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Different antibiotic treatments for group A streptococcal pharyngitis (Review)

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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

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; and (d) preventing complications (suppurative complications, acute rheumatic fever, post-streptococcal glomerulonephritis). To assess the evidence on the comparative incidence of adverse effects and the risk-benefit of antibiotic treatment for streptococcal pharyngitis.

Search methods

We searched CENTRAL (2016, Issue 3), MEDLINE Ovid (1946 to March week 3, 2016), Embase Elsevier (1974 to March 2016), and Web of Science Thomson Reuters (2010 to March 2016). We also searched clinical trials registers.

Selection criteria

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

Data collection and analysis

Two review authors independently screened trials for inclusion, and extracted data using standard methodological procedures as recommended by Cochrane. We assessed risk of bias of included studies according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* and used the GRADE tool to assess the overall quality of evidence for the outcomes.

Main results

We included 19 trials (5839 randomised participants); seven compared penicillin with cephalosporins, six compared penicillin with macrolides, three compared penicillin with carbacephem, one trial compared penicillin with sulphonamides, one trial compared clindamycin with ampicillin, and one trial compared azithromycin with amoxicillin in children. All included trials reported clinical outcomes. Reporting of randomisation, allocation concealment, and blinding was poor in all trials. The overall quality of the evidence assessed using the GRADE tool was low for the outcome 'resolution of symptoms' in the intention-to-treat (ITT) analysis and very low for the outcomes 'resolution of symptoms' of evaluable participants and for adverse events. We downgraded the quality of evidence mainly due to lack of (or poor reporting of) randomisation or blinding, or both, heterogeneity, and wide confidence intervals (CIs).

There was a difference in symptom resolution in favour of cephalosporins compared with penicillin (evaluable patients analysis odds ratio (OR) for absence of resolution of symptoms 0.51, 95% CI 0.27 to 0.97; number needed to treat to benefit (NNTB) 20, N = 5, n = 1660; very low quality evidence). However, this was not statistically significant in the ITT analysis (OR 0.79, 95% CI 0.55 to 1.12; N = 5, n = 2018; low quality evidence). Clinical relapse was lower for cephalosporins compared with penicillin (OR 0.55, 95% CI 0.30 to 0.99; NNTB 50, N = 4, n = 1386; low quality evidence), but this was found only in adults (OR 0.42, 95% CI 0.20 to 0.88; NNTB 33, N = 2, n = 770). There were no differences between macrolides and penicillin for any of the outcomes. One unpublished trial in children found a better cure rate for azithromycin in a single dose compared to amoxicillin for 10 days (OR 0.29, 95% CI 0.11 to 0.73; NNTB 18, N = 1, n = 482), but there was no difference between the groups in ITT analysis (OR 0.76, 95% CI 0.55 to 1.05; N = 1, n = 673) or at long-term follow-up (evaluable patients analysis OR 0.88, 95% CI 0.43 to 1.82; N = 1, n = 422). Children experienced more adverse events with azithromycin compared to amoxicillin (OR 2.67, 95% CI 1.78 to 3.99; N = 1, n = 673). Compared with penicillin carbacephem showed better symptom resolution post-treatment in adults and children combined (ITT analysis OR 0.70, 95% CI 0.49 to 0.99; NNTB 14, N = 3, n = 795), and in the subgroup analysis of children (OR 0.57, 95% CI 0.33 to 0.99; NNTB 8, N = 1, n = 233), but not in the subgroup analysis of adults (OR 0.75, 95% CI 0.46 to 1.22, N = 2, n = 562). Children experienced more adverse events with macrolides compared with penicillin (OR 2.33, 95% CI 1.06 to 5.15; N = 1, n = 489). Studies did not report on long-term complications so it was unclear if any class of antibiotics was better in preventing serious but rare complications.

Authors' conclusions

There were no clinically relevant differences in symptom resolution when comparing cephalosporins and macrolides with penicillin in the treatment of 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 than penicillin 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 regarded as a first choice treatment for both adults and children. All studies were in high-income countries with low risk of streptococcal complications, so there is need for trials in low-income countries and Aboriginal communities where risk of complications remains high.

PLAIN LANGUAGE SUMMARY

Different antibiotics for group A streptococcal pharyngitis

Review question

We wanted to know which antibiotic was more effective in treating sore throats caused by bacteria (group A beta-haemolytic streptococci (GABHS)).

Background

Most sore throats are caused by viruses, but many people carry throat bacteria, sometimes causing bacterial throat infection.

GABHS infection can have serious complications including rheumatic fever and kidney disease. Antibiotics are often prescribed to prevent complications, but provide modest benefit for sore throat, even if GABHS are present. Most throat infections are self-limiting and complication risks is extremely low for most people in high-income countries. However, sometimes antibiotics are needed. Penicillin, a cheap antibiotic, has been used to treat GABHS for many years. GABHS resistance to penicillin is rare.

Search date

We searched the literature to March 2016.

Study characteristics

We included 19 trials (18 publications) that involved 5835 people. Trials studied different antibiotics for people with sore throat who tested positive for GABHS, and were aged from one month to 80 years. Nine trials included only children; and nine included people aged 12 years or older. Most studies were published over 15 years ago; all but one reported on clinical outcomes.

Study funding sources

Thirteen trials were supported by drug study funding - some received grants - others included people employed by drug companies. Five studies did not report funding.

Key results

Antibiotic effects were similar, and all caused side effects (such as nausea and vomiting, rash), but there was no strong evidence to show meaningful differences between antibiotics. Studies did not report on long-term complications so it was unclear if any class of antibiotics was better in preventing serious but rare complications.

All studies were in high-income countries with low risk of streptococcal complications, so there is a need for trials in low-income countries and Aboriginal communities where risk remains high. Our review supports the use of penicillin as a first choice antibiotic in patients with throat infections caused by GABHS.

Quality of the evidence

Evidence quality was low or very low for all outcomes when macrolides or cephalosporins were compared with penicillin. Evidence quality was downgraded because of concerns about randomisation and blinding, wide confidence intervals (estimates were not very precise) and statistical differences among studies that may impact on the validity of the estimate. Most study authors did not report enough information about methods to be sure there was no bias.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Cephalosporins compared to penicillin for group A streptococcal pharyngitis

Patient or population: group A streptococcal pharyngitis
Setting: outpatients
Intervention: cephalosporin
Comparison: penicillin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with penicillin	Risk with Cephalosporin				
Resolution of symptoms post-treatment (ITT analysis)	Study population 245 per 1,000	204 per 1,000 (151 to 267)	OR 0.79 (0.55 to 1.12)	2018 (5 RCTs)	⊕⊕◯◯ LOW [12]	
Resolution of symptoms post-treatment (ITT analysis) - Adults	Study population 320 per 1,000	268 per 1,000 (220 to 322)	OR 0.78 (0.60 to 1.01)	1163 (2 RCTs)	⊕⊕◯◯ LOW [12]	
Resolution of symptoms post-treatment (ITT analysis) - Children	Study population 167 per 1,000	143 per 1,000 (74 to 258)	OR 0.83 (0.40 to 1.73)	855 (3 RCTs)	⊕◯◯◯ VERY LOW [123]	
Resolution of symptoms post-treatment (evaluable participants)	Study population 112 per 1,000	60 per 1,000 (33 to 109)	OR 0.51 (0.27 to 0.97)	1660 (5 RCTs)	⊕◯◯◯ VERY LOW [123]	

Incidence of relapse (evaluable participants)	Study population		OR 0.55 (0.30 to 0.99)	1386 (4 RCTs)	⊕⊕◯◯ LOW [12]
	46 per 1,000	26 per 1,000 (14 to 45)			
Adverse events (ITT analysis)	Study population		OR 0.94 (0.27 to 3.25)	1279 (3 RCTs)	⊕◯◯◯ VERY LOW [123]
	193 per 1,000	184 per 1,000 (61 to 438)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] unclear randomisation and blinding
[2] wide confidence intervals
[3] heterogeneity

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 GABHS sore throat pointed to the self-limiting nature of an acute sore throat (even in cases of positive GABHS culture) (Spinks 2013). Antibiotics provide only modest benefit when prescribed for 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 treatment with antibiotics for participants with proven presence, or a high likelihood of GABHS (Cooper 2001; Snow 2001). However, 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); 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 the comparative benefit-harm balance, costs, and local antimicrobial resistance patterns. Many guidelines recommend penicillin as a first choice, with erythromycin preferred for people who are allergic to penicillin (Cooper 2001; Snow 2001). To date, resistance of GABHS to penicillin has only been documented incidentally (Devi 2011; Gerber 2009b; Ibrahim 2014), and resistance to erythromycin is still low (Cooper 2001). Considering the growing problem of antibiotic resistance for other pathogens, this responsiveness of GABHS should not be endangered (Wise 1998). Penicillin and erythromycin are cheap and the most cost-effective option. Despite 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 people with 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 eligible antibiotics can guide choice. Therefore, to provide healthcare providers with sufficient information to make an evidence-based choice, both treatment benefits and adverse events are compared.

OBJECTIVES

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; and (d) preventing complications (suppurative complications, acute rheumatic fever, post-streptococcal glomerulonephritis). 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, rapid test or both.

Types of interventions

Antibiotics of one class compared with another class.

Types of outcome measures

The focus was on outcome measures relevant for patients.

Primary outcomes

1. Resolution of symptoms (cure or improvement of signs and symptoms, which could include sore throat, fever, feeling ill, etc.) post-treatment

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

For this update we searched the Cochrane Acute Respiratory Infections Group's Specialised Register (25 March 2016); the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 11), in the Cochrane Library (searched 25 March 2016); MEDLINE Ovid (1966 to March week 3 2016); Embase Elsevier (1974 to 25 March 2016) and Web of Science Thomson Reuters (2010 to 25 March 2016). Search strategies for previous versions of this review are presented in Appendix 1. Details of the current MEDLINE and CENTRAL search strategy are in Appendix 2, Embase is in Appendix 3, and Web of Science is in Appendix 4.

We did not impose any language or publication restrictions.

Searching other resources

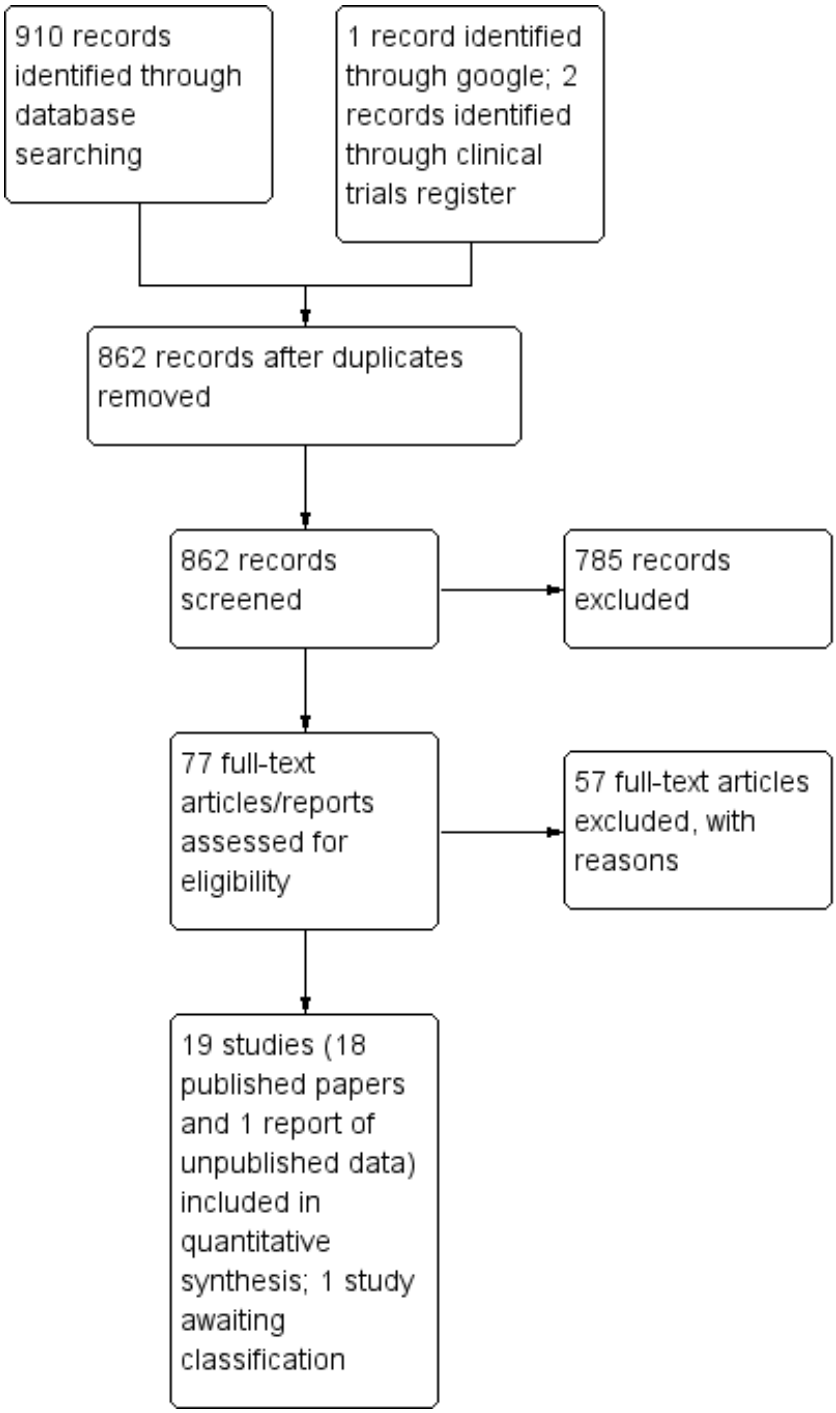
We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and the US National Institutes of Health Ongoing Trials Register for completed and ongoing trials (www.clinicaltrials.gov). We used the terms streptococcal AND pharyngitis (latest search 25 March 2016). 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 assessed all trials with relevant titles or abstracts, or both, identified by the search to determine which met the inclusion criteria. We excluded all trials that did not meet our inclusion criteria. Trials that were closely assessed for inclusion but subsequently excluded are listed in the Characteristics of excluded studies table. The search results are reported in a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (MVD, NK) independently extracted data, using a standard checklist we developed for 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 domains:

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: 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 Cochrane's risk of bias tool (Higgins 2011). The same review authors independently assessed each trial. We assessed risk of bias for: selection bias (random number generation and allocation concealment), performance and detection bias (blinding), attrition bias (incomplete outcome data), and reporting bias (selective reporting). We assessed studies as low risk of bias (methods clearly described and deemed adequate), high risk of bias (methods described and inadequate or not described and deemed likely to be inadequate), or unclear bias (insufficient information to assess the methods, however no obvious indication for use of inadequate methods).

Measures of treatment effect

We used Review Manager 5 software for statistical analysis and data pooling (RevMan 2014). If possible, we summarised data in a meta-analysis and performed analyses according to ITT analysis. This means that the number of participants randomised was used as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures. For dichotomous outcomes, we expressed results as ORs, with 95% CIs. For statistically significant results we calculated NNTB and NNTH where possible.

Unit of analysis issues

We did not include any cluster-randomised studies. All included studies reported outcomes at the level of the randomised unit, the individual patient.

Dealing with missing data

We assessed the impact of missing data on the overall outcome of the meta-analysis by comparing analysis of on-treatment (or evaluable patients) and ITT data.

Assessment of heterogeneity

We assessed heterogeneity among trial results by calculating a Chi^2 test (significance defined as $P < 0.10$) and the I^2 statistic (Higgins 2003).

Assessment of reporting biases

We did not identify a sufficient number of studies to assess the presence of publication bias by means of a funnel plot.

Data synthesis

We pooled dichotomous data using a random-effects model (Higgins 2011). We used a random-effects model for pooling (DerSimonian 1986), but in the absence of statistical heterogeneity (using a cut-off point of $I^2 < 20\%$), we also pooled data using the fixed-effect model and compared outcomes (Mantel 1959). We used RevMan 2014 software for pooling.

GRADE and 'Summary of findings' table

For assessment of the overall quality of evidence for the pooled studies, we used the GRADE approach (Atkins 2004), with GRADEpro software (GRADEproGDT 2014). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We created summary of findings tables for the following comparisons: cephalosporin versus penicillin (Summary of findings for the main comparison; Analysis 1.1; Analysis 1.2; Analysis 1.6; Analysis 1.8) and macrolide versus penicillin (Summary of findings 2; Analysis 2.1; Analysis 2.2; Analysis 2.5; Analysis 2.6). We assessed the quality of evidence for the primary outcome (resolution of symptoms, both ITT and evaluable patient analysis), and secondary outcomes (incidence of relapse and incidence of adverse events). We justified all decisions to down- or up-grade the quality of studies using

footnotes to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

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

We reported ITT data for clinical outcomes and 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 was analysed by including only evaluable participants; an ITT analysis would have seriously overestimated the importance of relapse, and results would not be relevant to clinical practice.

Sensitivity analysis

We performed a sensitivity analysis of the impact of heterogeneity on the overall effect estimate by first pooling all studies and subsequently removing studies one by one, starting with the studies that appeared (by inspection of the forest plot) to be contributing to the heterogeneity. We also performed sensitivity analysis by applying both random-effects and fixed-effect models in the absence of statistical heterogeneity ($I^2 < 20\%$). A meaningful sensitivity analysis was only possible for resolution of symptoms in the comparison of cephalosporin versus penicillin.

RESULTS

Description of studies

Results of the search

We retrieved 385 search results from our electronic searches to October 2012. We retrieved an additional 216 records in the December 2014 search and anther 258 records in the March 2016 search. We identified one additional trial through a Google search (Muller 1992). We identified two references to completed (unpublished) studies on ClinicalTrials.gov in the 2014 search (NCT00643149; NCT00393744). We reviewed a total of 77 trials for this review. Of these, 21 met the predefined inclusion criteria. Two of the 21 papers reported different outcomes of the same study and were considered as one single study (Norrby 2002). The unpublished report of one study registered and marked as completed on ClinicalTrials.gov was made available by Pfizer upon request in 2013 and was included in the 2016 update (NCT00643149). Of the two additional studies that we identified in the March 2016 search, we excluded one (Stillerman 1970), and one was available in abstract form only and is awaiting classification pending information from the authors (Eslami 2014). See PRISMA flow diagram (Moher 2009; Figure 1).

Included studies

We included 18 trials in the first version of this review (van Driel 2010). Henness 1982 reported two separate trials and we split this into two parts to clarify which trial was assessed (Henness 1982-study 1; Henness 1982-study 2). We identified one new study in the 2012 update (NCT00643149), and no new studies in the 2014 update. We did not add any new studies in the 2016 update. We included a total of 19 trials in this review. Most included trials were conducted in the 1990s, three in the 1980s (Henness 1982-study 1; Henness 1982-study 2; Randolph 1985), and two in the 1970s (Jackson 1973; Trickett 1973). Only two trials were more recent (Norrby 2002; NCT00643149). All but one trial reported clinical outcomes (Henness 1982-study 2).

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. We identified the NCT00643149 study through searching a clinical trials register and we subsequently obtained a report from the manufacturer.

All but two of the included studies compared penicillin with another antibiotic class. Henness 1982 compared penicillin V with cefadroxil in both study 1 and study 2, but added two additional study arms in study 2 (erythromycin, benzathine penicillin G/procaine penicillin). Jackson 1973 compared clindamycin with ampicillin and NCT00643149 compared azithromycin with amoxicillin.

The included trials investigated a total of 5839 randomised participants with acute GABHS tonsillopharyngitis. Participants' ages ranged from one month to 80 years. Nine trials included only, or predominantly, children (Disney 1992a; Disney 1992b; Henness 1982-study 1; Henness 1982-study 2; Jackson 1973; O'Doherty 1996; NCT00643149; Randolph 1985; Reed 1991). Ten trials included participants who were at least 12 years of age or older (Bachand 1991; Carbon 1995; Levenstein 1991; McCarty 1992a; Muller 1992; Nemeth 1999; Norrby 2002; Stein 1991; Trickett 1973; Watkins 1997). In Reed 1991, approximately 80% of participants were under 15 years of age and therefore included in the subgroup analysis for children. In Muller 1992, 90% of participants were aged over 12 years; however, because results were not stratified by 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 mostly performed first by a rapid immunoassay test and reconfirmed with a throat culture. In five trials, the confirmation of GABHS ton-

sillopharyngitis was carried out only by a throat culture (Henness 1982-study 1; Henness 1982-study 2; 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. Randolph 1985 reported clinical effect within the first 24 hours of treatment. NCT00643149 assessed clinical effects on days 24 to 28 after starting the study drug. Three trials reported on specific symptoms, such as sore throat and fever (Bachand 1991; Levenstein 1991; Randolph 1985). None reported data on the duration of illness. Henness 1982-study 2 did not report any clinical outcomes.

Twelve trials reported the incidence of clinical relapse (Bachand 1991; Carbon 1995; Disney 1992a; Disney 1992b; Levenstein 1991; McCarty 1992a; Muller 1992; Nemeth 1999; Norrby 2002; O'Doherty 1996; Reed 1991; Stein 1991). The definition of clinical relapse varied slightly; from "pretreatment signs and 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 1982-study 1). Two studies used the physician's assessment 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. Jackson 1973 only reported bacteriological outcomes and clinical adverse events.

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 13 trials.

The percentage of patients who dropped out before outcome measurement varied. Some studies did not seem to have any dropouts (Henness 1982-study 1; Henness 1982-study 2; Randolph 1985) or lost 20% or fewer of the randomised participants at the time of outcome evaluation (Carbon 1995; Disney 1992b; Jackson 1973; Levenstein 1991; Norrby 2002; NCT00643149; Reed 1991). Six studies reported drop out rates between 20% and 30% (Bachand 1991; McCarty 1992a; Muller 1992; Nemeth 1999; O'Doherty 1996; Stein 1991), and in Watkins 1997, reportedly 38% of patients dropped out before the end of the study. The most commonly reported reason for dropout was negative culture for GABHS.

Excluded studies

We excluded 57 studies. The most common reason for exclusion (38 trials) was no or inadequate blinding (Adam 1994; Adam 1995; Adam 1996; Adam 2000a; Adam 2000b; Adam 2001; Aujard 1995; Bottaro 2012; Cohen 2002; Denny 1953; Dykhuizen 1996; Esposito 2002; Feder 1999; Gerber 1986; Gooch 1993; Hamill 1993; Holm 1991; Howe 1997; Kuroki 2013; Lennon 2008; McCarty 1992b; McCarty 1994; Milatovic 1991; Milatovic 1993; Pacifico 1996; Perkins 1969; Pichichero 2000; Pichichero 2008; Portier 1990; Portier 1994; NCT00393744; Sakata 2008; Shapera 1973; Shvartzman 1993; Stillerman 1986; Tack 1997; Tack 1998; Uysal 2000). Seven trials did not compare at least two different classes of antibiotics (Breese 1974; Disney 1979; Matsen 1974; McIsaac 2004; Rimoin 2011; 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). Two trials did not report any clinical outcomes (Gerber 1999a; Stillerman 1970); one was a meta-analysis (Cruz 2011); two were reviews (Stelter 2014; Van Brusselen 2014); and four were not RCTs (Del Mar 2008; De Meyere 1992; Granizio 2008; Haverkorn 1971).

Risk of bias in included studies

Risk of bias assessment is reported in Characteristics of included studies and illustrated in Figure 2 and Figure 3. Only three trials reported ITT analysis for efficacy outcomes (Disney 1992a; Norrby 2002; Randolph 1985). 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.

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

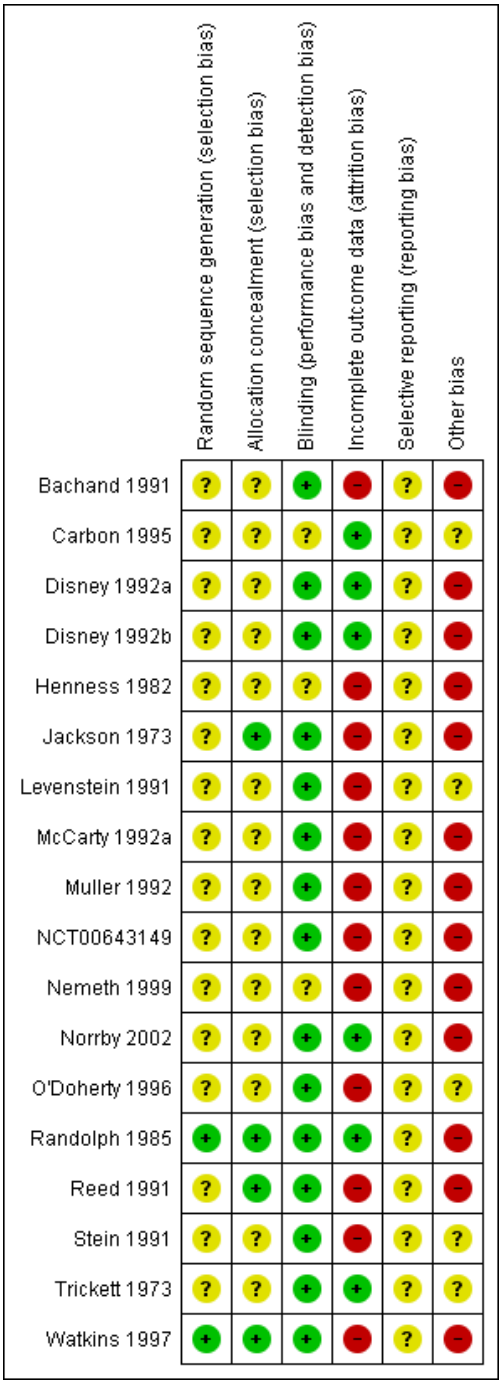
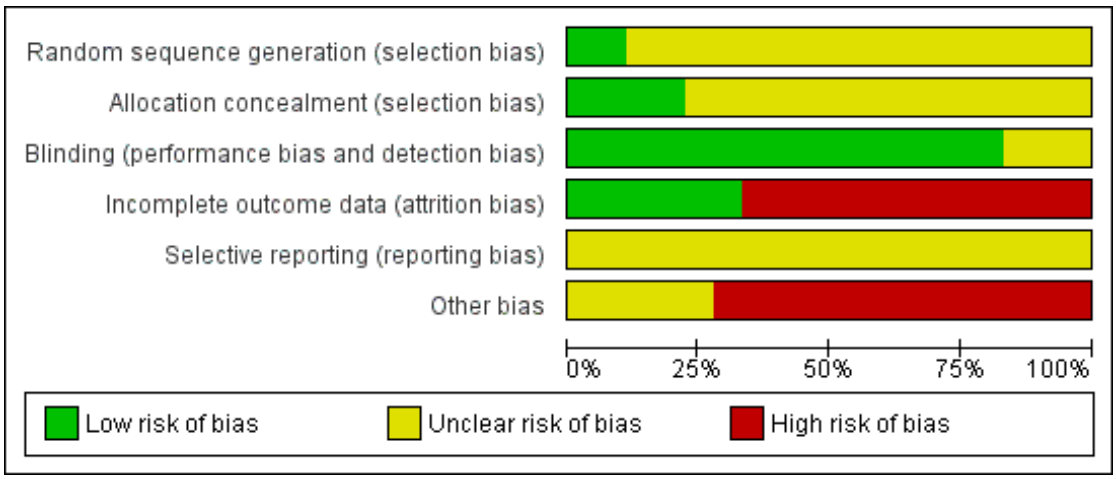


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All trials were randomised, but only four described methods of randomisation or allocation concealment, or both (Jackson 1973; Randolph 1985; Reed 1991; Watkins 1997).

Random sequence generation was described and deemed adequate in two studies (Randolph 1985; Watkins 1997) and not described (assessed as unclear risk) in the remaining studies.

Allocation concealment was described and assessed as adequate in four studies (Jackson 1973; Randolph 1985; Reed 1991; Watkins 1997) and not described (assessed as unclear risk) in the other studies.

Blinding

All trials were double-blinded and methods of blinding were described in 14 trials (Disney 1992a; Disney 1992b; Jackson 1973; Levenstein 1991; McCarty 1992a; Muller 1992; Norrby 2002; O'Doherty 1996; NCT00643149; Randolph 1985; Reed 1991; Stein 1991; Trickett 1973; Watkins 1997).

Blinding of participants and personnel was reported and assessed as low risk of bias in 15 trials (Bachand 1991; Disney 1992a; Disney 1992b; Jackson 1973; Levenstein 1991; McCarty 1992a; Muller 1992; NCT00643149; Norrby 2002; O'Doherty 1996; Randolph 1985; Reed 1991; Stein 1991; Trickett 1973; Watkins 1997). In four studies (Carbon 1995; Henness 1982-study 1; Henness 1982-study 2; Nemeth 1999) this was not reported and assessed as unclear risk of bias.

Blinding of outcome assessors was reported and assessed as low risk of bias in only one trial (Randolph 1985). This was not reported and hence assessed as unclear risk of bias in all other included studies.

Incomplete outcome data

The post-randomisation dropout rate was high in most trials. In 12 trials the proportion of dropouts was more than 20% (Bachand 1991; Henness 1982-study 1; Jackson 1973; Levenstein 1991; McCarty 1992a; Muller 1992; NCT00643149; Nemeth 1999; O'Doherty 1996; Reed 1991; Stein 1991; Watkins 1997), ranging from 21.5% in McCarty 1992a to 48.5% in 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, and therefore, these studies were assessed as high risk of attrition bias.

Only four trials reported an ITT analysis with all randomised participants included in the analysis of the clinical outcome (Disney 1992a; Disney 1992b; Norrby 2002; Randolph 1985). These trials had minimal to no dropouts (0 or 1 participant) and were assessed as low risk of attrition bias. Carbon 1995, Henness 1982-study 2 and Trickett 1973 were also assessed as low risk of attrition bias because of a low post-randomisation dropout rate.

None of the studies were assessed as unclear risk of attrition bias.

Selective reporting

All included studies were assessed as unclear risk for selective reporting; pre-publication protocols were not available.

Other potential sources of bias

Eleven trials reported sponsorship by a pharmaceutical company (Disney 1992a; Disney 1992b; Jackson 1973; McCarty 1992a; Muller 1992; Nemeth 1999; Norrby 2002; Randolph 1985; Reed 1991; Trickett 1973; Watkins 1997). NCT00643149 was unpublished and obtained from the company that conducted the trial (Pfizer). Authors of six trials were reported to be employees of a pharmaceutical company (Bachand 1991; Disney 1992b; Henness 1982-study 1; Henness 1982-study 2; Nemeth 1999; Watkins 1997), and in three of those, the employing pharmaceutical company was not reported as a funding source (Bachand 1991; Henness 1982-study 1; Henness 1982-study 2). These fourteen trials were assessed as high risk of bias in this domain. The remaining five trials did not mention funding sources and were assessed as 'unclear risk of bias' in this domain.

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

See: **Summary of findings for the main comparison** Cephalosporins compared to penicillin for group A streptococcal pharyngitis; **Summary of findings 2** Macrolides compared to penicillin for group A streptococcal pharyngitis

1. Cephalosporin versus penicillin

Six trials contributed to the pooled analysis within this comparison (Carbon 1995; Disney 1992a; Henness 1982-study 1; Nemeth 1999; Randolph 1985; Reed 1991). We assessed the overall quality of evidence for the primary outcome, resolution of symptoms post-treatment as low for the ITT analysis in the total study population and in the subgroup analysis for adults, but very low for the analysis of evaluable patients and ITT analysis in children. The quality of the pooled effect estimate was assessed as low for the outcome incidence of relapse (evaluable patients) and very low for the outcome adverse events (ITT analysis). We downgraded the quality due to unclear randomisation and blinding, wide confidence intervals, and heterogeneity when pooling the studies (see Summary of findings for the main comparison).

1.1. Primary outcome: Resolution of symptoms post-treatment

Six trials reported on the resolution of symptoms at various points in time (Carbon 1995; Disney 1992a; Henness 1982-study 1; Nemeth 1999; Randolph 1985; Reed 1991). See also Summary of findings for the main comparison.

Five trials measured resolution of symptoms at the end of treatment (2 to 15 days or more post-treatment); two trials in adults (Carbon 1995; Nemeth 1999), and three in children (Disney 1992b; Henness 1982-study 1; Reed 1991). The ITT analysis included 2018 participants and showed no difference between treatments (OR 0.79, 95% CI 0.55 to 1.12; low quality evidence; Analysis 1.1; Summary of findings for the main comparison). The effect in adults (OR 0.78, 95% CI 0.60 to 1.01; N = 2, n = 1163; low quality evidence) was similar to that in children (OR 0.83, 95% CI 0.40 to 1.73; N = 3, n = 855; low quality evidence).

The result of the analysis of evaluable participants only showed an effect in favour of treatment with cephalosporins (OR 0.51, 95% CI 0.27 to 0.97; ARD 0.05, NNTB 20, n = 1660; very low quality evidence; Analysis 1.2; Summary of findings for the main comparison). However, the estimates of effect in adults (OR 0.56, 95% CI 0.24 to 1.32; N = 2, n = 880) and in children (OR 0.46, 95% CI 0.14 to 1.52; N = 3, n = 780) analysed separately revealed no statistically significant differences between treatment groups.

We analysed the studies with reported pharmaceutical company sponsorship separately for the outcome resolution of symptoms post-treatment. Two studies that did not report funding sources showed a statistically significant effect in favour of cephalosporins (OR 0.47, 95% CI 0.27 to 0.81; ARD 0.02, NNTB 50; Carbon 1995; Disney 1992a). Pooling sponsored studies did not result in a significant difference between antibiotic groups (Henness 1982-study 1; Nemeth 1999; Reed 1991). See Analysis 1.9.

One trial in children (n = 138) also reported 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). See Analysis 1.3.

A sensitivity analysis revealed that in the ITT analysis, the trial by Disney 1992a contributed to the heterogeneity of the analysis in children. However, removing this trial from the analysis did not result in a significant change in the overall outcome. In a similar analysis for the evaluable patients only, the trial by Reed 1991 appeared to contribute most to the heterogeneity. After removing this trial, the I^2 statistic was no longer important. Pooling the two remaining trials in children showed a statistically significant benefit in favour of cephalosporins in children. However, the overall effect in all participants remained non-significant.

1.2. Secondary outcomes

1.2.1 Sore throat

One trial in children found no difference between treatment groups for resolution of sore throat (OR 0.97, 95% CI 0.23 to 4.04; n = 138; Analysis 1.4; Randolph 1985).

1.2.2 Fever

One trial in children found no difference between treatment groups for resolution of fever (OR 0.97, 95% CI 0.19 to 4.98; n = 138; Analysis 1.5; Randolph 1985).

1.2.3 Duration of illness

Not reported.

1.2.4 Incidence of relapse

In four trials (n = 1386) that reported the incidence of clinical relapse in evaluated participants there was a benefit of treatment with cephalosporins over penicillin in the total population (OR 0.55, 95% CI 0.30 to 0.99; ARD 0.02, NNTB 50; Carbon 1995; Disney 1992a; Nemeth 1999; Reed 1991). This was due to a difference in two trials in adults (OR 0.42, 95% CI 0.20 to 0.88; ARD 0.03, NNTB 33.3, n = 770; Carbon 1995; Nemeth 1999). There was no difference between trials in children (OR 0.89, 95% CI 0.33 to 2.45; n = 616; Analysis 1.6; Disney 1992a; Reed 1991).

1.2.5 Incidence of complications

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

1.2.6 Adverse events

Three trials in adults reported the incidence of adverse effects (Carbon 1995; Nemeth 1999; Reed 1991). There was significant heterogeneity among the trials. In the cephalosporin group, 212 of 788 participants reported adverse events, compared with 87 of 491 in the penicillin group. There was no difference between treatments (OR 0.94, 95% CI 0.27 to 3.25; Analysis 1.8).
The reported adverse events were predominantly gastrointestinal (diarrhoea, nausea and vomiting, constipation), but also vaginal moniliasis and headaches have been reported with both antibiotic classes (Carbon 1995; Nemeth 1999). Reed 1991 did not report the nature of the adverse events. None of the adverse events were serious. Carbon 1995 reported one patient with penicillin allergy.

2. Macrolide versus penicillin

Six trials contributed to the pooled analysis within this comparison (Bachand 1991; Levenstein 1991; Norrby 2002; O'Doherty 1996; Stein 1991; Watkins 1997). We assessed the overall quality of the evidence for the primary outcome, resolution of symptoms, and for incidence of relapse and for adverse events as low. We downgraded the quality due to unclear randomisation and blinding, and wide confidence intervals (see Summary of findings 2).

2.1 Primary outcome: Resolution of symptoms post-treatment

Five trials in adults (Bachand 1991; Levenstein 1991; Norrby 2002; Stein 1991; Watkins 1997), and one 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 treatment groups (OR 1.11, 95% CI 0.92 to 1.35; low quality evidence; Analysis 2.1; Summary of findings 2). The estimate of effect in adults (OR 1.07, 95% CI 0.86 to 1.34; N = 5, n = 1239) was similar to children (OR 1.25, 95% CI 0.85 to 1.84; n = 489). The analysis of evaluable participants only did not result in any significant differences between treatment groups (OR 0.79, 95% CI 0.57 to 1.09; n = 1159; low quality evidence; Analysis 2.2; Summary of findings 2). 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 funding sources did not show significant differences in results (Analysis 2.7).

2.2 Secondary outcomes

2.2.1 Sore throat

Two trials reported resolution of sore throat in adults, and found no difference between the treatments (OR 0.97, 95% CI 0.64 to 1.46; n = 371; Analysis 2.3; Bachand 1991; Levenstein 1991).

2.2.2 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; Analysis 2.4).

2.2.3 Duration of illness

Not reported.

2.2.4 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 relapse at day 15 to 56 post-treatment. The difference was not statistically significant (OR 1.21, 95% CI 0.48 to 3.03; Analysis 2.5; Summary of findings 2).

2.2.5 Incidence of complications

Not reported.

2.2.6 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 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; Summary of findings 2). In the trial in children, macrolides seemed to cause more adverse events than penicillin (OR 2.33, 95% CI 1.06 to 5.15; n = 489, NNTH 17.2; Analysis 2.6).

The reported adverse events were predominantly gastrointestinal (diarrhoea, nausea and vomiting, constipation, abdominal pain), but vaginal moniliasis and headaches and dizziness were also reported with both antibiotic classes. Rash was reported in patients taking penicillin (O'Doherty 1996). Most studies did not report any serious adverse events, but Levenstein 1991 reported two serious events - depression and balanitis.

3. Azithromycin versus amoxicillin

3.1 Primary outcome: Resolution of symptoms post-treatment

One trial (unpublished data provided by Pfizer) studied the effect of a single dose of azithromycin versus 10 days of amoxicillin in 673 children (NCT00643149). The clinical cure rate was reported for the 'bacteriological per protocol population' only, which was defined as those with GABHS-positive culture within 48 hours of treatment start, at least eight days of treatment (compliance) and available data at baseline. Effects were measured at 24 to 28 days after commencing treatment and on days 38 to 42. In the azithromycin group 239/245 participants achieved clinical cure at the first evaluation point versus 218/237 in the amoxicillin group (OR fixed-effect 0.29, 95% CI 0.11 to 0.73; NNTB 18; Analysis 3.2). The difference was not statistically significant in the ITT analysis (OR 0.76, 95% CI 0.55 to 1.05; Analysis 3.1).

3.2 Secondary outcomes

3.2.1 Sore throat

Not reported.

3.2.2 Fever

Not reported.

3.2.3 Duration of illness

Not reported.

3.2.4 Incidence of relapse

On days 38 to 45 after treatment commencement, the per protocol population was reduced to 223 in the azithromycin group and 199 in the amoxicillin group. The incidence of relapse did not differ between groups in the ITT analysis (OR 0.75, 95% CI 0.55 to 1.02; Analysis 3.3) or the bacteriological per protocol population (16/223 in the azithromycin group versus 16/199 in the amoxicillin group; OR 0.88, 95% CI 0.43 to 1.82; Analysis 3.4).

3.2.5 Incidence of complications

Not reported.

3.2.6 Adverse events

In total, 57.5% of participants in the azithromycin group and 56.3% in the amoxicillin group reported experiencing an adverse event. However, reported treatment-related adverse events were more prevalent in the azithromycin group (27.6%) than in the amoxicillin group (12.5%); (OR 2.67, 95% CI 1.78 to 3.99). The most commonly reported adverse events were related to the digestive system (diarrhoea, nausea, vomiting, abdominal pain) and were more common in patients treated with azithromycin (34.1%) than those treated with amoxicillin (16.1%). Rash was more common in the amoxicillin group (3.0% versus 0.6% in the azithromycin group). No deaths or serious adverse events were reported (Analysis 3.5).

4. Carbacephem versus penicillin

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

4.1 Primary outcome: Resolution of symptoms post-treatment

In the ITT analysis, more participants reported resolution of symptoms in the carbacephem group than in the penicillin group (OR for absence of symptom resolution post-treatment 0.70, 95% CI 0.49 to 0.99; n = 795, ARD 0.07, NNTB 14.3; Analysis 4.1). There was no difference in adults (OR 0.75, 95% CI 0.46 to 1.22;

n = 562); in children there was a beneficial effect from carbacephem (OR 0.57, 95% CI 0.33 to 0.99; n = 233, ARD 0.12, NNTB 8.3). The analysis of evaluable participants showed no differences between treatment groups (OR 0.62, 95% CI 0.38 to 1.01; n = 602; Analysis 4.2).

4.2 Secondary outcomes

4.2.1 Sore throat

Not reported.

4.2.2 Fever

Not reported.

4.2.3 Duration of illness

Not reported.

4.2.4 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; Analysis 4.3).

4.2.5 Incidence of complications

Not reported.

4.2.6 Adverse events

There were no differences in reported adverse events between 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 1992 reported that one participant was hospitalised for surgical drainage of a tonsillar abscess in the group treated with loracarbef one day after initiating therapy. See Analysis 4.4.

Reported adverse events were predominantly gastrointestinal (diarrhoea, nausea, vomiting) in all treatment groups. Headaches were reported in McCarty 1992a and Muller 1992, and vaginal moniliasis in McCarty 1992a. Rashes were reported in both treatment groups (Disney 1992b; Muller 1992).

5. Clindamycin versus ampicillin

Jackson 1973 compared treatment with clindamycin to ampicillin (n = 314). The only clinical outcome reported was adverse events.

5.1 Primary outcome: Resolution of symptoms post-treatment

Not reported.

5.2 Secondary outcomes

5.2.1 Sore throat

Not reported.

5.2.2 Fever

Not reported.

5.2.3 Duration of illness

Not reported.

5.2.4 Incidence of relapse

Not reported.

5.2.5 Incidence of complications

Not reported.

5.2.6 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; Analysis 5.1). Gastrointestinal adverse events (nausea or vomiting and loose stools) and rash or urticaria occurred in both treatment groups. No other events were reported.

6. Sulphonamide versus penicillin

One trial in adults was included in this comparison (Trickett 1973). It reported only on adverse events.

6.1 Primary outcome: Resolution of symptoms post-treatment

Not reported.

6.2 Secondary outcomes

6.2.1 Sore throat

Not reported.

6.2.2 Fever

Not reported.

6.2.3 Duration of illness

Not reported.

6.2.4 Incidence of relapse

Not reported.

6.2.5 Incidence of complications

Not reported.

6.2.6 Adverse events

Trickett 1973 reported eight events in participants treated with sulphonamides and six events in the penicillin group; Analysis 6.1. They found no difference between sulphonamide and penicillin (OR 1.37, 95% CI 0.43 to 4.34). Gastrointestinal disturbances, rash, (reversible) leukopenia and (reversible) liver and kidney function disturbances were reported in both treatment groups.

Penicillin allergy

We assessed the reporting of penicillin allergy in all included studies. Carbon 1995 reports one patient with a 'severe allergic reaction' in the penicillin group, but no further details are provided. Muller 1992 reported that one patient developed a rash and another experienced vomiting, both attributed to use of penicillin (although patients were then successfully switched to amoxicillin/clavulanate). However, in the loracarbef group, also one participant discontinued treatment because of a rash. Trickett 1973 reports one patient with a rash in the penicillin group, but two patients reported a rash in the trimethoprim/sulfamethoxazole group. None of the other studies included in this review specifically report penicillin allergy.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Macrolides compared to penicillin for group A streptococcal pharyngitis

Patient or population: group A streptococcal pharyngitis
Settings: outpatients
Intervention: macrolide
Comparison: penicillin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Penicillin	Macrolide				
Resolution of symptoms post-treatment (ITT analysis)	Study population		OR 1.11 (0.92 to 1.35)	1728 (6 RCTs)	⊕⊕◯◯ LOW[1,2]	
	423 per 1000	448 per 1000 (402 to 497)				
	Moderate					
	426 per 1000	451 per 1000 (405 to 500)				
Resolution of symptoms post-treatment (evaluable participants only)	Study population		OR 0.79 (0.57 to 1.09)	1159 (6 RCTs)	⊕⊕◯◯ LOW[1,2]	
	172 per 1000	141 per 1000 (106 to 185)				
	Moderate					
	161 per 1000	131 per 1000 (98 to 173)				

Incidence of relapse (evaluable participants)	Study population		OR 1.21 (0.48 to 3.03)	802 (6 RCTs)	⊕⊕◯◯ LOW[1,2]
	44 per 1000	53 per 1000 (22 to 123)			
	Moderate				
	109 per 1000	129 per 1000 (56 to 271)			
Adverse events (ITT analysis)	Study population		OR 1.19 (0.82 to 1.73)	1727 (6 RCTs)	⊕⊕◯◯ LOW[1,2]
	324 per 1000	363 per 1000 (282 to 453)			
	Moderate				
	286 per 1000	323 per 1000 (248 to 410)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ITT**: intention-to-treat; **OR**: odds ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Unclear randomisation.
[2]Wide confidence intervals.

DISCUSSION

Summary of main results

Our meta-analysis found generally low quality evidence (as per the GRADE assessment) that did not show clinically important differences in clinical outcomes when different classes of antibiotics were compared with penicillin in adults and children with pharyngitis caused by GABHS.

Resolution of symptoms

ITT analysis did not show any difference in resolution of symptoms between cephalosporins and penicillin. When only evaluable participants were included in the analysis (i.e. participants for whom an outcome was known) there seemed to be a benefit of cephalosporins over penicillin with regard to resolution of symptoms after treatment (number needed to treat to benefit (NNTB) 20). Subgroup analysis of adults and children (aged between one month and 17 years) did not reveal any significant differences, but this could be attributed to lack of sufficient power.

ITT analysis of carbacephem versus penicillin showed a benefit of carbacephem with regard to resolution of symptoms after treatment (NNTB 14.3). There was no significant benefit in the (large) adult subgroup, and the effect may be largely based on an observed effect in children (aged between six months and 12 years) (NNTB 8.3). The analysis of evaluable participants only did not reach statistical significance (but the estimated NNTB was likely to be high).

Pooling of trials comparing macrolides with penicillin did not result in any differences between groups in terms of resolution of symptoms. Only one unpublished trial in children aged between two and 12 years that compared a single dose of azithromycin with 10 days of amoxicillin found that more children on azithromycin were cured after 24 to 28 days than with amoxicillin. However, this effect was no longer significant in the ITT analysis.

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

Relapse

The incidence of relapse in evaluable participants seemed to be lower in participants treated with cephalosporins compared with penicillin, but the event rate was low (approximately 3.5%) and the NNTB 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, who seemed to experience more adverse events than children treated with penicillin (although this difference was not statistically significant, most likely due to insufficient power) or amoxicillin or ampicillin.

The results of our meta-analysis need to be considered in the context of morbidity (including serious complications) prevalence, concerns about rising antibiotic resistance, and economic constraints in all healthcare systems.

Penicillin allergy

Incidence of penicillin allergy was poorly if at all reported in the included trials. When a rash is reported in the penicillin group this is often also reported in the comparator group. The limited information about penicillin allergy may reflect the low incidence in the general population. Albin 2014 found that penicillin allergy was reported in 11.5% of patients in a retrospective chart review, but only 11.8% of those with a documented allergy had experienced an anaphylactic reaction. The incidence of true anaphylaxis has been reported as less than 0.01% (Battacharya 2010). It is also possible that patients with known penicillin allergies were excluded from the trials resulting in a low incidence of allergies during the trial. This exclusion was only explicitly mentioned in a few of the included studies.

Overall completeness and applicability of evidence

Although we searched several databases and scrutinised all references listed in identified reviews and publications of trials, we may have missed some trials. We contacted experts and pharmaceutical companies. One pharmaceutical company responded, but this did not result in additional data. An updated search in 2012 identified an unpublished study, and a report was provided by the manufacturer in 2013 (NCT00643149). This study was included in the 2014 update but we did not identify any new published or unpublished trials in a new search. As an analysis of unpublished data used in Cochrane Reviews suggested that searching for unpublished data generally does not uncover new data that are important to the conclusion of the review (van Driel 2009), the lack of further unpublished data may not have had an important impact on the results of our review.

Our meta-analysis focused on clinical outcomes. 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 clinical presentation into account. Gerber 1999a 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 in patients classified as clinically likely to be streptococcal carriers. 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 could not draw any conclusions concerning this outcome.

Our review included studies involving children and adults, but age ranges of participants in each study varied widely, and there was significant overlap. Therefore, it was not always possible to perform subgroup analyses based on age groups. It was not possible to draw conclusions about specific age groups. This would have been clinically relevant because GABHS is more common in children aged between five and 15 years (Worrall 2007).

Quality of the evidence

A strength of our review is that we included only randomised and double-blinded trials. This was intended to minimise risk of bias related to participant selection and reporting of outcomes. However, in spite of the lower risk of bias due to methodology, reporting of findings and transparency of 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 was difficult to assess because the process of randomisation and blinding was not described in most studies. For instance, only four studies described the method used to conceal allocation (Jackson 1973; Randolph 1985; Reed 1991; Watkins 1997).

It is surprising that resolution of sore throat, a key symptom in GABHS pharyngitis and important reason for patients to consult their doctor (van Driel 2006), was only reported as a separate outcome in one study (McCarty 1992a). Most studies however, assessed our primary outcome which is a composite endpoint consisting of a combination of symptoms including sore throat, fever, and feeling unwell. This is of course also of clinical relevance to patients.

The overall quality of the pooled evidence assessed with the GRADE tool was low for all outcomes in the comparison of macrolides versus penicillin and low or very low for the comparison cephalosporins versus penicillin. We downgraded the quality of evidence mainly because of lack of, or poor reporting of randomisation, or blinding, or both, heterogeneity and wide confidence intervals.

Potential biases in the review process

Pooling of outcomes was hampered by differences in outcome definitions among studies. Because most trials measured clinical outcomes 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 was considered separately. Very few trials reported on specific symptoms related to acute GABHS tonsillopharyngitis. Because symptom resolution is a subjective outcome, the interpretation may differ among trials, and pooling may therefore be inappropriate. However, differences between comparison groups in the same trial were not affected because they were measured in the same population.

We used ITT analysis of the selected outcomes for our meta-analyses. However, this may have underestimated the efficacy of treatment. Most trials reported numbers of participants randomised, but included only the evaluated participants in the outcome analysis. When reported, a common reason for post-randomisation exclusion was 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 was 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 did not seem relevant because it did not influence conclusions. However, for trials that did not report this, it was not possible to know if selective exclusions occurred. We checked if the analysis method influenced outcomes 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 cephalosporins and penicillin were compared, ITT analysis 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 (ORs) suggested that large benefits could be expected when treating patients with cephalosporins or carbacephems. However, these supposedly impressive effects expressed as a relative measure of risk (ORs) 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 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 prevalence 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

We found that although there seems to be some benefit of antibiotics with a wider spectrum, such as cephalosporins and carbacephem, this observed effect is not consistent across analysis methods and subgroups. Cephalosporins showed 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 were relatively high (20 for treatment with cephalosporins compared with penicillin), except perhaps for the effect of carbacephem in children (NNTB 8.3). There was no clinically meaningful difference between penicillin and the other classes of antibiotics studied with regard to rate of clinical relapse. However, cephalosporins seemed to reduce the 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).

Unpublished study, NCT00643149, concluded that a single dose of azithromycin was superior to 10 days of amoxicillin in children. However, the analysis was based on a per protocol population that had completed at least eight days of treatment. Results were based on those patients who responded bacteriologically, thus censoring patients with strains resistant to the allocated antibiotic. Because eradication rates were higher in the azithromycin arm this may have biased the analysis. The ITT analysis, which underestimates the effect, did not show any difference between groups. In addition, amoxicillin may not be an appropriate choice for the treatment of GABHS pharyngitis/tonsillitis, considering the implications of using wide spectrum antibiotics on resistance in the community.

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% confidence interval (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 review concluding that cephalosporins are superior to penicillin in treating GABHS pharyngitis, and therefore cephalosporins should be considered first choice (Casey 2004). However, in our review the absolute difference between the cephalosporin or penicillin, although not statistically significant, was 2.5%, which implies a NNTB of 40. Treating 40 patients with cephalosporins instead of penicillin would incur additional costs to healthcare systems and 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 been reported elsewhere (Casey 2004). However, in our review 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 weighting in the meta-analysis (Nemeth 1999); "worsening of, or absence of significant remission of, signs and 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 2004 included 35 trials; two-thirds were not blinded and reporting of randomisation and losses to follow-up was very poor, implying a high risk of bias (Gerber 2004). By restricting inclusion to double-blinded trials we ruled out one source of potential bias and improved methodological rigour. The Casey 2004 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 included studies with carbacephems, which have been advertised as a separate class of antibiotics (Cooper 1992). Casey 2004 reported 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 review). The trial populations included in Casey 2004, as in ours, may have been contaminated with chronic carriers of GABHS who had intercurrent viral pharyngitis (Gerber 2004), but it was not clear if this has implications for clinical practice. Gerber 1999b argued that the superior effectiveness of cephalosporins over penicillin observed in some studies may reflect a greater ability to eradicate the streptococcal carrier state rather than actual superior effectiveness of "bona fide acute GABHS pharyngitis".

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

AUTHORS' CONCLUSIONS

Implications for practice

Our review did not find clinically important differences in clinical outcomes when different classes of antibiotics were compared with penicillin in adults and children with pharyngitis caused by GABHS. The finding that carbacephems and cephalosporins may have some benefit over penicillin in terms of resolution of symptoms and incidence of relapse was inconsistent across analysis methods (only statistically significant for the evaluable patients analysis) and the NNTB was substantial. This is not compelling evidence to alter current guideline recommendations for 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 were too few 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 different antibiotics, penicillin can still be considered a first choice treatment for both adults and children.

Implications for research

The observed differences in clinical efficacy between adults and children needs further exploration. The currently available studies include different age ranges which makes it difficult to identify differential effects in various age groups. Individual patient data were unavailable; therefore, future studies reporting effects in distinct age groups may provide clinically relevant information. 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 for prevention of complications. Further studies with longer follow-up may be able to address this issue. Because 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 different treatment options may provide additional guidance for making treatment choices.

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* *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 US - 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 2 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 (pre-treatment signs and symptoms improved but not resolved); failure (pre-treatment signs and symptoms not improved or worsened and pathogen persisted); indeterminate (response could not be assigned); relapse/recurrence (pre-treatment 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

Bias	Authors' judgement	Support for judgement

Bachand 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Reported as "randomised (1:1)". Not described how sequence was generated
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"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 (attrition bias) All outcomes	High risk	26 participants prematurely discontinued and 38 were excluded from efficacy analysis (reasons reported) 29.7% post-randomisation dropout No ITT analysis (128 randomised and 90 included in efficacy analysis)
Selective reporting (reporting bias)	Unclear risk	"There was no evidence of investigator bias in any of the analyses."
Other bias	High risk	Funding: not reported, but author is employee of Abbott International Ltd

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 General Practice 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 (CTM), 200 mg twice a day for 5 days and a penicillin V (PEV)-like placebo three times a day for 10 days (n = 119); penicillin V (PEV) megaunit (600 mg) three times a day for 10 days and CTM-like placebo twice a day for 5 days (n = 125) - Duration of treatment: 15 days - Duration of follow-up: 90 days

Carbon 1995 (*Continued*)

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 antibiotic or relapsed (recurrence of fever and/or symptoms), or cured on day 10 but 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised", but no description of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported as "double blind, double dummy", but no description of how blinding of different administration frequency and duration was maintained
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 4 lost to follow-up (all in penicillin group). no ITT analysis (although reported in table that ITT, the numbers do not correspond to ITT)
Selective reporting (reporting bias)	Unclear risk	Only clinical success reported, no specific symptoms; Adverse events reported, but no ITT analysis. 3 participants in each group discontinued because of adverse events
Other bias	Unclear risk	Funding: not reported

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 US - Age: 4 to 17 yrs - Diagnosis: clinical tonsillitis or pharyngitis, throat cultures - Inclusion criteria: clinical tonsillopharyngitis and throat cultures strongly positive for GABHS - Exclusion criteria: concurrent enrolment of siblings, 2 or more sore throats in previous 6 months, treated with antibiotic 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 titres - Anti-DNase B titres
Notes	- Funding: grant from Lilly Research Laboratories, Indianapolis, Ind., US - Ethics approval: not mentioned - ITT analysis on 525 participants completing the protocol, no information on dropouts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised", but no description of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	"The participants were assigned...on a random schedule supplied by Eli Lilly and Co."
Blinding (performance bias and detection bias) All outcomes	Low risk	"...the physician and parents were not appraised as to who was in which group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No description of dropouts, 525 of 525 randomised patients reported ITT analysis for clinical outcome.

Disney 1992a (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Only clinical (and bacteriological) failure reported, no symptoms specified. No reporting of adverse events.
Other bias	High risk	Funding: grant from Lilly Research Laboratories, Indianapolis, Ind., US

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%) - Setting: 11 paediatric offices in US - 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 antibiotic, any antibiotic 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 > 25 kg) (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

Bias	**Authors' judgement**	**Support for judgement**

Disney 1992b (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Reported as "randomised (1:1), but no reporting of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo was administered twice daily to the loracarbef group to maintain double blind conditions."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"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.
Selective reporting (reporting bias)	Unclear risk	ITT for adverse events.
Other bias	High risk	Funding: Eli Lilly Company

Henness 1982

Methods	Study 1: - RCT - Double-blinded Study 2: - RCT, randomised - Double-blinded
Participants	Study 1: - Number of participants randomised: 214 (47 no *S.pyogenes*) - Number of evaluated participants: 162 (75.7%) - Number of dropouts: 3 lost to follow-up from evaluable participants - Setting: private paediatric practices in US - Age: 1 to 16 yrs - Diagnosis: throat culture - Inclusion criteria: acute untreated tonsillopharyngitis - Exclusion criteria: not reported Study 2: - Number of participants randomised: 198 - Number of evaluated participants: 198 - Number of dropouts: 0? - Setting: private paediatric practices in US - Age: 1 to 16 years - Diagnosis: throat culture - Inclusion criteria: acute untreated tonsillopharyngitis - Exclusion criteria: not reported

Henness 1982 (*Continued*)

Interventions	Study 1: - Groups: penicillin V suspension 8 mg/kg every 6 hours (n = 114); cefadroxil suspension 15 mg/kg twice daily (n = 100) - Duration of treatment: 10 days - Duration of follow-up: 27 to 43 days Study 2: - 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	Study 1: - 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 titres - Susceptibility studies Study 2: - Clinical outcomes: not reported - Bacteriological outcomes - Streptozyme titres - Susceptibility
Notes	Study 1: - Funding: not mentioned, author employee of Mead Johnson Pharmaceutical Division, Evansville, US - Ethics approval: not mentioned - First study in the publication - No ITT reported Study 2: - Funding: not mentioned, author employee of Mead Johnson Pharmaceutical Division, Evansville, US - Ethics approval: not mentioned - Second study in the publication - No ITT reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study 1: Reported as "randomised", but no description of randomisation sequence

Henness 1982 (*Continued*)

		Study 2: Reported as "randomised", but no description of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Study 1: "...participants were assigned randomly..." Study 2: Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study 1: Reported as "double blind", but no description of blinding. Study 2: Reported as "double blind", but no description of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study 1: 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) 24.3% post-randomisation dropout No ITT analysis for clinical outcomes. Study 2: No dropouts described; according to reported numbers no participants dropped out
Selective reporting (reporting bias)	Unclear risk	Study 1: Only clinical (and bacteriological) cure reported, no specific symptoms; no ITT. Adverse events not reported. Study 2: No clinical outcomes reported.
Other bias	High risk	Author is employee of Mead Johnson Pharmaceutical Division, Evansville, US

Jackson 1973

Methods	- RCT - Double-blinded
Participants	- Number of participants randomised: 314 (95 negative culture excluded from analysis) - Number of participants evaluated: 207 (70%) - Number of dropouts: 12 reported - Setting: not described

Jackson 1973 (*Continued*)

	- 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised", but no description of randomisation sequence
Allocation concealment (selection bias)	Low risk	"Labels for each group were randomised, sealed in sequentially numbered envelopes,..."
Blinding (performance bias and detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	95 negative cultures excluded after randomisation; 12 positive cultures excluded due to failure to return first follow-up culture (C7 and A5) 30% post-randomisation dropout
Selective reporting (reporting bias)	Unclear risk	Only clinical outcome for post-streptococcal sequelae. ITT for adverse events.
Other bias	High risk	Funding: Upjohn Company

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 (51.4%) - 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 (pre-treatment 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" - No ITT for efficacy, but ITT for adverse effects

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised" but no description of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described.

Levenstein 1991 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Description of medication and placebo to ensure blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts accounted for the bacteriological outcome analysis, but not for the clinical outcome analysis (only 125 of 243 randomised participants included in clinical outcome analysis) 48.6% post-randomisation dropout No ITT for clinical outcomes.
Selective reporting (reporting bias)	Unclear risk	Safety analysis on all 243 randomised participants; clinical and bacteriological outcome on only 125 participants
Other bias	Unclear risk	Funding: not reported

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 (78.4%) - 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 $\geq$ 177 µmol/L, 2.0 mg/dL), physical or mental condition that might preclude evaluation of response, possible future need for other systemic antibiotic during study, use of antibiotic therapy within 3 days of pre therapy evaluation, use of other investigational agents within previous 28 days, hypersensitivity to beta-lactam antibiotic
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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised"; no description of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"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 (attrition bias) All outcomes	High risk	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) 21.6% post-randomisation dropout No ITT for clinical outcome.
Selective reporting (reporting bias)	Unclear risk	ITT for adverse events analysis.
Other bias	High risk	Funding: Eli Lilly and Company

Muller 1992

Methods	- RCT - Double-blind
Participants	- Number of enrolled participants: 344 - Number of participants randomised: 344 - Number of participants evaluated: 239 (69.5%) - Number of dropouts: 105 (31%) - Setting: study centres in Europe and Israel - Age: 3 to 80 years (mean 28.2) 10.8% < 12 years, 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 antibiotic < 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 to 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 loracarbef = 22 (13.0%) and penicillin V = 19 (10.9%) patients. Headache and nausea/vomiting were the only 2 events reported during therapy by more than 2% of the total population. Headache was reported by loracarbef = 5/169 (3.0%) and by penicillin V = 4/175 (2.3%) (P = 0.696). Nausea or vomiting was reported by loracarbef = 2/169 (1.2%) and by penicillin

Muller 1992 (*Continued*)

	V = 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"with placebo twice daily to maintain double-blind conditions."
Incomplete outcome data (attrition bias) All outcomes	High risk	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 (loracarbef = 37, penicillin V = 3); 12 patients in each group received either insufficient therapy, had no follow-up data (lost to follow-up) or had incomplete data; loracarbef = 3 patients and penicillin V = 1 were disqualified from the efficacy analysis due to protocol violations; loracarbef = 1 patient was disqualified for efficacy evaluation because of the use of another antibiotic during the study period, and loracarbef = 1 patient could not be evaluated because the post-therapy evaluation was performed 22 days after discontinuing therapy
Selective reporting (reporting bias)	Unclear risk	All indicated outcomes are reported.
Other bias	High risk	Funding: grants from Lilly Research Centre Ltd.

NCT00643149

Methods	- RCT - non-inferiority trial - 15 May 2003 to 22 May 2004

NCT00643149 (*Continued*)

Participants	- Number of participants enrolled: target 626 (313 per arm) - Number of participants randomised: 693 - Number of evaluated (treated) participants: 673 (337 azithromycin and 336 amoxicillin) - Number of participants discontinued: 125 (56 azithromycin and 69 amoxicillin) - Age: Children 2 to 12 years - Setting: Multicentre: 33 centres in North America (6 sites in Canada, 19 in US), Latin America (3 sites in Costa Rica, 1 in Guatamala), and India (4 sites); Paediatric outpatients - Acute pharyngitis/tonsillitis based on "erythematous pharyngeal mucosa or thick exudate covering the pharynx and tonsillar area, and at least one of the following signs or symptoms: sore/scratchy throat; pain on swallowing; chills and/or fever; cervical adenopathy; scarlet fever rash on the face and skin folds, or red tongue with prominent papillae ("strawberry tongue")." - Positive rapid antigen detection test or positive culture for GABHS - GABHS pharyngitis/tonsillitis (tested for susceptibility to azithromycin and amoxicillin)
Interventions	- Azithromycin SR 60 mg/kg single dose (n = 337); bacteriological per protocol population (n = 245) - Amoxicillin 45 mg/kg twice daily for 10 days (n = 336); bacteriological per protocol population (n = 237)
Outcomes	- Bacteriological cure (primary outcome) - Clinical success - Compliance - Adverse events - Time points of assessment: "Test of Cure" at 24 to 28 days after starting study drug; and long term follow-up on days 38 to 45
Notes	- Report provided by Pfizer - Study supported and conducted by Pfizer - Protocol No: A0661071 - Outcomes only reported for "Bacteriological Per Protocol Population", i.e. positive GABHS culture at recruitment or within 48hrs of starting treatment, at least 8 days of study medication and assessment at baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo matched to the active treatment.

NCT00643149 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	- In total 693 randomised; 20 were not treated due to insufficient drug supply at study site (no more information given) - Of 673 patients treated 125 patients discontinued (56 in azithromycin group and 69 in amoxicillin group); reasons for discontinuation provided (more dropout due to adverse events in azithromycin arm (4.7% versus 0.9%) and more lack of efficacy in amoxicillin arm (8.3% versus 3.3%))
Selective reporting (reporting bias)	Unclear risk	All outcomes reported.
Other bias	High risk	Study supported and conducted by Pfizer

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 US and Canada - Age: =/> 13 years - Diagnosis: rapid antigen test, throat culture - 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 antibiotic 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 four times a day (n = 305); cefdinir 300 mg twice a day (n = 304); penicillin V 250 mg four times a day (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 antibiotic therapy required); failure (absence of significant remission of signs and symptoms or need for further antibiotic therapy); relapse (worsening of, or absence of significant remission of, signs and symptoms 17 to 24 days post-therapy or need for further antibiotic 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised", but no description of the randomisation sequence
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned in a 1:1:1 ratio.."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"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 (attrition bias) All outcomes	High risk	Dropouts 275: no GABHS at admission culture (194); failure to return or noncompliance (not specified in which group) 30% dropout No ITT analysis for clinical outcomes.
Selective reporting (reporting bias)	Unclear risk	Only clinical cure reported, no symptoms specified. Adverse events analysed by ITT: 21 participants discontinued due to adverse events (cefdinir = 17 and penicillin V = 4); difference between both groups not significant
Other bias	High risk	Funding: Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan (first author is employee)

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 hypokalaemia, 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 antibiotic within 7 days prior to study entry; pregnancy, lactation, hypersensitivity to study antibiotic, infection with a pathogen known to be resistant to study drugs, concurrent treatment with other antibiotic 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 pre-infection state of all infection-related signs and symptoms, without additional antibiotic) ; failure (infection-related signs and symptoms unchanged or worsened, or clinical improvement but required additional antibiotic, 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 - 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

Norrby 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Reported as "randomised (1:1)"; Randomisation not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Blinding was maintained by masking the tablets in capsules and matching placebo capsules where appropriate."
Incomplete outcome data (attrition bias) All outcomes	Low risk	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
Selective reporting (reporting bias)	Unclear risk	Cure was predefined clinical outcome; adverse events reported
Other bias	High risk	Funding: Aventis Pharma

O'Doherty 1996

Methods	- RCT - Double-blinded - Double-dummy
Participants	- Number of participants enrolled: 489 (92 negative culture) (Azithromycin 20 mg = 160; Azithromycin 10 mg = 166; Penicillin V = 163) - Number of participants evaluated: 358 - Number of dropouts: 131 excluded (Azithromycin 20 mg = 57; Azithromycin 10 mg = 43; Penicillin V = 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 - Exclusion criteria: within 72 hours prior to the study other antibiotic 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

O'Doherty 1996 (*Continued*)

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: azithromycin 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised", but no description of randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Matched placebo suspensions or solutions were administered to maintain blinding of the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	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) 27% post-randomisation dropout No ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Only clinical (and bacteriological) cure reported, no specific symptoms in outcome analysis Adverse events reported with ITT analysis.

O'Doherty 1996 (*Continued*)

Other bias	Unclear risk	Funding: not reported

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 paediatric office - Age: 2 to 20 years - Diagnosis: throat culture - Inclusion criteria: clinically suggestive GABHS pharyngitis - Exclusion criteria: history of hypersensitivity to penicillin or cephalosporins, antibiotic 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"All participants were then assigned by a table of random numbers..."
Allocation concealment (selection bias)	Low risk	"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."
Blinding (performance bias and detection bias) All outcomes	Low risk	See above.

Randolph 1985 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts (all randomised participants evaluated).
Selective reporting (reporting bias)	Unclear risk	Specific signs and symptoms reported. No reporting of adverse events.
Other bias	High risk	Funding: Mead Johnson and Company

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 US - 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, antibiotic in the previous 3 days
Interventions	- Groups: cefaclor 20 mg/kg/day in 3 doses (n = 60); penicillin VK 20 mg/kg/day 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 US - Informed consent obtained - Ethics approval not mentioned - No ITT reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.

Reed 1991 (*Continued*)

Allocation concealment (selection bias)	Low risk	"The patient was given a prescription that used a code number to identify the medication to be used."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The identity of the antibiotic was unknown to the physician and to the patient, and was randomised by a coding sheet that was available only to the pharmacists dispensing the study medication."
Incomplete outcome data (attrition bias) All outcomes	High risk	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), could not be evaluated according to investigator (cefaclor 3 and penicillin 5) 20% post-randomisation dropout No ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Only clinical (and bacteriological) outcome reported, no specific symptom outcomes reported Adverse events reported; no ITT analysis.
Other bias	High risk	Funding: Eli Lily & Company, Indianapolis, Indiana US

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

Stein 1991 (*Continued*)

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 - Bacteriological outcomes - Blood haematology and chemistry - Urinalysis - Serology (antistreptolysin-O titres, anti-DNase B titres)
Notes	- Funding: not reported - Ethics approval: not mentioned - No ITT for efficacy, but ITT for adverse effects

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random number code" was used, but unclear how it was generated
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"In order to maintain blinding of the study placebo capsules were alternated with clarithromycin capsules every six hours."
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts 33 (26%); no description of reasons; no ITT for clinical outcomes
Selective reporting (reporting bias)	Unclear risk	Clinical (and bacteriological) cure rate reported, no specific symptoms. Adverse events reported with ITT analysis.
Other bias	Unclear risk	Funding: not reported

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, antibiotic other than study drugs during the trial period, inadequate folate reserves, malabsorption syndrome, haemolytic anaemia, anti-convulsant therapy (dilantin, primidone), antibiotic 1 week preceding acute streptococcal infection, renal insufficiency, abnormal liver function, low platelets, total white cells, neutrophils, haemoglobin, hematocrit; glucose-6-phosphate dehydrogenase deficiency, 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 - Liver function: Serum Glutamic Oxaloacetic Transaminase (SGOT) or Aspartate transaminase (AST)
Notes	- Funding: medication supplied by Hoffmann-LaRoche Inc. - Ethics approval: not mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported as "randomised" but no description of randomisation sequence; "both groups were evenly matched as to age, sex, physical condition, and concurrent diagnoses."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	"all test medications were supplied in individually coded bottles of identical appearance and were administered according to the randomised double blind code."
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 dropouts: lost to follow-up, failed to take medication or negative on strep A tests (not specified per group). No ITT analysis.

Trickett 1973 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Cure rates reported, not individual symptoms. Adverse events mentioned, but not tested.
Other bias	Unclear risk	Funding: medication supplied by Hoffmann-LaRoche Inc.

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 antibiotic other than the study antibiotic; hypersensitivity to macrolides, penicillins, cephalosporins, pregnancy, breast-feeding, systemic antibiotic 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

Bias	**Authors' judgement**	**Support for judgement**

Watkins 1997 (*Continued*)

Random sequence generation (selection bias)	Low risk	Sequence generated by computer programme.
Allocation concealment (selection bias)	Low risk	"The randomisation list was not provided to the investigators until the study was complete.."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double dummy design" "This was accomplished by giving two bottles to each patient, one containing 20 tablets (dirithromycin or placebo) and one containing 40 capsules (penicillin or placebo). "
Incomplete outcome data (attrition bias) All outcomes	High risk	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) 38% post-randomisation dropout No ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Only clinical cure reported, no specific symptoms. Adverse events reported with ITT.
Other bias	High risk	Funding: Eli Lilly and Company (2 authors are employees)

GABHS: group A beta-haemolytic streptococcus
ITT: intention-to-treat analysis
kg: kilogram weight
lb: pound weight
RCT: randomised controlled trial
SD: standard deviation

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
Bottaro 2012	Open-label study
Breese 1974	Did not compare 2 different classes of antibiotics
Cohen 2002	Not double-blinded
Cruz 2011	Meta-analysis
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 2 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 1999a	Did not report any clinical outcomes
Gooch 1993	Not double-blinded
Granizio 2008	Pooled analysis; not original studies

(*Continued*)

Hamill 1993	Not double-blinded
Haverkorn 1971	Not RCT Did not compare 2 different classes of antibiotics
Holm 1991	Not double-blinded
Howe 1997	Not double-blinded
Kuroki 2013	Open-label study
Lennon 2008	Not double-blinded (investigator blinded only)
Matsen 1974	Did not compare 2 different classes of antibiotics
McCarty 1992b	Not double-blinded
McCarty 1994	Not double-blinded
McIsaac 2004	Did not compare 2 different classes of antibiotics
Milatovic 1991	Not double-blinded
Milatovic 1993	Not double-blinded
NCT00393744	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
Rimoin 2011	Did not compare 2 different classes of antibiotics
Roos 1997	Recurrent sore throat
Sakata 2008	Not double-blinded
Shapera 1973	Not double-blinded
Shvartzman 1993	Not double-blinded

(*Continued*)

Siegel 1961	Did not compare 2 different classes of antibiotics
Standaert 1997	Not only acute GABHS tonsillopharyngitis
Stelter 2014	Review of results of tonsillectomy
Stillerman 1970	No information on blinding and no data on clinical outcomes
Stillerman 1986	Not double-blinded
Tack 1997	Not double-blinded
Tack 1998	Not double-blinded
Uysal 2000	Not double-blinded
Van Brusselen 2014	Review of tonsillitis guidelines
Zwart 2000	Did not compare 2 different classes of antibiotics

GABHS: group A beta-haemolytic streptococci
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Eslami 2014

Methods	"To compare clinical and bacteriologic responses to intramuscular benzathine penicillin G (BPG) and single dose of amoxicillin in Group A streptococcal (GAS) pharyngitis."
Participants	"571 children from 6 to 15 years old age, with pharyngitis, who were admitted to 45 elementary and guidance schools from 7 regions of Education Organization in North-East of Iran, Mashhad. They were screened for enrolment and if he/she presented pharyngitis with clinical criteria of sore throat, erythema, exudate and tender or enlarged anterior cervical lymph nodes. Exclusion criteria included reports of antibiotic use, negative throat culture for GAS and history of allergy to the drugs."
Interventions	"...intramuscular benzathine penicillin G (BPG) and single dose of amoxicillin in Group A streptococcal (GAS) pharyngitis..." "Results: In the amoxicillin group, treatment failure was more than the penicillin group (18.9% vs. 6.4%, respectively) but the difference was not statistically significant ($P < 0.05$). Both drugs were significantly effective in reducing pharyngitis manifestations but penicillin was significantly more effective in reducing exudate than amoxicillin."
Outcomes	Clinical and bacteriologic responses.
Notes	No information on study design provided in the available abstract. Authors contacted for details

RCT: randomised controlled trial

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, Random, 95% CI)	0.97 [0.34, 2.74]
3.1 Children	1	138	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.34, 2.74]
4 Sore throat (ITT analysis)	1	138	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.23, 4.04]
5 Fever (ITT analysis)	1	138	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.19, 4.98]
6 Incidence of relapse (evaluable participants)	4	1386	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.30, 0.99]
6.1 Adults	2	770	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.20, 0.88]
6.2 Children	2	616	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.45]
7 Complications (ITT analysis)	1	244	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Adverse events (ITT analysis)	3	1279	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.27, 3.25]
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. Azithromycin versus amoxicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure at 24-28 days (ITT)	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
1.1 Children	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
2 Clinical cure at 24-28 days (bacteriological per protocol population)	1	482	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.73]
2.1 Children	1	482	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.73]
3 Relapse on day 38-45 (ITT)	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.02]
3.1 Children	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.02]
4 Relapse on day 38-45 (bacteriological per protocol)	1	422	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.82]
4.1 Children	1	422	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.82]
5 Adverse events (all patients)	1	673	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [1.78, 3.99]
5.1 Children	1	673	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [1.78, 3.99]

Comparison 4. 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 5. 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 6. Sulfonamide versus penicillin

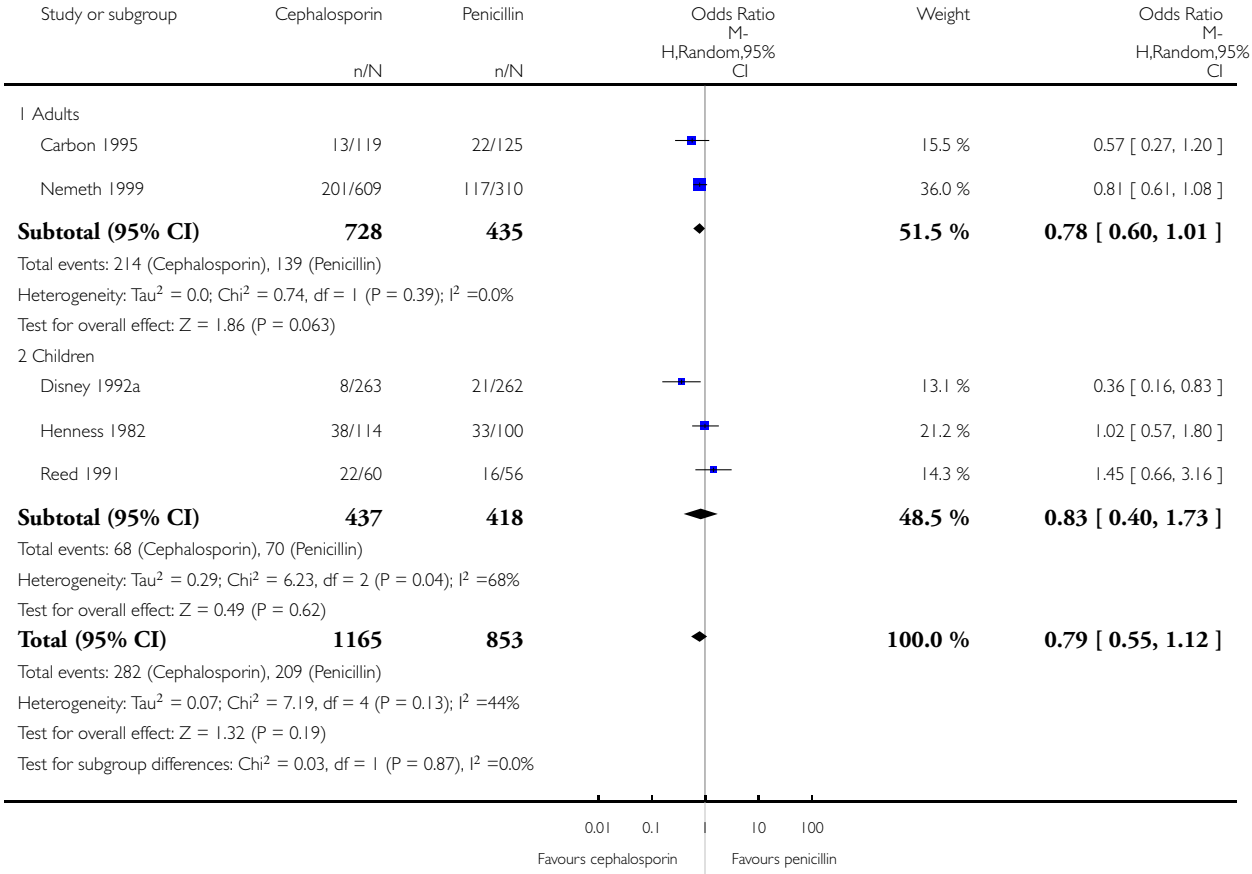
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events (ITT analysis)	1	87	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.43, 4.34]

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)

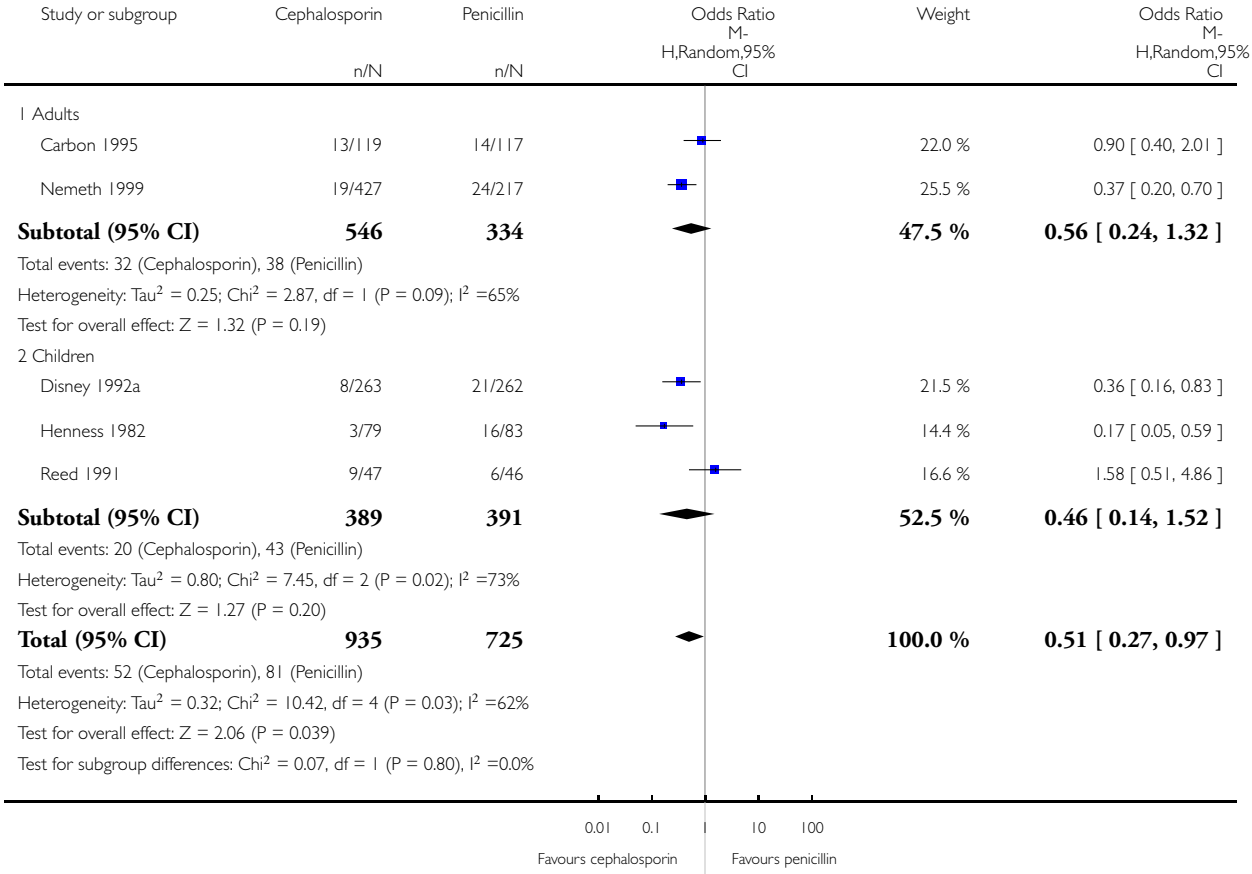


Analysis 1.2. Comparison 1 Cephalosporin versus penicillin, Outcome 2 Resolution of symptoms post-treatment (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

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

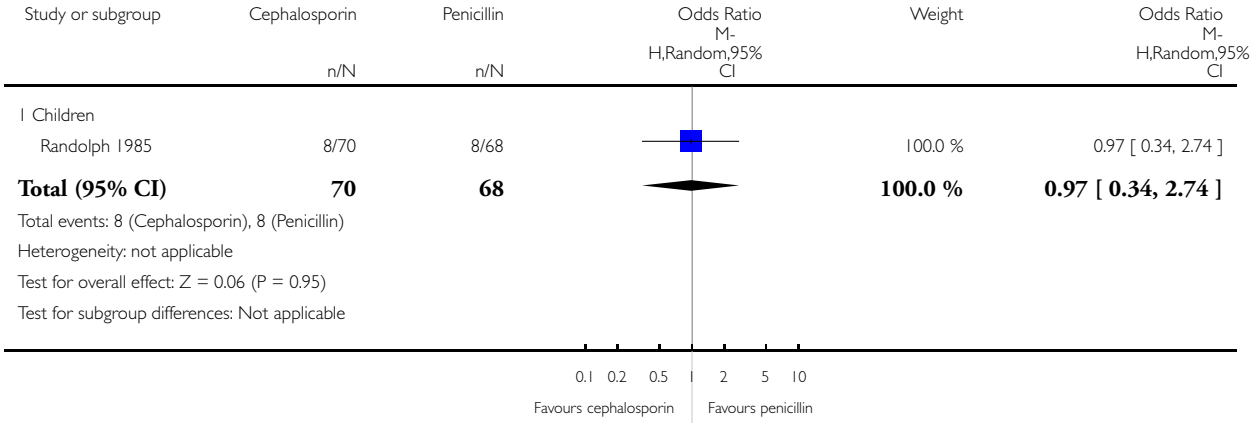


Analysis 1.3. Comparison 1 Cephalosporin versus penicillin, Outcome 3 Resolution of symptoms within 24 hours of treatment (ITT analysis).

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)

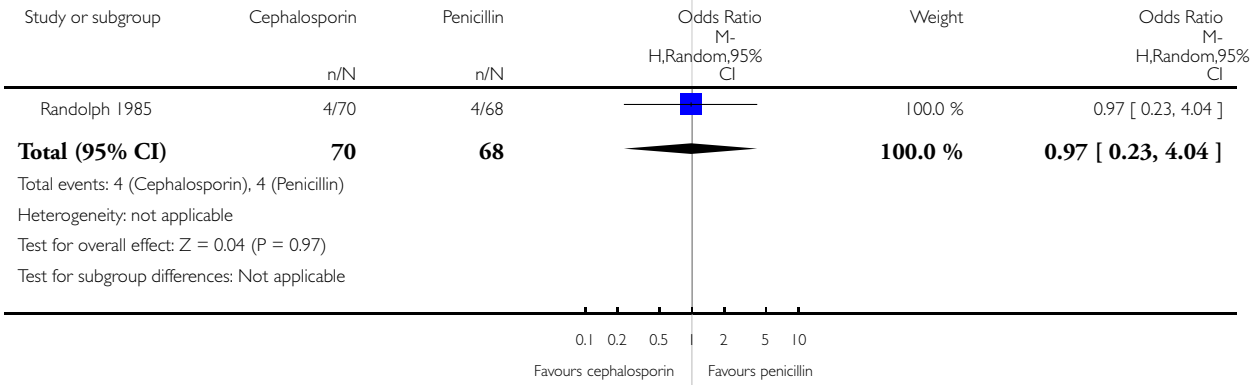


Analysis 1.4. Comparison 1 Cephalosporin versus penicillin, Outcome 4 Sore throat (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 4 Sore throat (ITT analysis)

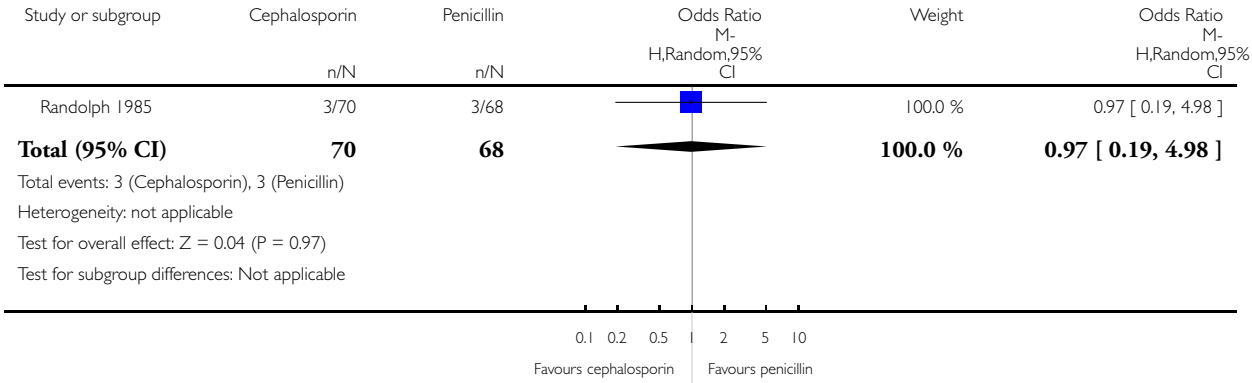


Analysis 1.5. Comparison 1 Cephalosporin versus penicillin, Outcome 5 Fever (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 5 Fever (ITT analysis)

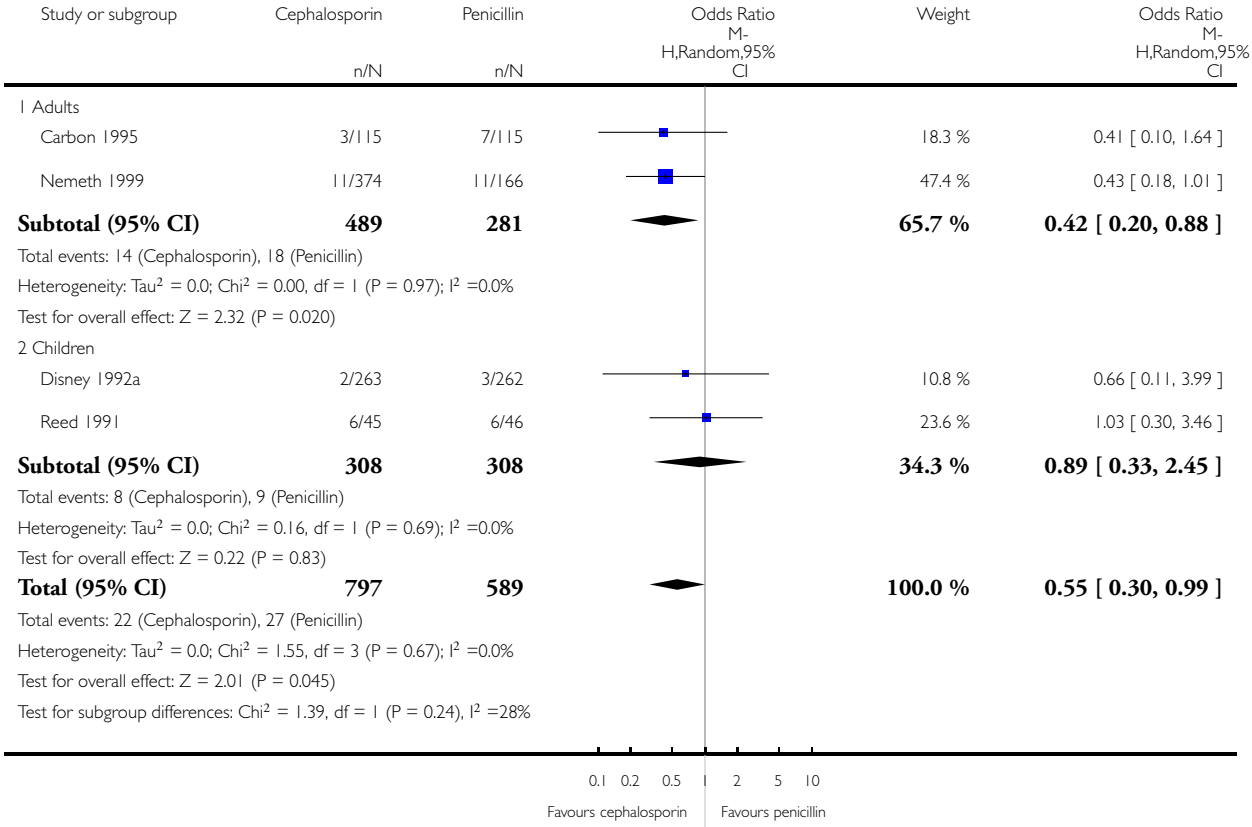


Analysis 1.6. Comparison 1 Cephalosporin versus penicillin, Outcome 6 Incidence of relapse (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 1 Cephalosporin versus penicillin

Outcome: 6 Incidence of relapse (evaluable participants)



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,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Carbon 1995	0/119	0/125			Not estimable
Total (95% CI)	**119**	**125**			**Not estimable**

Total events: 0 (Cephalosporin), 0 (Penicillin)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

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	14/119	34/125		33.1 %	0.36 [0.18, 0.71]
Nemeth 1999	183/609	48/310		35.7 %	2.34 [1.65, 3.34]
Reed 1991	13/60	13/56		31.1 %	0.91 [0.38, 2.19]
Total (95% CI)	**788**	**491**		**100.0 %**	**0.94 [0.27, 3.25]**

Total events: 210 (cephalosporin), 95 (penicillin)

Heterogeneity: $Tau^2 = 1.09$; $Chi^2 = 24.36$, df = 2 ($P<0.00001$); $I^2 = 92\%$

Test for overall effect: Z = 0.10 (P = 0.92)

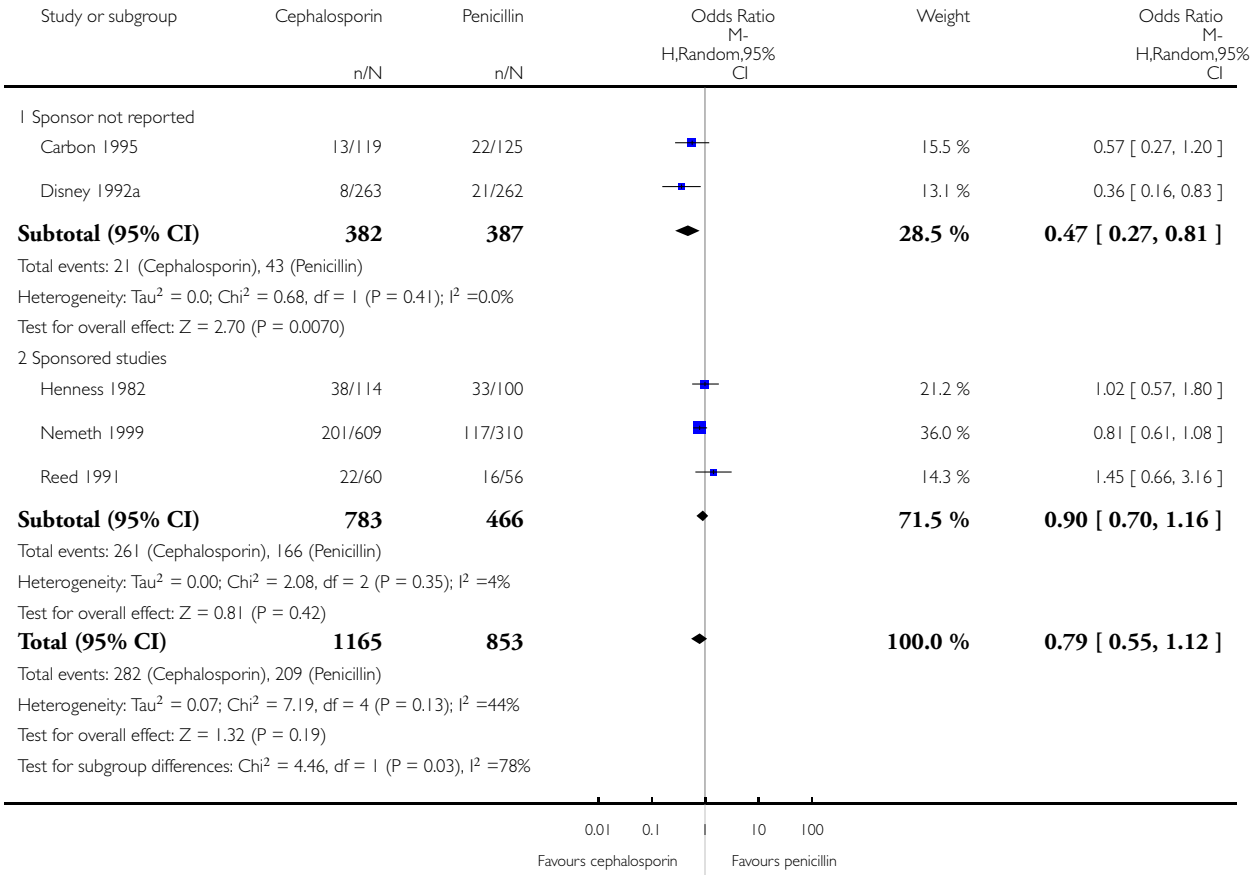
Test for subgroup differences: Not applicable

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)

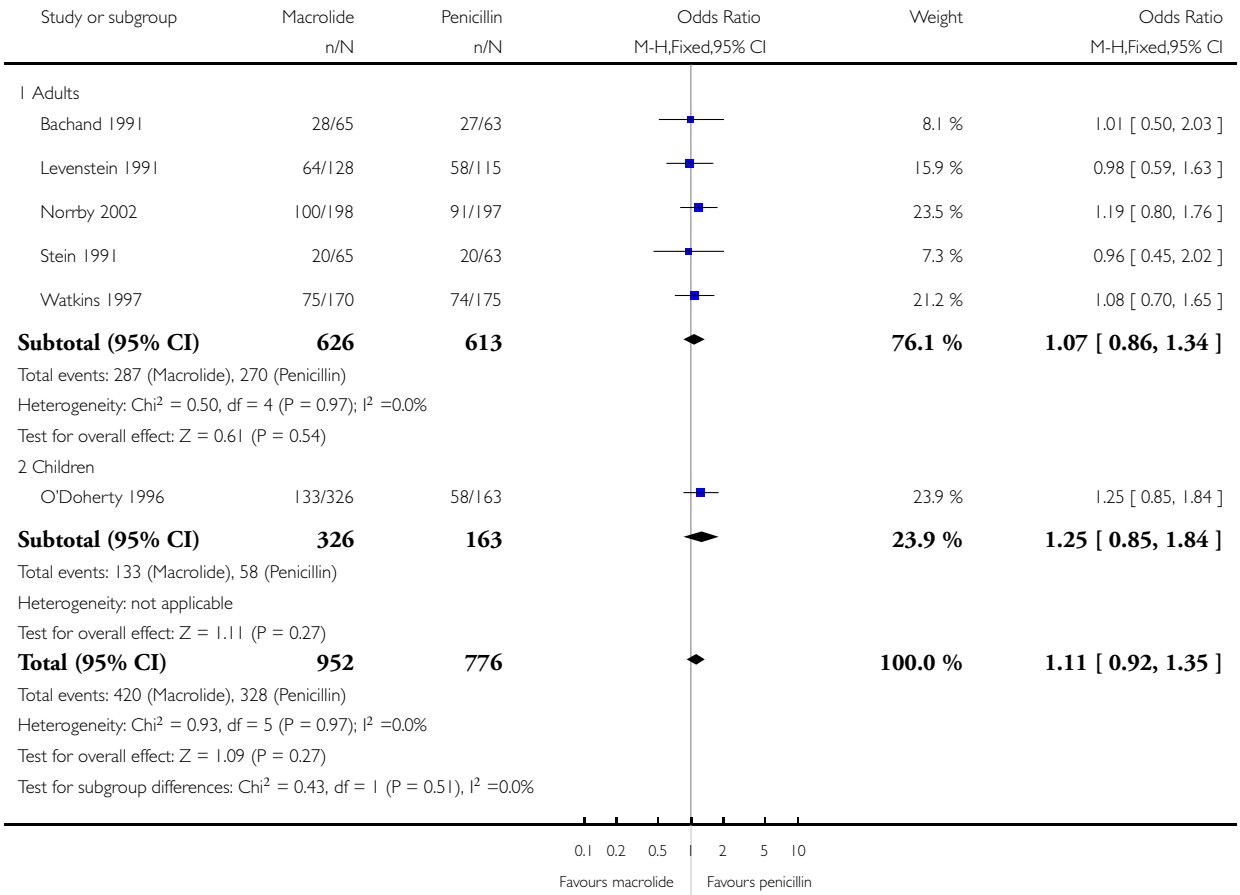


Analysis 2.1. Comparison 2 Macrolide versus penicillin, Outcome 1 Resolution of symptoms post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

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



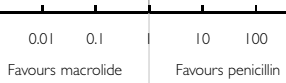
Analysis 2.2. Comparison 2 Macrolide versus penicillin, Outcome 2 Resolution of symptoms post-treatment (evaluable participants only).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

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

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 Adults					
Bachand 1991	6/43	11/47		11.1 %	0.53 [0.18, 1.59]
Levenstein 1991	3/67	1/58		1.3 %	2.67 [0.27, 26.41]
Norrby 2002	17/115	13/119		13.3 %	1.41 [0.65, 3.06]
Stein 1991	2/47	5/48		5.8 %	0.38 [0.07, 2.08]
Watkins 1997	26/121	35/136		31.6 %	0.79 [0.44, 1.41]
Subtotal (95% CI)	**393**	**408**		**63.1 %**	**0.88 [0.59, 1.31]**
Total events: 54 (Macrolide), 65 (Penicillin)					
Heterogeneity: Chi^2 = 4.24, df = 4 (P = 0.37); I^2 =6%					
Test for overall effect: Z = 0.65 (P = 0.52)					
2 Children					
O'Doherty 1996	33/226	28/132		36.9 %	0.64 [0.36, 1.11]
Subtotal (95% CI)	**226**	**132**		**36.9 %**	**0.64 [0.36, 1.11]**
Total events: 33 (Macrolide), 28 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.60 (P = 0.11)					
Total (95% CI)	**619**	**540**		**100.0 %**	**0.79 [0.57, 1.09]**
Total events: 87 (Macrolide), 93 (Penicillin)					
Heterogeneity: Chi^2 = 5.07, df = 5 (P = 0.41); I^2 =1%					
Test for overall effect: Z = 1.44 (P = 0.15)					
Test for subgroup differences: Chi^2 = 0.85, df = 1 (P = 0.36), I^2 =0.0%					

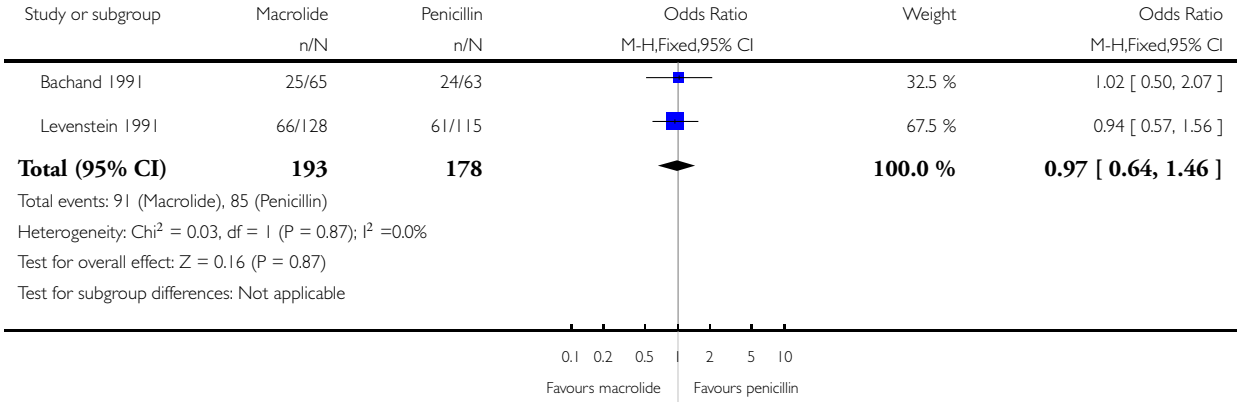


Analysis 2.3. Comparison 2 Macrolide versus penicillin, Outcome 3 Sore throat post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

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

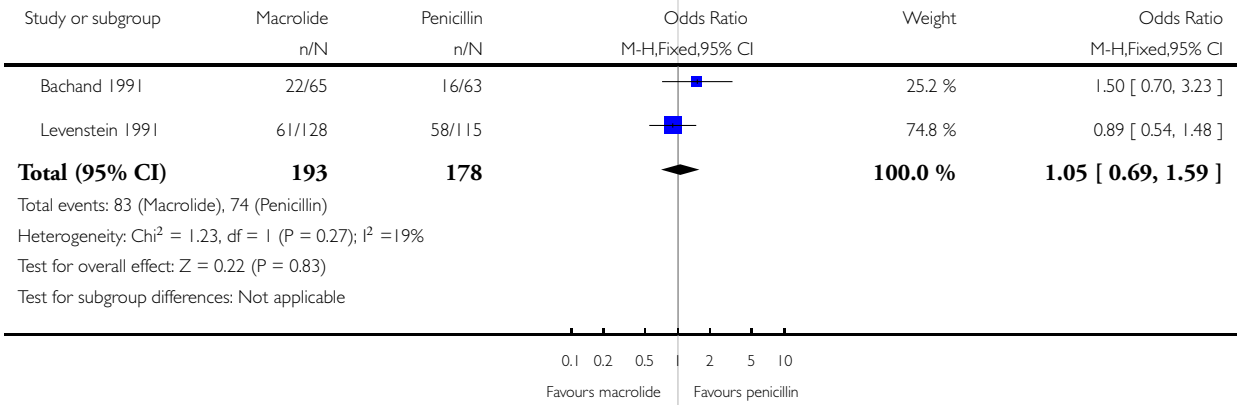


Analysis 2.4. Comparison 2 Macrolide versus penicillin, Outcome 4 Fever post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 4 Fever post-treatment (ITT analysis)

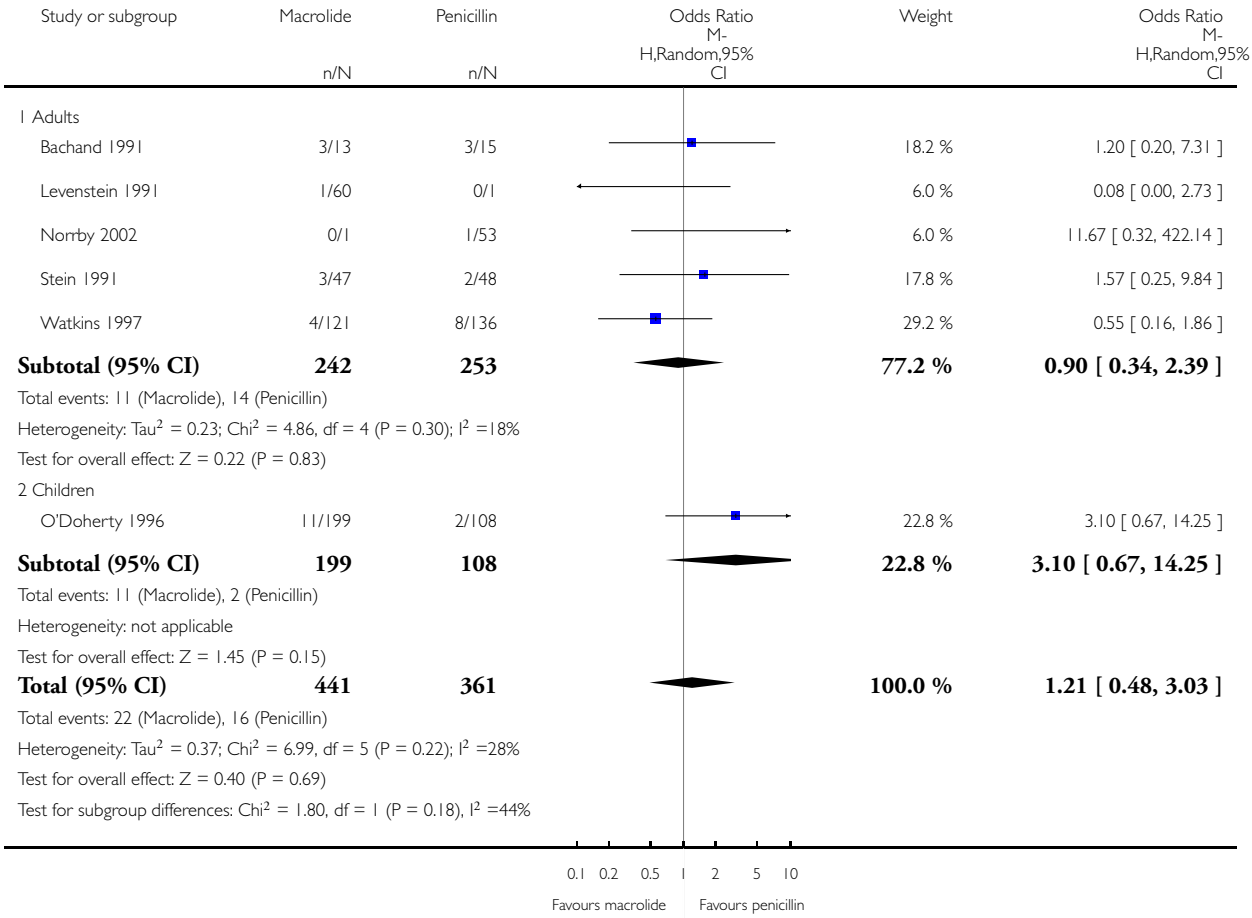


Analysis 2.5. Comparison 2 Macrolide versus penicillin, Outcome 5 Incidence of relapse (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 5 Incidence of relapse (evaluable participants)

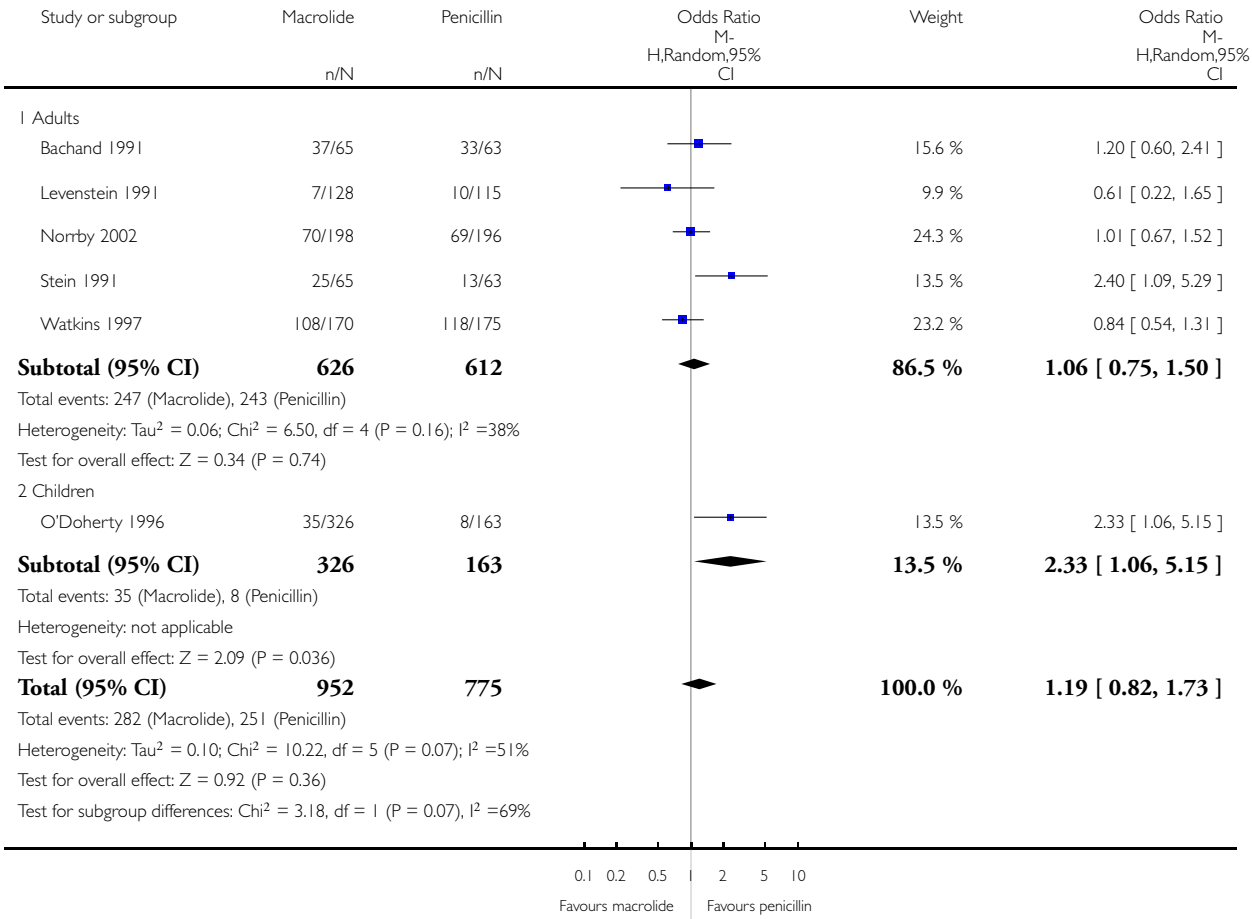


Analysis 2.6. Comparison 2 Macrolide versus penicillin, Outcome 6 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 2 Macrolide versus penicillin

Outcome: 6 Adverse events (ITT analysis)



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 = 0.00, df = 1 (P = 0.99), I^2 =0.0%					

Analysis 3.1. Comparison 3 Azithromycin versus amoxicillin, Outcome 1 Clinical cure at 24-28 days (ITT).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Azithromycin versus amoxicillin

Outcome: 1 Clinical cure at 24-28 days (ITT)

Study or subgroup	Azithromycin n/N	Amoxicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Children					
NCT00643149	98/337	118/336		100.0 %	0.76 [0.55, 1.05]
Total (95% CI)	**337**	**336**		**100.0 %**	**0.76 [0.55, 1.05]**
Total events: 98 (Azithromycin), 118 (Amoxicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.094)					
Test for subgroup differences: Not applicable					

Analysis 3.2. Comparison 3 Azithromycin versus amoxicillin, Outcome 2 Clinical cure at 24-28 days (bacteriological per protocol population).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Azithromycin versus amoxicillin

Outcome: 2 Clinical cure at 24-28 days (bacteriological per protocol population)

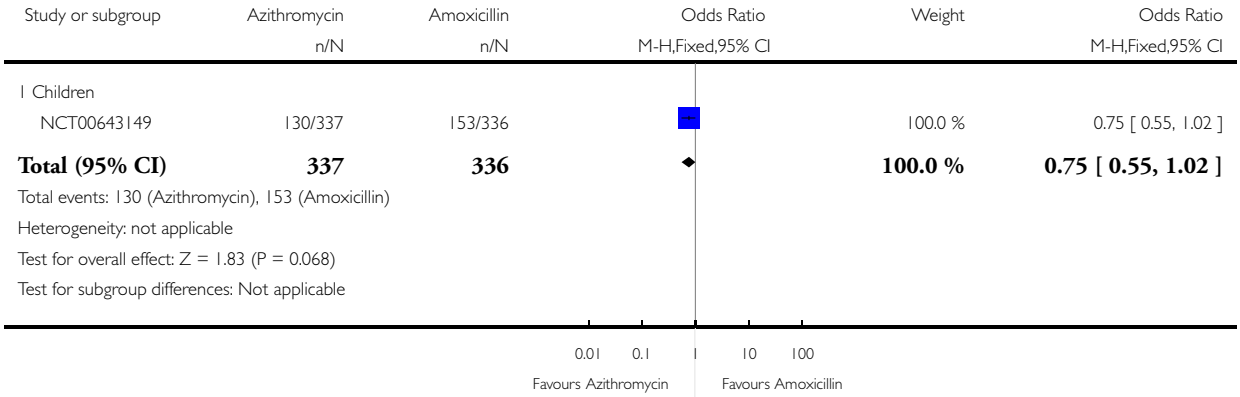
Study or subgroup	Azithromycin n/N	Amoxicillin n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Children					
NCT00643149	6/245	19/237		100.0 %	0.29 [0.11, 0.73]
Total (95% CI)	**245**	**237**		**100.0 %**	**0.29 [0.11, 0.73]**
Total events: 6 (Azithromycin), 19 (Amoxicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.61 (P = 0.0092)					
Test for subgroup differences: Not applicable					

Analysis 3.3. Comparison 3 Azithromycin versus amoxicillin, Outcome 3 Relapse on day 38-45 (ITT).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Azithromycin versus amoxicillin

Outcome: 3 Relapse on day 38-45 (ITT)

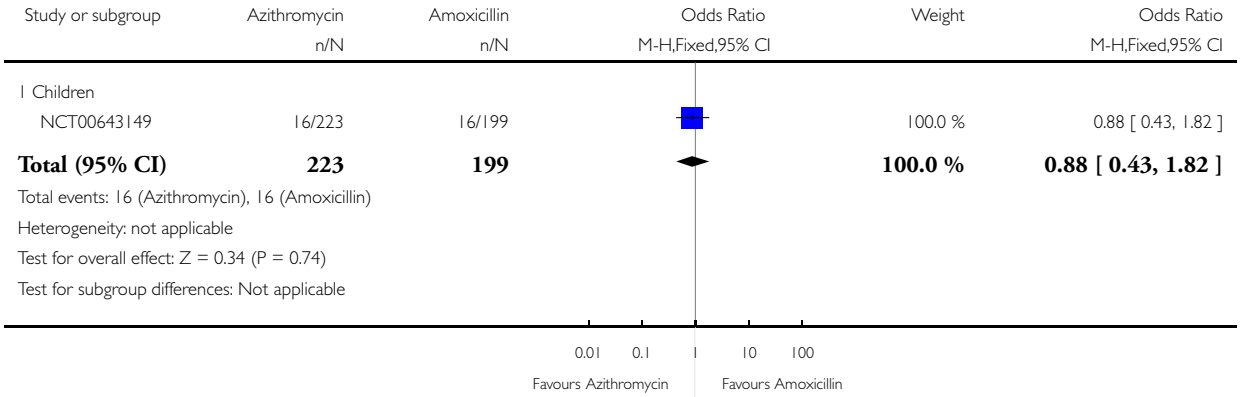


Analysis 3.4. Comparison 3 Azithromycin versus amoxicillin, Outcome 4 Relapse on day 38-45 (bacteriological per protocol).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Azithromycin versus amoxicillin

Outcome: 4 Relapse on day 38-45 (bacteriological per protocol)

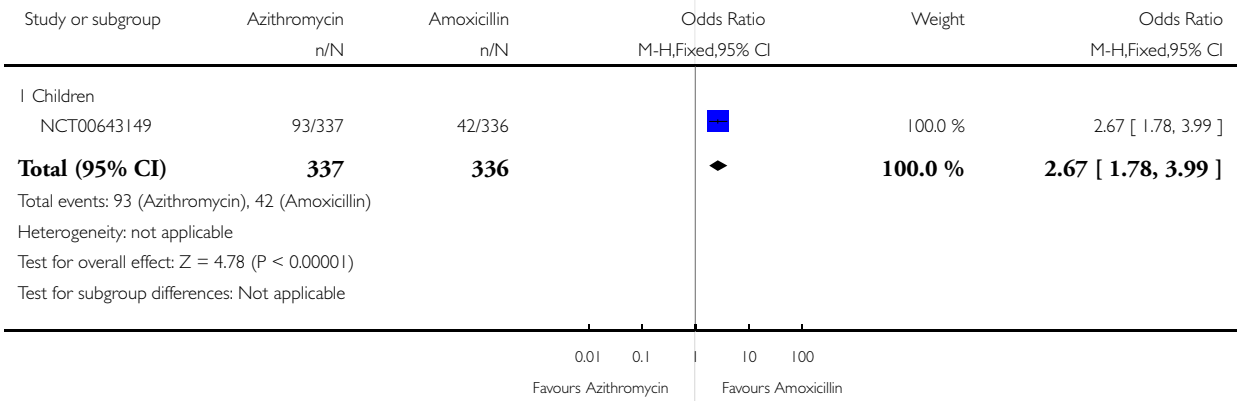


Analysis 3.5. Comparison 3 Azithromycin versus amoxicillin, Outcome 5 Adverse events (all patients).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 3 Azithromycin versus amoxicillin

Outcome: 5 Adverse events (all patients)



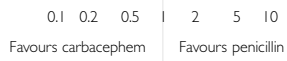
Analysis 4.1. Comparison 4 Carbacephem versus penicillin, Outcome 1 Resolution of symptoms post-treatment (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 4 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)					
Test for subgroup differences: $Chi^2 = 0.54$, df = 1 (P = 0.46), $I^2 = 0.0\%$					

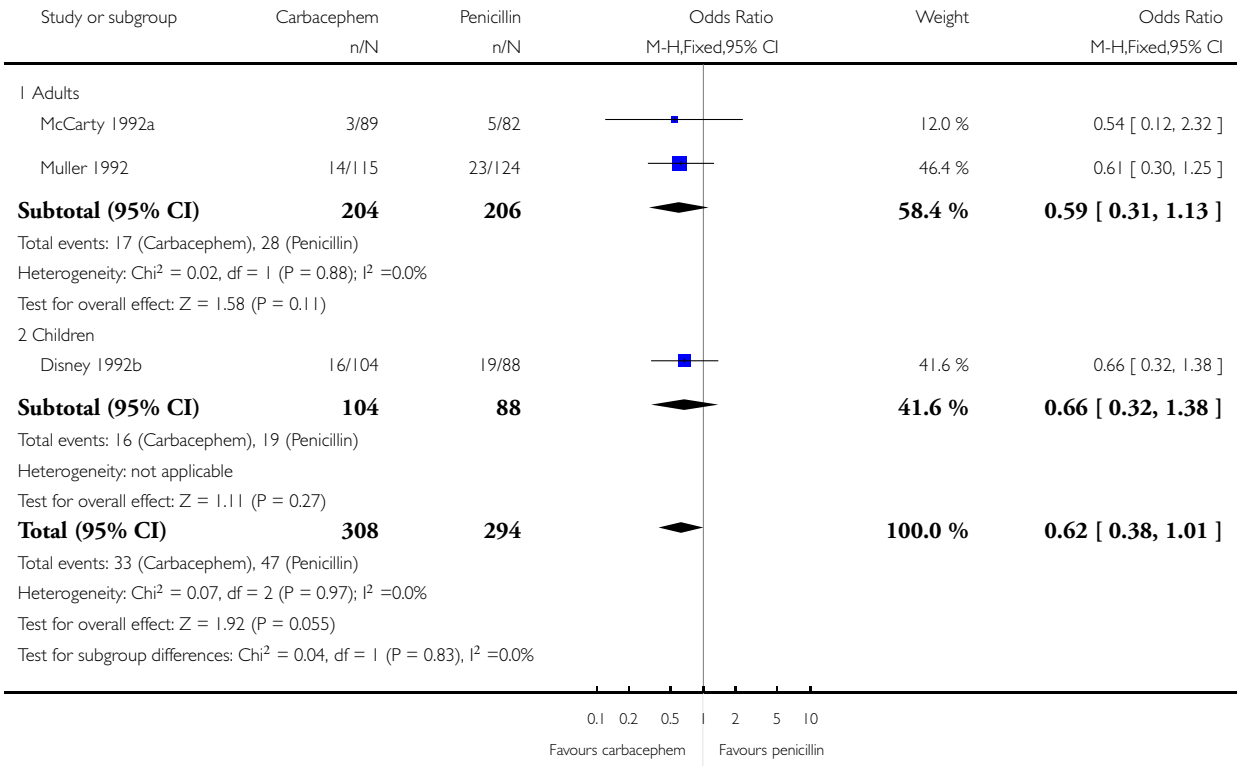


Analysis 4.2. Comparison 4 Carbacephem versus penicillin, Outcome 2 Resolution of symptoms post-treatment (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 4 Carbacephem versus penicillin

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



Analysis 4.3. Comparison 4 Carbacephem versus penicillin, Outcome 3 Incidence of relapse (evaluable participants).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 4 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)

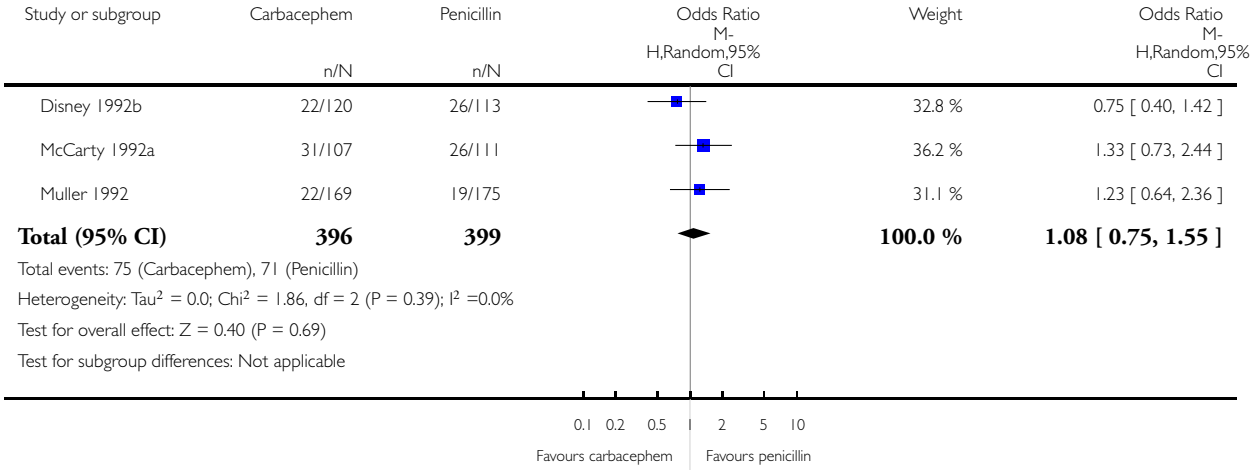
Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Carbacephem versus penicillin, Outcome 4 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 4 Carbacephem versus penicillin

Outcome: 4 Adverse events (ITT analysis)

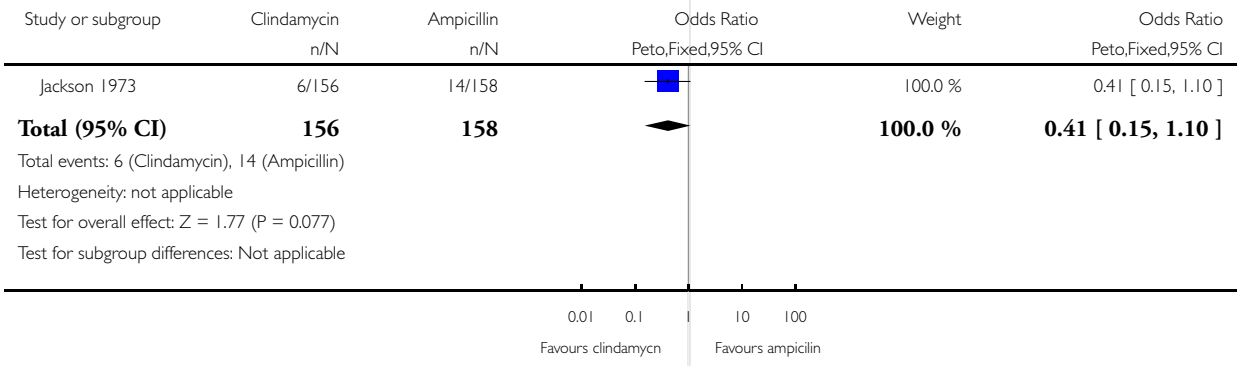


Analysis 5.1. Comparison 5 Clindamycin versus ampicillin, Outcome 1 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 5 Clindamycin versus ampicillin

Outcome: 1 Adverse events (ITT analysis)

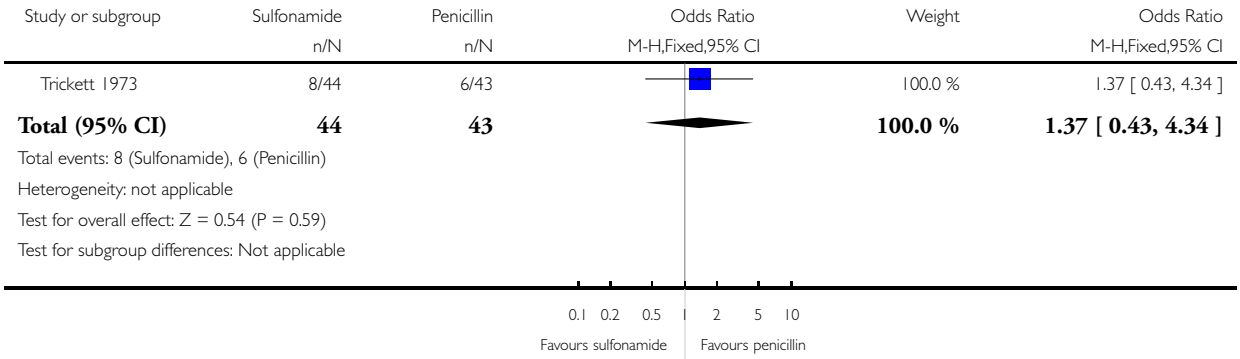


Analysis 6.1. Comparison 6 Sulfonamide versus penicillin, Outcome 1 Adverse events (ITT analysis).

Review: Different antibiotic treatments for group A streptococcal pharyngitis

Comparison: 6 Sulfonamide versus penicillin

Outcome: 1 Adverse events (ITT analysis)



APPENDICES

Appendix 1. Previous searches

Our 2012 review update used the search strategy described below. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 19 October 2012), which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to October week 4, 2012), EMBASE (1974 to October 2012) and Web of Science (2010 to October 2012).

In 2010 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 3).

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.

Appendix 2. MEDLINE and CENTRAL search strategy

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 (throat* adj3 (infect* or inflam*)).tw.
10 (strep* adj3 (throat* or pharyng*)).tw.
11 Streptococcal Infections/
12 Streptococcus pyogenes/
13 ("group a" adj5 streptococc*).tw.
14 gabhs.tw.
15 or/11-14
16 (throat* or pharyng*).tw.
17 15 and 16
18 1 or 2 or 3 or 4 or 5 or 7 or 8 or 9 or 10 or 17
19 exp Anti-Bacterial Agents/
20 (antibacterial* or anti bacterial*).tw.
21 antibiotic*.tw.
22 exp beta-lactams/
23 exp aminoglycosides/
24 exp Macrolides/
25 exp Quinolones/
26 exp Sulfonamides/
27 exp Tetracyclines/

28 (aminoglycoside* or amoxicillin* or amoxycillin* or ampicillin* or azithromycin* or benzylpenicillin* or beta-lactam* or beta-lactam* or cefaclor* or cefadroxil or cefalexin or cefdinir or cefditoren or cefixime or cefpodoxime or cefprozil or ceftibuten or ceftriaxone or cefuroxime or cephalosporin* or clarithromycin or clavulanic acid* or clindamycin or co-amoxyclav* or doripenem or doxycycline or eratapenem or erythromycin or imipenem or lincomycin or macrolide* or meropenem or moxifloxacin or penicillin* or phenoxymethylpenicillin* or piperacillin* or quinolone* or roxithromycin* or sulfamethoxazole* or sulfonimide* or tetracycline* or ticarcillin or trimethoprim*).tw,nm.
29 or/19-28
30 18 and 29
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 2011)

Appendix 3. Embase.com (Elsevier) search strategy

#31 #22 AND #30
#30 #25 NOT #29
#29 #26 NOT #28
#28 #26 AND #27
#27 'human'/de
#26 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#25 #23 OR #24
#24 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
#23 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#22 #16 AND #21
#21 #17 OR #18 OR #19 OR #20
#20 aminoglycoside*:ab,ti OR amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR ampicillin*:ab,ti OR azithromycin*:ab,ti OR benzylpenicillin*:ab,ti OR 'beta-lactam':ab,ti OR 'beta-lactams':ab,ti OR betalactam*:ab,ti OR cefaclor*:ab,ti OR cefadroxil:ab,ti OR cefalexin:ab,ti OR cefdinir:ab,ti OR cefditoren:ab,ti OR cefixime:ab,ti OR cefpodoxime:ab,ti OR cefprozil:ab,ti OR ceftibuten:ab,ti OR ceftriaxone:ab,ti OR cefuroxime:ab,ti OR cephalosporin*:ab,ti OR clarithromycin:ab,ti OR 'clavulanic acid':ab,ti OR clindamycin:ab,ti OR 'co-amoxyclav':ab,ti OR doripenem:ab,ti OR doxycycline:ab,ti OR eratapenem:ab,ti OR erythromycin:ab,ti OR imipenem:ab,ti OR lincomycin:ab,ti OR
macrolide*:ab,ti OR meropenem:ab,ti OR moxifloxacin:ab,ti OR penicillin*:ab,ti OR phenoxymethylpenicillin*:ab,ti OR piperacillin*:ab,ti OR quinolone*:ab,ti OR roxithromycin*:ab,ti OR sulfamethoxazole*:ab,ti OR
sulfonimide*:ab,ti OR tetracycline*:ab,ti OR ticarcillin:ab,ti OR trimethoprim*:ab,ti
#19 'beta lactam antibiotic'/exp OR 'aminoglycoside antibiotic agent'/exp OR 'macrolide'/exp OR 'quinolone derivative'/exp OR 'sulfonamide'/exp OR 'tetracycline derivative'/exp
#18 antibiotic*:ab,ti OR antibacterial*:ab,ti OR 'anti-bacterial':ab,ti OR 'anti-bacterials':ab,ti
#17 'antibiotic agent'/exp
#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #15
#15 #13 AND #14
#14 throat*:ab,ti OR pharyngit*:ab,ti
#13 #9 OR #10 OR #11 OR #12
#12 gabhs:ab,ti
#11 ('group a' NEXT/5 streptococc*):ab,ti
#10 'streptococcus pyogenes'/de
#9 'streptococcus infection'/de OR 'group a streptococcal infection'/de
#8 (strep* NEAR/3 (throat* OR pharyngit*)):ab,ti
#7 'streptococcal pharyngitis'/de
#6 'sore throat':ab,ti OR 'sore throats':ab,ti OR (throat* NEAR/3 (infect* OR inflam*)):ab,ti
#5 'sore throat'/de
#4 tonsillit*:ab,ti OR tonsillopharyngit*:ab,ti
#3 'tonsillitis'/de

#2 pharyngit*:ab,ti OR nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti
#1 'pharyngitis'/de OR 'rhinopharyngitis'/de OR 'viral pharyngitis'/de

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

# 6	**18**	#4 AND #3 Refined by: Publication Years=(2011 OR 2010 OR 2012) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 5	**297**	#4 AND #3 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 4	**1,296,034**	Topic=(random* or placebo* or crossover* or "cross over" or ((singl* or doubl*) NEAR/1 blind*) or allocat*) OR Title=(trial) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 3	**1,398**	#2 AND #1 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 2	**350,460**	Topic=(antibiotic* or anti-bacterial* or antibacterial* or aminoglycoside* or amoxicillin* or amoxycillin* or ampicillin* or azithromycin* or benzylpenicillin* or beta-lactam* or betalactam* or cefaclor* or cefadroxil or cefalexin or cefdinir or cefditoren or cefixime or cefpodoxime or cefprozil or ceftibuten or ceftriaxone or cefuroxime or cephalosporin* or clarithromycin or "clavulanic acid*" or clindamycin or co-amoxyclav* or doripenem or doxycycline or eratapenem or erythromycin or imipenem or lincomycin or macrolide* or meropenem or moxifloxacin or penicillin* or phenoxymethylpenicillin* or piperacillin* or quinolone* or roxithromycin* or sulfamethoxazole* or sulfonimide* or tetracycline* or ticarcillin or trimethoprim*) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 1	**2,840**	Topic=(pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit* or tonsillopharyngit* or "sore throat" or "sore throats" or (throat NEAR/2 (infect* or inflam*))) AND Topic=(streptococc* or gabhs) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*

WHAT'S NEW

Date	Event	Description
25 March 2016	New search has been performed	We updated the searches and identified two new studies. We excluded one of the studies (Stillerman 1970). Further details have been requested from the authors of the other identified study (Eslami 2014), which is currently inserted in the 'Studies awaiting classification' section
25 March 2016	New citation required but conclusions have not changed	The review conclusions remain unchanged.

HISTORY

Date	Event	Description
5 December 2014	New search has been performed	This review update includes the Pfizer 2011 study that was identified in the 2013 review publication and had been awaiting classification until data became available. We did not identify any new studies for inclusion in the 2014 updated search. We identified three new trials for exclusion (Kuroki 2013; Stelter 2014; Van Brusselen 2014). The review conclusions remain unchanged.
5 December 2014	New citation required but conclusions have not changed	Our conclusions remain unchanged. In this update we added a 'Summary of findings' tables and integrated GRADE assessment into the text of the review
19 October 2012	New search has been performed	The updated searches identified five new references. Four studies were excluded (Bottaro 2012; Cruz 2011; Rimoin 2011; NCT00393744), and we requested results from one completed unpublished study (NCT00643149).
19 October 2012	New citation required but conclusions have not changed	Our conclusions remain unchanged.
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.

ST conducted the searches for this review.

MVD and NK selected trials for the original version of the review. MVD and ADS reviewed searches for the subsequent updates.

HH assisted with the selection process.

MVD, ADS, 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. MVD updated the review.

All review authors contributed to the discussion and the editing.

DECLARATIONS OF INTEREST

Mieke L van Driel: None known.

An IM De Sutter: None known.

Hilde Habraken: None known.

Sarah Thorning: None known.

Thierry Christiaens: None known

SOURCES OF SUPPORT

Internal sources

- None received, Other.

External sources

- None received, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2010 review, outcomes were split into primary and secondary. The composite outcome 'resolution of symptoms' was included as a primary outcome.

In the 2014 update, the risk of bias assessment tool was changed from the Jadad score to the Cochrane risk of bias assessment tool. We also included a GRADE assessment using the GRADEPro software and added a description of the GRADE assessment of the overall quality of the evidence to the methods section and text of the review.

Following advice from the Statistical Editor, we changed the analysis method for pooling to a random-effects model as the default. To be consistent with our protocol (van Driel 2003), we also used a fixed-effect model if there was no substantial heterogeneity, and compared results in a sensitivity analysis. This was mentioned as a sensitivity analysis in the protocol (van Driel 2003) and is now described in the Methods section as a subgroup analysis.

We performed subgroup analyses for adults and children where appropriate because this is relevant to clinicians; this was added to the Methods section.

Sensitivity analysis: Our protocol planned sensitivity analyses for patients in different settings, per carrier status, or diagnostic criteria (throat culture or rapid test), publication status (published versus unpublished studies, studies published as abstract versus full text articles, year of publication). These were replaced with sensitivity analysis of the impact of heterogeneity and of applying a random-effects and fixed-effect model.

Sensitivity analysis according to methodological quality rated on the Jadad score (van Driel 2003) was abandoned with the introduction of the Cochrane risk of bias assessment.

The 2016 author team was changed to include Sarah Thorning as an author. Natalja Keber no longer contributed to the review and was removed as an author.

The outcome 'incidence of relapse' was added to the Summary of findings table for cephalosporins compared to penicillin.

INDEX TERMS

Medical Subject Headings (MeSH)

*Streptococcus pyogenes; Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Cephalosporins [therapeutic use]; Clindamycin [therapeutic use]; Macrolides [therapeutic use]; Penicillins [therapeutic use]; Pharyngitis [*drug therapy; microbiology]; Randomized Controlled Trials as Topic; Streptococcal Infections [*drug therapy; microbiology]; Sulfonamides [therapeutic use]

MeSH check words

Adult; Child; Humans