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Different antibiotic treatments for group A streptococcal pharyngitis (Review)

van Driel ML, De Sutter AIM, Keber N, Habraken H, Christiaens T

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[Intervention Review]

Different antibiotic treatments for group A streptococcal pharyngitis

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ABSTRACT

Background

Antibiotics provide only modest benefit in treating sore throat, although effectiveness increases in participants with positive throat swabs for group A beta-haemolytic streptococci (GABHS). It is unclear which antibiotic is the best choice if antibiotics are indicated.

Objectives

We assessed the comparative efficacy of different antibiotics on clinical outcomes, relapse, complications and adverse events in GABHS tonsillopharyngitis.

Search methods

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2010, Issue 3) which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to July Week 4, 2010) and EMBASE (1974 to August 2010).

Selection criteria

Randomised, double-blind trials comparing different antibiotics reporting at least one of the following: clinical cure, clinical relapse, complications, adverse events.

Data collection and analysis

Two authors independently screened trials for inclusion and extracted data.

Main results

Seventeen trials (5352 participants) were included; 16 compared with penicillin (six with cephalosporins, six with macrolides, three with carbacephem and one with sulfonamides), one trial compared clindamycin and ampicillin. Randomisation reporting, allocation concealment and blinding were poor.

There was no difference in symptom resolution between cephalosporins and penicillin (intention-to-treat (ITT) analysis; N = 5; n = 2018; odds ratio for absence of resolution of symptoms (OR) 0.79, 95% confidence interval (CI) 0.55 to 1.12). Clinical relapse was lower with cephalosporins (N = 4; n = 1386; OR 0.55, 95% CI 0.31 to 0.99); overall number needed to treat to benefit (NNTB) 50), but found only in adults (OR 0.42, 95% CI 0.20 to 0.88; NNTB 33). There were no differences between macrolides and penicillin. Carbacephem showed better symptom resolution post-treatment (N = 3; n = 795; OR 0.70, 95% CI 0.49 to 0.99; NNTB 14), but only in children (N = 2; n = 233; OR 0.57, 95% CI 0.33 to 0.99; NNTB 8.3). Children experienced more adverse events with macrolides (N = 1, n = 489; OR 2.33; 95% CI 1.06 to 5.15).

Authors' conclusions

Evidence is insufficient for clinically meaningful differences between antibiotics for GABHS tonsillopharyngitis. Limited evidence in adults suggests cephalosporins are more effective than penicillin for relapse, but the NNTB is high. Limited evidence in children suggests carbacephem is more effective for symptom resolution. Data on complications are too scarce to draw conclusions. Based on these results and considering the low cost and absence of resistance, penicillin can still be recommended as first choice.

PLAIN LANGUAGE SUMMARY

Different antibiotics for group A streptococcal pharyngitis

Pharyngitis or tonsillitis, a throat infection that usually presents with a sore throat, is a common upper respiratory tract infection. Most sore throats are caused by viruses, but sometimes bacteria are involved. Many people carry bacteria in their throat without becoming ill. However, sometimes a bacterial throat infection can occur.

Infection with a specific type of bacteria, group A beta-haemolytic streptococci (GABHS) is linked to serious complications such as acute rheumatic fever or kidney disease (post-streptococcal glomerulonephritis). In order to prevent these complications antibiotics are often prescribed to treat patients presenting to their doctor with a sore throat. A previous Cochrane review found that there is only a modest benefit of antibiotics for treating an acute sore throat, even if group A beta-haemolytic streptococci (GABHS) are present. Most throat infections, even with bacteria, are self-limiting and the risk of complications is extremely low in most populations studied (in low-income countries). However, sometimes antibiotics may be indicated.

We found 17 trials with a total of 5352 participants that studied the effects of different classes of antibiotics on resolution of symptoms in patients with a sore throat and a positive culture for GABHS. Our review found that the effects of these antibiotics are very similar. All antibiotics studied also cause undesired side effects (such as nausea and vomiting, rash), but there was no strong evidence for meaningful differences between the antibiotics. The studies did not report on long-term complications and therefore it is unclear if any class of antibiotics is better in preventing these serious but rare complications.

As all the identified studies were carried out in populations in high-income countries with a low risk of streptococcal complications, there is a need for trials in populations where this risk is still very high (low-income countries and Aboriginal communities). Penicillin has been used for a very long time but resistance of the GABHS to penicillin has never been reported. Also, penicillin is a cheap antibiotic. Our review therefore supports the use of penicillin as a first choice antibiotic in patients with acute throat infections caused by GABHS.

BACKGROUND

Description of the condition

Pharyngitis is a common upper respiratory tract infection. Antibiotics are often prescribed to treat this condition. Patients usually consult a physician with the complaint of sore throat. A previous Cochrane review comparing the effect of antibiotics to placebo in participants with or without group A beta-haemolytic streptococci (GABHS) sore throat (Del Mar 2009) pointed to the self-limiting nature of an acute sore throat (even in case of positive GABHS culture). Antibiotics provide only modest benefit when prescribed for

the condition 'sore throat'. The effect of antibiotic treatment was increased in participants with positive throat swabs for GABHS. The streptococci-positive participants are only a small proportion of all participants with 'sore throat'. Nevertheless, in many countries antibiotics are prescribed for most people who have a 'sore throat' (Cars 2001; Linder 2001). Given the high consumption of antibiotics for this condition a rational approach would be to reserve a treatment with antibiotics for participants with proven presence or a high likelihood of group A streptococci (Cooper 2001; Snow 2001). But clinical scoring systems are somewhat limited in their ability to correctly target GABHS positive patients (McIsaac 1998) and the usefulness of rapid assay tests depends on the prevalence of GABHS in the population (Sonnad 1999) and justification of its cost-effectiveness is unclear (Gerber 2004; Neuner 2003).

Description of the intervention

The slight benefit of treatment with antibiotics in patients with GABHS sore throat may be considered relevant. When antibiotics are indicated a choice needs to be made. In that case several aspects need to be considered, such as comparative benefit-harm balance, costs and local antimicrobial resistance patterns. Many guidelines recommend penicillin as a first choice, with erythromycin preferred for penicillin-allergic participants (Cooper 2001; Snow 2001). To date, resistance of GABHS to penicillin has not been documented (Gerber 2009) and resistance to erythromycin is still low (Cooper 2001). Considering the growing problem of antibiotic resistance for other pathogens, this responsiveness of group A streptococci should not be endangered (Wise 1998). Penicillin and erythromycin are cheap and the most cost-effective option. In spite of this, physicians continue to prescribe broad-spectrum antibiotics, including recently marketed ones. It is not clear if these antibiotics have any substantial clinical benefit over penicillin (and erythromycin).

Why it is important to do this review

Internationally, guidelines recommend using penicillin as first choice when choosing to treat acute sore throat (suspected to be caused by GABHS) with antibiotics (Matthys 2007). However, some argue that cephalosporins are more effective and should therefore be preferred (Casey 2004). Many physicians argue that occurrence of penicillin allergy should be taken into account when making a choice for an antibiotic. This review looked for evidence of penicillin allergy occurring in the available trials. In addition, in the presence of documented penicillin allergy, the side effect profile of the eligible antibiotics can guide choice. Therefore, in order to provide healthcare providers with sufficient information to make an evidence-based choice, both treatment benefits and adverse events are compared.

OBJECTIVES

1. To assess the evidence on the comparative efficacy of different antibiotics in: (a) alleviating symptoms (pain, fever); (b) shortening the duration of the illness; (c) preventing relapse; (d) preventing complications (suppurative complications, acute rheumatic fever, post-streptococcal glomerulonephritis).

2. To assess the evidence on the comparative incidence of adverse effects and the risk-benefit of antibiotic treatment for streptococcal pharyngitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, controlled trials comparing at least two different classes of antibiotics.

Types of participants

Adults and children of all ages presenting with symptoms of sore throat and with an infection caused by GABHS confirmed by a throat culture and/or rapid test.

Types of interventions

Antibiotic of one class compared with another class.

Types of outcome measures

The focus is on outcome measures that are relevant for the patient.

Primary outcomes

1. Resolution of symptoms (cure or improvement of signs and symptoms, such as sore throat, fever, feeling ill, etc.).

Secondary outcomes

1. Sore throat.
2. Fever.
3. Duration of illness.
4. Incidence of relapse.
5. Incidence of complications (suppurative complications, acute rheumatic fever, post-streptococcal glomerulonephritis).
6. Adverse events.

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2010, Issue 3) which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to July Week 4, 2010) and EMBASE (1974 to August 2010).

The following search strategy was used to search MEDLINE and CENTRAL. The MEDLINE search terms were combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2009). The search terms were adapted for EMBASE (Appendix 1).

MEDLINE (Ovid)

1 exp Pharyngitis/
2 pharyngit*.tw.
3 Nasopharyngitis/
4 nasopharyngit*.tw.
5 rhinopharyngit*.tw.
6 tonsillit*.tw.
7 tonsillopharyngit*.tw.
8 sore throat*.tw.
9 (strep* adj3 throat*).tw.
10 Streptococcal Infections/
11 "group a beta hemolytic streptococc*".tw.
12 "group a beta haemolytic streptococc*".tw.
13 gabhs.tw.
14 or/10-13
15 throat*.tw.
16 14 and 15
17 1 or 2 or 3 or 4 or 5 or 7 or 8 or 9 or 16
18 exp Anti-Bacterial Agents/
19 (antibacterial* or anti bacterial*).tw.
20 antibiotic*.tw.
21 or/18-20
22 17 and 21

There were no language or publication restrictions.

Searching other resources

We also searched reference sections of the identified reviews and trials for additional trials; independent sources of drug information (journals of the International Society of Drug Bulletins (electronically and by hand); and proceedings of meetings and conferences for additional references of trials. We contacted pharmaceutical companies producing antibiotics applied in treating pharyngitis for published or unpublished trials on their products; and experts in the field for additional references.

Data collection and analysis

Selection of studies

Two review authors (MVD, NK) independently read all trials with relevant titles and/or abstracts identified by the search, in order to determine which ones met the inclusion criteria. We excluded all trials failing to meet our inclusion criteria.

Data extraction and management

Two review authors (MVD, NK) independently extracted data, using a standard checklist developed by the review authors for the purpose of the review. The standard data extraction form included the following general information: published/unpublished, title, authors, source, contact address, country, language of publication, year of publication, duplicate publications, sponsoring, and setting. It also included data on the following:

1. Methods: randomisation procedure, allocation, blinding (participants, people administering treatment, outcome assessors), duration of study, design, analysis (intention-to-treat (ITT)).
2. Participants: number, age, diagnostic criteria, history, baseline characteristics.
3. Interventions: interventions (dose, route, timing, duration), comparison group.
4. Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up.
5. Results: for outcomes and times of assessment (including a measure of variation).

Assessment of risk of bias in included studies

Two review authors (MVD, NK) assessed the methodological quality of the included trials by using the Risk of bias tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009) which assesses randomisation, blinding and dropouts. Two review authors (MVD, NK) independently scored each trial.

Measures of treatment effect

We used Review Manager software for statistical analysis. If possible, we summarised data in a meta-analysis and analyses were performed according to ITT analysis. This means that the number of participants randomised was used as the denominator for each outcome. The participants for whom an outcome was not reported were considered as treatment failures. For dichotomous outcomes we expressed results as odds ratios (OR), with 95% confidence intervals (CI). If possible, for statistically significant results we calculated the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH).

Assessment of heterogeneity

We assessed heterogeneity between trial results by calculating a Chi^2 test (significant defined as $P < 0.10$) and a Higgins I^2 statistic (Higgins 2003). A fixed-effect model (Mantel 1959) was used for pooling, but in the presence of statistical heterogeneity (using a cut-off point of I^2 statistic > 20%) the data were pooled with the random-effects model (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We stratified the trials into sub-categories according to the comparisons between different classes of antibiotics. For each comparison the predefined outcomes were reported and pooled, if possible, in a meta-analysis. Subgroup analyses were performed for trials with children versus adults.

We report ITT data for the clinical outcomes in the analysis section. We also report on analysis of evaluable participants (i.e. only including in the analysis participants for whom outcome reporting was complete) to illustrate any differences between analysis methods. Analysis of relapse incidence is analysed by including only evaluable participants, as an ITT analysis would seriously overestimate the importance of relapse and the results would not be relevant to clinical practice.

RESULTS

Description of studies

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

We retrieved 136 search results from our electronic searches. A total of 60 trials were considered for the review. One additional trial was identified through a Google search (Muller 1992). Of these, 18 met the predefined inclusion criteria. Two of the 18 papers reported different outcomes of the same study and are thus considered as one single study (Norrby 2002). Thus, 17 trials were included in the review.

Included studies

Most of the included trials were conducted in the 1990s, two in the 1980s (Henness 1982a; Randolph 1985) and two in the 1970s (Jackson 1973; Trickett 1973). Only one trial was more recent (Norrby 2002).

Contacting pharmaceutical companies did not result in any additional published or unpublished data (only one company replied), neither did contacting authors or experts in the field.

All included studies compared penicillin with another antibiotic class. None of the identified studies compared macrolides with antibiotics other than penicillin.

The included trials investigated a total of 5352 participants with acute GABHS tonsillopharyngitis. The age of participants ranged from one month to 80 years. Seven trials included only or predominantly paediatric participants (Disney 1992a; Disney 1992b; Henness 1982a; Henness 1982b; O'Doherty 1996; Randolph 1985; Reed 1991), nine trials included participants who were at least 12 years or older (Bachand 1991; Carbon 1995; Levenstein 1991; McCarty 1992a; Nemeth 1999; Norrby 2002; Stein 1991; Trickett 1973; Watkins 1997). Two other trials included a wider range of participants aged one month or older. In the study by Reed approximately 80% of participants were under 15 years of age (Reed 1991) and therefore included in the subgroup analysis for children. In Muller 1992 90% of participants were over 12 years old and as results were not stratified per age group this study was included in the adult subgroup analysis.

All trials included only participants with confirmed acute GABHS tonsillopharyngitis. Confirmation of the presence of GABHS in participants with clinical signs of tonsillopharyngitis was in most cases performed first by a rapid immunoassay test and then reconfirmed with a throat culture. In five trials the confirmation of GABHS tonsillopharyngitis was carried out only by a throat culture (Henness 1982a; Henness 1982b; Jackson 1973; Randolph 1985; Trickett 1973) and in two trials only with a rapid immunoassay test (O'Doherty 1996; Stein 1991). All but one trial reported on clinical outcomes. Trickett 1973 only reported bacteriological outcomes, but was included in the meta-analysis on adverse effects.

Clinical outcomes, in most studies defined as complete resolution of signs and symptoms (Characteristics of included studies) were assessed at various time points, but mostly measured between five to 10 days following the end of antibiotic treatment. Therefore, post-treatment the outcome "post-treatment clinical efficacy" (i.e. assessment of signs and symptoms after completion of the treatment course) was pooled. One trial reported clinical effect within the first 24 hours of treatment (Randolph 1985). Three trials reported on specific symptoms, such as sore throat and fever (Bachand 1991; Levenstein 1991; Randolph 1985). None of the trials reported data on the duration of illness.

Ten trials reported the incidence of clinical relapse (Bachand 1991; Carbon 1995; Disney 1992a; Disney 1992b; McCarty 1992a; Muller 1992; Nemeth 1999; O'Doherty 1996; Reed 1991; Stein 1991). The definition of clinical relapse varies slightly between trials; from "pretreatment signs & symptoms resolved but reappeared" Bachand 1991; Carbon 1995; Disney 1992b; Levenstein 1991; McCarty 1992a; Muller 1992; Nemeth 1999; Norrby 2002; Stein 1991) or "initial improvement or alleviation of symptoms, but subsequent worsening or recurrence" (McCarty 1992a; Watkins 1997) to "new infection with different serotype" (Disney 1992a). One study defined clinical cure as "clinical improvement within first 24 hours of therapy and all follow-up cultures no *S. pyogenes*" (Henness 1982a). Two studies used the physician's as-

sessment of symptoms as outcome (Randolph 1985; Reed 1991). Four trials reported complications occurring during longer follow-up (Carbon 1995; Jackson 1973; McCarty 1992a; Muller 1992). Fifteen trials mentioned adverse effects reported during treatment.

The use of antipyretic analgesics was allowed in four trials (Bachand 1991; Disney 1992b; Muller 1992; Watkins 1997), prohibited in two (Carbon 1995; Randolph 1985) and not stated in the other 11 trials.

Excluded studies

Forty-nine trials were excluded from analysis. The most common reason for exclusion (35 trials) was no or inadequate blinding (Adam 1994; Adam 1995; Adam 1996; Adam 2000a; Adam 2000b; Adam 2001; Aujard 1995; Cohen 2002; Denny 1953; Dykhuizen 1996; Esposito 2002; Feder 1999; Gerber 1986; Gooch 1993; Hamill 1993; Holm 1991; Howe 1997; Lennon 2008; McCarty 1992b; McCarty 1994; Milatovic 1991; Milatovic 1993; Pacifico 1996; Perkins 1969; Pichichero 2000; Pichichero 2008; Portier 1990; Portier 1994; Sakata 2008; Shapera 1973; Shvartzman 1993; Stillerman 1986; Tack 1997; Tack 1998; Uysal 2000). Six trials did not compare at least two different classes of antibiotics (Breese 1974; Disney 1979; Matsen 1974; McIsaac 2004; Siegel 1961; Zwart 2000). In two trials the included participants did not exclusively have acute GABHS tonsillopharyngitis (Davies 1995; Standaert 1997) and one trial included patients with recurrent tonsillitis (Roos 1997). One trial did not report any clinical outcomes (Gerber 1999) and four trials were not randomised controlled trials (RCTs) (Del Mar 2008; De Meyere 1992; Granizio 2008; Haverkorn 1971).

Risk of bias in included studies

Risk of bias assessment is reported in the Characteristics of included studies table. Only three trials (Disney 1992a; Norrby 2002; Randolph 1985) reported an ITT analysis for the efficacy outcomes. One trial reported carrying out an ITT analysis, but post-randomisation exclusions were not included in the efficacy analysis (Carbon 1995). All trial authors used an ITT analysis for adverse effects.

Allocation

All trials were randomised, but only three described the method of randomisation and/or allocation concealment (Jackson 1973; Randolph 1985; Watkins 1997).

Blinding

All the trials were double-blinded, and the method of blinding was described in 13 of the 17 trials (Disney 1992a; Disney 1992b; Jackson 1973; Levenstein 1991; McCarty 1992a; Muller 1992; Norrby 2002; O'Doherty 1996; Randolph 1985; Reed 1991; Stein 1991; Trickett 1973; Watkins 1997).

Incomplete outcome data

The post-randomisation dropout rate was high in most trials. In 11 trials (Bachand 1991; Henness 1982a; Jackson 1973; Levenstein 1991; McCarty 1992a; Nemeth 1999; Muller 1992; Norrby 2002; O'Doherty 1996; Stein 1991; Watkins 1997) the proportion of dropouts was more than 20%, ranging from 21.5% (McCarty 1992a) to 48.5% (Levenstein 1991). In the outcome analysis most trials included only participants with complete outcome data. This may have had an important impact on the effect measured. Only three trials performed an ITT analysis with all randomised participants included in the analysis of the clinical outcome (Disney 1992a; Norrby 2002; Randolph 1985). These three trials all have minimal to no dropouts (0 or 1 participant).

Selective reporting

Most trials reported a composite outcome of "clinical cure". This is a relevant outcome for clinical practice, but the definition of cure may have differed in the included trials.

Other potential sources of bias

Ten trials reported that they were sponsored by a pharmaceutical company (Disney 1992b; Jackson 1973; McCarty 1992a; Muller 1992; Nemeth 1999; Norrby 2002; Randolph 1985; Reed 1991; Trickett 1973; Watkins 1997). Authors of six trials were reported as employees of a pharmaceutical company (Bachand 1991; Disney 1992b; Henness 1982a; Henness 1982b; Nemeth 1999; Watkins 1997); and in three of those trials the employing pharmaceutical company was not reported as a funding source (Bachand 1991; Henness 1982a; Henness 1982b). The remaining five trials did not mention their funding source.

Six trials mentioned that ethics approval was obtained for the study (Bachand 1991; Levenstein 1991; Muller 1992; Nemeth 1999; Norrby 2002; O'Doherty 1996) and seven trials reported- that informed consent was obtained from participants or guardians (Levenstein 1991; McCarty 1992a; Muller 1992; Nemeth 1999; Norrby 2002; O'Doherty 1996; Reed 1991).

Effects of interventions

1. Cephalosporin versus penicillin

Resolution of symptoms

Six trials (Carbon 1995; Disney 1992a; Nemeth 1999; Henness 1982a; Randolph 1985; Reed 1991) reported on the resolution of symptoms at various points in time.

Five trials measured resolution of symptoms at the end of treatment (two to 15 days or more post-treatment), two trials in adults (Carbon 1995; Nemeth 1999) and three in children (Disney 1992b; Henness 1982a; Reed 1991). The ITT analysis included 2018 participants and showed no difference between treatments (OR 0.79; 95% CI 0.55 to 1.12). The effect in adults (N = 2; n = 1163; OR 0.78; 95% CI 0.60 to 1.01) was similar to that in children (N = 3; n = 855; OR 0.83; 95% CI 0.40 to 1.73).

The result of the analysis of evaluable participants only (n = 1660) showed an effect in favour of treatment with cephalosporins (OR 0.51; 95% CI 0.27 to 0.97; absolute risk difference (ARD) 0.05; NNTB 20). However, the estimates of effect in adults (N = 2; n = 880; OR 0.56; 95% CI 0.24 to 1.32) and in children (N = 3; n = 780; OR 0.46; 95% CI 0.14 to 1.52) analysed separately revealed no statistically significant differences between treatment groups.

We analysed the studies with reported pharmaceutical company sponsorship separate from the studies that did not mention any industry involvement for the outcome resolution of symptoms post-treatment. The two studies that did not report their funding source (Carbon 1995; Disney 1992a) showed a statistically significant effect in favour of cephalosporins (OR 0.47; 95% CI 0.27 to 0.81; ARD 0.02; NNTB 50). The sponsored studies pooled together (Henness 1982a; Nemeth 1999; Reed 1991) did not result in a significant difference between the two groups of antibiotics.

One trial in children (n = 138) also reported the resolution of symptoms within 24 hours of treatment (Randolph 1985) and found no difference between treatment groups (OR 0.97; 95% CI 0.34 to 2.74).

Sore throat

One trial in children (Randolph 1985) found no difference between treatment groups for resolution of sore throat (n = 138; OR 0.97; 95% CI 0.23 to 4.04).

Fever

One trial in children (Randolph 1985) found no difference between treatment groups for resolution of fever (n = 138; OR 0.97; 95% CI 0.19 to 4.98).

Incidence of relapse

In four trials (n = 1386) that reported the incidence of clinical relapse in evaluated participants (Carbon 1995; Disney 1992a; Nemeth 1999; Reed 1991) there was a benefit of treatment with cephalosporins over penicillin in the total population (OR 0.55; 95% CI 0.31 to 0.99; ARD 0.02; NNTB 50). This was due to a difference in the two trials in adults (Carbon 1995; Nemeth 1999) (n = 770; OR 0.42; 95% CI 0.20 to 0.88; ARD 0.03; NNTB 33.3). There was no difference in the two trials in children (Disney 1992a; Reed 1991) (n = 616; OR 0.89; 95% CI 0.33 to 2.43).

Complications

In one trial in adults (Carbon 1995) no complications were reported in the cephalosporin group (119 participants) or the penicillin group (125 participants).

Adverse events

Three trials in adults reported the incidence of adverse effects (Carbon 1995; Nemeth 1999; Reed 1991). There was significant heterogeneity between the trials. In the cephalosporin group 212 of 788 participants reported adverse events, compared to 87 of 491 in the penicillin group. There was no difference between the two treatments (OR 0.99; 95% CI 0.31 to 3.16).

2. Macrolide versus penicillin

Resolution of symptoms post-treatment

Five trials in adults (Bachand 1991; Levenstein 1991; Norrby 2002; Stein 1991; Watkins 1997) and one trial in children (O'Doherty 1996) investigated the resolution of symptoms at various points in time post-treatment. In the ITT analysis of 1728 participants there were no differences between the two treatment groups (OR 1.11; 95% CI 0.92 to 1.35). The estimate of effect in adults (N = 5; n = 1239; OR 1.07; 95% CI 0.86 to 1.34) was similar to that in the trial in children (n = 489; OR 1.25; 95% CI 0.85 to 1.84). The analysis of evaluable participants only did not result in any significant differences between treatment groups (n = 1159; OR 0.79; 95% CI 0.57 to 1.09). The estimate for the five trials in adults (n = 801) was OR 0.88; 95% CI 0.59 to 1.31 and one trial in children (n = 358) was OR 0.64; 95% CI 0.36 to 1.11.

ITT analysis of pharmaceutical industry sponsored trials versus trials that did not report their funding source does not show significant differences in results.

Sore throat

Two trials in adults (n = 371) reported the resolution of sore throat in adults (n = 371) (Bachand 1991; Levenstein 1991) and found no difference between the two treatments (OR 0.97; 95% CI 0.64 to 1.46).

Fever

Resolution of fever at two to 10 days post-treatment was reported in two trials with 371 adult participants (Bachand 1991; Levenstein 1991). All participants in both groups were free of fever

at the time they were evaluated (45 participants in the macrolide group and 39 in the penicillin group; OR 1.05; 95% CI 0.69 to 1.59).

Incidence of relapse

Incidence of clinical relapse was evaluated in six trials, five trials in adults (Bachand 1991; Levenstein 1991; Norrby 2002; Stein 1991; Watkins 1997) and one in children (O'Doherty 1996). Twenty-two of 441 participants in the macrolide group and 16 of 361 in the penicillin group reported a relapse at day 15 to 56 post-treatment. The difference was not statistically significant (OR 1.21; 95% CI 0.48 to 3.03).

Adverse events

In the six trials (n = 1727), five in adults and one in children (O'Doherty 1996), that reported on the incidence of adverse events, there were no statistically significant differences between the treatment groups: 282 events were reported in the macrolide group and 251 in the penicillin group (OR 1.19; 95% CI 0.82 to 1.73). In the trial in children (n = 489) macrolides seemed to cause more adverse events than penicillin (OR 2.33; 95% CI 1.06 to 5.15; NNTH 17.2).

3. Carbacephem versus penicillin

Three trials are included in this comparison (n = 795): one in children (Disney 1992b), one in adults (McCarty 1992a) and one in a population of adults and children (but predominantly adults as 90% were older than 12 years) (Muller 1992).

Resolution of symptoms post-treatment

In the ITT analysis more participants reported resolution of symptoms in the carbacephem group than in the penicillin group (n = 795; OR for absence of symptom resolution post-treatment 0.70; 95% CI 0.49 to 0.99; ARD 0.07; NNTB 14.3). In adult participants there was no difference (n = 562; OR 0.75; 95% CI 0.46 to 1.22) and in children there was a beneficial effect of carbacephem (n = 233; OR 0.57; 95% CI 0.33 to 0.99; ARD 0.12; NNTB 8.3). The analysis of evaluable participants showed no differences between treatment groups (n = 602; OR 0.62; 95% CI 0.38 to 1.01).

Incidence of relapse

There were no differences in the incidence of clinical relapse between groups treated with carbacephem or penicillin (21 events in 267 participants treated with carbacephem and 16 in 256 participants treated with penicillin; OR 1.27; 95% CI 0.64 to 2.50).

Adverse events

There were no differences in reported adverse events between the treatments (75 events reported in 396 participants treated with carbacephem and 71 in 399 participants treated with penicillin; OR 1.08; 95% CI 0.75 to 1.55). Muller reported that one participant was hospitalised for surgical drainage of a tonsillar abscess in the group treated with loracarbef one day after initiating therapy (Muller 1992).

4. Clindamycin versus ampicillin

One trial compared treatment with clindamycin to ampicillin (Jackson 1973) (n = 314). The only outcome reported is adverse events. Six participants reported adverse events in the group treated with clindamycin (156 participants) and 14 participants experienced adverse events in the ampicillin group (158 participants). The difference was not statistically significant (OR 0.41; 95% CI 0.15 to 1.10). No other clinical outcomes were reported.

5. Sulfonamide versus penicillin

One trial in adults was included in this comparison (Trickett 1973). It reported only on adverse events (eight events reported in participants treated with sulphonamides and six events in the penicillin group) and found no difference between sulphonamide and penicillin (OR 1.37; 95% CI 0.43 to 4.34).

6. Penicillin allergy

Muller reports that one patient developed a rash and one patient experienced vomiting, both attributed to use of penicillin (although the patient was then successfully switched to amoxicillin/clavulanate). However, in the loracarbef group also one participant discontinued treatment because of a rash (Muller 1992). None of the other included trials reported on penicillin allergy.

DISCUSSION

Summary of main results

Our meta-analysis shows that there is generally no strong evidence for clinically important differences in clinical outcomes when comparing different classes of antibiotics with penicillin in adults and children with pharyngitis caused by GABHS.

Resolution of symptoms

Intention to treat (ITT) analysis does not show any difference in resolution of symptoms between cephalosporins and penicillin. When only evaluable participants are included in the analysis (i.e. participants for whom an outcome was known) there seems to be a

benefit of cephalosporins over penicillin with regard to resolution of symptoms after treatment (NNTB 20). Subgroup analysis of adults and children did not reveal any significant differences, but this can be attributed to lack of sufficient power.

ITT analysis of the comparison between carbacephem and penicillin showed a benefit of carbacephem with regard to resolution of symptoms after treatment with a NNTB of 14.3. There is no significant benefit in the (large) adult subgroup, and the effect may thus be largely based on an observed effect in children (NNTB 8.3). The analysis of evaluable participants only does not reach statistical significance (but the estimated NNTB is likely to be high).

Other comparisons with penicillin (macrolides or clindamycin or sulfonamides) did not report clinical outcomes for this meta-analysis.

Relapse

The incidence of relapse in evaluable participants seems to be lower in participants treated with cephalosporins compared with penicillin, but the event rate is low (approximately 3.5%) and the NNTB is quite high (NNTB 50). There were no differences in relapse rate between other antibiotics and penicillin.

Adverse events

Adverse events occurred at a similar rate in all treatment groups, except children treated with macrolides seemed to experience more adverse events than children treated with penicillin (although this difference was not statistically significant, most likely due to insufficient power).

The results of our meta-analysis are not clear cut and need to be discussed in the context of morbidity (including serious complications) prevalence, concerns for rising antibiotic resistance and economic constraints in all healthcare systems.

Overall completeness and applicability of evidence

Although we have searched several databases and scrutinised all references listed in identified reviews and publications of trials, we may have missed some trials. We have contacted experts and pharmaceutical companies. One pharmaceutical company responded, but this did not result in additional data. This additional search did not yield any new published or unpublished trials. As an analysis of unpublished data used in Cochrane Reviews suggests that generally, searching for unpublished data does not uncover new data that are important to the conclusion of the review (van Driel 2009), the lack of unpublished data may not have had an important impact on the results of our review.

Our meta-analysis focuses on clinical outcomes only. Reviews that report bacteriological outcomes point to the superiority of cephalosporins over penicillin with regard to eradication of GABHS (Brunton 2006; Casey 2004). However, this does not take the clinical presentation into account. Gerber et al found no difference in bacteriologic treatment success rates between cefadroxil and penicillin groups among participants classified clinically as likely to have true GABHS pharyngitis, but cephalosporins seemed to be more successful in eradicating GABHS is patients classified clinically as likely to be streptococcal carriers (Gerber 1999). Contamination of treatment groups by such chronic GABHS carriers contributes to the apparent superiority of cephalosporins in studies focusing on bacteriological outcomes (Shulman 2004). This is of very limited clinical relevance. To our knowledge chronic streptococcal carriage is not linked to higher risk of developing GABHS pharyngitis and hence eradication of streptococci in carriers is not a treatment goal. Information on complications is scarcely reported and therefore we cannot draw any conclusions concerning this outcome.

Quality of the evidence

A strong point of our review is that we included only randomised and double-blinded trials. This was intended to minimise the risk of bias related to selection of participants and reporting of outcomes. However, in spite of the lower risk of bias due to methodology, reporting of the findings and transparency of the analyses in the trials were often unsatisfactory. Patient characteristics were poorly reported and outcomes poorly or not at all defined. Dropout rates in some studies were very high (> 20%).

The overall risk of bias in included studies is difficult to assess because the process of randomisation and blinding is not described in most studies. For instance, only four studies (Jackson 1973; Randolph 1985; Reed 1991; Watkins 1997) described the method used to conceal allocation.

It is surprising that "resolution of sore throat", a key symptom in GABHS pharyngitis, is only reported as a separate outcome in one study (McCarty 1992a). Most studies assess the "whole clinical picture" of the clinical presentation of pharyngitis, which is a combination of symptoms including sore throat, fever and feeling unwell. Assessment of the effect of antibiotics on the full range of signs and symptoms is therefore clinically relevant.

Potential biases in the review process

Pooling of the different outcomes is hampered by the differences of outcome definitions across studies. As most trials measure clinical outcome within two weeks of the end of antibiotic treatment, they were pooled for the outcome 'resolution of symptoms post-treatment'. The trial that reported symptom resolution within the first 24 hours of treatment is considered separately. Very few trials report on specific symptoms related to acute GABHS tonsillopharyngitis. As 'symptom resolution' is a subjective outcome, the interpretation may be different across trials and pooling may therefore be inappropriate. However, differences between comparison groups in the same trial will not be affected (as they are measured in the same population).

The results of this meta-analysis are based on ITT analysis of the selected outcomes. However, this may underestimate the efficacy of treatment. Most trials reported the number of participants randomised, but included only the evaluated participants in the outcome analysis. When reported, a common reason for post-randomisation exclusion is a negative throat culture, suggesting that another pathogen caused the signs and symptoms of acute tonsillopharyngitis. Including these GABHS-negative participants in the analysis could bias the results if exclusion is not similar in both treatment groups. Some trials reported exclusions per group and show that this is not the case. When comparing two efficacious treatments this potential underestimation does not seem relevant as it will not influence the conclusions. However, for the trials that do not report this, it is not possible to know if selective exclusions occurred. We checked if the method of analysis influenced outcome by performing both ITT and analysis of evaluable participants for the outcome resolution of symptoms post-treatment. This showed different results in two comparisons. When comparing cephalosporins and penicillin, ITT analysis for this outcome yielded a non-significant result, whereas analysis of evaluable participants showed a benefit of cephalosporins over penicillin. The opposite occurred in the analysis of effect on the same outcome in participants treated with carbacephem versus penicillin; where ITT analysis showed a statistically significant difference and the evaluable participants analysis did not, most likely due to a reduction in the number of participants included in the analysis (resulting in reduced statistical power). Analysing only evaluable participants implies a high risk of bias as there may have been a selective dropout. On the other hand, the ITT analysis can be considered as a conservative estimate of the true effect.

The estimated odds ratios suggest that large benefits can be expected when treating patients with cephalosporins or carbacephems. But these supposedly impressive effects expressed as a relative measure of risk (expressed as an OR) do not always translate into a clinically meaningful difference. For example, the estimated OR of 0.55 for the incidence of relapse in cephalosporins compared with penicillin, suggests that the risk of relapse could be halved by treating patients with cephalosporins. However, the associated absolute risk difference is 0.02, resulting in a NNTB of 50, which means that 50 patients need to be treated with broad-spectrum more expensive antibiotics to prevent one additional relapse.

Calculating the absolute risk difference and the NNTB is therefore a useful method to assess the clinical importance of a relative risk. The interpretation of the NNTBs (how many patients needed to treat is acceptable) is however, not clear cut and depends on assessment of benefit and harm and also cost-effectiveness.

All the trials in our review were performed in high-income countries. The incidence of suppurative and other complications (which are rare in high-income countries) as well as antimicrobial resistance rates may be different in low-income countries or specific communities with high prevalences of GABHS tonsillitis (Hanna 2010). Therefore, studies performed in low-income and high prevalence communities are needed.

Agreements and disagreements with other studies or reviews

Our review shows that although there seems to be some benefit of antibiotics with a wider spectrum, i.e. cephalosporins and carbacephem, this observed effect is not consistent across analysis methods and studied subgroups. Cephalosporins show a benefit regarding resolution of symptoms only in the analysis of evaluable participants and carbacephem is superior to penicillin for this outcome only in the ITT analysis (attributable to an effect in children treated with a carbacephem). The NNTBs associated with the observed effects are relatively high (20 for treatment with cephalosporins compared with penicillin), except perhaps for the effect of carbacephem in children (NNTB 8.3). There is no clinically meaningful difference between penicillin and the other classes of antibiotics that have been studied with regard to rate of clinical relapse. However, cephalosporins seem to reduce relapse rate (NNTB 50), especially in adults (NNTB 30).

The effects observed in cephalosporins and carbacephems and not in the other antibiotic classes can be explained by the fact that although they are considered different classes of antibiotics, carbacephems chemically closely resemble cephalosporins (Cooper 1992).

Interpretation of these findings for clinical practice is not straightforward. One could argue that our meta-analysis points to a superior efficacy of cephalosporins over penicillin, especially in adults where the upper limit of the 95% CI is 1.01 (P = 0.06) in the ITT analysis. The population size may not have been large enough to reach statistical significance. This finding is in line with an earlier meta-analysis concluding that cephalosporins are superior to penicillin in treating GABHS pharyngitis and therefore cephalosporins should be considered first choice (Casey 2004). But in our meta-analysis the absolute difference between the two groups (cephalosporin or penicillin) although not statistically significant is only 2.5% which implies a NNTB of 40. Treating 40 patients with cephalosporins instead of penicillin would incur an additional cost to the healthcare system as well as add to the risk of developing antibiotic resistance, especially in broad spectrum antibiotics such as cephalosporins.

The observed superior effect of cephalosporins in reducing the rate of relapse has also been reported in another meta-analysis (Casey 2004). However, in our meta-analysis it is only observed in adults and may be biased by the rather liberal definition of relapse in the study that accounts for 49% of the weighting in the meta-analysis (Nemeth 1999); "worsening of, or absence of significant remission of, signs & symptoms 17 to 24 days post-therapy or need for further AB therapy", whereas in other studies "recurrence of symptoms" after initial remission was required. The NNTB of 33 participants that need to be treated with cephalosporins rather

than penicillin to prevent one participant experiencing relapse illustrates the limited clinical relevance of this statistically significant result.

How can the differences between Casey's meta-analysis and ours be explained? Casey included 35 trials; two thirds of those were not blinded and reporting of randomisation and losses to follow up was very poor implying a high risk of bias (Gerber 2004b). By restricting the inclusion to double-blinded trials we ruled out one source of potential bias and improved the methodological rigour of the meta-analysis. Casey's subgroup analysis of double-blinded studies generated an OR similar to ours (although with a much narrower CI, OR 0.43; 95% CI 0.25 to 0.71), but it included studies with carbacephems, which have been advertised as a separate class of antibiotics (Cooper 1992). Casey reports an analysis of evaluable patients, whereas ITT analysis may be more appropriate especially with important numbers of dropouts (which is the case in many of the trials included in our meta-analysis). The trial populations included in Casey's review, as in ours, may have been contaminated with chronic carriers of GABHS who had intercurrent viral pharyngitis (Gerber 2004b) but it is not clear if this has implications for clinical practice.

We found no differences in the incidence of adverse events and data on long-term follow up and the occurrence of complications was insufficient. Therefore, costs and antimicrobial resistance patterns are important in making a choice.

stantial. This is insufficiently convincing evidence to alter current guideline recommendations for the treatment of patients with GABHS tonsillopharyngitis. Moreover, we found no clinically important differences in occurrence of adverse events and data on the incidence of complications are too scarce to draw conclusions.

Antibiotics have a limited effect in the treatment of patients with acute sore throat, even in the presence of GABHS. However, if antibiotics are to be prescribed, based on these results and taking into consideration the costs and antimicrobial resistance patterns of the different antibiotics, penicillin can still be considered first choice in both adults and children.

Implications for research

The observed differences in clinical efficacy between adults and children needs further exploration. Prevention of serious complications such as acute rheumatic fever and acute glomerulonephritis are often mentioned as arguments in favour of antibiotic use. However, the current data do not provide information about the impact of different antibiotics on the prevention of complications. Further studies with longer follow up might be able to address this issue. As these complications seem to be more prevalent in low-income and high-risk communities (for example, Australian Indigenous communities), studies in these specific high-risk communities are needed. Economic analysis of the cost-effectiveness of the different treatment options can provide additional guidance for making a choice.

AUTHORS' CONCLUSIONS

Implications for practice

Although there seem to be indications that carbacephems and cephalosporins might have some benefit over penicillin in terms of resolution of symptoms and incidence of relapse, the findings are inconsistent across analysis methods and the NNTB are sub-

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REFERENCES

References to studies included in this review

Bachand 1991 ***{published data only}***
Bachand RT Jr. A comparative study of clarythromycin and penicillin VK in the treatment of outpatients with streptococcal pharyngitis. *Journal of Antimicrobial Chemotherapy* 1991;**27**(Suppl A):75–82.

Carbon 1995 ***{published data only}***
Carbon C, Chatelin A, Bingen E, Zuck P, Rio Y, Guetat F, et al. A double-blind randomized trial comparing the efficacy and safety of a 5-day course of cefotiam hexetil with that of a 10-day course of penicillin V in adult patients with pharyngitis caused by group A beta-haemolytic streptococci. *Journal of Antimicrobial Chemotherapy* 1995;**35**(6):843–54.

Disney 1992a ***{published data only}***
Disney FA, Dillon H, Blumer JL, Dudding BA, McLinn SE, Nelson DB, et al. Cephalexin and penicillin in the treatment of group A beta-hemolytic streptococcal throat infections. *American Journal of Diseases of Children* 1992; **146**(11):1324–7.

Disney 1992b ***{published data only}***
Disney FA, Hanfling MJ, Hausinger SA. Loracarbef (LY163892) vs. penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis. *Pediatric Infectious Disease Journal* 1992;**11**(Suppl 8):20–6.

Henness 1982a ***{published data only}***
Henness DM. A clinical experience with cefadroxil in

upper respiratory tract infection. *Journal of Antimicrobial Chemotherapy* 1982;**10**(Suppl B):125–35.

Henness 1982b ***{published data only}***
Henness DM. A clinical experience with cefadroxil in upper respiratory tract infection. *Journal of Antimicrobial Chemotherapy* 1982;**10**(Suppl B):125–35.

Jackson 1973 ***{published data only}***
Jackson H. A comparative study of clindamycin palmitate and ampicillin in the treatment of group A beta hemolytic streptococcal pharyngitis. *Clinical Pediatrics* 1973;**12**(8): 501–3.

Levenstein 1991 ***{published data only}***
Levenstein JH. Clarythromycin versus penicillin in the treatment of streptococcal pharyngitis. *Journal of Antimicrobial Chemotherapy* 1991;**27**(Suppl A):67–74.

McCarty 1992a ***{published data only}***
McCarty J. Loracarbef versus penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis in an adult population. *American Journal of Medicine* 1992;**92**(Suppl 6A):74–9.

Muller 1992 ***{published data only}***
Muller O, Spirer Z, Wettich K. Loracarbef versus penicillin V in the treatment of Streptococcal pharyngitis and tonsillitis. *Infection* 1992;**20**(5):301–8.

Nemeth 1999 ***{published data only}***
Nemeth MA, McCarty J, Gooch III WM, Henry D, Keyserling CH, Tack KJ. Comparison of cefdinir and penicillin for the treatment of streptococcal pharyngitis. *Clinical Therapeutics* 1999;**21**(11):1873–81.

Norrby 2002 ***{published data only}***
Norrby SR, Chang J, Stewart JA, Brumpt I, Conway DP. Relief of symptoms in patients with group A b-hemolytic streptococcus tonsillopharyngitis: comparison between telithromycin and penicillin V. *Scandinavian Journal of Infectious Diseases* 2003;**35**(4):223–5.
Norrby SR, Rabie WJ, Bacart P, Mueller O, Leroy B, Rangaraju M, et al. Efficacy of short-course therapy with the ketolide telithromycin compared with 10 days of penicillin V for the treatment of pharyngitis/tonsillitis. *Scandinavian Journal of Infectious Diseases* 2002;**33**(12):883–90.

O'Doherty 1996 ***{published data only}***
O'Doherty B, and the Paediatric Azithromycin Study Group. Azithromycin versus penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/ tonsillitis. *European Journal of Clinical Microbiology and Infectious Diseases* 1996;**15**(9):718–24.

Randolph 1985 ***{published data only}***
Randolph MF, Gerber MA, DeMeo KK, Wright BS. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *Journal of Pediatrics* 1985;**106**(6):870–5.

Reed 1991 ***{published data only}***
Reed BD, Huck W, Zazove P. Treatment of beta-hemolytic streptococcal pharyngitis with cefaclor or penicillin; efficacy and interaction with beta-lactamase-producing organisms in the pharynx. *Journal of Family Practice* 1991;**32**(2):138–44.

Stein 1991 ***{published data only}***
Stein GE, Christensen S, Mummaw N. Comparative study of clarythromycin and penicillin V in the treatment of streptococcal pharyngitis. *European Journal of Clinical Microbiology and Infectious Diseases* 1991;**10**(11):949–53.

Trickett 1973 ***{published data only}***
Trickett PC, Dineen P, Mogabgab W. Clinical experience: respiratory tract. Trimethoprim-sulfamethoxazole versus penicillin G in the treatment of group A beta-hemolytic streptococcal pharyngitis and tonsillitis. *The Journal of Infectious Diseases* 1973;**128**(Suppl):693–5.

Watkins 1997 ***{published data only}***
Watkins VS, Smietana M, Conforti PM, Sides GD, Huck W. Comparison of dirithromycin and penicillin for treatment of streptococcal pharyngitis. *Antimicrobial Agents and Chemotherapy* 1997;**41**(1):72–5.

References to studies excluded from this review

Adam 1994 ***{published data only}***
Adam D, Hostalek U. Effectiveness and tolerance of cefixime in comparison with penicillin V in bacterial pharyngitis and tonsillitis in children. Cefixime Study Group. *Klinische Padiatrie* 1994;**206**(1):26–9.

Adam 1995 ***{published data only}***
Adam D, Hostalek U, Troster K. 5-day cefixime therapy for bacterial pharyngitis and/or tonsillitis: comparison with 10-day penicillin V therapy. *Infection* 1995;**22**(Suppl 2):83–6.

Adam 1996 ***{published data only}***
Adam D, Scholz H, and the Pharyngitis Study Group. Five days of erythromycin estolate versus ten days of penicillin V in the treatment of group A Streptococcal tonsillopharyngitis in children. *European Journal of Clinical Microbiology and Infectious Diseases* 1996;**15**(9):712–7.

Adam 2000a ***{published data only}***
Adam D, Scholz H, Helmerking M. Comparison of short-course (5 day) cefuroxime axetil with a standard 10 day oral penicillin V regimen in the treatment of tonsillopharyngitis. *The Journal of Antimicrobial Chemotherapy* 2000;**45**(Suppl): 23–30.

Adam 2000b ***{published data only}***
Adam D, Scholz H, Helmerking M. Short-course antibiotic treatment of 4782 culture-proven cases of group A streptococcal tonsillopharyngitis and incidence of poststreptococcal sequelae. *The Journal of Infectious Diseases* 2000;**182**(2):509–16.

Adam 2001 ***{published data only}***
Adam D, Scholz H, Helmerking M. Five days ceftibuten versus 10 days penicillin in the treatment of 2099 patients with A-streptococcal tonsillopharyngitis [Fünf Tage Ceftibuten im Vergleich zu zehn Tagen Penicillin V in der Therapie der A–Streptokokken–Tonsillopharyngitis]. *Fortschritte der Medizin* 2001;**119**(Suppl 2):63–70.

Aujard 1995 ***{published data only}***
Auyard Y, Boucot I, Brahimi N, Chiche D, Bingen E. Comparative efficacy and safety of four-day cefuroxime

axetil and ten-day penicillin treatment of group A beta-hemolytic streptococcal pharyngitis in children. *Pediatric Infectious Disease Journal* 1995;**14**(4):295–300.

Breese 1974 ***{published data only}***
Breese BB, Disney FA, Talpey WB, Green JL. Treatment of Streptococcal pharyngitis with amoxicillin. *Journal of Infectious Diseases* 1974;**129**(Suppl):178–80.

Cohen 2002 ***{published data only}***
Cohen R, Reinert P, De La Rocque F, Levy C, Boucherat M, Robert M, et al. Comparison of two dosages of azithromycin for three days versus penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2002;**21**:297–303.

Davies 1995 ***{published data only}***
Davies HD, Low DE, Schwartz B, Scriver S, Fletcher A, O'Rourke K, et al. Evaluation of short-course therapy with cefixime or rifampin for eradication of pharyngeally carried group A Streptococci. *Clinical Infectious Diseases* 1995;**21**: 1294–6.

De Meyere 1992 ***{published data only}***
de Meyere M, Mervielde I, Bogaert M. Use of antibiotics in acute sore throat [Het nut van antibiotica bij acute keelpijn]. *Nederlands Tijdschrift Voor Geneeskunde* 1992; **136**(47):2314–7.

Del Mar 2008 ***{published data only}***
Del Mar C. Once- daily amoxycillin eradicates group A beta-hemolytic strep as well as penicillin twice a day. *Journal of Pediatrics* 2008;**153**(5):725.

Denny 1953 ***{published data only}***
Denny FW, Wannamaker LW, Hahn EO. Comparative effects of penicillin, aureomycin and terramycin on Streptococcal tonsillitis and pharyngitis. *Pediatric Infectious Disease* 1953;**11**:7–14.

Disney 1979 ***{published data only}***
Disney FA, Breese BB, Francis AB, Green JL. The use of cefaclor in the treatment of beta-haemolytic streptococcal throat infections in children. *Postgraduate Medical Journal* 1979;**55**(Suppl 4):50–2.

Dykhuizen 1996 ***{published data only}***
Dykhuizen RS, Golder D, Reid TMS, Gould IM. Phenoxymethyl penicillin versus co-amoxiclav in the treatment of acute streptococcal pharyngitis, and the role of beta-lactamase activity in saliva. *Journal of Antimicrobial Chemotherapy* 1996;**37**:133–8.

Esposito 2002 ***{published data only}***
Esposito S, Marchisio P, Bosis S, Droghetti R, Mattina R, Principi N, et al. Comparative efficacy and safety of 5-day cefaclor and 10-day amoxycillin treatment of group A Streptococcal pharyngitis in children. *International Journal of Antimicrobial Agents* 2002;**20**:28–33.

Feder 1999 ***{published data only}***
Feder HM Jr, Gerber MA, Randolph MF, Stelmach PS, Kaplan EL. Once-daily therapy for Streptococcal pharyngitis with amoxicillin. *Pediatrics* 1999;**103**:47–51.

Gerber 1986 ***{published data only}***
Gerber MA, Randolph MF, Chanatry J, Wright LL, Anderson LR, Kaplan EL. Once daily therapy for streptococcal pharyngitis with cefadroxil. *Journal of Pediatrics* 1986;**109**(3):531–7.

Gerber 1999 ***{published data only}***
Gerber MA, Tanz RR, Kabat W, Bell GL, Siddiqui PN, Lerer TJ, et al. Potential mechanisms for failure to eradicate group A Streptococci from the pharynx. *Pediatrics* 1999; **104**(4):911–7.

Gooch 1993 ***{published data only}***
Gooch WM 3rd, McLinn SE, Arnovitz GH, Pichichero ME, Kumar A, Kaplan A, et al. Efficacy of cefuroxime axetil suspension compared with that of penicillin V suspension in children with group A streptococcal pharyngitis. *Antimicrobial Agents and Chemotherapy* 1993;**37**(2):159–63.

Granizio 2008 ***{published data only}***
Granizio JJ, Gimenez MJ, Barberan J, Coronel J, Gimeno M, Aguilar L. Efficacy of cefditoren in the treatment of upper respiratory tract infections: a pooled analysis of six clinical trials. *Revista Espanola de Quimioterapia* 2008;**21** (1):14–21.

Hamill 1993 ***{published data only}***
Hamill J. Multicentre evaluation of azithromycin and penicillin V in the treatment of acute Streptococcal pharyngitis and tonsillitis in children. *Journal of Antimicrobial Chemotherapy* 1993;**31**(Suppl E):89–94.

Haverkorn 1971 ***{published data only}***
Haverkorn MJ, Valkenburg HA, Goslings WR. Streptococcal pharyngitis in the general population. I. A controlled study of Streptococcal pharyngitis and its complications in the Netherlands. *Journal of Infectious Diseases* 1971;**124**(4):339–47.

Holm 1991 ***{published data only}***
Holm SE, Roos K, Stromberg A. A randomized study of treatment of Streptococcal pharyngotonsillitis with cefadroxil or phenoxymethylpenicillin (penicillin V). *Pediatric Infectious Disease Journal* 1991;**10**(Suppl 10): 68–71.

Howe 1997 ***{published data only}***
Howe RW, Millar MR, Coast J, Whitfield M, Peters TJ, Brookes S. A randomized controlled trial of antibiotics on symptom resolution in patients presenting to their general practitioner with a sore throat. *British Journal of General Practice* 1997;**47**:280–4.

Lennon 2008 ***{published data only}***
Lennon DR, Farrell E, Martin DR, Stewart JM. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-hemolytic streptococcal pharyngitis. *Archives of Disease in Childhood* 2008;**93**(6):474–8.

Matsen 1974 ***{published data only}***
Matsen JM, Torstenson O, Siegel SE, Bacaner H. Use of available dosage forms of cephalexin in clinical comparison with phenoxymethyl penicillin and benzathine penicillin in the treatment of streptococcal pharyngitis in children. *Antimicrobial Agents and Chemotherapy* 1974;**6**(4):501–6.

McCarty 1992b ***{published data only}***
McCarty JM, Renteria A. Treatment of pharyngitis and tonsillitis with cefprozil: review of three multicenter trials. *Clinical Infectious Diseases* 1992;**14**(Suppl 2):224–30.

McCarty 1994 ***{published data only}***
McCarty JM. Comparative efficacy and safety of cefprozil versus penicillin, cefaclor and erythromycin in the treatment of Streptococcal pharyngitis and tonsillitis. *European Journal of Clinical Microbiology and Infectious Diseases* 1994; **13**(10):846–50.

McIsaac 2004 ***{published data only}***
McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. *Journal of the American Medical Association* 2004;**291**(13):1587–95.

Milatovic 1991 ***{published data only}***
Milatovic D. Evaluation of cefadroxil, penicillin and erythromycin in the treatment of streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 1991;**10**(Suppl):61–3.

Milatovic 1993 ***{published data only}***
Milatovic D, Adam D, Hamilton H, Materman E. Cefprozil versus penicillin V in the treatment of Streptococcal tonsillopharyngitis. *Antimicrobial Agents and Chemotherapy* 1993;**37**(8):1620–3.

Pacifico 1996 ***{published data only}***
Pacifico L, Scopetti F, Ranucci A, Pataracchia M, Savignoni F, Chiesa C. Comparative efficacy and safety of 3-day azithromycin and 10-day penicillin V treatment of group A beta-hemolytic Streptococcal pharyngitis in children. *Antimicrobial Agents and Chemotherapy* 1996;**40**(4):1005–8.

Perkins 1969 ***{published data only}***
Perkins RL, Glontz GE, Saslaw S. Cephaloglycin: Crossover absorption studies and clinical evaluation. *Clinical Pharmacology and Therapeutics* 1969;**10**(2):244–9.

Pichichero 2000 ***{published data only}***
Pichichero ME, Gooch WM 3rd. Comparison of cefdinir and penicillin V in the treatment of pediatric streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2000;**19**(Suppl 12):171–3.

Pichichero 2008 ***{published data only}***
Pichichero ME, Casey JR, Block SL, Guttendorf R, Flanner H, Markowitz D, et al. Pharmacodynamic analysis and clinical trial of amoxicillin sprinkle administered once daily for 7 days compared to penicillin v potassium administered four times daily for 10 days in the treatment of tonsillopharyngitis due to streptococcus pyogenes in children. *Antimicrobial Agents and Chemotherapy* 2008;**52** (7):2512–20.

Portier 1990 ***{published data only}***
Portier H, Chavanet P, Gouyon JB, Guetat F. Five day treatment of pharyngotonsillitis with cefpodoxime proxetil. *Journal of Antimicrobial Chemotherapy* 1990;**26**(Suppl E): 79–85.

Portier 1994 ***{published data only}***
Portier H, Chavanet P, Waldner-Combernoux A, Kisterman JP, Grey PC, Ichou F, et al. Five versus ten days treatment of Streptococcal pharyngotonsillitis: A randomized controlled trial comparing cefpodoxime proxetil and phenoxymethyl penicillin. *Scandinavian Journal of Infectious Diseases* 1994; **26**(1):59–66.

Roos 1997 ***{published data only}***
Roos K, Larsson P. Loracarbef versus phenoxymethylpenicillin in the treatment of recurrent Streptococcal pharyngotonsillitis. *Scandinavian Journal of Infectious Diseases* 1997;**29**(2):141–5.

Sakata 2008 ***{published data only}***
Sakata H. Comparative study of 5-day cefcapene-pivoxil and 10-day amoxicillin or cefcapene-pivoxil for treatment of group A streptococcal pharyngitis in children. *Journal of Infection & Chemotherapy* 2008;**14**(3):208–12.

Shapera 1973 ***{published data only}***
Shapera RM, Hable KA, Matsen JM. Erythromycin therapy twice daily for streptococcal pharyngitis. Controlled comparison with erythromycin or penicillin phenoxymethyl four times daily or penicillin G benzathine. *Journal of the American Medical Association* 1973;**226**(5):531–5.

Shvartzman 1993 ***{published data only}***
Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. *BMJ* 1993;**306**(6886):1170–2.

Siegel 1961 ***{published data only}***
Siegel AC, Johnson EE, Stollerman GH. Controlled studies of Streptococcal pharyngitis in a pediatric population. *New England Journal of Medicine* 1961;**265**(12):559–65.

Standaert 1997 ***{published data only}***
Standaert BB, Finney KMA, Taylor MT, Coleman RT, Horowitz CL, Walter SM, et al. Comparison between cefprozil and penicillin to eradicate pharyngeal colonization of group A beta-hemolytic streptococci. *Pediatric Infectious Disease Journal* 1998;**17**(1):39–43.

Stillerman 1986 ***{published data only}***
Stillerman M. Comparison of oral cephalosporins with penicillin therapy for Group A streptococcal pharyngitis. *Pediatric Infectious Disease Journal* 1986;**5**(6):649–54.

Tack 1997 ***{published data only}***
Tack KJ, Hendrick JA, Rothstein E, Nemeth MA, Keyserling C, Pichichero ME. A study of 5-day treatment for streptococcal pharyngitis in children. Cefdinir Pediatric Study Group. *Archives of Pediatric and Adolescent Medicine* 1997;**151**(1):45–9.

Tack 1998 ***{published data only}***
Tack KJ, Henry DC, Gooch WM, Brink DN, Keyserling CH, The Cefdinir Pharyngitis Study Group. Five-day cefdinir treatment for Streptococcal pharyngitis. *Antimicrobial Agents and Chemotherapy* 1998;**42**(5):1073–5.

Uysal 2000 ***{published data only}***
Uysal S, Sanack R, Sunbul M. A comparison of the efficacy of cefuroxime axetil and intramuscular benzathine penicillin

for treating streptococcal tonsillopharyngitis. *Annals of Tropical Paediatrics* 2000;**20**:199–202.

Zwart 2000 ***{published data only}***
Zwart S, Sachs APE, Ruijs GJHM, Gubbels JW, Hoes AW, et al. Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. *BMJ* 2000;**320**(7228):150–4.

Additional references

Brunton 2006
Brunton S, Pichichero M. Considerations in the Use of Antibiotics for Streptococcal Pharyngitis. *Journal of Family Practice* 2006;**55**(Suppl 7):9–16.

Cars 2001
Cars O, Mölstad S, Melander A. Variation in antibiotic use in the European Union. *Lancet* 2001;**357**(9271):1851–3.

Casey 2004
Casey JR, Pichichero ME. Meta-analysis of cephalosporin versus penicillin treatment of group A Streptococcal tonsillopharyngitis in children. *Pediatrics* 2004;**113**:866-82.

Cooper 1992
Cooper RD. The carbacephems: a new beta-lactam antibiotic class. *American Journal of Medicine* 1992;**92** (Suppl):2–6.

Cooper 2001
Cooper RJ, Hoffman JR, Bartlett JG, Besser JG, Gonzales R, Hickner JM, et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. *Annals of Internal Medicine* 2001;**134**(6):509–17.

Del Mar 2009
Del Mar C, Glasziou PP, Spinks A. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD000023.pub3]

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

Gerber 1999
Gerber MA, Tanz RR, Kabat W, Bell GL, Lerer TJ, Lepow ML, et al. Potential mechanisms for failure to eradicate group A Streptococci from the pharynx. *Pediatrics* 1999; **104**:911–7.

Gerber 2004
Gerber MA, Shulman ST. Rapid diagnosis of pharyngitis caused by group A Streptococci. *Clinical Microbiology Reviews* 2004;**17**(3):571–80.

Gerber 2009
Gerber MA, Baltimore RS, Eaton CB, Gewitz MSM, Rowley AH, Shulman ST, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis. A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation* 2009;**119**(11):1541.

Hanna 2010
Hanna J, Clark MF. Acute rheumatic fever in Indigenous people in North Queensland: some good news at last?. *Medical Journal of Australia* 2010;**192**(10):581–4.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DJ. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [DOI: 10.1136/bmj.327.7414.557]

Higgins 2009
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: Wiley-Blackwell, 2009.

Lefebvre 2009
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: Wiley-Blackwell, 2009.

Linder 2001
Linder JA, Stafford RS. Antibiotic treatment of adults with sore throat by community primary care physicians. A National Survey, 1989-1999. *Journal of the American Medical Association* 2001;**286**(10):1181–6.

Mantel 1959
Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**:719–48.

Matthys 2007
Matthys J, De Meyere M, van Driel ML, De Sutter A. Differences among international pharyngitis guidelines: not just academic. *Annals of Family Medicine* 2007;**5**:436–43. [DOI: 10.1370/afm.741]

McIsaac 1998
McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *Canadian Medical Association Journal* 1998; **158**:75–83.

Neuner 2003
Neuner JM, Hamel MB, Phillips RS, Bona K, Aronson MD. Diagnosis and management of adults with pharyngitis: a cost-effectiveness analysis. *Annals of Internal Medicine* 2003;**139**(2):113–22.

Shulman 2004
Shulman ST, Gerber MA. So what's wrong with penicillin for Strep throat?. *Pediatrics* 2004;**113**:1816–9. [DOI: 10.1542/peds.113.6.1816]

Snow 2001
Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR. Principles of appropriate antibiotic use for acute pharyngitis in adults. *Annals of Internal Medicine* 2001;**134**(6):506–8.

Sonnad 1999
Sonnad SS, Zarkower N, Varney G. Rapid antigen testing for group A beta-hemolytic Streptococcus: a meta-

analysis evaluation of test performance (Meeting Abstract). *Annual Meeting of the International Society of Technology Assessment in Health Care* 1999;**15**:122. [PUBMED: http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102194100.html]

van Driel 2009

van Driel ML, De Sutter A, De Maeseneer J, Christiaens T. Searching for unpublished trials in Cochrane reviews may not be worth the effort. *Journal of Clinical Epidemiology* 2009;**62**(8):838–44.

Wise 1998

Wise R, Hart T, Cars O, Streulens M, Helmuth R, Huovinen P, et al. Antimicrobial resistance. Is a major threat to public health. *BMJ* 1998;**317**(7159):609–10.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bachand 1991

Methods	- RCT, randomised 1:1 - double-blinded - double-dummy
Participants	- number of randomised participants: 128 (108 *S. pyogenes* positive) - number of participants evaluated: 90 - number of dropouts: 38 (29.7%) - setting: 17 clinical centres USA - age: 12 to 62 years - diagnosis: rapid immunoassay test, throat culture - inclusion criteria: confirmed GABHS pharyngitis - exclusion criteria: risk for pregnancy or lactation, weight < 34 kg, no sore throat with at least one sign of streptococcal pharyngitis, negative rapid immunoassay test, overall poor health, hypersensitivity to erythromycin or penicillin, renal impairment or hepatic disease, history of rheumatic fever or cardiac valvular disease, rash suggestive of scarlet fever, active eye inflammation, treated with systemic antibiotic within two weeks/an investigational drug within four weeks/ long-acting injectable penicillin within six weeks prior to trial, concurrent antimicrobial agents
Interventions	- groups: clarithromycin, 250 mg (2 x 125 mg) caps 12 hourly (n = 65); penicillin VK 250 mg (2 x 125 mg) caps 6 hourly (n = 63) - duration of therapy: 80% > 10 days - duration of follow-up: 15 to 56 days
Outcomes	- clinical outcomes at 2 to 10 days post-treatment: cure (pre-treatment signs and symptoms resolved and pathogen eradicated); improvement (pretreatment signs and symptoms improved but not resolved); failure (pretreatment signs and symptoms not improved or worsened and pathogen persisted); indeterminate (response could not be assigned); relapse/recurrence (pretreatment signs and symptoms resolved but reappeared and pathogen recurred) - relapse at 15 to 56 days post-treatment - adverse effects - bacteriological outcomes - serology
Notes	- funding: not reported, but author is employee of Abbott International Ltd. - ethics approval: "the protocol was approved by local ethics committees" - no ITT for efficacy reported - no ITT reported

Risk of bias

Item	Authors' judgement	Description

Bachand 1991 (*Continued*)

Adequate sequence generation?	Unclear	Reported as "randomized (1:1)". Not described how sequence was generated
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"To maintain the double-blind nature of the study, placebos were administered and all drugs were placed in identical grey opaque capsules."
Incomplete outcome data addressed? All outcomes	Unclear	26 participants prematurely discontinued and 38 were excluded from efficacy analysis (reasons reported) No ITT analysis (128 randomised and 90 included in efficacy analysis)
Free of selective reporting?	Unclear	"There was no evidence of investigator bias in any of the analyses."

Carbon 1995

Methods	- RCT - double-blinded - double-dummy
Participants	- number of participants enrolled: 250 - number of participants randomised: 240 - number of participants evaluated: 236 - number of dropouts: 4 (2%) - setting: 60 French GP clinics - age: > 15 yrs - diagnosis: rapid antigen test, throat culture - inclusion criteria: fever =/> 38 °C, odynophagia, erythema or purulent exudate of pharynx, at least one tender submaxillary lymph node, rapid antigen test positive for GABHS, followed by positive throat culture - exclusion criteria: allergy to beta-lactams, pregnancy, lactation, chronic tonsillitis, antibiotics in 5 days preceding randomisation, no written consent
Interventions	- groups: cefotiam hexetil, 200 mg bid for 5 days and PEV placebo tid for 10 days (n = 119); Penicillin V megaunit (600 mg) tid for 10 days and CTM placebo bid for 5 days (n = 125) - duration of treatment: 15 days - duration of follow-up: 90 days
Outcomes	- clinical outcomes: success = cure (complete resolution of fever and symptoms) on days 10 and 30 or improvement on day 10 and cure on day 30 without further antibiotics); - failure = no response to therapy on day 10, or improvement on day 10 but required further AB or relapsed (recurrence of fever and/or symptoms), or cured on day 10 but

Carbon 1995 (*Continued*)

	subsequent relapse - relapse assessed on day 90 - adverse effects - bacteriological outcomes
Notes	- funding: not reported - ethics approval: not mentioned - described as ITT analysis for efficacy, but post-randomisation exclusions not included in analyses

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of randomisation sequence
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Unclear	Reported as "double blind, double dummy", but no description of how blinding of different administration frequency and duration was maintained
Incomplete outcome data addressed? All outcomes	Yes	Dropouts: 4 lost to follow up (all in P group)
Free of selective reporting?	Unclear	Only clinical success reported, no specific symptoms; no ITT analysis (although reported in table that ITT, the numbers to not correspond to ITT) Adverse events reported, but no ITT analysis. 3 participants in each group discontinued because of adverse events

Disney 1992a

Methods	- RCT - double-blinded
Participants	- number of participants eligible: 654 - number of participants randomised: 525 - number of participants evaluated: 525 - number of dropouts: not specified - setting: 7 paediatric practices in USA - age: 4 to 17 yrs - diagnosis: clinical tonsillitis or pharyngitis, throat cultures - inclusion criteria: clinical tonsillopharyngitis and throat cultures strongly positive for

Disney 1992a (*Continued*)

	GABHS - exclusion criteria: concurrent enrolment of siblings, two or more sore throats in previous 6 months, treated with AB in previous 2 weeks, throat culture negative for GABHS
Interventions	- groups: cephalexin 27 mg/kg 4 times per day (n = 263); penicillin 27 mg/kg 4 times per day (n = 262) - duration of treatment: 10 days - duration of follow-up: 32 to 35 days
Outcomes	- clinical outcomes: clinical failure (not defined) at 32 to 35 days - clinical relapse (new infection with different serotype) - bacteriological outcomes - antistreptolysin-O titers - anti-DNase B titers
Notes	- funding: not reported - ethics approval: not mentioned - ITT analysis on 525 participants completing the protocol, no information on dropouts

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of randomisation sequence
Allocation concealment?	Unclear	"The participants were assigned...on a random schedule supplied by Eli Lilly and Co.,..."
Blinding? All outcomes	Yes	"...the physician and parents were not appraised as to who was in which group."
Incomplete outcome data addressed? All outcomes	No	No description of dropouts ITT analysis for clinical outcome
Free of selective reporting?	No	Only clinical (and bacteriological) failure reported, no symptoms specified No reporting of adverse events

Disney 1992b

Methods	- RCT, randomised 1:1 - double-blinded - double-dummy
Participants	- number of participants enrolled: 233 (19 negative culture) - number of evaluated participants: 192 - number of dropouts: 31 (13%)

Disney 1992b (*Continued*)

	- setting: 11 paediatric offices in USA - age: 6 months to 12 years - diagnosis: rapid antigen test, throat culture - inclusion criteria: clinical diagnosis of acute streptococcal pharyngitis/ tonsillitis, inflammation and swelling, with or without fever =/> 38°C or exudate, rapid antigen test or throat culture positive for GABHS, history of compliance - exclusion criteria: history of renal impairment (serum creatinine =/>177 µmol/l, 2. 0 mg/dl), any condition that could preclude evaluation of response, requirement for systemic AB, any AB therapy within 3 days of start, hypersensitivity to penicillins and/ or cephalosporins
Interventions	- groups: loracarbef oral suspension, 15 mg/kg/day 2 divided doses, or 200 mg caps 2 per day (patient > 25kg) (n = 120); penicillin VK oral suspension 20 mg/kg/day 4 doses, daily max. 500 mg or 250 mg caps 4 per day (patient > 25 kg) (n = 113) - duration of treatment: 10 days - duration of follow-up: 4 to 5 weeks
Outcomes	- clinical outcomes at 3 to 5 days post-treatment: cure (absence of presenting signs/symptoms); significant improvement (persistence of signs/symptoms); failure (insignificant change in signs/symptoms); relapse (recurrence of one or more signs/symptoms) - relapse at 5 to 6 weeks post-treatment - adverse effects - bacteriological outcomes
Notes	- funding: Eli Lilly Company - ethics approval: not mentioned - no ITT reported for efficacy, but ITT for adverse events

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized (1:1), but no reporting of randomisation sequence
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"Placebo was administered twice daily to the loracarbef group to maintain double blind conditions."
Incomplete outcome data addressed? All outcomes	Yes	"unevaluable": 16 in Loracarbef group and 25 in Penicillin group (negative pre therapy culture, insufficient therapy, incomplete data, lost to follow up, late for visit, concomitant use of other antibiotic) No ITT for clinical outcome

Disney 1992b (*Continued*)

Free of selective reporting?	No	ITT for adverse events

Henness 1982a

Methods	- RCT - double-blinded
Participants	- number of participants randomised: 214 (47 no *S. pyogenes*) - number of evaluated participants: 162 - number of dropouts: 3 lost to follow-up from evaluable participants - setting: private paediatric practices in USA - age: 1 to 16 yrs - diagnosis: throat culture - inclusion criteria: acute untreated tonsillopharyngitis - exclusion criteria: not reported
Interventions	- groups: penicillin V suspension 8 mg/kg every 6 hours (n = 114); cefadroxil suspension 15mg/kg twice daily (n = 100) - duration of treatment: 10 days - duration of follow-up: 27 to 43 days
Outcomes	- clinical outcomes: cure (clinical improvement within first 24 hours of therapy and all follow-up cultures no *S. pyogenes*); failure (illness consistent with streptococcal infection and positive throat culture at 4 days post-therapy); carrier (asymptomatic with same type S. pyogenes in throat culture obtained between 5 to 33 days post-therapy) - bacteriological outcomes - complete blood counts - urinalysis - streptozyme titers - susceptibility studies
Notes	- funding: not mentioned, author employee of Mead Johnson Pharmaceutical Division, Evansville, USA - ethics approval: not mentioned - first study in the publication - no ITT reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of randomisation sequence
Allocation concealment?	Unclear	"...participants were assigned randomly..."
Blinding? All outcomes	Unclear	Reported as "double blind", but no description of blinding

Henness 1982a (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	52 participants discontinued (cefadroxil 35 and penicillin 17); reasons: negative culture (Total 47; cefadroxil 31 and penicillin 16), lost to follow up (Total 3; cefadroxil 2 and penicillin 1), Other (Total 2; cefadroxil 2 and penicillin 0) No ITT analysis for clinical outcomes
Free of selective reporting?	Unclear	Only clinical (and bacteriological) cure reported, no specific symptoms; no ITT Adverse events not reported

Henness 1982b

Methods	- RCT, randomised - double-blinded
Participants	- number of participants randomised: 198 - number of evaluated participants: 198 - number of dropouts: 0? - setting: private paediatric practices in USA - age: 1 to 16 years - diagnosis: throat culture - inclusion criteria: acute untreated tonsillopharyngitis - exclusion criteria: not reported
Interventions	- groups: penicillin V suspension 10 mg/kg every 8 hours (n = 50); cefadroxil suspension 15 mg/kg twice daily (n = 50); erythromycin 15 mg/kg orally twice daily (n = 49); benzathine penicillin G (900,000 U) and procaine penicillin (300,000 U) once intramuscular - duration of treatment: 10 days for all oral treatments - duration of follow-up: 27 to 43 days
Outcomes	-clinical outcomes: not reported - bacteriological outcomes - streptozyme titers - susceptibility
Notes	- funding: not mentioned, author employee of Mead Johnson Pharmaceutical Division, Evansville, USA - ethics approval: not mentioned - second study in the publication - no ITT reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of randomisation sequence

Henness 1982b (*Continued*)

Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Unclear	Reported as "double blind", but no description of blinding
Incomplete outcome data addressed? All outcomes	Unclear	No dropouts described; according to reported numbers no participants dropped out
Free of selective reporting?	Unclear	No clinical outcomes reported

Jackson 1973

Methods	- RCT - double-blinded
Participants	- number of participants randomised: 314 (95 negative culture excluded from analysis) - number of participants evaluated: 207 - number of dropouts: 12 reported - setting: not described - age: not described - diagnosis: throat culture - inclusion criteria: child in weight range 11.4 to 45.4 kg , pharyngitis, positive culture or white blood count >10,000 - exclusion criteria: allergy to penicillin or lincomycin, received any antibiotics within previous 6 weeks
Interventions	- groups: clindamycin daily dose 150 to 450 mg (n = 156); ampicillin daily dose 750 to 2000 mg (n = 158) - duration of treatment: 10 days - duration of follow-up: 26 to 28 days post-therapy
Outcomes	- adverse effects - bacteriological outcomes
Notes	- funding: Upjohn Company - ethics approval: not mentioned - ITT for adverse events

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of randomisation sequence
Allocation concealment?	Yes	"Labels for each group were randomized, sealed in sequentially numbered envelopes,....."

Jackson 1973 (*Continued*)

Blinding? All outcomes	Yes	See above
Incomplete outcome data addressed? All outcomes	Unclear	95 negative cultures excluded after randomisation; 12 positive cultures excluded due to failure to return first follow up culture (C7 and A5)
Free of selective reporting?	No	Only clinical outcome for poststreptococcal sequelae ITT for adverse events

Levenstein 1991

Methods	- RCT - double-blinded - double-dummy
Participants	- number of participants enrolled: 243 (82 *S. pyogenes* negative) - number of participants evaluated in clinical outcome analysis: 125 - number of dropouts: 28 (12%) - setting: multicenter (Australia, New Zealand, Chile, South Africa) outpatient clinics - age: 13 to 59 years - diagnosis: rapid antigen test, throat culture - inclusion criteria: body weight =/> 50 kg, ability to swallow capsules, sore throat with at least one other sign of streptococcal pharyngitis (pharyngeal erythema/exudate, cervical lymph node tenderness, fever), positive rapid immunoassay for GABHS antigen - exclusion criteria: hypersensitivity to erythromycin or penicillin, previous course clarithromycin or penicillin VK in this trial, renal impairment or history of glomerulonephritis, history of hepatic disease or liver enzyme elevation, history of cardiac valvular disease, rash symptomatic of scarlet fever, history of allergies and/or asthma
Interventions	- groups: clarithromycin, 250 mg capsules every 12 hours (n = 128); penicillin VK, 250 mg caps every 6 hours (n = 115) - duration of treatment: clarithromycin 8 to 10 days; penicillin VK 10 to 14 days - duration of follow-up: 15 to 56 days
Outcomes	- clinical outcomes at 2 to 10 days post-treatment: cure (pretreatment signs and symptoms resolved); improvement (symptoms improved but not totally resolved); failure (symptoms not improved or worsened); indeterminate (clinical response could not be assigned because of non-compliance or other reasons) - relapse 15 to 56 days post-treatment - adverse effects - bacteriological outcomes - blood haematology and chemistry - urinalysis
Notes	- funding: not reported - informed consent obtained - ethics approval: " the study was approved by local ethics committees"

Levenstein 1991 (*Continued*)

	- no ITT for efficacy, but ITT for adverse effects

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Reported as "randomized" but no description of randomisation sequence
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Description of medication and placebo to ensure blinding
Incomplete outcome data addressed? All outcomes	Unclear	drop outs accounted for the bacteriological outcome analysis, but not for the clinical outcome analysis (only 125 of 243 randomised participants included in clinical outcome analysis) No ITT for clinical outcomes
Free of selective reporting?	No	Safety analysis on all 243 randomised participants; clinical and bacteriological outcome on only 125 participants

McCarty 1992a

Methods	- RCT - double-blinded - double-dummy
Participants	- number of enrolled participants: 218 - number of participants randomised: 218 (31 negative culture) - number of participants evaluated: 171 - number of dropouts: 47 (22%) - setting: 12 study centres in North America - age: > 12 years - diagnosis: rapid antigen test, throat culture - inclusion criteria: clinical diagnosis of streptococcal pharyngitis or tonsillitis - inflammation of pharynx and tonsils with pain in the throat, with or without fever or exudate, rapid antigen test or throat culture positive for GABHS - exclusion criteria: pregnancy, lactation, history of renal impairment (serum creatinine levels =/> 177 µmol/L, 2.0 mg/dL), physical or mental condition that might preclude evaluation of response, possible future need for other systemic AB during study, use of AB therapy within 3 days of pre therapy evaluation, use of other investigational agents within previous 28 days, hypersensitivity to beta-lactam AB

McCarty 1992a (*Continued*)

Interventions	- groups: loracarbef oral suspension 15 mg/kg/day 2 doses, daily max. 375 mg, or 200 mg caps 2 per day (n = 107); penicillin VK oral suspension 20 mg/kg/day 4 doses daily max. 500 mg, or 250 mg caps 4 per day (n = 111) - duration of treatment: 10 days - duration of follow-up: 28 to 35 days
Outcomes	- clinical outcomes at 3 to 5 days post-treatment: cure (total alleviation of difficulty in swallowing, pharyngeal pain); improvement (substantial improvement in signs and symptoms); failure (signs and symptoms not substantially alleviated); relapse (initial improvement or alleviation of symptoms, but subsequent worsening or recurrence); unable to evaluate - relapse at 28 to 35 days post-treatment - adverse effects - bacteriological outcomes
Notes	- funding: Eli Lilly and Company - informed consent obtained - ethics approval: not mentioned - no ITT reported for efficacy, but ITT reported for adverse events

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized"; no description of randomisation sequence
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"In order to maintain blinding, placebo was administered twice daily to participants in the loracarbef group so that all participants received 4 doses daily."
Incomplete outcome data addressed? All outcomes	Unclear	Dropouts: 18 in loracarbef group and 29 in penicillin group. Reasons for dropout: negative culture (L12 and P19) insufficient therapy, incomplete data, use of other antibiotic, noncompliance, lack of post-therapy culture) No ITT for clinical outcome
Free of selective reporting?	No	ITT for adverse events analysis

Muller 1992

Methods	RCT double-blind
Participants	- number of enrolled participants: 344 - number of participants randomised: 344 - number of participants evaluated: 239 - number of dropouts: 105 (31%) - setting: study centres in Europe and Israel - age: 3 to 80 yrs (mean 28.2) 10.8% < 12 yrs, 2.0% > 65 yrs - diagnosis: rapid antigen test and confirmed by throat culture -inclusion criteria:clinical diagnosis of streptococcal pharyngitis or tonsillitis and a positive rapid streptococcal antigen test. Selections were made on the basis of a demonstrated history of therapeutic compliance on the part of the patient and/or the patient's parent/guardian -exclusion criteria: pregnant or nursing or history of renal impairment; any condition, including significant underlying disease or concomitant infection, which in the opinion of the investigator could have precluded evaluation of response; anticipated need for systemic antibiotics; use of AB < 3 days; or hypersensitivity to penicillins and/or cephalosporins
Interventions	- Groups: 1) loracarbef (n = 169) suspension of 15 mg/kg/day in 2 divided doses up to a max daily dose 375 mg or as a 200 mg capsule twice daily, with placebo twice daily to maintain double-blind conditions. 2) penicillin V (n = 175 suspension of 20 mg/kg/day in 4 divided doses up to a max daily dose of 500 mg or as 250 mg capsules 4 times daily - duration of treatment: 10 days - duration of follow-up: 38 to 45 days - Concomitant medication for treatment of underlying diseases or conditions was allowed with the exception of systemic antibiotics. During therapy paracetamol was used by 5.5% of the patients
Outcomes	- Clinical outcomes at days 4 to 6: the patients' symptomatic responses and adherence to the treatment regimen; at days 13-15): physical examination to determine symptomatic response to therapy; at days 38 to 45: physical examination to evaluate possible recurrence of pharyngitis or tonsillitis. Throat cultures were required at every observation period - Global symptomatic response based on symptom score (difficulty in swallowing, pharyngeal pain, pharyngeal redness, tonsillar inflammation, tonsillar swelling, and temperature): cure, improvement [substantial], failure, relapse, or unable to evaluate - Relapse: no definition given - A patient was discontinued from the study if the pathogen isolated from initial culture was resistant to study antibiotic; if there was obvious symptomatic failure of the study antibiotic at any time during treatment; if there was a significant adverse event or a clinically significant alteration in a laboratory parameter; if a patient or parent/guardian wished to withdraw from the study; if the blinding was broken for safety reasons; or if the patient had an elevated pre-therapy serum creatinine - Adverse events: At least one adverse event was reported by L = 22 (13.0%) and P = 19 (10.9%) patients. Headache and nausea/vomiting were the only two events reported during therapy by more than 2% of the total population. Headache was reported by L = 5/169 (3.0%) and by P = 4/175 (2.3%) (P = 0.696). Nausea or vomiting was reported

Muller 1992 (*Continued*)

	by L = 2/169 (1.2%) and by P = 5/175 (2.9%) (P = 0.272). Few patients (approximately 5% of the total population) reported adverse events during the 28 to 35 day post-therapy follow-up period
Notes	- Funding: grants from Lilly Research Centre Ltd. - Informed consent obtained - Ethics: "conducted according to ethical committee guidelines, including the Declaration of Helsinki (1983 Venice Amendment)." -No ITT analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"with placebo twice daily to maintain double-blind conditions"
Incomplete outcome data addressed? All outcomes	Yes	54 of the 169 (31.9%) loracarbef-treated and 51/115 (29.1%) penicillin-treated patients did not qualify for efficacy evaluation. The most common reasons for disqualification in each therapy group were bacteriological (L = 37, P = 3); 12 patients in each group received either insufficient therapy, had no follow-up data (lost to follow-up), or had incomplete data; L = 3 patients and P = 1 were disqualified from the efficacy analysis due to protocol violations; L = 1 patient was disqualified for efficacy evaluation because of the use of another antibiotic during the study period, and L = 1 patient was unevaluable because the post-therapy evaluation was performed 22 days after discontinuing therapy
Free of selective reporting?	Yes	All indicated outcomes are reported

Nemeth 1999

Methods	- RCT, randomised 1:1:1 - double-blinded - double-dummy
Participants	- number of participants enrolled: 919 - number of positive throat cultures susceptible to study drugs: 725 - number of participants evaluated: 644 - number of dropouts: 275 (30%) - setting: 25 study centres in USA and Canada - age: =/>13 years - diagnosis: rapid antigen test, throat culture

Nemeth 1999 (*Continued*)

	- inclusion criteria: throat culture positive for GABHS, at least 1 clinical sign or symptom of pharyngitis - exclusion criteria: pregnancy, history of rheumatic fever or rheumatic heart disease, peritonsillar abscess or invasive disease, hypersensitivity to beta-lactam drugs, hepatic disease, hepatic enzyme levels or serum creatinine > 2 times upper limit of normal, another systemic AB within 3 days before first dose of study medication or for which < 5 half-lives had elapsed, enrolled in this study previously, received another investigational drug within 4 weeks before study admission
Interventions	- groups: cefdinir 600 mg QID (n = 305); cefdinir 300 mg BID (n = 304); penicillin V 250 mg QID (n = 310) - duration of treatment 10 days - duration of follow-up 17 to 24 days post-therapy
Outcomes	- clinical outcomes at day 4 to 9 after treatment: cure (all signs and symptoms absent or in satisfactory remission and no further AB therapy required); failure (absence of significant remission of signs and symptoms or need for further AB therapy); relapse (worsening of, or absence of significant remission of, signs and symptoms 17 to 24 days post-therapy or need for further AB therapy) - relapse at day 17 to 24 after treatment - adverse effects - bacteriological outcomes
Notes	- funding: Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan (first author is employee) - informed consent obtained - ethics approval: institutional review board approval obtained at each site - no ITT for efficacy reported, but ITT for adverse events

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of the randomisation sequence
Allocation concealment?	Unclear	"Patients were randomly assigned in a 1:1:1 ratio.."
Blinding? All outcomes	Unclear	"All participants took the same number of capsules daily. All regimens were administered for 10 days." No description of the appearance of the capsules
Incomplete outcome data addressed? All outcomes	Unclear	Dropouts 275: no GABHS at admission culture (194); failure to return or noncompliance (not specified in which group) No ITT analysis for clinical outcomes

Nemeth 1999 (*Continued*)

Free of selective reporting?	Unclear	Only clinical cure reported, no symptoms specified Adverse events analysed by ITT: 21 participants discontinued due to adverse events (C17 and P4); difference C-P NS

Norrby 2002

Methods	- RCT, randomised 1:1 - double-blinded - double-dummy
Participants	- number of participants enrolled: 398 - number of participants randomised: 396 (1 negative culture) - number of participants evaluated: 395 - number of dropouts: 34 (9%) - setting: 62 centres in 10 countries (Europe, New Zealand, S. Africa) - age: 15 to 74 years - diagnosis: rapid antigen test, throat culture - inclusion criteria: clinical signs and symptoms of acute pharyngitis/tonsillitis, including sore throat and 1 or more others; presumed diagnosis of acute GABHS pharyngitis/tonsillitis, based on positive rapid antigen detection test or throat culture within 24 hours prior to starting study medication - exclusion criteria: infection of deep tissues of upper respiratory tract or subpharyngeal respiratory tract; head or neck cancer; history of rheumatic heart disease or valve disease, infectious mononucleosis, rash; immunocompromised, impaired renal or hepatic function, history heart rhythm diseases, severe hypokalemia, any concomitant condition likely to preclude assessment of treatment response, non-streptococcal or viral pharyngitis/tonsillitis, chronic streptococcal carrier, environmental risk of reinfection, treatment with penicillin V, systemic or local AB within 7 days prior to study entry; pregnancy, lactation, hypersensitivity to study AB, infection with a pathogen known to be resistant to study drugs, concurrent treatment with other AB or probenecid, or any medication that may interact with study medication
Interventions	- groups: telithromycin 800 mg oral once daily (n = 198); penicillin V 500 mg oral 3 times daily (n = 197) - duration of treatment: telithromycin 5 days; penicillin V 10 days - duration of follow-up: 38 to 45 days
Outcomes	- clinical outcomes at day 16 to 20: cure (improvement, disappearance or return to preinfection state of all infection-related signs and symptoms, without additional AB) ; failure (infection-related signs and symptoms unchanged or worsened, or clinical improvement but required additional AB, developed new clinical findings consistent with active infection); indeterminate (missing post-treatment information, discontinued early for reasons unrelated to study drug) - relapse at day 38 to 45 - adverse effects - bacteriological outcomes

Norrby 2002 (*Continued*)

	- blood haematology - urinalysis - mean symptom score reported in second publication; no SD reported
Notes	- funding: Aventis Pharma - informed consent obtained - ethics approval: "approved by and independent ethics committee in each country" - modified ITT (1 patient with negative GABHS excluded) - 2 publications of same study with different outcomes

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Reported as "randomized (1:1)"; Randomisation not described
Blinding? All outcomes	Yes	"Blinding was maintained by masking the tablets in capsules and matching placebo capsules where appropriate."
Incomplete outcome data addressed? All outcomes	Unclear	ITT for clinical outcomes excluded one randomised patient with negative culture; 34 participants discontinued, mainly due to withdrawal of consent or adverse events; not clear how these reasons were distributed in the 2 groups
Free of selective reporting?	Unclear	Cure was predefined clinical outcome; adverse events reported

O'Doherty 1996

Methods	- RCT - double-blinded - double-dummy
Participants	- number of participants enrolled: 489 (92 negative culture) (A20 mg = 160; A10 mg = 166; P = 163) - number of participants evaluated: 358 - number of dropouts: 131 excluded (A20 = 57; A10 = 43; P = 31) (27%) - setting: 19 outpatient clinical centres (Europe) - age: 2 to 13 years - diagnosis: clinical examination, rapid antigen test - inclusion criteria: clinical signs and symptoms suggestive of GABHS pharyngitis/tonsillitis, rapid antigen test positive for GABHS

O'Doherty 1996 (*Continued*)

	- exclusion criteria: within 72 hours prior to the study other AB which could interfere with evaluation of therapy, hypersensitivity to macrolide or beta-lactam antibiotic, terminal illness or other serious disease, any gastrointestinal condition that might affect drug absorption, other investigational drug in the previous month or long-acting penicillin injections within the previous 6 weeks
Interventions	- groups: azithromycin suspension single oral dose 10 mg/kg (n = 166); azithromycin suspension one single dose 20 mg/kg (n = 160); penicillin V solution 50 mg/ml orally 4 times daily (total daily dose 500 to 1000 mg) (n = 163) - duration of treatment: azythromycin 3 days; penicillin V 10 days - duration of follow-up: 28 to 30 days
Outcomes	- clinical outcomes at day 12 to 14 : cure; improvement; failure; relapse - relapse at day 28 to 30 - adverse effects - bacteriological outcomes - blood haematology and chemistry - urinalysis
Notes	- funding: not reported - informed consent obtained - ethics approval: institutional review board approval obtained - definition of outcomes not reported - no ITT for efficacy, but ITT for adverse effects

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized", but no description of randomisation sequence
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"Matched placebo suspensions or solutions were administered to maintain blinding of the study."
Incomplete outcome data addressed? All outcomes	Unclear	Dropout 131 participants: absence of pathogen (azithromycin 20 mg = 36; azithromycin 10 mg = 30; penicillin = 26), deviation from protocol (azithromycin 20 mg = 10; azithromycin 10 mg = 8; penicillin = 3), adverse event (azithromycin 20 mg = 11; azithromycin 10 mg = 5; penicillin = 2) No ITT analysis

O'Doherty 1996 (*Continued*)

Free of selective reporting?	Unclear	Only clinical (and bacteriological) cure reported, no specific symptoms in outcome analysis Adverse events reported with ITT analysis

Randolph 1985

Methods	- RCT - double-blinded
Participants	- number of eligible participants: 260 - number of randomised participants: 194 - number of participants evaluated: 194 - number of dropouts: 0 - setting: a private pediatric office - age: 2 to 20 years - diagnosis: throat culture - inclusion criteria: clinically suggestive GABHS pharyngitis - exclusion criteria: history of hypersensitivity to penicillin or cephalosporins, AB within previous 72 hours
Interventions	- groups: cefadroxil 250 mg in 3 doses over next 18 to 24 hours (n = 70); penicillin V 250 mg in 3 doses over next 18 to 24 hours (n = 68); placebo (n = 56) - duration of treatment: 10 days - duration of follow-up: 4 weeks (only results from examination 18 to 24 hours after initiation of treatment reported)
Outcomes	- clinical outcomes 24 hours after treatment start assessed by physician: improvement - sore throat (numbers only reported in graph) - fever (numbers only reported in graph) - bacteriological outcomes
Notes	- funding: Mead Johnson and Company - ethics approval: not mentioned - ITT analysis reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"All participants were then assigned by a table of random numbers..."
Allocation concealment?	Yes	"Randomization of treatment regimens was performed by a study nurse so that the evaluating physician, parents and participants were unaware of which agent was dispensed."

Randolph 1985 (*Continued*)

Blinding? All outcomes	Yes	See above
Incomplete outcome data addressed? All outcomes	Yes	No dropouts (all randomised participants evaluated)
Free of selective reporting?	Unclear	Specific signs and symptoms reported No reporting of adverse events

Reed 1991

Methods	- RCT - double-blinded
Participants	- number of participants enrolled and randomised: 116 - number of evaluated participants: 93 - number of dropouts: 23 (20%) - setting: 4 primary care offices in USA - age: > 1 month - diagnosis: rapid test, throat culture - inclusion criteria: sore throat or poor eating, rapid test positive for GABHS - exclusion criteria: allergy to penicillin or cephalosporins, pregnancy, history of renal or hepatic impairment, significant underlying disease or concomitant infection that could preclude evaluation of response to treatment, AB in the previous 3 days
Interventions	- groups: cefaclor 20 mg/kg/d in 3 doses (n = 60); penicillin VK 20 mg/kg/d in 3 doses (n = 56) - duration of treatment: 10 days - duration of follow-up: 28 to 30 days post-therapy
Outcomes	- clinical outcomes (not defined; according to clinician's impression at 2 days after treatment completion): cure, improvement, relapse, failure - relapse at day 28 to 30 - adverse effects - bacteriological outcomes - beta-lactamase enzyme production
Notes	- funding: Eli Lily & Company, Indianapolis, Indiana USA - informed consent obtained - ethics approval not mentioned - no ITT reported

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described

Reed 1991 (*Continued*)

Allocation concealment?	Yes	"The patient was given a prescription that used a code number to identify the medication to be used."
Blinding? All outcomes	Yes	"The identity of the antibiotic was unknown to the physician and to the patient, and was randomized by a coding sheet that was available only to the pharmacists dispensing the study medication."
Incomplete outcome data addressed? All outcomes	Unclear	Dropouts 23: no GABHS on culture (cefaclor 6 and penicillin 2), insufficient therapy (cefaclor 0 and penicillin 1), no follow up culture (cefaclor 3 and penicillin 0), other antibiotic (cefaclor 1 and penicillin 2), unevaluable according to investigator (cefaclor 3 and penicillin 5) No ITT analysis
Free of selective reporting?	Unclear	Only clinical (and bacteriological) outcome reported, no specific symptom outcomes reported Adverse events reported; no ITT analysis

Stein 1991

Methods	- RCT - double-blinded - double-dummy
Participants	- number of participants enrolled and randomised: 128 (clarithromycin 65 and penicillin 63) - number of participants with *S. pyogenes*: 109 - number of participants evaluated: 95 (clarithromycin 47 and penicillin 48) - number of dropouts: 33 (26%) - setting: multicentre (not specified) - age: 12 to 58 years - diagnosis: clinical examination, rapid immunoassay test - inclusion criteria: signs and symptoms of streptococcal throat infection, rapid immunoassay test positive for GABHS antigen - exclusion criteria: age < 12 years, pregnancy, lactation, hypersensitivity to erythromycin or penicillin, receiving antibiotics, impaired renal or liver function
Interventions	- groups: clarithromycin 250 mg capsule every 12 hours (n = 65); penicillin V 250 mg capsule every 6 hours (n = 63) - duration of treatment: 10 days - duration of follow-up: 29 to 35 days
Outcomes	- clinical outcomes at day 5 to 7 and at day 14 to 16: cure (complete resolution of signs and symptoms); improved (considerable resolution of presenting signs and symptoms); failure (no improvement) - relapse at day 29 to 35 - adverse effects

Stein 1991 (*Continued*)

	- bacteriological outcomes - blood haematology and chemistry - urinalysis - serology (antistreptolysin-O titers, anti-DNase B titres)
Notes	- funding: not reported - ethics approval: not mentioned - no ITT for efficacy, but ITT for adverse effects

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"random number code" was used, but unclear how it was generated
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"In order to maintain blinding of the study placebo capsules were alternated with clarithromycin capsules every six hours."
Incomplete outcome data addressed? All outcomes	No	Dropouts 33; no description of reasons; no ITT for clinical outcomes
Free of selective reporting?	Unclear	Clinical (and bacteriological) cure rate reported, no specific symptoms Adverse events reported with ITT analysis

Trickett 1973

Methods	- RCT - double-blinded - double-dummy
Participants	- number of enrolled participants: 96 - number of participants evaluated: 87 - number of dropouts: 9 (9%) - setting: 3 institutions (regular clinics + emergency rooms) - age: > 16 years - diagnosis: throat culture - inclusion criteria: acute sore throat suggestive of acute streptococcal pharyngitis and/or tonsillitis, throat culture positive for GABHS - exclusion criteria: pregnancy, breast-feeding, AB other than study drugs during the trial period, inadequate folate reserves, malabsorption syndrome, haemolytic anaemia, anti-convulsant therapy (dilantin, primidone), AB 1 week preceding acute streptococcal infection, renal insufficiency, abnormal liver function, low platelets, total white cells, neutrophils, haemoglobin, hematocrit; glucose-6-phosphate dehydrogenase deficiency,

Trickett 1973 (*Continued*)

	systemic lupus erythematosus, history of idiosyncratic or allergic reactions to any of the drugs
Interventions	- groups: sulphamethoxazole (SMZ) 400 mg and trimethoprim (TMP) 80 mg 2 tablets 4 times per day (n = 48); penicillin G 250 mg 1 tablet 4 times per day (n = 48) - duration of therapy: 10 days - duration of follow-up: 28 days
Outcomes	- no clinical outcomes reported - adverse effects - bacteriological outcomes - urinalysis - creatinine - SGOT
Notes	- funding: medication supplied by Hoffmann-LaRoche Inc. - ethics approval: not mentioned

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Reported as "randomized" but no description of randomisation sequence; "both groups were evenly matched as to age, sex, physical condition, and concurrent diagnoses."
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	"all test medications were supplied in individually coded bottles of identical appearance and were administered according to the randomized double blind code."
Incomplete outcome data addressed? All outcomes	Unclear	9 dropouts: lost to follow up, failed to take medication or negative on strep A tests (not specified per group) No ITT analysis
Free of selective reporting?	Unclear	Cure rates reported, not individual symptoms Adverse events mentioned, but not tested

Watkins 1997

Methods	- RCT - double-blinded - double-dummy
Participants	- number of participants randomised: 345 (dirithromycin 170 and penicillin 175) - number of participants evaluated: 257 (dirithromycin 121 and penicillin 136) - number of dropouts: 66 in each group (38%) - setting: 15 clinical centres in North America - age: > 12 years - diagnosis: rapid antigen test, throat culture - inclusion criteria: weight > 81 lb, positive throat culture, informed consent, ability to return for follow-up, negative pregnancy test and use of a reliable method of contraception during therapy and for 30 days thereafter - exclusion criteria: any condition precluding evaluation of response to treatment, systemic AB other than the study AB; hypersensitivity to macrolides, penicillins, cephalosporins, pregnancy, breast-feeding, systemic AB in 7 days before study; participation in a previous dirithromycin study or any study involving and investigational drug in the 30 days prior to this study
Interventions	- groups: dirithromycin, 500 mg once daily (n = 170); penicillin VK 250 mg 4 times daily (n = 175) - duration of treatment: 10 days - duration of follow-up: 3 to 5 weeks post-treatment
Outcomes	- clinical outcomes 3 to 5 days post-treatment: cure (elimination of signs and symptoms) ; improvement (significant but incomplete resolution of signs and symptoms); relapse (worsening of signs and symptoms after initial improvement); failure (no improvement in signs and symptoms during treatment) - clinical relapse at 3 to 5 weeks post-treatment not reported - adverse effects - bacteriological outcomes
Notes	- funding: Eli Lilly and Company (2 authors are employees) - ethics approval: not mentioned - no ITT for efficacy, but ITT for adverse effects

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Sequence generated by computer program.
Allocation concealment?	Yes	"The randomization list was not provided to the investigators until the study was complete.."
Blinding? All outcomes	Yes	"Double dummy design" "This was accomplished by giving two bottles to each patient, one containing 20 tablets

Watkins 1997 (*Continued*)

		(dirithromycin or placebo) and one containing 40 capsules (penicillin or placebo). "
Incomplete outcome data addressed? All outcomes	Unclear	Description of dropouts in each group: lack of efficacy (dirithromycin 20; penicillin 26) , lost to follow up (dirithromycin 4; penicillin 1), patient's decision (dirithromycin 3; penicillin 0), entry criteria exclusion (dirithromycin 25; penicillin 22), protocol violation (dirithromycin 8; penicillin 8) , adverse event (dirithromycin 6; penicillin 9) No ITT analysis
Free of selective reporting?	Unclear	Only clinical cure reported, no specific symptoms Adverse events reported with ITT

GABHS: Group A beta-hemolytic streptococcus
ITT: intention to treat analysis
SD: Standard deviation
BID: twice a day
TID: three times a day
QID: four times a day
kg: kilogram weight
lb: pound weight

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

Study	Reason for exclusion
Adam 1994	not double-blinded
Adam 1995	not double-blinded
Adam 1996	not double-blinded
Adam 2000a	not double-blinded
Adam 2000b	not double-blinded
Adam 2001	not double-blinded
Aujard 1995	not double-blinded

(*Continued*)

Breese 1974	did not compare two different classes of antibiotics
Cohen 2002	not double-blinded
Davies 1995	not only acute GABHS tonsillopharyngitis
De Meyere 1992	not RCT
Del Mar 2008	commentary of RCT
Denny 1953	not double-blinded
Disney 1979	did not compare two different classes of antibiotics
Dykhuizen 1996	not double-blinded
Esposito 2002	not double-blinded
Feder 1999	not double-blinded
Gerber 1986	not double-blinded
Gerber 1999	did not report any clinical outcomes
Gooch 1993	not double-blinded
Granizio 2008	pooled analysis; not original studies
Hamill 1993	not double-blinded
Haverkorn 1971	not RCT did not compare two different classes of antibiotics
Holm 1991	not double-blinded
Howe 1997	not double-blinded
Lennon 2008	not double-blinded (investigator blinded only)
Matsen 1974	did not compare two different classes of antibiotics
McCarty 1992b	not double-blinded
McCarty 1994	not double-blinded
McIsaac 2004	did not compare two different classes of antibiotics
Milatovic 1991	not double-blinded

(*Continued*)

Milatovic 1993	not double-blinded
Pacifico 1996	not double-blinded
Perkins 1969	not double-blinded
Pichichero 2000	not double-blinded
Pichichero 2008	not double-blinded (investigator blinded only)
Portier 1990	not double-blinded
Portier 1994	not double-blinded
Roos 1997	recurrent sore throat
Sakata 2008	not double-blinded
Shapera 1973	not double-blinded
Shvartzman 1993	not double-blinded
Siegel 1961	did not compare two different classes of antibiotics
Standaert 1997	not only acute GABHS tonsillopharyngitis
Stillerman 1986	not double-blinded
Tack 1997	not double-blinded
Tack 1998	not double-blinded
Uysal 2000	not double-blinded
Zwart 2000	did not compare two different classes of antibiotics

DATA AND ANALYSES

Comparison 1. Cephalosporin versus penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of symptoms post-treatment (ITT analysis)	5	2018	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.12]
1.1 Adults	2	1163	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
1.2 Children	3	855	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.40, 1.73]
2 Resolution of symptoms post-treatment (evaluable participants)	5	1660	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.27, 0.97]
2.1 Adults	2	880	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.24, 1.32]
2.2 Children	3	780	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.14, 1.52]
3 Resolution of symptoms within 24 hours of treatment (ITT analysis)	1	138	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.34, 2.74]
3.1 Children	1	138	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.34, 2.74]
4 Sore throat (ITT analysis)	1	138	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.23, 4.04]
5 Fever (ITT analysis)	1	138	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.19, 4.98]
6 Incidence of relapse (evaluable participants)	4	1386	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.31, 0.99]
6.1 Adults	2	770	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.20, 0.88]
6.2 Children	2	616	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.33, 2.43]
7 Complications (ITT analysis)	1	244	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Adverse events (ITT analysis)	3	1279	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.31, 3.16]
9 Resolution of symptoms ITT (subgroup sponsored versus no sponsor reported)	5	2018	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.12]
9.1 Sponsor not reported	2	769	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.27, 0.81]
9.2 Sponsored studies	3	1249	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.70, 1.16]

Comparison 2. Macrolide versus penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of symptoms post-treatment (ITT analysis)	6	1728	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.92, 1.35]
1.1 Adults	5	1239	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.34]
1.2 Children	1	489	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.84]
2 Resolution of symptoms post-treatment (evaluable participants only)	6	1159	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.09]
2.1 Adults	5	801	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.31]

2.2 Children	1	358	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.36, 1.11]
3 Sore throat post-treatment (ITT analysis)	2	371	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.46]
4 Fever post-treatment (ITT analysis)	2	371	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.59]
5 Incidence of relapse (evaluable participants)	6	802	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.48, 3.03]
5.1 Adults	5	495	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.34, 2.39]
5.2 Children	1	307	Odds Ratio (M-H, Random, 95% CI)	3.10 [0.67, 14.25]
6 Adverse events (ITT analysis)	6	1727	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.73]
6.1 Adults	5	1238	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.50]
6.2 Children	1	489	Odds Ratio (M-H, Random, 95% CI)	2.33 [1.06, 5.15]
7 Resolution of symptoms ITT (subgroup sponsored versus no-sponsor reported)	6	1728	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.92, 1.35]
7.1 Sponsor not reported	3	860	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.84, 1.48]
7.2 Sponsored studies	3	868	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.85, 1.46]

Comparison 3. Carbacephem versus penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of symptoms post-treatment (ITT analysis)	3	795	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.49, 0.99]
1.1 Adults	2	562	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.46, 1.22]
1.2 Children	1	233	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.33, 0.99]
2 Resolution of symptoms post-treatment (evaluable participants)	3	602	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 1.01]
2.1 Adults	2	410	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.13]
2.2 Children	1	192	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.32, 1.38]
3 Incidence of relapse (evaluable participants)	3	523	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.64, 2.50]
4 Adverse events (ITT analysis)	3	795	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.75, 1.55]

Comparison 4. Clindamycin versus ampicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events (ITT analysis)	1	314	Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.15, 1.10]

Comparison 5. Sulfonamide versus penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events (ITT analysis)	1	87	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.43, 4.34]

Analysis 1.1. Comparison 1 Cephalosporin versus penicillin, Outcome 1 Resolution of symptoms post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 1 Resolution of symptoms post-treatment (ITT analysis)

Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adults					
Carbon 1995	13/119	22/125		15.5 %	0.57 [0.27, 1.20]
Nemeth 1999	201/609	117/310		36.0 %	0.81 [0.61, 1.08]
Subtotal (95% CI)	**728**	**435**		**51.5 %**	**0.78 [0.60, 1.01]**
Total events: 214 (cephalosporin), 139 (penicillin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.74$, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 1.86 (P = 0.063)					
2 Children					
Disney 1992a	8/263	21/262		13.1 %	0.36 [0.16, 0.83]
Henness 1982a	38/114	33/100		21.2 %	1.02 [0.57, 1.80]
Reed 1991	22/60	16/56		14.3 %	1.45 [0.66, 3.16]
Subtotal (95% CI)	**437**	**418**		**48.5 %**	**0.83 [0.40, 1.73]**
Total events: 68 (cephalosporin), 70 (penicillin)					
Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 6.23$, df = 2 (P = 0.04); I^2 =68%					
Test for overall effect: Z = 0.49 (P = 0.62)					
Total (95% CI)	**1165**	**853**		**100.0 %**	**0.79 [0.55, 1.12]**
Total events: 282 (cephalosporin), 209 (penicillin)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 7.19$, df = 4 (P = 0.13); I^2 =44%					
Test for overall effect: Z = 1.32 (P = 0.19)					

Analysis 1.2. Comparison 1 Cephalosporin versus penicillin, Outcome 2 Resolution of symptoms post-treatment (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 2 Resolution of symptoms post-treatment (evaluable participants)

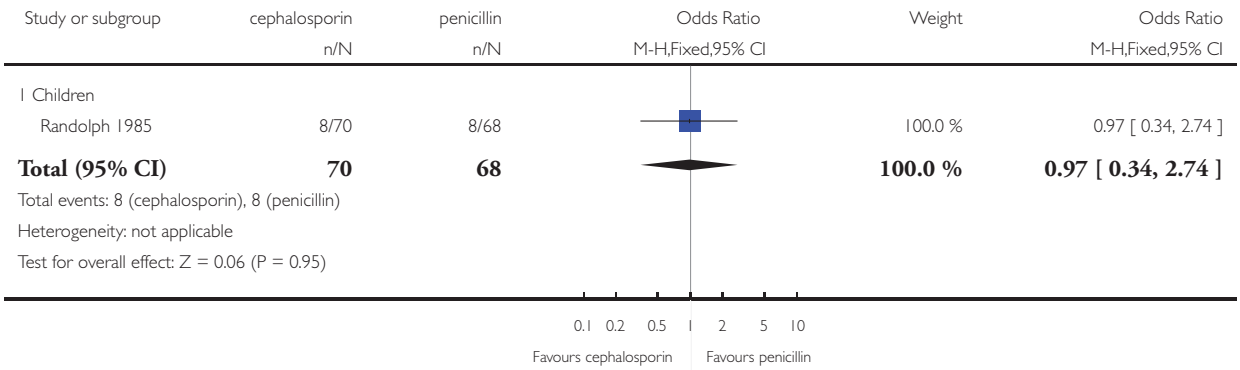
Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adults					
Carbon 1995	13/119	14/117		22.0 %	0.90 [0.40, 2.01]
Nemeth 1999	19/427	24/217		25.5 %	0.37 [0.20, 0.70]
Subtotal (95% CI)	**546**	**334**		**47.5 %**	**0.56 [0.24, 1.32]**
Total events: 32 (cephalosporin), 38 (penicillin)					
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 2.87$, df = 1 (P = 0.09); $I^2 = 65\%$					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Children					
Disney 1992a	8/263	21/262		21.5 %	0.36 [0.16, 0.83]
Henness 1982a	3/79	16/83		14.4 %	0.17 [0.05, 0.59]
Reed 1991	9/47	6/46		16.6 %	1.58 [0.51, 4.86]
Subtotal (95% CI)	**389**	**391**		**52.5 %**	**0.46 [0.14, 1.52]**
Total events: 20 (cephalosporin), 43 (penicillin)					
Heterogeneity: $Tau^2 = 0.80$; $Chi^2 = 7.45$, df = 2 (P = 0.02); $I^2 = 73\%$					
Test for overall effect: Z = 1.27 (P = 0.20)					
Total (95% CI)	**935**	**725**		**100.0 %**	**0.51 [0.27, 0.97]**
Total events: 52 (cephalosporin), 81 (penicillin)					
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 10.42$, df = 4 (P = 0.03); $I^2 = 62\%$					
Test for overall effect: Z = 2.06 (P = 0.039)					

Analysis 1.3. Comparison 1 Cephalosporin versus penicillin, Outcome 3 Resolution of symptoms within 24 hours of treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 3 Resolution of symptoms within 24 hours of treatment (ITT analysis)

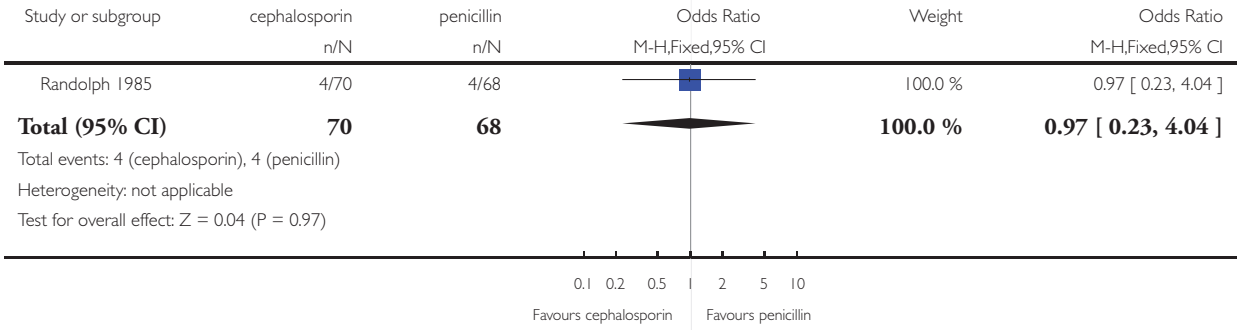


Analysis 1.4. Comparison 1 Cephalosporin versus penicillin, Outcome 4 Sore throat (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 4 Sore throat (ITT analysis)



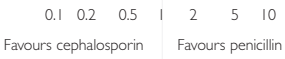
Analysis 1.5. Comparison 1 Cephalosporin versus penicillin, Outcome 5 Fever (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 5 Fever (ITT analysis)

Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Randolph 1985	3/70	3/68		100.0 %	0.97 [0.19, 4.98]
Total (95% CI)	**70**	**68**		**100.0 %**	**0.97 [0.19, 4.98]**
Total events: 3 (cephalosporin), 3 (penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					



Analysis 1.6. Comparison 1 Cephalosporin versus penicillin, Outcome 6 Incidence of relapse (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 6 Incidence of relapse (evaluable participants)

Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Adults					
Carbon 1995	3/115	7/115		22.9 %	0.41 [0.10, 1.64]
Nemeth 1999	11/374	11/166		49.7 %	0.43 [0.18, 1.01]
Subtotal (95% CI)	**489**	**281**		**72.7 %**	**0.42 [0.20, 0.88]**
Total events: 14 (cephalosporin), 18 (penicillin)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.021)					
2 Children					
Disney 1992a	2/263	3/262		10.0 %	0.66 [0.11, 3.99]
Reed 1991	6/45	6/46		17.3 %	1.03 [0.30, 3.46]
Subtotal (95% CI)	**308**	**308**		**27.3 %**	**0.89 [0.33, 2.43]**

(*Continued* . . .)

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Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 8 (cephalosporin), 9 (penicillin)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.22 (P = 0.82)					
Total (95% CI)	**797**	**589**		**100.0 %**	**0.55 [0.31, 0.99]**
Total events: 22 (cephalosporin), 27 (penicillin)					
Heterogeneity: Chi^2 = 1.55, df = 3 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 1.99 (P = 0.047)					

Analysis 1.7. Comparison 1 Cephalosporin versus penicillin, Outcome 7 Complications (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 7 Complications (ITT analysis)

Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Carbon 1995	0/119	0/125		0.0 [0.0, 0.0]
Total (95% CI)	**119**	**125**		**0.0 [0.0, 0.0]**
Total events: 0 (cephalosporin), 0 (penicillin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.8. Comparison 1 Cephalosporin versus penicillin, Outcome 8 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 8 Adverse events (ITT analysis)

Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Carbon 1995	16/119	34/125		33.3 %	0.42 [0.22, 0.80]
Nemeth 1999	183/609	48/310		36.0 %	2.34 [1.65, 3.34]
Reed 1991	13/60	13/56		30.8 %	0.91 [0.38, 2.19]
Total (95% CI)	**788**	**491**		**100.0 %**	**0.99 [0.31, 3.16]**

Total events: 212 (cephalosporin), 95 (penicillin)

Heterogeneity: $Tau^2 = 0.94$; $Chi^2 = 22.00$, df = 2 (P = 0.00002); $I^2 = 91\%$

Test for overall effect: Z = 0.02 (P = 0.98)

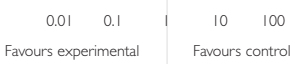
Analysis 1.9. Comparison 1 Cephalosporin versus penicillin, Outcome 9 Resolution of symptoms ITT (subgroup sponsored versus no sponsor reported).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 9 Resolution of symptoms ITT (subgroup sponsored versus no sponsor reported)

Study or subgroup	cephalosporin n/N	penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Sponsor not reported					
Carbon 1995	13/119	22/125		15.5 %	0.57 [0.27, 1.20]
Disney 1992a	8/263	21/262		13.1 %	0.36 [0.16, 0.83]
Subtotal (95% CI)	**382**	**387**		**28.5 %**	**0.47 [0.27, 0.81]**
Total events: 21 (cephalosporin), 43 (penicillin)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.70 (P = 0.0070)					
2 Sponsored studies					
Henness 1982a	38/114	33/100		21.2 %	1.02 [0.57, 1.80]
Nemeth 1999	201/609	117/310		36.0 %	0.81 [0.61, 1.08]
Reed 1991	22/60	16/56		14.3 %	1.45 [0.66, 3.16]
Subtotal (95% CI)	**783**	**466**		**71.5 %**	**0.90 [0.70, 1.16]**
Total events: 261 (cephalosporin), 166 (penicillin)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.08$, df = 2 (P = 0.35); $I^2 = 4\%$					
Test for overall effect: Z = 0.81 (P = 0.42)					
Total (95% CI)	**1165**	**853**		**100.0 %**	**0.79 [0.55, 1.12]**
Total events: 282 (cephalosporin), 209 (penicillin)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 7.19$, df = 4 (P = 0.13); $I^2 = 44\%$					
Test for overall effect: Z = 1.32 (P = 0.19)					

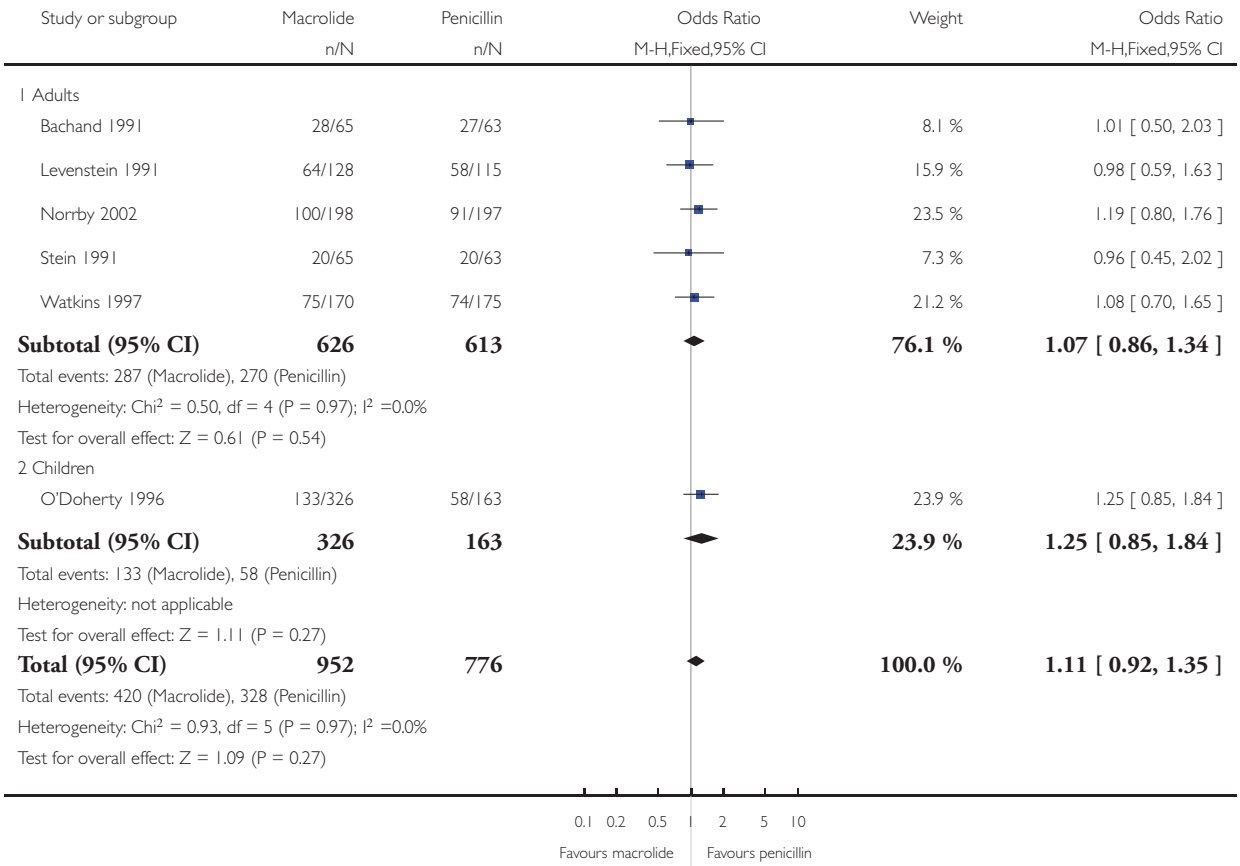


Analysis 2.1. Comparison 2 Macrolide versus penicillin, Outcome 1 Resolution of symptoms post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 1 Resolution of symptoms post-treatment (ITT analysis)

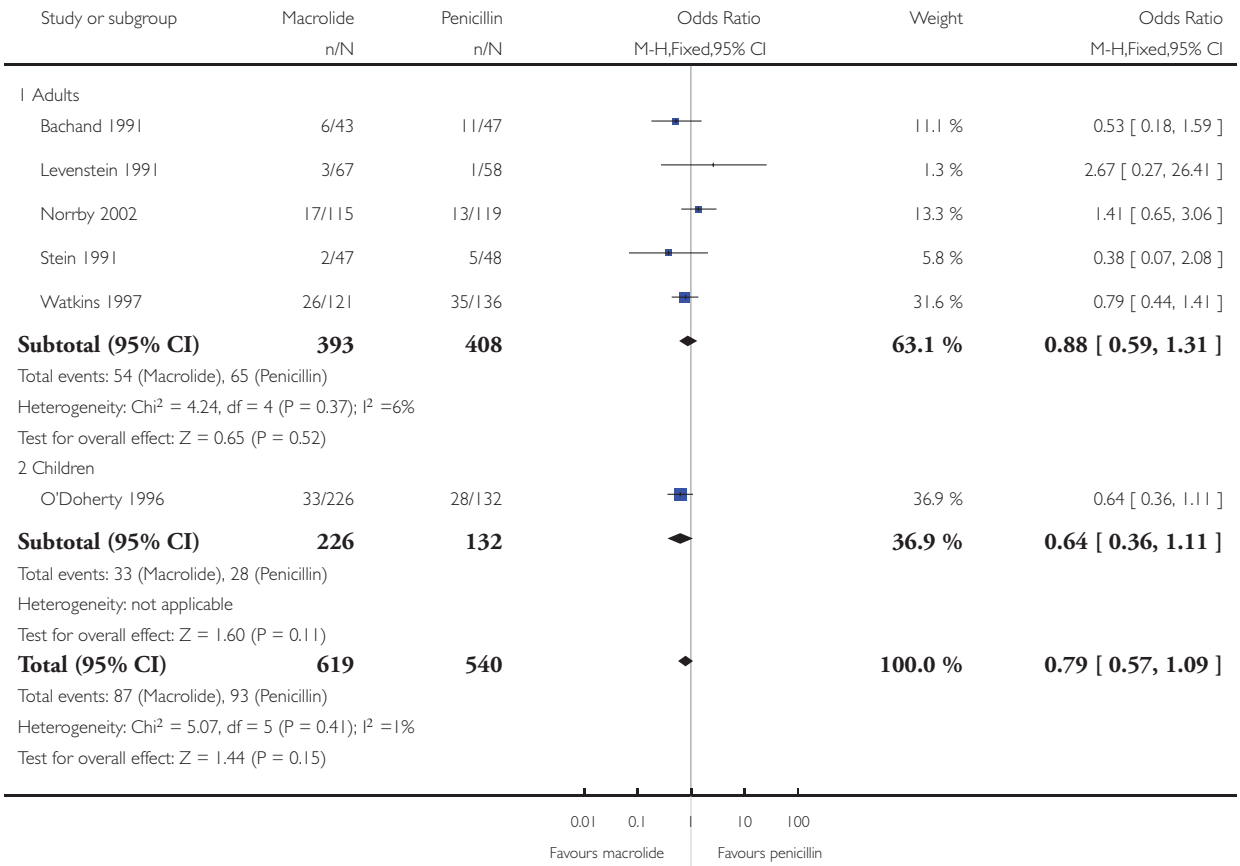


Analysis 2.2. Comparison 2 Macrolide versus penicillin, Outcome 2 Resolution of symptoms post-treatment (evaluable participants only).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 2 Resolution of symptoms post-treatment (evaluable participants only)



Analysis 2.3. Comparison 2 Macrolide versus penicillin, Outcome 3 Sore throat post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

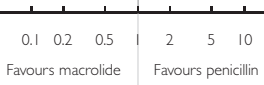
Outcome: 3 Sore throat post-treatment (ITT analysis)

Study or subgroup	Macrolide n/N	Penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bachand 1991	25/65	24/63		32.5 %	1.02 [0.50, 2.07]
Levenstein 1991	66/128	61/115		67.5 %	0.94 [0.57, 1.56]
Total (95% CI)	**193**	**178**		**100.0 %**	**0.97 [0.64, 1.46]**

Total events: 91 (Macrolide), 85 (Penicillin)

Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 0.16 (P = 0.87)



Analysis 2.4. Comparison 2 Macrolide versus penicillin, Outcome 4 Fever post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 4 Fever post-treatment (ITT analysis)

Study or subgroup	Macrolide n/N	Penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bachand 1991	22/65	16/63		25.2 %	1.50 [0.70, 3.23]
Levenstein 1991	61/128	58/115		74.8 %	0.89 [0.54, 1.48]
Total (95% CI)	**193**	**178**		**100.0 %**	**1.05 [0.69, 1.59]**

Total events: 83 (Macrolide), 74 (Penicillin)

Heterogeneity: Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =19%

Test for overall effect: Z = 0.22 (P = 0.83)

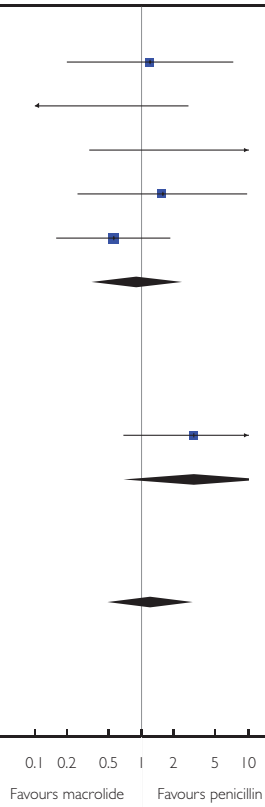
Analysis 2.5. Comparison 2 Macrolide versus penicillin, Outcome 5 Incidence of relapse (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 5 Incidence of relapse (evaluable participants)

Study or subgroup	Macrolide n/N	Penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adults					
Bachand 1991	3/13	3/15		18.2 %	1.20 [0.20, 7.31]
Levenstein 1991	1/60	0/1		6.0 %	0.08 [0.00, 2.73]
Norrby 2002	0/1	1/53		6.0 %	11.67 [0.32, 422.14]
Stein 1991	3/47	2/48		17.8 %	1.57 [0.25, 9.84]
Watkins 1997	4/121	8/136		29.2 %	0.55 [0.16, 1.86]
Subtotal (95% CI)	**242**	**253**		**77.2 %**	**0.90 [0.34, 2.39]**
Total events: 11 (Macrolide), 14 (Penicillin)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 4.86$, df = 4 (P = 0.30); $I^2 = 18\%$					
Test for overall effect: Z = 0.22 (P = 0.83)					
2 Children					
O'Doherty 1996	11/199	2/108		22.8 %	3.10 [0.67, 14.25]
Subtotal (95% CI)	**199**	**108**		**22.8 %**	**3.10 [0.67, 14.25]**
Total events: 11 (Macrolide), 2 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
Total (95% CI)	**441**	**361**		**100.0 %**	**1.21 [0.48, 3.03]**
Total events: 22 (Macrolide), 16 (Penicillin)					
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 6.99$, df = 5 (P = 0.22); $I^2 = 28\%$					
Test for overall effect: Z = 0.40 (P = 0.69)					



Analysis 2.6. Comparison 2 Macrolide versus penicillin, Outcome 6 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 6 Adverse events (ITT analysis)

Study or subgroup	Macrolide n/N	Penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adults					
Bachand 1991	37/65	33/63		15.6 %	1.20 [0.60, 2.41]
Levenstein 1991	7/128	10/115		9.9 %	0.61 [0.22, 1.65]
Norrby 2002	70/198	69/196		24.3 %	1.01 [0.67, 1.52]
Stein 1991	25/65	13/63		13.5 %	2.40 [1.09, 5.29]
Watkins 1997	108/170	118/175		23.2 %	0.84 [0.54, 1.31]
Subtotal (95% CI)	**626**	**612**		**86.5 %**	**1.06 [0.75, 1.50]**
Total events: 247 (Macrolide), 243 (Penicillin)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 6.50, df = 4 (P = 0.16); I^2 =38%					
Test for overall effect: Z = 0.34 (P = 0.74)					
2 Children					
O'Doherty 1996	35/326	8/163		13.5 %	2.33 [1.06, 5.15]
Subtotal (95% CI)	**326**	**163**		**13.5 %**	**2.33 [1.06, 5.15]**
Total events: 35 (Macrolide), 8 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.036)					
Total (95% CI)	**952**	**775**		**100.0 %**	**1.19 [0.82, 1.73]**
Total events: 282 (Macrolide), 251 (Penicillin)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 10.22, df = 5 (P = 0.07); I^2 =51%					
Test for overall effect: Z = 0.92 (P = 0.36)					

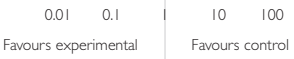
Analysis 2.7. Comparison 2 Macrolide versus penicillin, Outcome 7 Resolution of symptoms ITT (subgroup sponsored versus no-sponsor reported).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 7 Resolution of symptoms ITT (subgroup sponsored versus no-sponsor reported)

Study or subgroup	Macrolide n/N	Penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Sponsor not reported					
Levenstein 1991	64/128	58/115		15.9 %	0.98 [0.59, 1.63]
O'Doherty 1996	133/326	58/163		23.9 %	1.25 [0.85, 1.84]
Stein 1991	20/65	20/63		7.3 %	0.96 [0.45, 2.02]
Subtotal (95% CI)	**519**	**341**		**47.1 %**	**1.11 [0.84, 1.48]**
Total events: 217 (Macrolide), 136 (Penicillin)					
Heterogeneity: Chi^2 = 0.72, df = 2 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 Sponsored studies					
Bachand 1991	28/65	27/63		8.1 %	1.01 [0.50, 2.03]
Norrby 2002	100/198	91/197		23.5 %	1.19 [0.80, 1.76]
Watkins 1997	75/170	74/175		21.2 %	1.08 [0.70, 1.65]
Subtotal (95% CI)	**433**	**435**		**52.9 %**	**1.12 [0.85, 1.46]**
Total events: 203 (Macrolide), 192 (Penicillin)					
Heterogeneity: Chi^2 = 0.20, df = 2 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
Total (95% CI)	**952**	**776**		**100.0 %**	**1.11 [0.92, 1.35]**
Total events: 420 (Macrolide), 328 (Penicillin)					
Heterogeneity: Chi^2 = 0.93, df = 5 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 1.09 (P = 0.27)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					



Analysis 3.1. Comparison 3 Carbacephem versus penicillin, Outcome 1 Resolution of symptoms post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Carbacephem versus penicillin

Outcome: 1 Resolution of symptoms post-treatment (ITT analysis)

Study or subgroup	Carbacephem n/N	Penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adults					
McCarty 1992a	21/107	34/111		25.1 %	0.55 [0.30, 1.03]
Muller 1992	68/169	74/175		44.4 %	0.92 [0.60, 1.41]
Subtotal (95% CI)	**276**	**286**		**69.5 %**	**0.75 [0.46, 1.22]**
Total events: 89 (Carbacephem), 108 (Penicillin)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 1.72, df = 1 (P = 0.19); I^2 =42%					
Test for overall effect: Z = 1.15 (P = 0.25)					
2 Children					
Disney 1992b	32/120	44/113		30.5 %	0.57 [0.33, 0.99]
Subtotal (95% CI)	**120**	**113**		**30.5 %**	**0.57 [0.33, 0.99]**
Total events: 32 (Carbacephem), 44 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.99 (P = 0.047)					
Total (95% CI)	**396**	**399**		**100.0 %**	**0.70 [0.49, 0.99]**
Total events: 121 (Carbacephem), 152 (Penicillin)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 2.60, df = 2 (P = 0.27); I^2 =23%					
Test for overall effect: Z = 2.03 (P = 0.042)					

Analysis 3.2. Comparison 3 Carbacephem versus penicillin, Outcome 2 Resolution of symptoms post-treatment (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Carbacephem versus penicillin

Outcome: 2 Resolution of symptoms post-treatment (evaluable participants)

Study or subgroup	Carbacephem n/N	Penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Adults					
McCarty 1992a	3/89	5/82		12.0 %	0.54 [0.12, 2.32]
Muller 1992	14/115	23/124		46.4 %	0.61 [0.30, 1.25]
Subtotal (95% CI)	**204**	**206**		**58.4 %**	**0.59 [0.31, 1.13]**
Total events: 17 (Carbacephem), 28 (Penicillin)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 1.58 (P = 0.11)					
2 Children					
Disney 1992b	16/104	19/88		41.6 %	0.66 [0.32, 1.38]
Subtotal (95% CI)	**104**	**88**		**41.6 %**	**0.66 [0.32, 1.38]**
Total events: 16 (Carbacephem), 19 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
Total (95% CI)	**308**	**294**		**100.0 %**	**0.62 [0.38, 1.01]**
Total events: 33 (Carbacephem), 47 (Penicillin)					
Heterogeneity: Chi^2 = 0.07, df = 2 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 1.92 (P = 0.055)					

Analysis 3.3. Comparison 3 Carbacephem versus penicillin, Outcome 3 Incidence of relapse (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Carbacephem versus penicillin

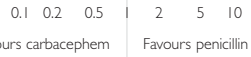
Outcome: 3 Incidence of relapse (evaluable participants)

Study or subgroup	Carbacephem n/N	Penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Disney 1992b	9/84	5/70		32.6 %	1.56 [0.50, 4.89]
McCarty 1992a	5/75	3/67		19.8 %	1.52 [0.35, 6.63]
Muller 1992	7/108	8/119		47.6 %	0.96 [0.34, 2.75]
Total (95% CI)	**267**	**256**		**100.0 %**	**1.27 [0.64, 2.50]**

Total events: 21 (Carbacephem), 16 (Penicillin)

Heterogeneity: $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 0.69 (P = 0.49)



Analysis 3.4. Comparison 3 Carbacephem versus penicillin, Outcome 4 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Carbacephem versus penicillin

Outcome: 4 Adverse events (ITT analysis)

Study or subgroup	Carbacephem n/N	Penicillin n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Disney 1992b	22/120	26/113		32.8 %	0.75 [0.40, 1.42]
McCarty 1992a	31/107	26/111		36.2 %	1.33 [0.73, 2.44]
Muller 1992	22/169	19/175		31.1 %	1.23 [0.64, 2.36]
Total (95% CI)	**396**	**399**		**100.0 %**	**1.08 [0.75, 1.55]**

Total events: 75 (Carbacephem), 71 (Penicillin)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.86$, df = 2 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 0.40 (P = 0.69)

Analysis 4.1. Comparison 4 Clindamycin versus ampicillin, Outcome 1 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 4 Clindamycin versus ampicillin

Outcome: 1 Adverse events (ITT analysis)

Study or subgroup	Clindamycin n/N	Ampicillin n/N	Odds Ratio Peto,Fixed,95% CI	Weight	Odds Ratio Peto,Fixed,95% CI
Jackson 1973	6/156	14/158		100.0 %	0.41 [0.15, 1.10]
Total (95% CI)	**156**	**158**		**100.0 %**	**0.41 [0.15, 1.10]**
Total events: 6 (Clindamycin), 14 (Ampicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.077)					
Test for subgroup differences: Not applicable					

Analysis 5.1. Comparison 5 Sulfonamide versus penicillin, Outcome 1 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 5 Sulfonamide versus penicillin

Outcome: 1 Adverse events (ITT analysis)

Study or subgroup	Sulfonamide n/N	Penicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Trickett 1973	8/44	6/43		100.0 %	1.37 [0.43, 4.34]
Total (95% CI)	**44**	**43**		**100.0 %**	**1.37 [0.43, 4.34]**
Total events: 8 (Sulfonamide), 6 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					

APPENDICES

Appendix 1. Embase.com search strategy

28. #24 AND #27
27. #25 OR #26
26. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl*) NEAR/2 (mask* OR blind*)):ab,ti
25. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
24. #20 AND #23
23. #21 OR #22
22. antibiotic*:ab,ti OR antibacterial*:ab,ti OR (anti NEAR/1 bacterial*):ab,ti
21. 'antibiotic agent'/exp
20. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #19
19. #17 AND #18
18. throat*:ab,ti
17. #13 OR #14 OR #15 OR #16
16. gabhs:ab,ti
15. ('group a beta haemolytic' NEAR/1 streptococc*):ab,ti
14. ('group a beta hemolytic' NEAR/1 streptococc*):ab,ti
13. 'streptococcus infection'/de OR 'group a streptococcal infection'/de
12. (strep* NEAR/3 throat*):ab,ti
11. (sore NEAR/1 throat*):ab,ti
10. 'sore throat'/exp
9. tonsillopharyngit*:ab,ti
8. 'streptococcal pharyngitis'/exp
7. tonsillit*:ab,ti
6. 'tonsillitis'/exp
5. nasopharyngit*:ab,ti
4. rhinopharyngit*:ab,ti
3. 'rhinopharyngitis'/exp
2. pharyngit*:ab,ti
1. 'pharyngitis'/exp

WHAT'S NEW

Last assessed as up-to-date: 10 August 2010.

Date	Event	Description
9 December 2010	Amended	Contact details updated.

Evid.-Based Child Health **7:1**: 16–81 (2011)

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 10, 2010

Date	Event	Description
6 October 2010	Amended	Contact details updated.
31 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MVD wrote the protocol. All authors contributed to final editing of the protocol.

MVD and NK selected trials.

MVD and NK independently performed quality assessment.

MVD and NK performed data extraction with support from ADS. MVD analysed the data.

MVD wrote the draft review and addressed the reviewers' comments. All review authors contributed to the discussion and the editing.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of General Practice and Primary Health Care, University of Ghent, Belgium.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Streptococcus pyogenes; Age Factors; Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Cephalosporins [therapeutic use]; Clindamycin [therapeutic use]; Macrolides [therapeutic use]; Penicillins [therapeutic use]; Pharyngitis [*drug therapy; microbiology]; Streptococcal Infections [*drug therapy; microbiology]; Sulfonamides [therapeutic use]

MeSH check words

Adult; Child; Humans