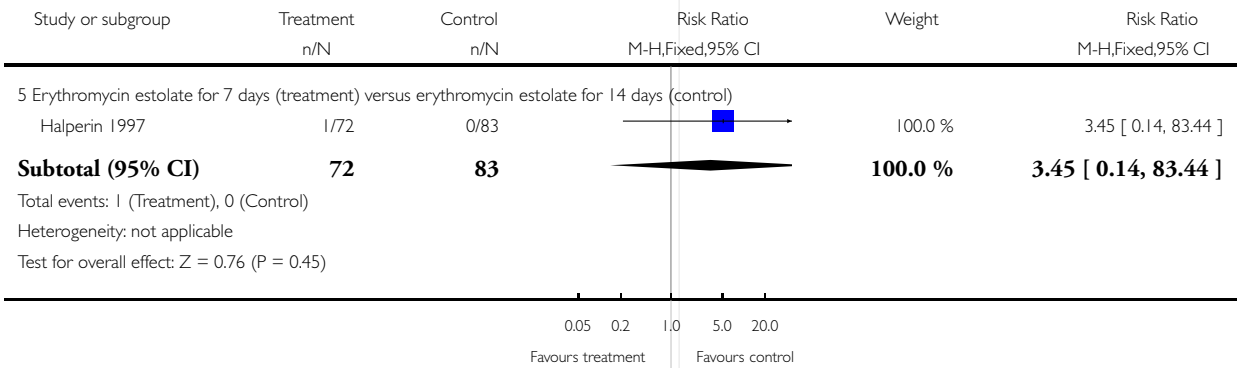
Outcome: 7 Bacteriological relapse



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 7 Bacteriological relapse



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 7 Bacteriological relapse

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
6 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	0/51	0/53		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**51**	**53**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

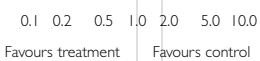
Analysis 1.8. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 8 Respiratory complications.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 8 Respiratory complications

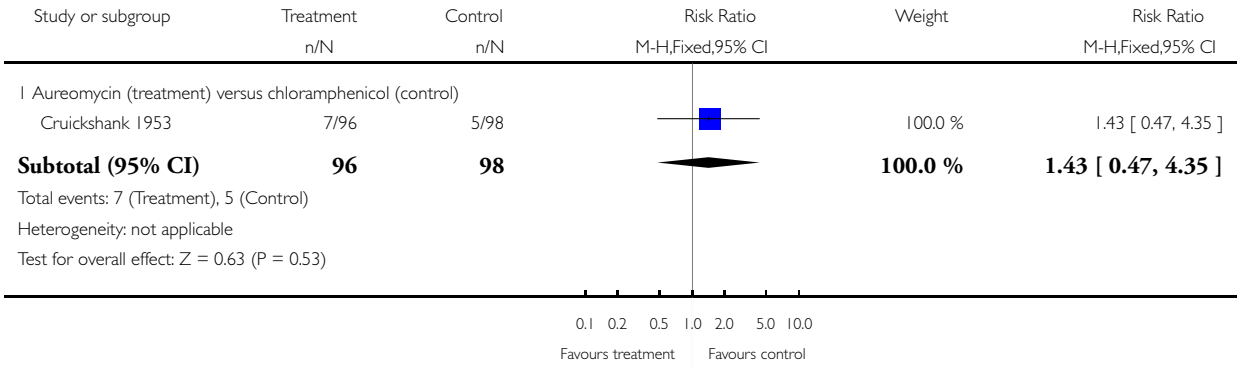
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Aureomycin (treatment) versus chloramphenicol (control)					
Cruickshank 1953	7/96	5/98		100.0 %	1.43 [0.47, 4.35]
Subtotal (95% CI)	**96**	**98**		**100.0 %**	**1.43 [0.47, 4.35]**
Total events: 7 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 8 Respiratory complications

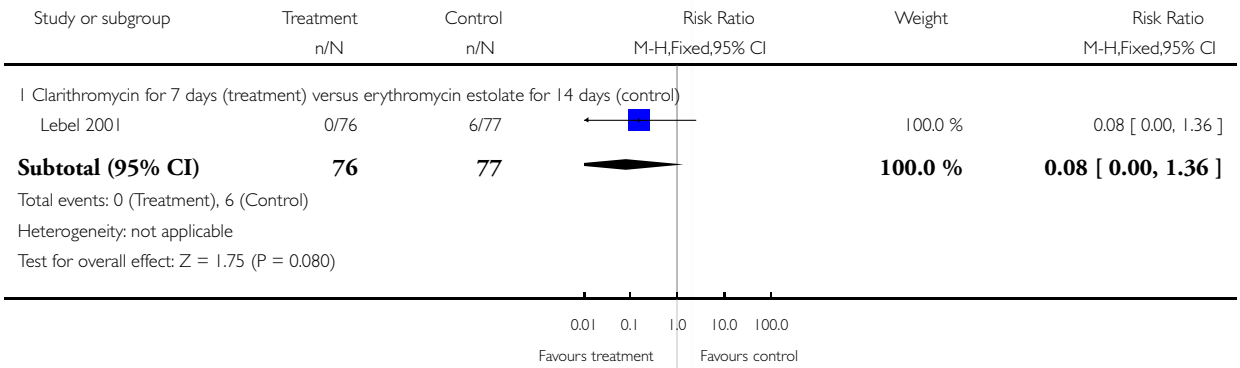


Analysis 1.9. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 9 Complications (otitis media).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

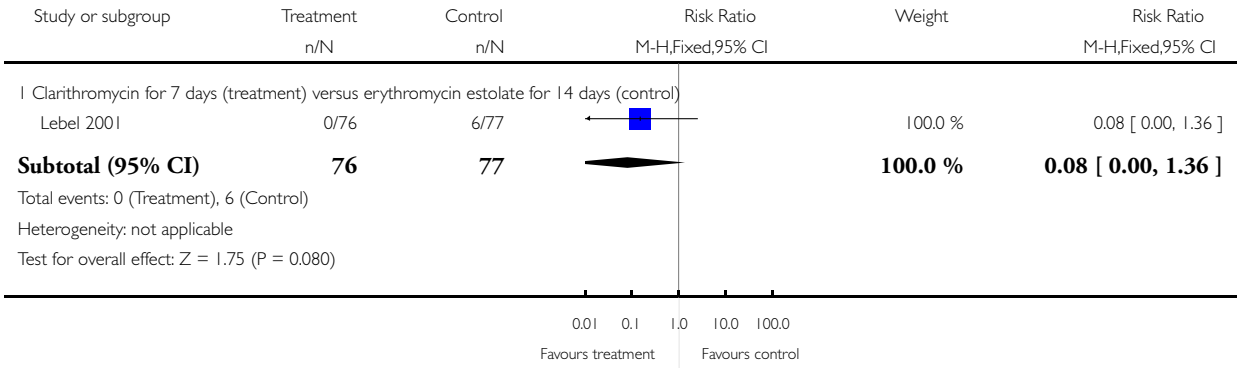
Outcome: 9 Complications (otitis media)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 9 Complications (otitis media)

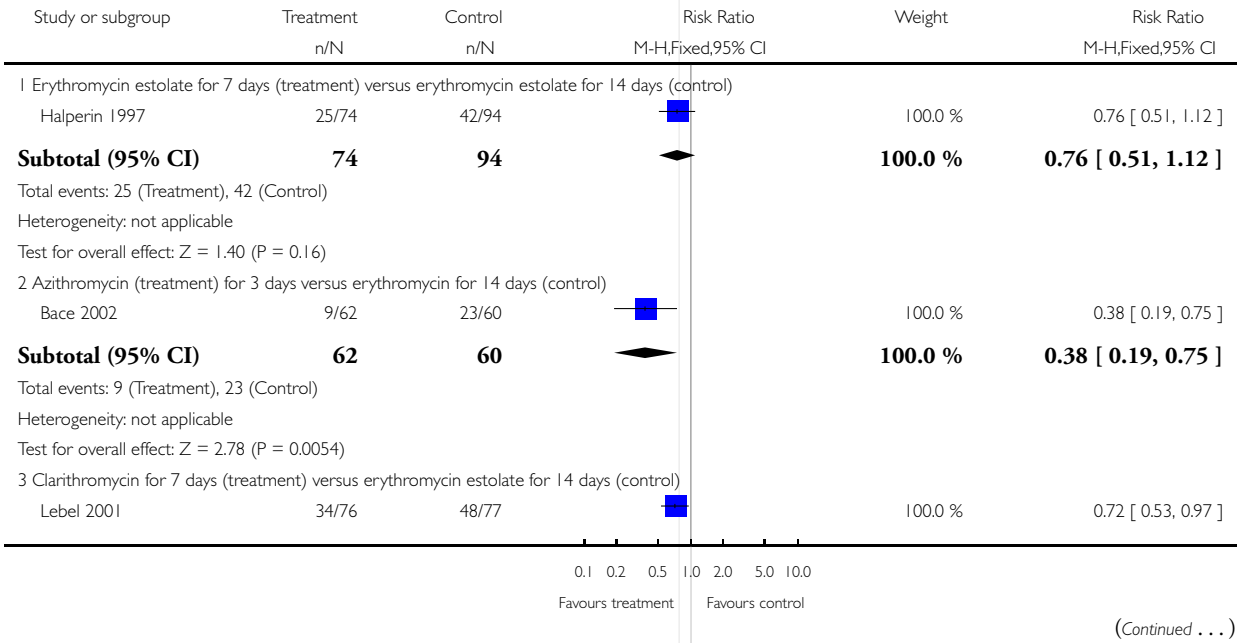


Analysis 1.10. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 10 All side effects.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 10 All side effects



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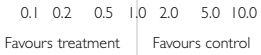
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**76**	**77**		**100.0 %**	**0.72 [0.53, 0.97]**
Total events: 34 (Treatment), 48 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.033)					
4 Ampicillin for 6 days (treatment) versus chloramphenicol for 6 days (control)					
Strangert 1969	21/76	11/72		100.0 %	1.81 [0.94, 3.48]
Subtotal (95% CI)	**76**	**72**		**100.0 %**	**1.81 [0.94, 3.48]**
Total events: 21 (Treatment), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.076)					
5 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)					
Hoppe 1992	11/93	16/97		100.0 %	0.72 [0.35, 1.46]
Subtotal (95% CI)	**93**	**97**		**100.0 %**	**0.72 [0.35, 1.46]**
Total events: 11 (Treatment), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					
6 Aureomycin (chlortetracycline) (treatment) versus chloramphenicol (control)					
Cruickshank 1953	15/96	12/98		100.0 %	1.28 [0.63, 2.58]
Subtotal (95% CI)	**96**	**98**		**100.0 %**	**1.28 [0.63, 2.58]**
Total events: 15 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

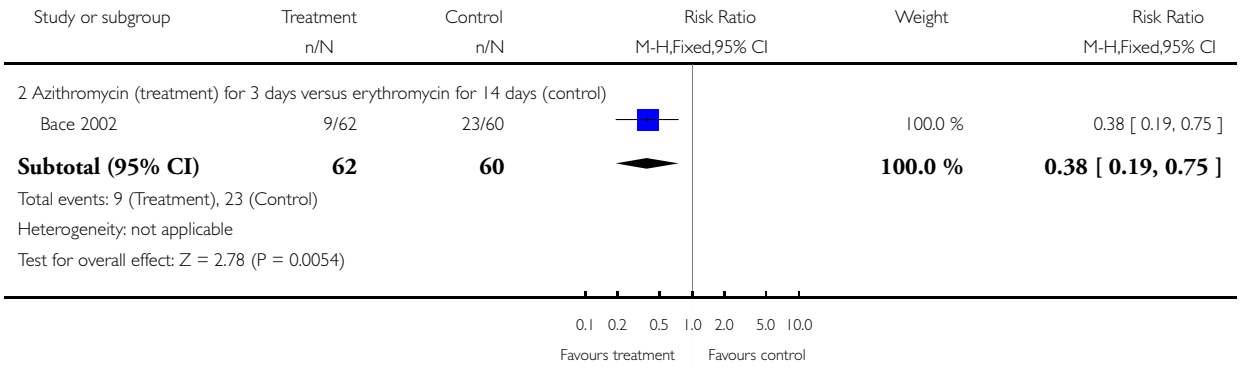
Outcome: 10 All side effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	25/74	42/94		100.0 %	0.76 [0.51, 1.12]
Subtotal (95% CI)	**74**	**94**		**100.0 %**	**0.76 [0.51, 1.12]**
Total events: 25 (Treatment), 42 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

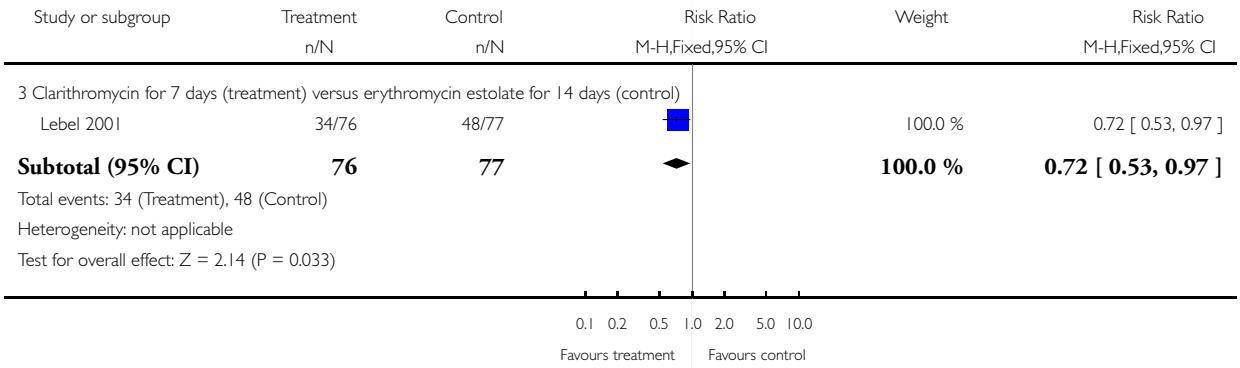
Outcome: 10 All side effects



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 10 All side effects

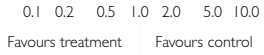


Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 10 All side effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
4 Ampicillin for 6 days (treatment) versus chloramphenicol for 6 days (control)					
Strangert 1969	21/76	11/72		100.0 %	1.81 [0.94, 3.48]
Subtotal (95% CI)	**76**	**72**		**100.0 %**	**1.81 [0.94, 3.48]**
Total events: 21 (Treatment), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.076)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

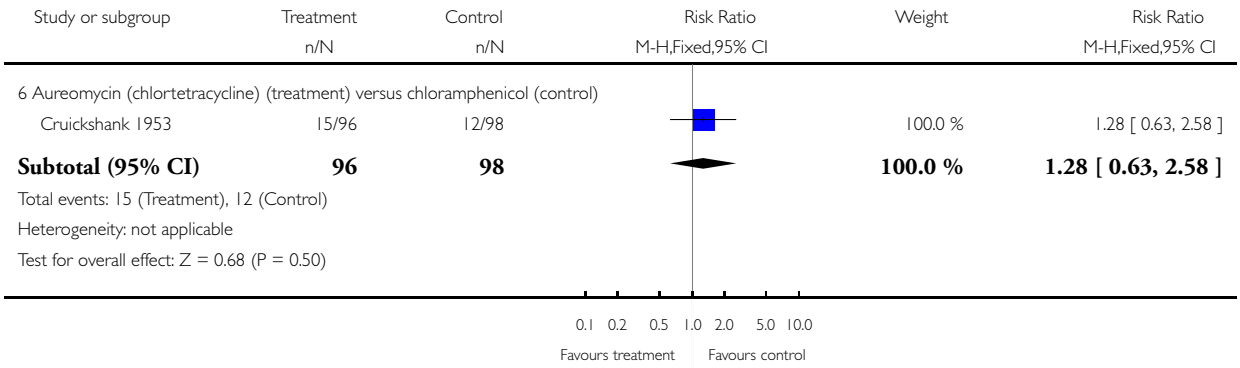
Outcome: 10 All side effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
5 Erythromycin estolate for 14 days (treatment) versus erythromycin ethylsuccinate for 14 days (control)					
Hoppe 1992	11/93	16/97		100.0 %	0.72 [0.35, 1.46]
Subtotal (95% CI)	**93**	**97**		**100.0 %**	**0.72 [0.35, 1.46]**
Total events: 11 (Treatment), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 10 All side effects

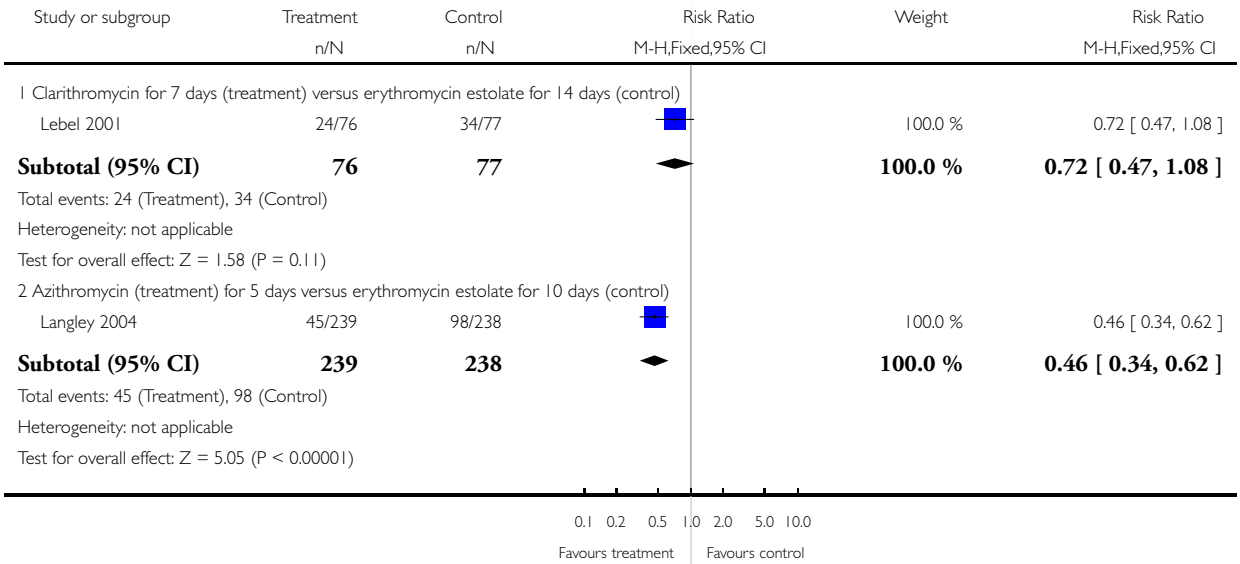


Analysis 1.11. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 11 Gastro-intestinal system side effects.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 11 Gastro-intestinal system side effects



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 11 Gastro-intestinal system side effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Clarithromycin for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Lebel 2001	24/76	34/77		100.0 %	0.72 [0.47, 1.08]
Subtotal (95% CI)	**76**	**77**		**100.0 %**	**0.72 [0.47, 1.08]**
Total events: 24 (Treatment), 34 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.58 (P = 0.11)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours treatment Favours control

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 11 Gastro-intestinal system side effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	45/239	98/238		100.0 %	0.46 [0.34, 0.62]
Subtotal (95% CI)	**239**	**238**		**100.0 %**	**0.46 [0.34, 0.62]**
Total events: 45 (Treatment), 98 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.05 (P < 0.00001)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0

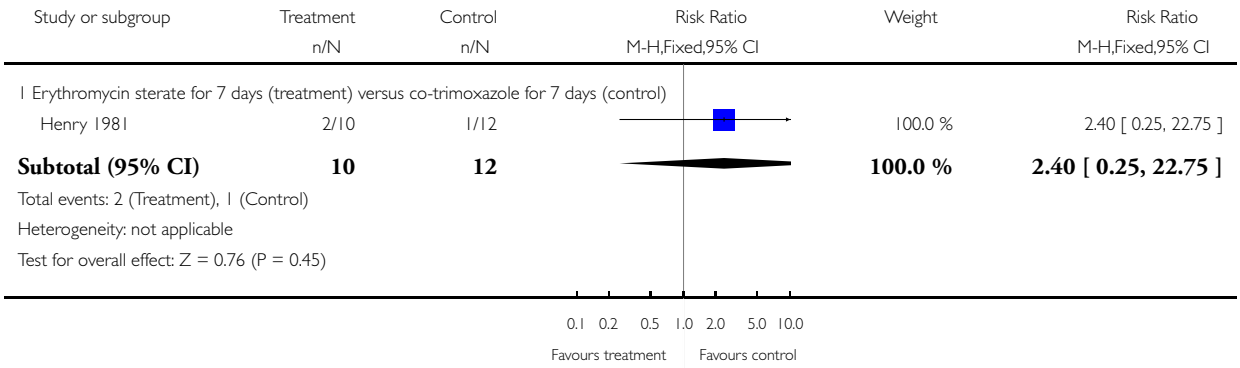
Favours treatment Favours control

Analysis 1.12. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 12 Side effects (diarrhoea).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

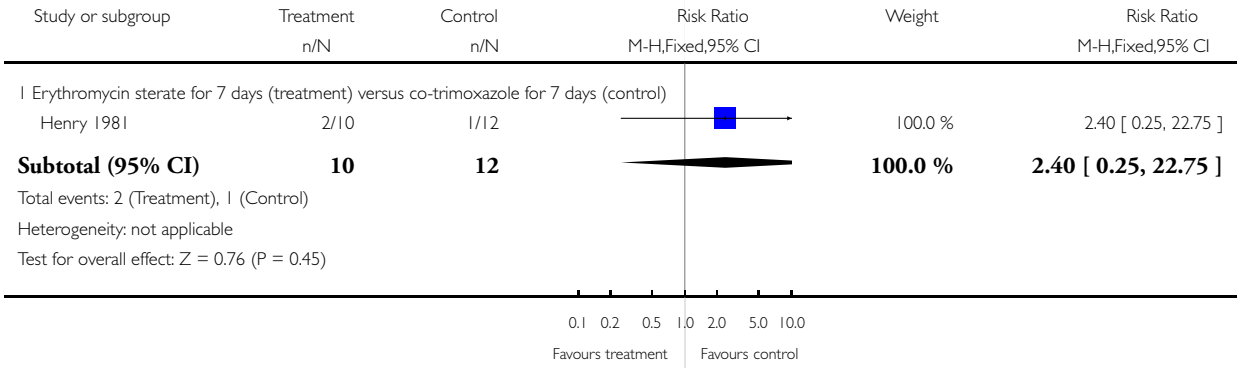
Outcome: 12 Side effects (diarrhoea)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 12 Side effects (diarrhoea)

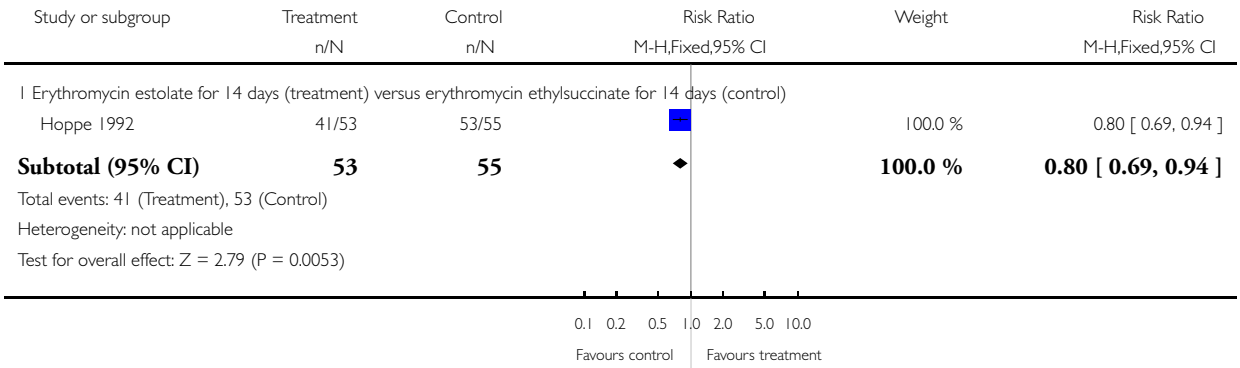


Analysis 1.13. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 13 Compliance (detected by antimicrobial activity in urine).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

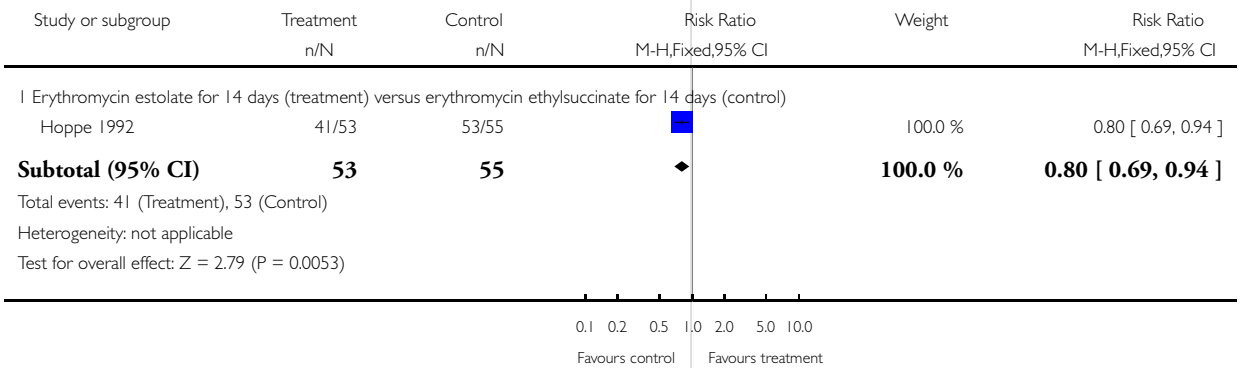
Outcome: 13 Compliance (detected by antimicrobial activity in urine)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 13 Compliance (detected by antimicrobial activity in urine)



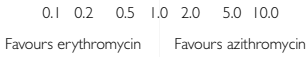
Analysis 1.14. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 14 Compliance (presented as number of children who took 100% of prescribed doses).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 14 Compliance (presented as number of children who took 100% of prescribed doses)

Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	215/239	131/238		100.0 %	1.63 [1.45, 1.85]
Subtotal (95% CI)	**239**	**238**		**100.0 %**	**1.63 [1.45, 1.85]**
Total events: 215 (Azithromycin), 131 (Erythromycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.87 (P < 0.00001)					



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 14 Compliance (presented as number of children who took 100% of prescribed doses)

Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	215/239	131/238		100.0 %	1.63 [1.45, 1.85]
Subtotal (95% CI)	**239**	**238**		**100.0 %**	**1.63 [1.45, 1.85]**
Total events: 215 (Azithromycin), 131 (Erythromycin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.87 (P < 0.00001)					

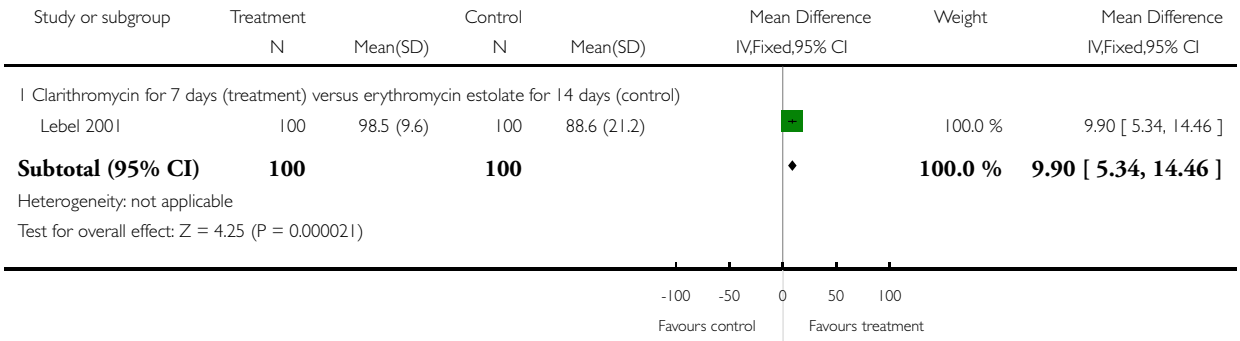
0.1 0.2 0.5 1.0 2.0 5.0 10.0
Favours erythromycin
Favours azithromycin

Analysis 1.15. Comparison 1 Antibiotics for treatment of whooping cough, Outcome 15 Compliance (presented as percentage of drugs taken).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

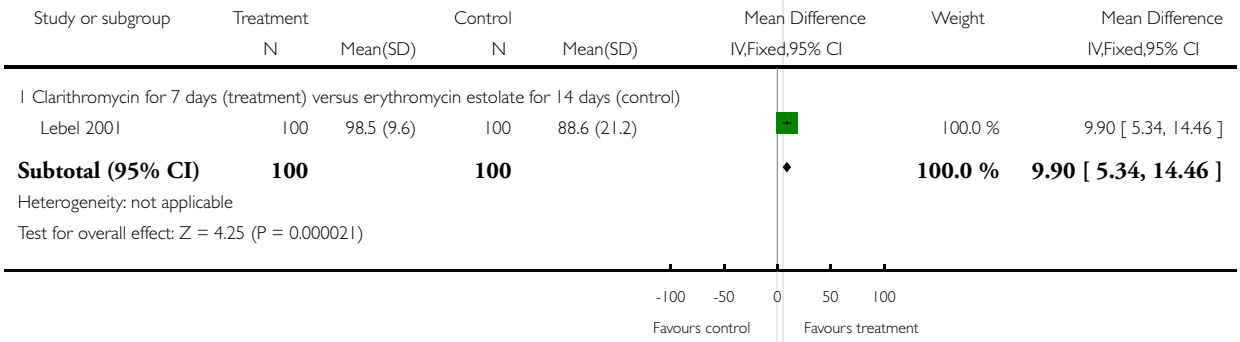
Outcome: 15 Compliance (presented as percentage of drugs taken)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 1 Antibiotics for treatment of whooping cough

Outcome: 15 Compliance (presented as percentage of drugs taken)



Analysis 2.1. Comparison 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis, Outcome 1 Presence of any sign or symptoms of whooping cough.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 1 Presence of any sign or symptoms of whooping cough

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	73/74	93/94		100.0 %	1.00 [0.96, 1.03]
Subtotal (95% CI)	**74**	**94**		**100.0 %**	**1.00 [0.96, 1.03]**
Total events: 73 (Treatment), 93 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 1 Presence of any sign or symptoms of whooping cough

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	73/74	93/94		100.0 %	1.00 [0.96, 1.03]
Subtotal (95% CI)	**74**	**94**		**100.0 %**	**1.00 [0.96, 1.03]**
Total events: 73 (Treatment), 93 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0
Favours 3-7 days
Favours 14 days

Analysis 2.2. Comparison 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis, Outcome 2 Microbiological eradication.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 2 Microbiological eradication

Study or subgroup	3 to 7 days n/N	10 to 14 days n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bace 2002	20/20	24/25		17.9 %	1.04 [0.92, 1.16]
Halperin 1997	68/69	83/84		61.1 %	1.00 [0.96, 1.03]
Langley 2004	53/53	53/53		0.0 %	0.0 [0.0, 0.0]
Lebel 2001	31/31	22/23		21.0 %	1.05 [0.94, 1.17]
Total (95% CI)	**173**	**185**		**100.0 %**	**1.02 [0.98, 1.06]**
Total events: 172 (3 to 7 days), 182 (10 to 14 days)					
Heterogeneity: Chi^2 = 1.35, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					

Analysis 2.3. Comparison 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis, Outcome 3 Microbiological eradication.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 3 Microbiological eradication

Study or subgroup	3 to 7 days n/N	10 to 14 days n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Halperin 1997	68/69	83/84		74.4 %	1.00 [0.96, 1.03]
Langley 2004	53/53	53/53		0.0 %	0.0 [0.0, 0.0]
Lebel 2001	31/31	22/23		25.6 %	1.05 [0.94, 1.17]
Total (95% CI)	**153**	**160**		**100.0 %**	**1.01 [0.97, 1.05]**
Total events: 152 (3 to 7 days), 158 (10 to 14 days)					
Heterogeneity: Chi^2 = 0.94, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 0.53 (P = 0.60)					

Analysis 2.4. Comparison 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis, Outcome 4 Bacteriological relapse.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 4 Bacteriological relapse

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	1/72	0/83		100.0 %	3.45 [0.14, 83.44]
Subtotal (95% CI)	**72**	**83**		**100.0 %**	**3.45 [0.14, 83.44]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
2 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	0/51	0/53		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**51**	**53**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Total (95% CI)	**123**	**136**		**100.0 %**	**3.45 [0.14, 83.44]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 4 Bacteriological relapse

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin estolate for 7 days (treatment) versus erythromycin estolate for 14 days (control)					
Halperin 1997	1/72	0/83		100.0 %	3.45 [0.14, 83.44]
Subtotal (95% CI)	**72**	**83**		**100.0 %**	**3.45 [0.14, 83.44]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 4 Bacteriological relapse

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Azithromycin (treatment) for 5 days versus erythromycin estolate for 10 days (control)					
Langley 2004	0/51	0/53		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**51**	**53**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Analysis 2.5. Comparison 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis, Outcome 5 All side effects.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 5 All side effects

Study or subgroup	3 to 7 days n/N	14 days n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bace 2002	9/62	23/60		21.6 %	0.38 [0.19, 0.75]
Halperin 1997	25/74	42/94		34.2 %	0.76 [0.51, 1.12]
Lebel 2001	34/76	48/77		44.1 %	0.72 [0.53, 0.97]
Total (95% CI)	**212**	**231**		**100.0 %**	**0.66 [0.52, 0.83]**
Total events: 68 (3 to 7 days), 113 (14 days)					
Heterogeneity: Chi^2 = 3.31, df = 2 (P = 0.19); I^2 =40%					
Test for overall effect: Z = 3.58 (P = 0.00035)					

Analysis 2.6. Comparison 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis, Outcome 6 All side effects.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 2 Antibiotics 3 to 7 days versus antibiotics for 10 to 14 days in treatment of whooping cough (subgroup analysis

Outcome: 6 All side effects

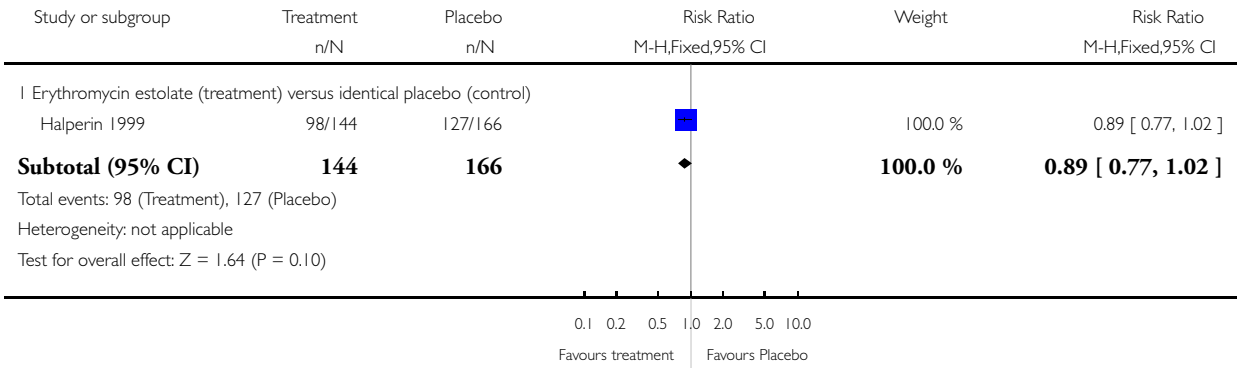
Study or subgroup	3 to 7 days n/N	14 days n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Halperin 1997	25/74	43/94		44.3 %	0.74 [0.50, 1.09]
Lebel 2001	34/76	48/77		55.7 %	0.72 [0.53, 0.97]
Total (95% CI)	**150**	**171**		**100.0 %**	**0.73 [0.57, 0.93]**
Total events: 59 (3 to 7 days), 91 (14 days)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 2.59 (P = 0.0096)					

Analysis 3.1. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 1 All (any) clinical symptoms.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

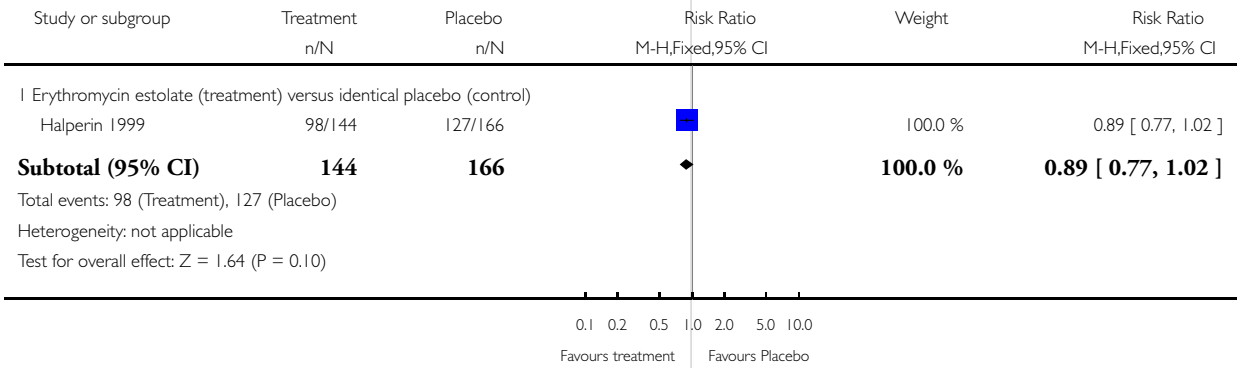
Outcome: 1 All (any) clinical symptoms



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 1 All (any) clinical symptoms

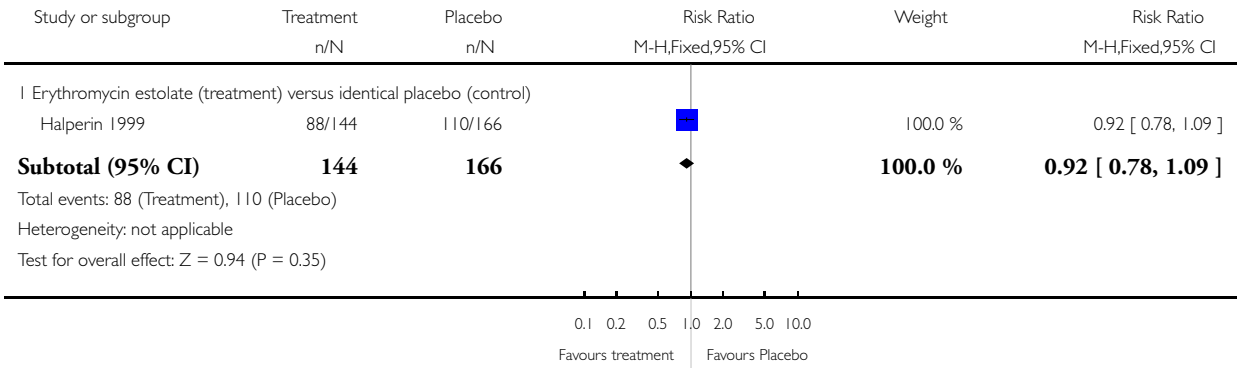


Analysis 3.2. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 2 Presence of all (any) cough.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

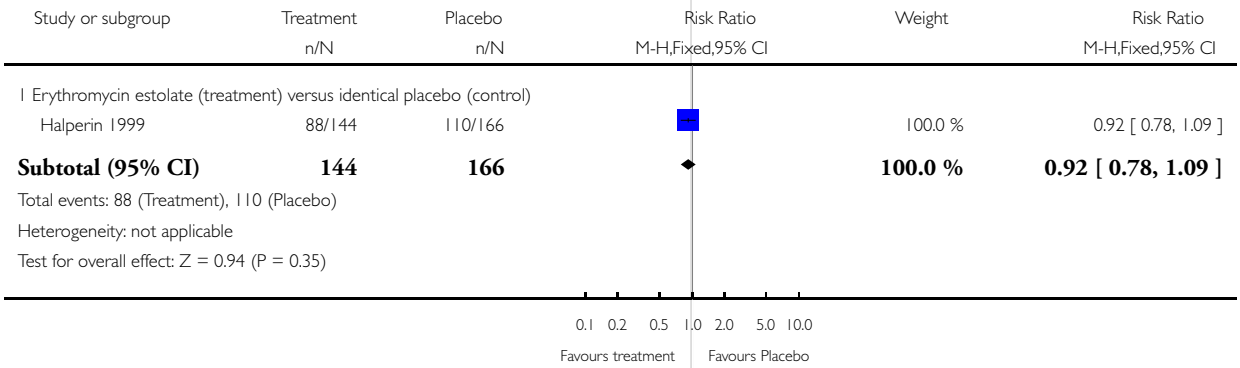
Outcome: 2 Presence of all (any) cough



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 2 Presence of all (any) cough

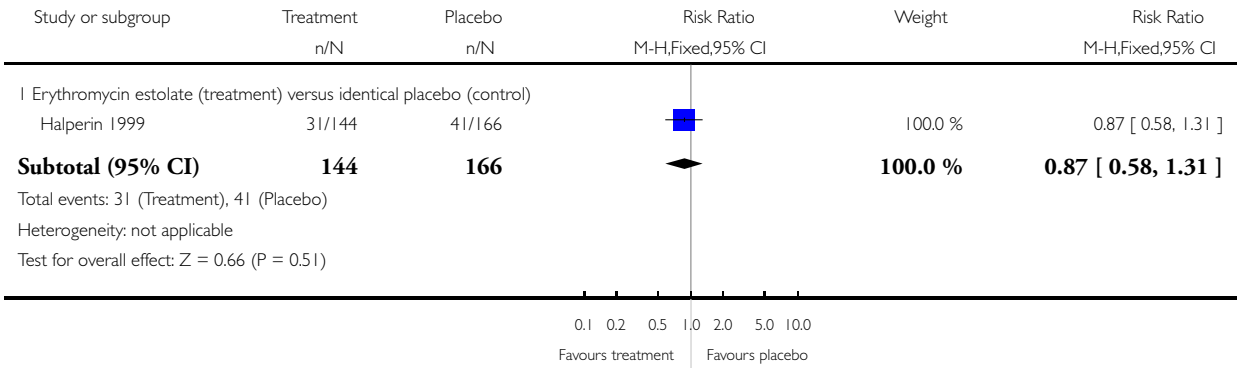


Analysis 3.3. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 3 Paroxysmal cough.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

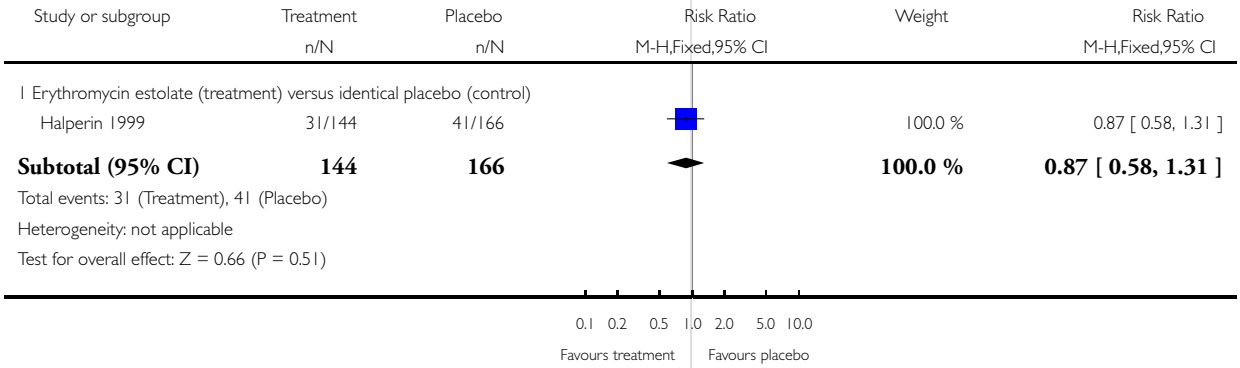
Outcome: 3 Paroxysmal cough



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 3 Paroxysmal cough

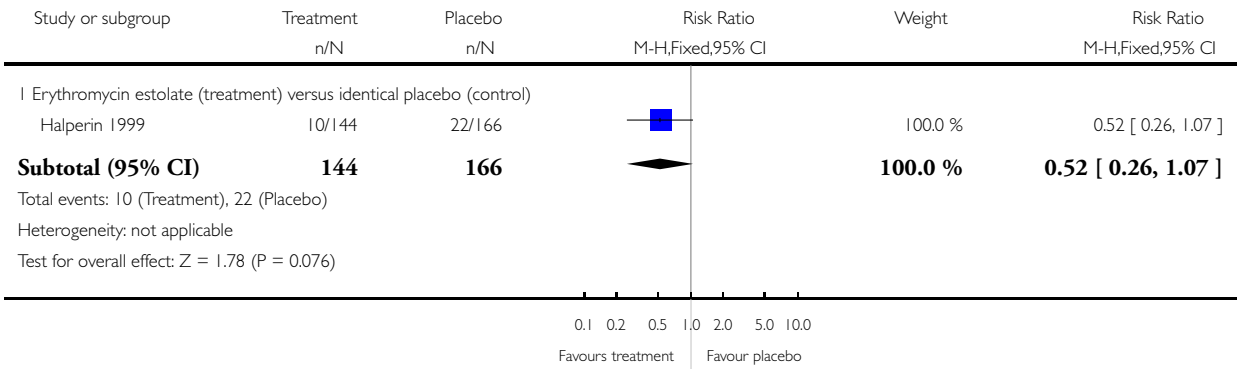


Analysis 3.4. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 4 Frequency of whoop in contacts.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

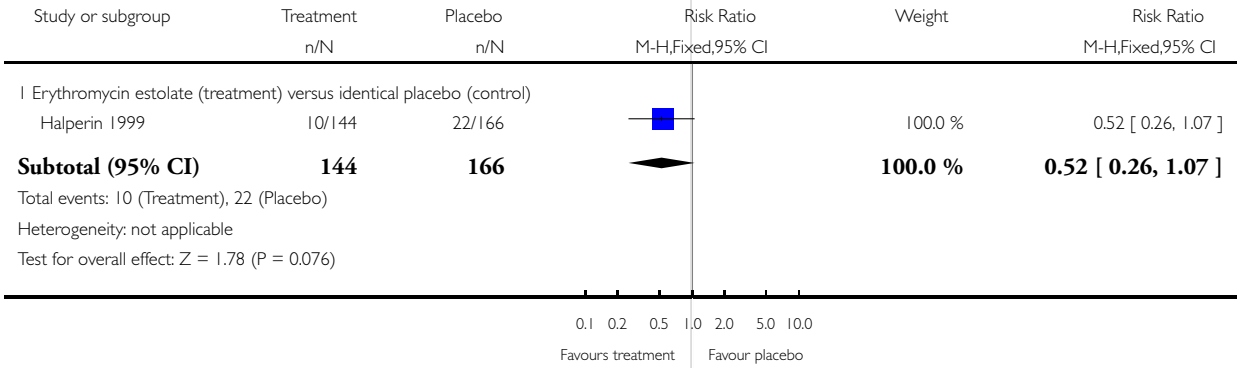
Outcome: 4 Frequency of whoop in contacts



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 4 Frequency of whoop in contacts

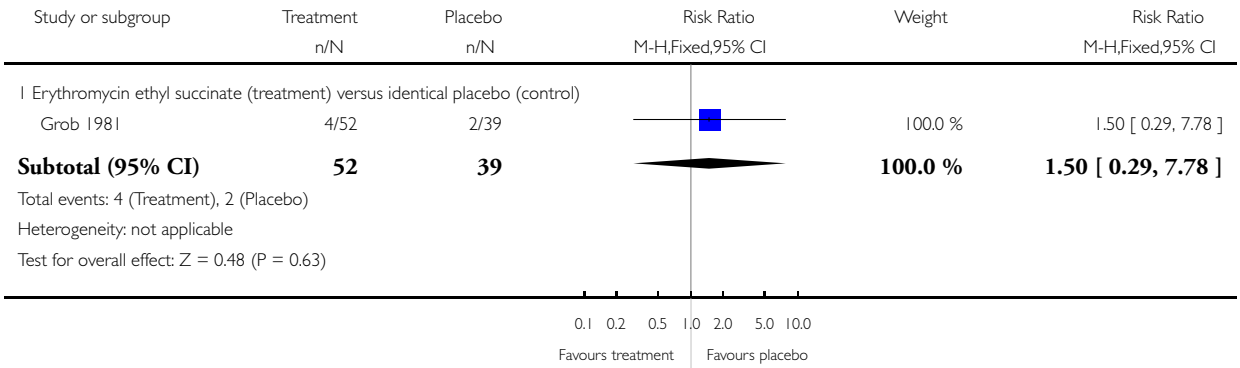


Analysis 3.5. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 5 Frequency of whooping cough in contacts.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

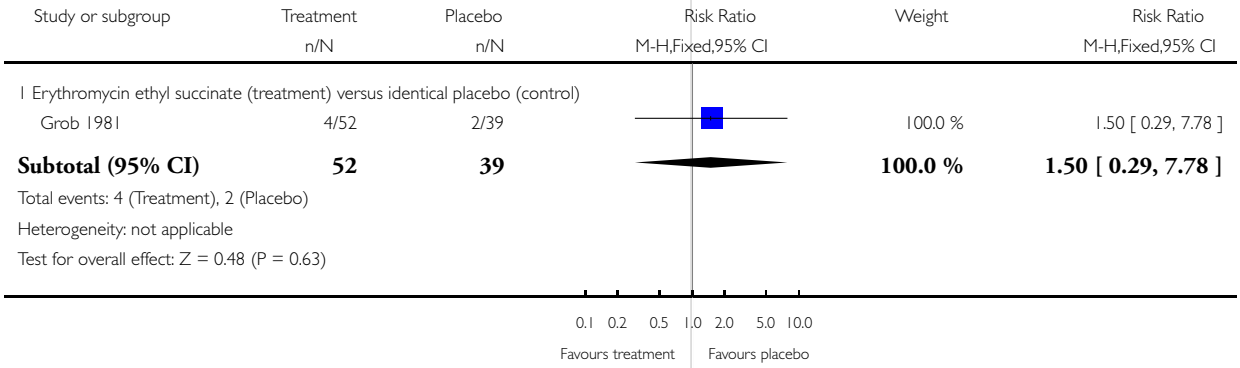
Outcome: 5 Frequency of whooping cough in contacts



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 5 Frequency of whooping cough in contacts



Analysis 3.6. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 6 Frequency of whooping cough in vaccinated contacts.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 6 Frequency of whooping cough in vaccinated contacts

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin ethyl succinate (treatment) versus identical placebo (control)					
Grob 1981	0/32	0/28		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**32**	**28**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 6 Frequency of whooping cough in vaccinated contacts

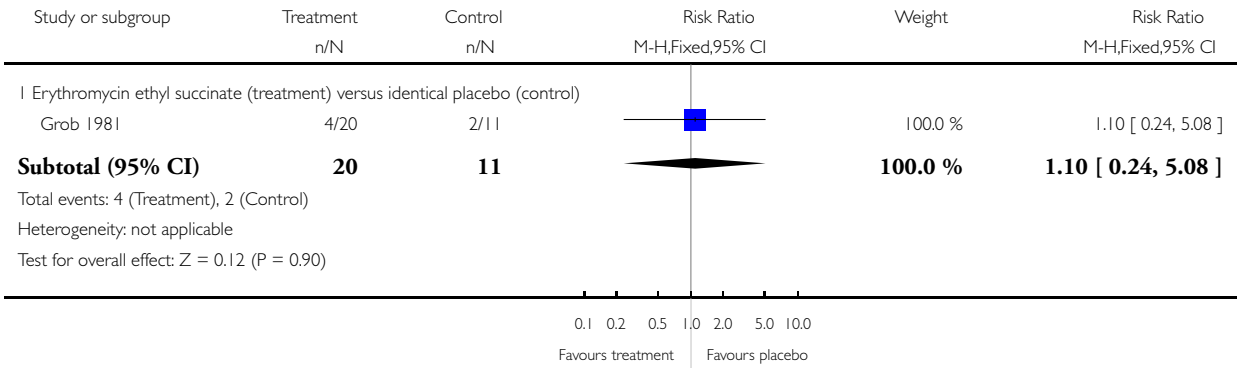
Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Erythromycin ethyl succinate (treatment) versus identical placebo (control)					
Grob 1981	0/32	0/28		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**32**	**28**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					

Analysis 3.7. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 7 Frequency of whooping cough in unvaccinated contacts.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

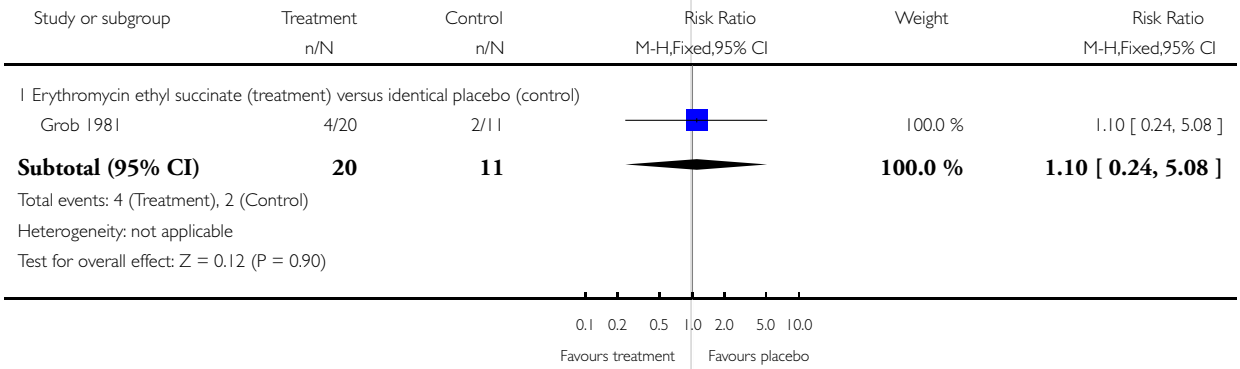
Outcome: 7 Frequency of whooping cough in unvaccinated contacts



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 7 Frequency of whooping cough in unvaccinated contacts

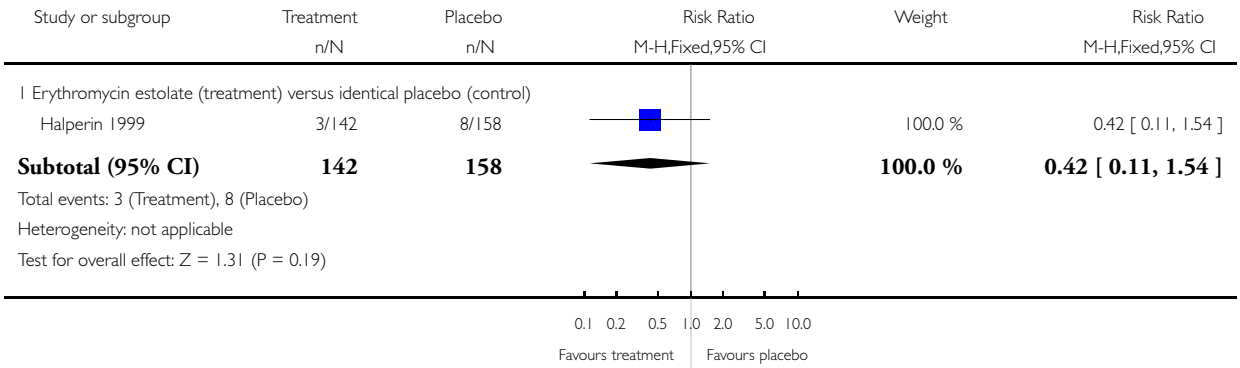


Analysis 3.8. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 8 Culture positive after prophylaxis in contacts (attack rate post-prophylaxis).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

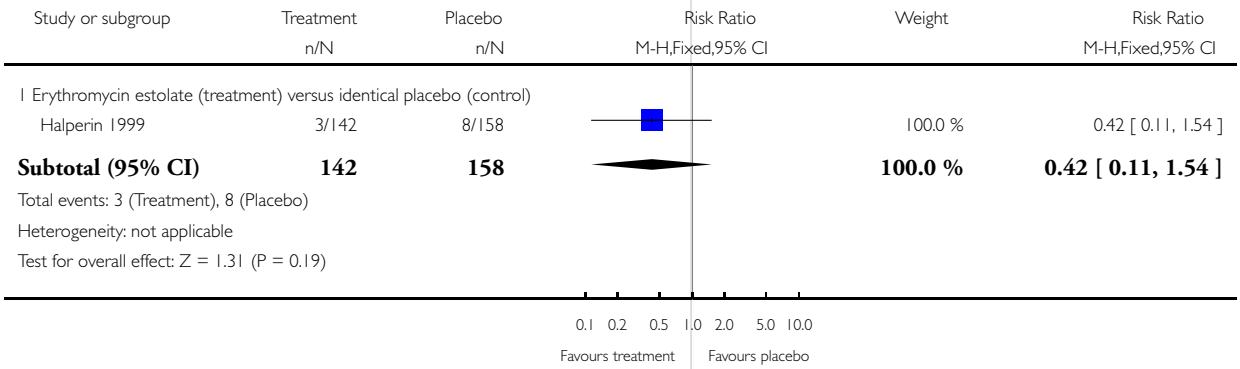
Outcome: 8 Culture positive after prophylaxis in contacts (attack rate post-prophylaxis)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 8 Culture positive after prophylaxis in contacts (attack rate post-prophylaxis)

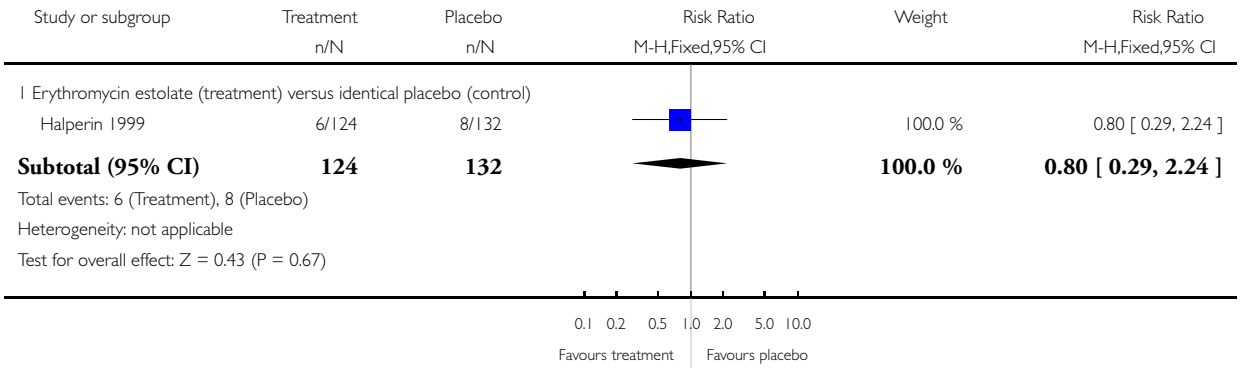


Analysis 3.9. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 9 Culture positive or paroxysmal cough > 2 weeks after prophylaxis in contacts (attack rate post-prophylaxis).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

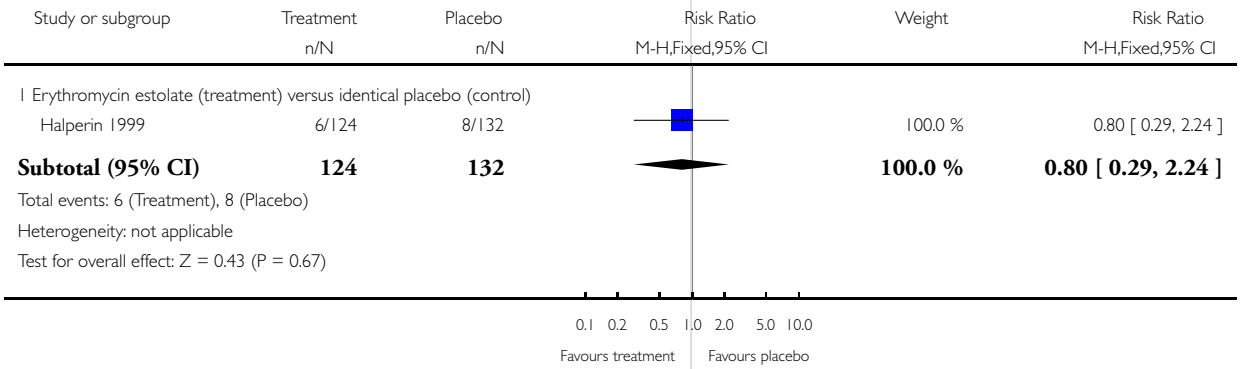
Outcome: 9 Culture positive or paroxysmal cough > 2 weeks after prophylaxis in contacts (attack rate post-prophylaxis)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 9 Culture positive or paroxysmal cough > 2 weeks after prophylaxis in contacts (attack rate post-prophylaxis)

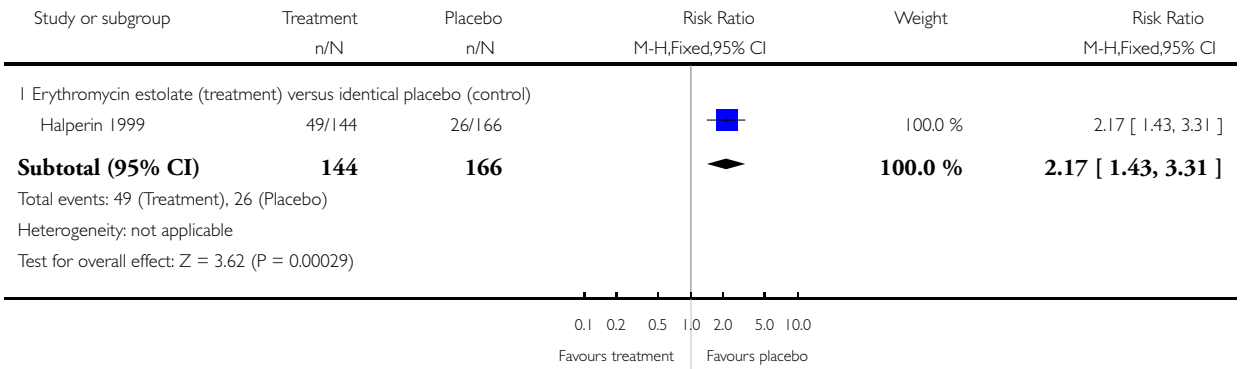


Analysis 3.10. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 10 All (any) side effects.

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

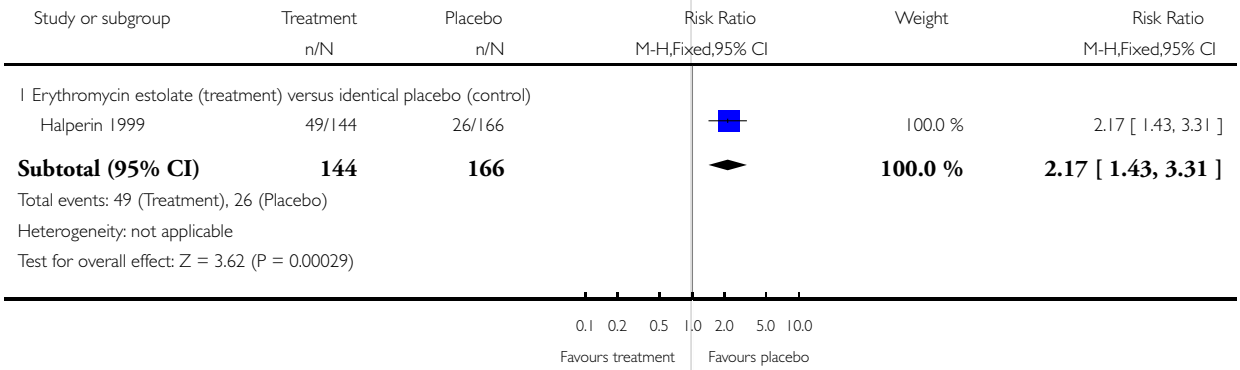
Outcome: 10 All (any) side effects



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 10 All (any) side effects

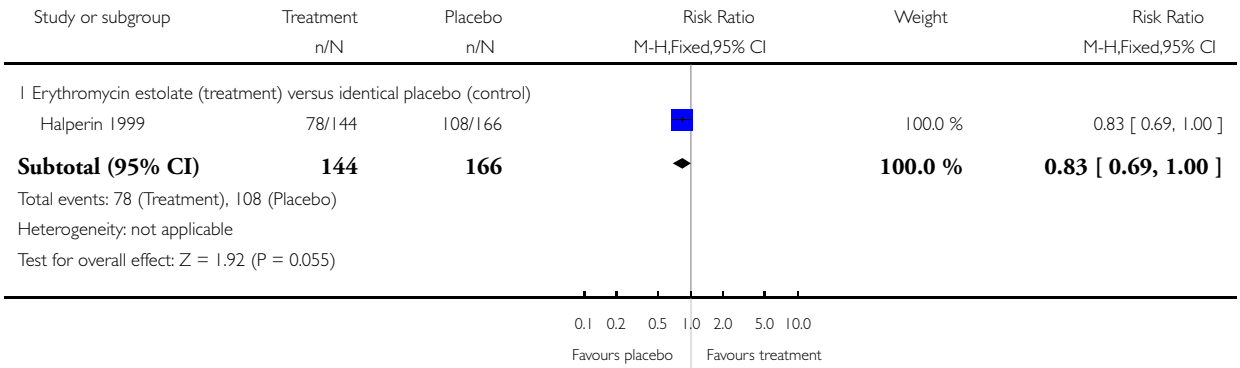


Analysis 3.11. Comparison 3 Antibiotic for prophylaxis of whooping cough, Outcome 11 Compliance (> 90% of doses).

Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

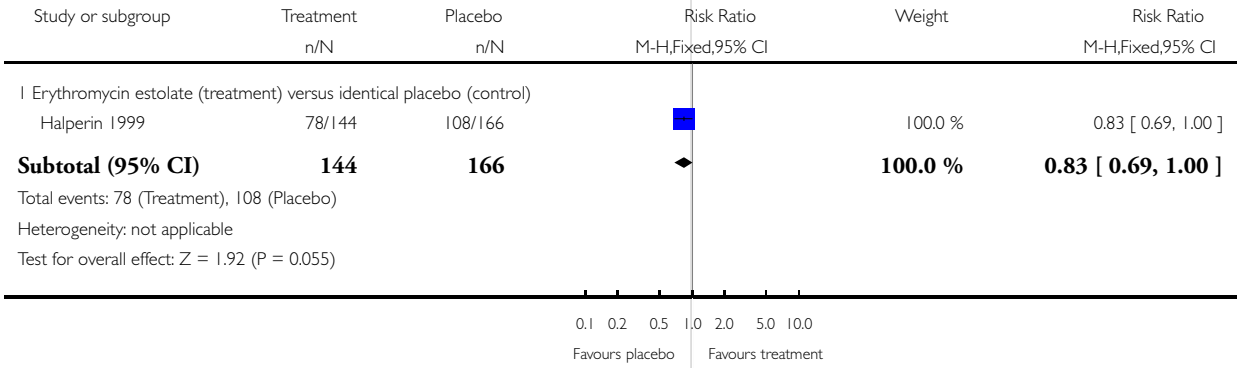
Outcome: 11 Compliance (> 90% of doses)



Review: Antibiotics for whooping cough (pertussis)

Comparison: 3 Antibiotic for prophylaxis of whooping cough

Outcome: 11 Compliance (> 90% of doses)



APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL
#1 pertus*
#2 whoop*
#3 whooping cough: (MeSH descriptor: explode all trees)
#4 whooping and cough
#5 #1 or #2 or #3 or #4
#6 antibiotic*
#7 Anti-Bacterial Agents (MeSH descriptor: explode all trees)
#8 antibimicrob*
#9 #6 or #7 or #8
#10 #5 and #9

Appendix 2. EMBASE search strategy

EMBASE (Embase.com)
1 'randomized controlled trial'/exp
2 'randomization'/exp AND [1974-2007]/py
3 'controlled study'/exp
4 'multicenter study'/exp
5 'phase 3 clinical trial'/exp
6 'phase 4 clinical trial'/exp
7 'single blind procedure'/exp
8 'double blind procedure'/exp
9 random* OR crossover OR 'cross over' OR 'cross-over' OR factorial OR volunteer AND [1974-2007]/py
13 (singl*:ab,ti OR doubl*:ab,ti OR trebl*:ab,ti OR tripl*:ab,ti) AND (blind*:ab,ti OR mask*:ab,ti) AND [1974-2007]/py
15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #13
16 human:de AND [1974-2007]/py
17 animal:de OR nonhuman:de AND [1974-2007]/py
18 #16 AND #17
19 #17 NOT #18 AND [1974-2007]/py
20 #15 NOT #19 AND [embase]/lim AND [1974-2007]/py
21 (('pertussis'/exp) OR (whoop* AND [1974-2007]/py) OR (pertuss* AND [1974-2007]/py) OR ('bordetella pertussis'/exp)) AND (('antibiotic agent'/exp) OR (antibiotic* AND [1974-2007]/py) OR (antimicrob* AND [1974-2007]/py))
22 #20 AND #21

WHAT'S NEW

Last assessed as up-to-date: 1 April 2007.

21 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2005

4 March 2007	New search has been performed	In this 2007 substantive update: (1) A single new randomised controlled trial was included (Langley 2004) for treatment of whooping cough. (2) No new RCT was found for prophylaxis of whooping cough. (3) This Cochrane review has been considerably revised and updated.
20 February 2004	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Sultan Altunaiji (SA) conceived the idea for the review. He designed and co-ordinated the screening of search results, retrieval of papers and screening retrieved papers against inclusion criteria, abstracting data from papers, appraising the quality of papers and trial methodology. He was also responsible for writing to authors for additional information, obtaining and screening data on unpublished studies, data entry into RevMan, analysis of data, clinical perspectives, policy and consumer perspectives, and writing the review.

Renata Kukuruzovic (RK), John Massie (JM) and Nigel Curtis (NC) contributed to screening search results, retrieval of papers and screening retrieved papers against inclusion criteria, abstracting data from papers, appraising quality of papers, trial methodology, obtaining and screening data on unpublished studies, analysis of data, policy and consumer perspectives, and writing the review.

DECLARATIONS OF INTEREST

None known.

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- No sources of support supplied

External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Azithromycin [therapeutic use]; Bordetella pertussis; Clarithromycin [therapeutic use]; Contact Tracing; Erythromycin [therapeutic use]; Erythromycin Estolate [therapeutic use]; Erythromycin Ethylsuccinate [therapeutic use]; Randomized Controlled Trials as Topic; Trimethoprim-Sulfamethoxazole Combination [therapeutic use]; Whooping Cough [*drug therapy; *prevention & control; transmission]

MeSH check words

Humans; Infant