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Different antibiotic treatments for group A streptococcal pharyngitis (Review)

van Driel ML, De Sutter AIM, Thorning S, Christiaens T

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TABLE OF CONTENTS

[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 their effectiveness increases in people with positive throat swabs for group A beta-haemolytic streptococci (GABHS). It is unclear which antibiotic is the best choice if antibiotics are indicated. This is an update of a review first published in 2010, and updated in 2013, 2016, and 2020.

Objectives

To assess the comparative efficacy of different antibiotics in: (a) alleviating symptoms (pain, fever); (b) shortening the duration of the illness; (c) preventing clinical relapse (i.e. recurrence of symptoms after initial resolution); 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 the following databases up to 3 September 2020: CENTRAL (2020, Issue 8), MEDLINE Ovid (from 1946), Embase Elsevier (from 1974), and Web of Science Thomson Reuters (from 2010). We also searched clinical trial registers on 3 September 2020.

Selection criteria

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

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 the risk of bias of included studies according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* and used the GRADE approach to assess the overall certainty of the evidence for the outcomes. We have reported the intention-to-treat analysis, and also performed an analysis of evaluable participants to explore the robustness of the intention-to-treat results.

Main results

We included 19 trials reported in 18 publications (5839 randomised participants): six trials compared penicillin with cephalosporins; six compared penicillin with macrolides; three compared penicillin with carbacephem; one compared penicillin with sulphonamides; one compared clindamycin with ampicillin; and one compared azithromycin with amoxicillin in children. All participants had confirmed acute

GABHS tonsillopharyngitis, and ages ranged from one month to 80 years. Nine trials included only, or predominantly, children. Most trials were conducted in an outpatient setting. Reporting of randomisation, allocation concealment, and blinding was poor in all trials. We downgraded the certainty of the evidence mainly due to lack of (or poor reporting of) randomisation or blinding, or both; heterogeneity; and wide confidence intervals.

Cephalosporins versus penicillin

We are uncertain if there is a difference in symptom resolution (at 2 to 15 days) for cephalosporins versus penicillin (odds ratio (OR) for absence of symptom resolution 0.79, 95% confidence interval (CI) 0.55 to 1.12; 5 trials; 2018 participants; low-certainty evidence). Results of the sensitivity analysis of evaluable participants differed (OR 0.51, 95% CI 0.27 to 0.97; 5 trials; 1660 participants; very low-certainty evidence). We are uncertain if clinical relapse may be lower for cephalosporins compared with penicillin (OR 0.55, 95% CI 0.30 to 0.99; number needed to treat for an additional beneficial outcome (NNTB) 50; 4 trials; 1386 participants; low-certainty evidence). Very low-certainty evidence showed no difference in reported adverse events.

Macrolides versus penicillin

We are uncertain if there is a difference between macrolides and penicillin for resolution of symptoms (OR 1.11, 95% CI 0.92 to 1.35; 6 trials; 1728 participants; low-certainty evidence). Sensitivity analysis of evaluable participants resulted in an OR of 0.79, 95% CI 0.57 to 1.09; 6 trials; 1159 participants). We are uncertain if clinical relapse may be different (OR 1.21, 95% CI 0.48 to 3.03; 6 trials; 802 participants; low-certainty evidence).

Azithromycin versus amoxicillin

Based on one unpublished trial in children, we are uncertain if resolution of symptoms is better with azithromycin in a single dose versus amoxicillin for 10 days (OR 0.76, 95% CI 0.55 to 1.05; 1 trial; 673 participants; very low-certainty evidence). Sensitivity analysis for per-protocol analysis resulted in an OR of 0.29, 95% CI 0.11 to 0.73; 1 trial; 482 participants; very low-certainty evidence). We are also uncertain if there was a difference in relapse between groups (OR 0.88, 95% CI 0.43 to 1.82; 1 trial; 422 participants; very low-certainty evidence). Adverse events were more common with azithromycin compared to amoxicillin (OR 2.67, 95% CI 1.78 to 3.99; 1 trial; 673 participants; very low-certainty evidence).

Carbacephem versus penicillin

There is low-certainty evidence that compared with penicillin, carbacephem may provide better symptom resolution post-treatment in adults and children (OR 0.70, 95% CI 0.49 to 0.99; NNTB 14.3; 3 trials; 795 participants).

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

We are uncertain if there are clinically relevant differences in symptom resolution when comparing cephalosporins and macrolides with penicillin in the treatment of GABHS tonsillopharyngitis. Low-certainty evidence in children suggests that carbacephem may be more effective than penicillin for symptom resolution. There is insufficient evidence to draw conclusions regarding the other comparisons in this review. Data on complications were too scarce to draw conclusions. These results do not demonstrate that other antibiotics are more effective than penicillin in the treatment of GABHS pharyngitis. All studies were conducted in high-income countries with a low risk of streptococcal complications, so there is a need for trials in low-income countries and Aboriginal communities, where the 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, which sometimes causes 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 resolve without treatment, and complication risks are extremely low for most people in high-income countries. However, sometimes antibiotics are needed. Penicillin, an inexpensive antibiotic, has been used to treat GABHS for many years. GABHS resistance to penicillin is rare.

Search date

We searched the literature to 3 September 2020.

Study characteristics

We included 19 trials (18 publications) that involved 5839 people. The included 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 10 trials included people aged 12 years or older. Most studies were published over 15 years ago, and all but one reported on outcome measures relevant for patients.

Study funding sources

Twelve trials reported funding from drug companies. Authors of six trials (in five publications) were employed by drug companies. Seven trials (in six publications) did not report funding sources.

Key results

Antibiotic effects were similar, and all antibiotics 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, therefore it was unclear if any class of antibiotics was better in preventing serious but rare complications.

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

Certainty of the evidence

We judged the certainty of the evidence as low or very low for all outcomes when macrolides or cephalosporins were compared with penicillin. We have concerns about the rigour of the study methods, the fact that estimates were not very precise and about the differences between studies.

SUMMARY OF FINDINGS

Summary of findings 1. Cephalosporins versus penicillin for group A streptococcal pharyngitis

Cephalosporins versus 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)	Certainty of the evidence (GRADE)	Comments
	Risk with penicillin	Risk with cephalosporin				
Resolution of symptoms post-treatment (ITT analysis)	Study population		OR 0.79 (0.55 to 1.12)	2018 (5 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcome measured at 2 to 15 days or more post-treatment. Subgroup analyses: Adults: OR 0.78 (0.60 to 1.01; 2 trials; 1163 participants; low-certainty evidence) Children: OR 0.83 (0.40 to 1.73; 3 trials; 855 participants; very low-certainty evidence) Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
	245 per 1000	204 per 1000 (151 to 267)				
Resolution of symptoms post-treatment (evaluable participants)	Study population		OR 0.51 (0.27 to 0.97)	1660 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Outcome measured at 2 to 15 days or more post-treatment. Note: The 'evaluable participants' analysis includes only those randomised participants for whom an outcome was reported.
	112 per 1000	60 per 1000 (33 to 109)				
Incidence of relapse (evaluable participants)	Study population		OR 0.55 (0.30 to 0.99)	1386 (4 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcome measured at 17 to 90 days post-treatment. Note: The 'evaluable participants' analysis includes only those randomised participants for whom an outcome was reported.
	46 per 1000	26 per 1000 (14 to 45)				

Adverse events (ITT analysis)	Study population		OR 0.94 (0.27 to 3.25)	1279 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
	193 per 1000	184 per 1000 (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; **ITT**: intention-to-treat; **OR**: odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to unclear randomisation and blinding.
[b]Downgraded 1 level due to wide confidence intervals.
[c]Downgraded 1 level due to heterogeneity.

Summary of findings 2. Macrolides versus penicillin for group A streptococcal pharyngitis

Macrolides versus penicillin for group A streptococcal pharyngitis

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with penicillin	Risk with macrolide				
Resolution of symptoms post-treatment (ITT analysis)	Study population		OR 1.11 (0.92 to 1.35)	1728 (6 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcome measured at 2 to 20 days post-treatment. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
	423 per 1000	448 per 1000 (402 to 497)				

Resolution of symptoms post-treatment (evaluable participants)	Study population 172 per 1000	141 per 1000 (106 to 185)	OR 0.79 (0.57 to 1.09)	1159 (6 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcome measured at 2 to 20 days post-treatment. Note: The 'evaluable participants' analysis includes only those randomised participants for whom an outcome was reported.
Incidence of relapse (evaluable participants)	Study population 44 per 1000	53 per 1000 (22 to 123)	OR 1.21 (0.48 to 3.03)	802 (6 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcome measured between 15 and 56 days post-treatment. Note: The 'evaluable participants' analysis includes only those randomised participants for whom an outcome was reported.
Adverse events (ITT analysis)	Study population 324 per 1000	363 per 1000 (282 to 453)	OR 1.19 (0.82 to 1.73)	1727 (6 RCTs)	⊕⊕⊖⊖ LOW[a,b]	A subgroup analysis based on 1 trial with 489 participants shows that children experienced more adverse events with macrolides compared with penicillin (OR 2.33, 95% CI 1.06 to 5.15). However, the test for subgroup differences was not significant. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.

*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 certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to unclear randomisation.
[b]Downgraded 1 level due to wide confidence intervals.

Summary of findings 3. Azithromycin versus amoxicillin for group A streptococcal pharyngitis

Azithromycin versus amoxicillin for group A streptococcal pharyngitis

Patient or population: group A streptococcal pharyngitis
Setting: paediatric outpatient departments

Intervention: azithromycin
Comparison: amoxicillin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with amoxicillin	Risk with azithromycin				
Clinical cure (ITT analysis)	Study population		OR 0.76 (0.55 to 1.05)	673 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Outcomes measured at 24 to 28 days after commencing treatment. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
	351 per 1000	291 per 1000 (229 to 362)				
Clinical cure (bacteriological per protocol-analysis)	Study population		OR 0.29 (0.11 to 0.73)	482 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Outcomes measured at 24 to 28 days after commencing treatment. Note: The 'bacteriological per protocol population' 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.
Relapse (ITT analysis)	Study population		OR 0.75 (0.55 to 1.02)	673 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Outcomes measured at 38 to 45 days after commencing treatment. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
	455 per 1000	385 per 1000 (315 to 460)				
Relapse (bacteriological per protocol analysis)	Study population		OR 0.88 (0.43 to 1.82)	422 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Outcomes measured at 38 to 45 days after commencing treatment. Note: The 'bacteriological per protocol population' 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.
Adverse events (ITT analysis)	Study population		OR 2.67 (1.78 to 3.99)	673 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	Outcomes measured at 38 to 45 days after commencing treatment. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We
	125 per 1000	276 per 1000 (203 to 363)				

considered the participants for whom an outcome was not reported as treatment failures.

*__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; **ITT**: intention-to-treat; **OR**: odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to unclear randomisation.
[b]Downgraded 1 level due to wide confidence interval.
[c]Downgraded 1 level due to unpublished data only.

Summary of findings 4. Carbacephem versus penicillin for group A streptococcal pharyngitis

Carbacephem versus penicillin for group A streptococcal pharyngitis

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with penicillin	Risk with carbacephem				
Resolution of symptoms post-treatment (ITT analysis)	Study population 381 per 1000	301 per 1000 (232 to 379)	OR 0.70 (0.49 to 0.99)	795 (3 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcomes measured at 3 to 6 days post-treatment. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
Resolution of symptoms post-treatment	Study population 160 per 1000	106 per 1000	OR 0.62 (0.38 to 1.01)	602 (3 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcomes measured at 3 to 6 days post-treatment.

(evaluable participants)		(67 to 161)				Note: The 'evaluable participants' analysis includes only those randomised participants for whom an outcome was reported.
Incidence of relapse (evaluable participants)	Study population		OR 1.27 (0.64 to 2.50)	523 (3 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcomes measured at 28 to 45 days post-treatment. Note: The 'evaluable participants' analysis includes only those randomised participants for whom an outcome was reported.
	63 per 1000	78 per 1000 (41 to 143)				
Adverse events (ITT analysis)	Study population		OR 1.08 (0.75 to 1.55)	795 (3 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Outcomes measured at 28 to 45 days post-treatment. Note: The ITT analysis uses the number of participants randomised as the denominator for each outcome. We considered the participants for whom an outcome was not reported as treatment failures.
	178 per 1000	189 per 1000 (140 to 251)				

*__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; **ITT**: intention-to-treat; **OR**: odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to unclear randomisation.
[b]Downgraded 1 level due to wide confidence interval.

BACKGROUND

Description of the condition

Pharyngitis is a common upper respiratory tract infection for which antibiotics are often prescribed. 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).

Description of the intervention

Antibiotics provide only modest benefit when prescribed for sore throat (Spinks 2013). The effect of antibiotic treatment was increased in participants with positive throat swabs for GABHS. Only a small proportion of individuals with a sore throat are streptococci-positive. 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 those 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). 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.

How the intervention might work

When prescribing an antibiotic, several factors 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 2009; 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 inexpensive 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

Antimicrobial resistance is a global emergency warranting the judicious and appropriate use of antibiotics, especially for self-limiting conditions (O'Neill 2016). International guidelines recommend using penicillin as the first choice when choosing to treat people with an acute sore throat (suspected to be caused by GABHS) with antibiotics (eTG 2019; Matthys 2007). However, some argue that cephalosporins are more effective and should therefore be preferred (Casey 2004). Many physicians argue that the occurrence of penicillin allergy should be taken into account when choosing an antibiotic. In this review we sought evidence of penicillin allergy in the available trials. In addition, in the presence of documented penicillin allergy, the side effect profile of eligible antibiotics can guide choice. The burden of GABHS is higher in some communities, such as low-income countries, or first nations populations in Australia. Appropriate treatment in the context of strong antimicrobial stewardship is needed to provide healthcare providers with sufficient information to make an evidence-based choice (May 2016). Both treatment benefits and adverse events need to be compared and taken into account.

OBJECTIVES

To assess the comparative efficacy of different antibiotics in: (a) alleviating symptoms (pain, fever); (b) shortening the duration of the illness; (c) preventing clinical relapse (i.e. recurrence of symptoms after initial resolution); 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, and reporting at least one of the following: clinical cure, clinical relapse, or complications and/or adverse events.

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 Central Register of Controlled Trials (CENTRAL 2020, Issue 8), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register (searched 3 September 2020), MEDLINE Ovid (1946 to 3 September 2020), Embase Elsevier (1974 to 3 September 2020), and Web of Science Thomson Reuters (2010 to 3 September 2020). We also searched clinical trials registers: the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/default.aspx) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) for completed and ongoing trials. We used the terms streptococcal AND pharyngitis (latest search 3 September 2020). Search strategies for previous versions of the review are presented in Appendix 1. Details of the current search strategy for MEDLINE and CENTRAL are in Appendix 2; for Embase in Appendix 3; and for Web of Science in Appendix 4.

We did not impose any language or publication restrictions.

Searching other resources

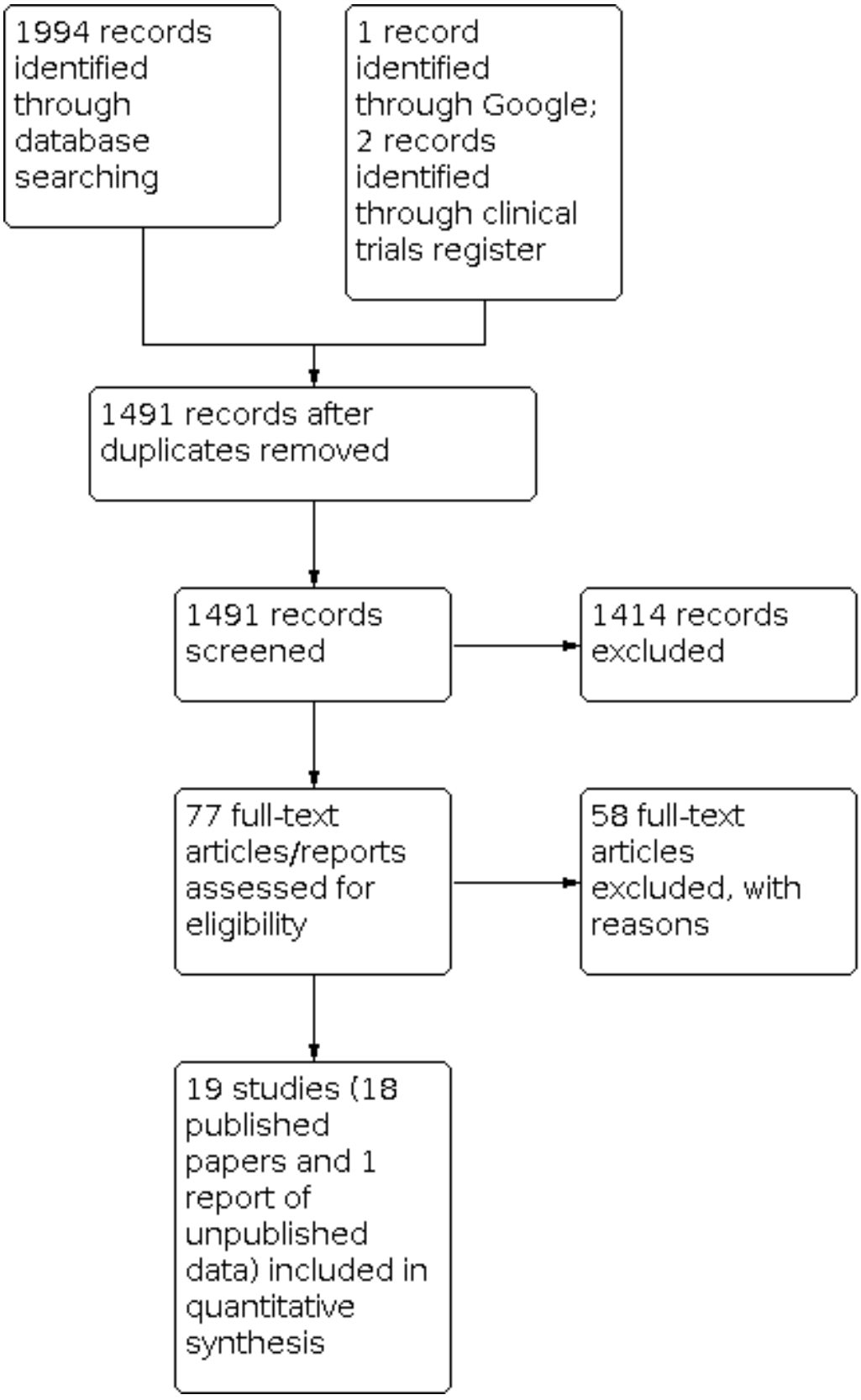
We also searched the reference sections of the identified reviews and trials for additional trials; independent sources of drug information (journals of the International Society of Drug Bulletins (electronically and by hand)); and proceedings of meetings and conferences for additional references to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

Data collection and analysis

Selection of studies

In this update two review authors (MVD, ADS) independently assessed all trials identified by the search with relevant titles or abstracts, or both, to determine which potentially met the inclusion criteria. We reviewed the full texts of these potentially eligible papers to assess them for inclusion in our review. We excluded all trials that did not meet our inclusion criteria. We list trials that were assessed for inclusion by reading the full texts but subsequently excluded in the Characteristics of excluded studies table. We reported the search results in a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

In this update two review authors (MVD, ADS) independently extracted data in pairs, using a standard checklist developed specifically for the review. The 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 categories.

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

In this update two review authors (MVD, ADS) independently assessed the methodological quality of the included trials using Cochrane's 'Risk of bias' tool (Higgins 2011). We assessed risk of bias for the following domains: 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 risk of bias (insufficient information to assess the methods, but no obvious indication for use of inadequate methods).

Measures of treatment effect

For dichotomous outcomes, we expressed results as odds ratios (ORs) with 95% confidence intervals (CIs). For statistically significant results, we calculated number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (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 participant.

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 participants) and ITT data.

Assessment of heterogeneity

We assessed heterogeneity amongst trials by calculating a Chi^2 test (significance defined as $P < 0.10$) and 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 (DerSimonian 1986). 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 results (Mantel 1959). We used Review Manager 5 software for pooling (Review Manager 2020).

We performed analyses according to ITT analysis, meaning 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. The outcome 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.

Subgroup analysis and investigation of heterogeneity

We stratified the trials into subcategories according to the comparisons between different classes of antibiotics. We performed subgroup analyses for trials with children versus adults.

Sensitivity analysis

We assessed the impact of missing data by performing analyses of on-treatment (or evaluable) participants and comparing results with the ITT analyses. We assessed 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. A meaningful sensitivity analysis of the impact of heterogeneity was only possible for resolution of symptoms in the comparison of cephalosporins versus penicillin.

Summary of findings and assessment of the certainty of the evidence

We created four 'Summary of findings' tables for the following comparisons: cephalosporins versus penicillin (Summary of findings 1; Analysis 1.1; Analysis 1.2; Analysis 1.7; Analysis 1.9); macrolides versus penicillin (Summary of findings 2; Analysis 2.1; Analysis 2.2; Analysis 2.6; Analysis 2.7); azithromycin versus amoxicillin (Summary of findings 3; Analysis 3.1; Analysis 3.3; Analysis 3.5); and carbacephem versus penicillin (Summary of findings 4; Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4). We used the GRADE approach to assess the overall certainty of evidence for the pooled studies (Atkins 2004), employing GRADEpro GDT software (GRADEpro GDT). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We assessed the certainty of evidence for the primary outcome (resolution of symptoms, both ITT and evaluable participant analysis) and secondary outcomes (incidence of relapse and incidence of adverse events). We justified all decisions to down- or upgrade the certainty of the evidence using footnotes to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We retrieved 136 search results from our electronic searches in July 2010, van Driel 2010, and 249 in October 2012, van Driel 2013, but no new trials were included. In the 2016 update we retrieved 474 records from our electronic searches until March 2016, and included one new trial (van Driel 2016). In this 2020 update we retrieved 629 records from our electronic searches to 3 September 2020. We did not identify any new trials for inclusion.

We identified one additional trial through a Google search (Muller 1992). We identified two references to completed (unpublished) studies on ClinicalTrials.gov in the 2016 search (NCT00393744; NCT00643149).

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 which was initially available in abstract form only was excluded after review of the full paper in the 2020 update (Eslami 2014). See the PRISMA flow diagram (Figure 1) (Moher 2009).

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). We did not add any new studies in the 2016 or this 2020 update. As data became available we included the unpublished study (NCT00643149) in this 2020 update, resulting in a total of 19 trials in the current review. Most of the included trials were conducted in the 1990s; three were conducted 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 (NCT00643149; Norrby 2002). All but one trial reported clinical outcome (Henness 1982-study 2).

Contacting pharmaceutical companies did not result in any additional published or unpublished data (only one company replied), nor 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; NCT00643149; O'Doherty 1996; 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 were 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 of the included trials involved 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 tonsillopharyngitis 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 (Henness 1982-study 2) reported on clinical outcomes. Trickett 1973 reported only bacteriological outcomes to assess efficacy, 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. Consequently, 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). No studies 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 participants who dropped out before outcome measurement varied. Some trials seemed not 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; NCT00643149; Norrby 2002; Reed 1991). Six studies reported dropout rates of between 20% and 30% (Bachand 1991; McCarty 1992a; Muller 1992; Nemeth 1999; O'Doherty 1996; Stein 1991), and in Watkins 1997, reportedly 38% of participants dropped out before the end of the study. The most commonly reported reason for dropout was negative culture for GABHS.

Excluded studies

We excluded 58 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; Eslami 2014; 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; NCT00393744; Pacifico 1996; Perkins 1969; Pichichero 2000; Pichichero 2008; Portier 1990; Portier 1994; Sakata 2008; Shapera 1973; Shvartzman 1993; Stillerman 1986; Tack 1997; Tack 1998; Uysal 2000). 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 participants with recurrent tonsillitis (Roos 1997). Two trials did not report any clinical outcomes (Gerber 1999a; Stillerman 1970); one study was a meta-analysis (Llerena 2011); two studies were reviews (Stelter 2014; Van Brusselen 2014); and four studies were not randomised controlled trials (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 postrandomisation 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.

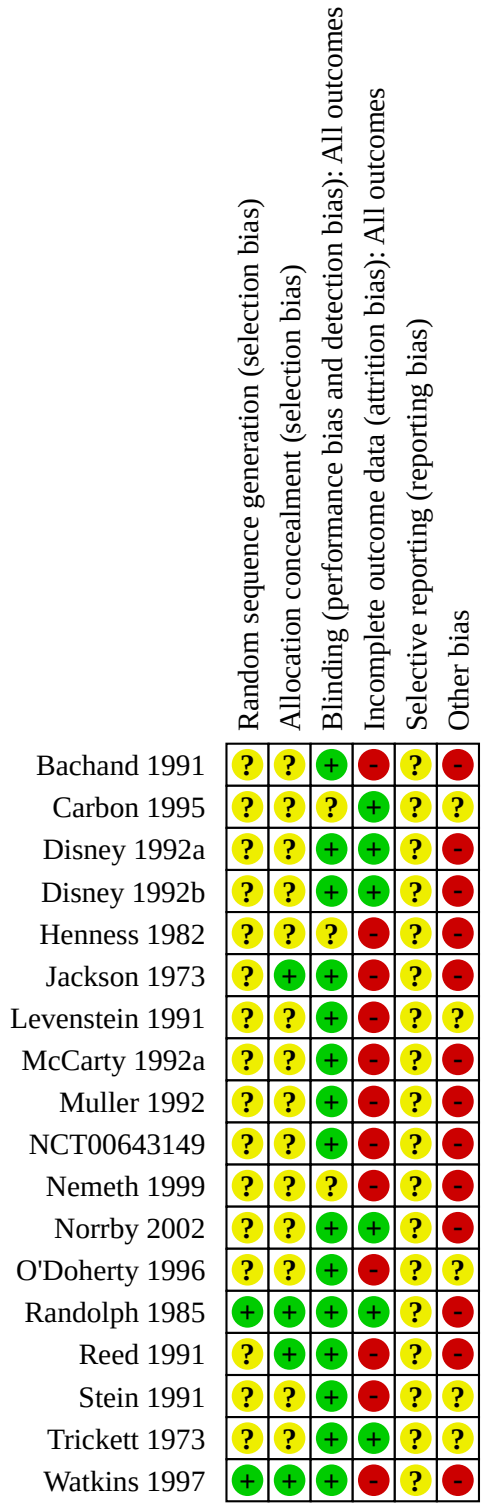
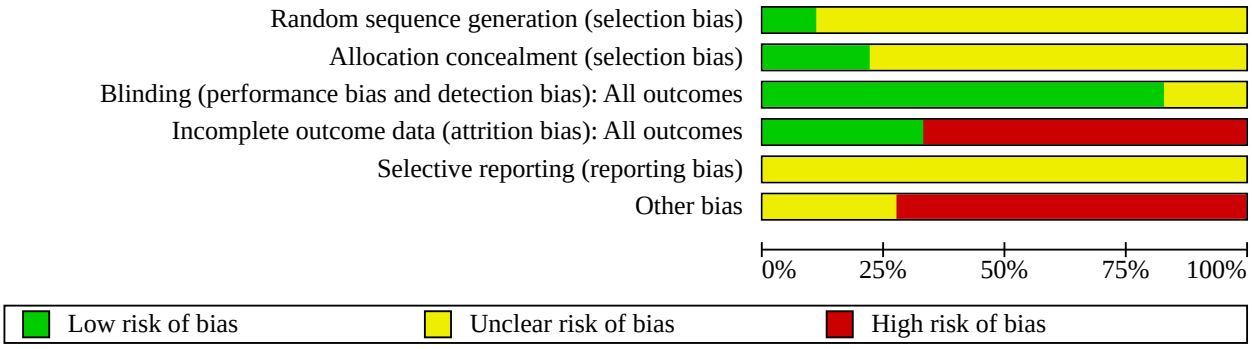


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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; NCT00643149; Norrby 2002; O'Doherty 1996; 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 the studies were assessed as at 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 the other included studies.

Incomplete outcome data

The postrandomisation 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. Most trials included only participants with complete outcome data in the outcome analysis. This may have had an important impact on the effect measured, therefore these studies were assessed as at 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 at low risk of attrition bias. We also assessed Carbon 1995, Henness 1982-study 2, and Trickett 1973 as at low risk of attrition bias due to a low postrandomisation dropout rate.

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

Selective reporting

We assessed all included studies as at unclear risk of reporting bias, as pre-publication protocols were not available.

Other potential sources of bias

Eleven published 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 was obtained from the company that conducted the trial (Pfizer). The authors of six trials (in five publications) were reported to be employees of a pharmaceutical company (Bachand 1991; Henness 1982-study 1; Henness 1982-study 2; NCT00643149; Nemeth 1999; Watkins 1997); in three of these trials, the employing pharmaceutical company was not reported as a funding source (Bachand 1991; Henness 1982-study 1; Henness 1982-study 2). We assessed the 14 trials (in 13 publications) reporting pharmaceutical company funding and/or including a pharmaceutical company employee in the authorship as at high risk of other bias (Bachand 1991; Disney 1992a; Disney 1992b; Henness 1982; Jackson 1973; McCarty 1992a; Muller 1992; NCT00643149; Nemeth 1999; Norrby 2002; Randolph 1985; Reed 1991; Watkins 1997). Trickett 1973 reported only receiving medication from a pharmaceutical company. Five trials (Carbon 1995; Henness 1982; Levenstein 1991; O'Doherty 1996; Stein 1991; Trickett 1973) did not report funding sources or pharmaceutical company authorship, and were assessed as unclear risk of bias for 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 1** Cephalosporins versus penicillin for group A streptococcal pharyngitis; **Summary of findings 2** Macrolides versus penicillin for group A streptococcal pharyngitis; **Summary of findings 3** Azithromycin versus amoxicillin for group A streptococcal pharyngitis; **Summary of findings 4** Carbacephem versus penicillin for group A streptococcal pharyngitis

Comparison 1: cephalosporins 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 certainty 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 participants and ITT analysis in children. We assessed the certainty of the pooled effect estimate as low for the outcome incidence of relapse (evaluable participants) and very low for the outcome adverse events (ITT analysis). We downgraded the certainty due to unclear randomisation and blinding, wide confidence intervals, and heterogeneity amongst studies when pooled. See Summary of findings 1.

Primary outcome

1. Resolution of symptoms post-treatment

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

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 (odds ratio (OR) 0.79, 95% confidence interval (CI) 0.55 to 1.12; 5 trials; 2018 participants; low-certainty evidence; Analysis 1.1; Summary of findings 1). The effect in adults (OR 0.78, 95% CI 0.60 to 1.01; 2 trials; 1163 participants; low-certainty evidence; Analysis 1.1) was similar to that in children (OR 0.83, 95% CI 0.40 to 1.73; 3 trials; 855 participants; very low-certainty evidence; Analysis 1.1); however, the test for subgroup differences was not significant (P = 0.87).

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; absolute risk difference (ARD) 0.05; NNTB 20; 5 trials; 1660 participants; very low-certainty evidence; Analysis 1.2; Summary of findings 1). However, the estimates of effect in adults (OR 0.56, 95% CI 0.24 to 1.32; 2 trials; 880 participants; very low-certainty evidence; Analysis 1.2) and in children (OR 0.46, 95% CI 0.14 to 1.52; 3 trials; 780 participants; very low-certainty evidence; Analysis 1.2), when analysed separately, revealed no statistically significant differences between treatment groups.

One trial in children 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; 1 trial; 138 participants; very low-certainty evidence; Analysis 1.3).

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; 2 trials; 769 participants; very low-certainty evidence; Analysis 1.4) (Carbon 1995; Disney 1992a). Pooling sponsored studies did not result in a significant difference between antibiotic groups (OR 0.90, 95% CI 0.70 to 1.16; 3 trials; 1249 participants; very low-certainty evidence; Analysis 1.4) (Henness 1982-study 1; Nemeth 1999; Reed 1991).

A sensitivity analysis revealed that in the ITT analysis, the trial by Disney 1992a contributed to the heterogenity 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 participants only, the trial by Reed 1991 appeared to contribute the most to the heterogeneity. After removal of 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 on all participants remained non-significant.

Secondary outcomes

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; 1 trial; 138 participants; very low-certainty evidence; Analysis 1.5) (Randolph 1985).

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; 1 trial; 138 participants; very low-certainty evidence; Analysis 1.6) (Randolph 1985).

3. Duration of illness

Not reported.

4. Incidence of relapse

In four trials that reported the incidence of clinical relapse in evaluated participants (Carbon 1995; Disney 1992a; Nemeth 1999; Reed 1991), treatment with cephalosporins resulted in less relapse than treatment with penicillin in the total population (OR 0.55, 95% CI 0.30 to 0.99; ARD 0.02; NNTB 50; 4 trials; 1386 participants; low-certainty evidence). 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; 2 trials; 770 participants; low-certainty evidence; Analysis 1.7; Summary of findings 1) (Carbon 1995; Nemeth 1999). There was no difference in two trials in children (OR 0.89, 95% CI 0.33 to 2.45; 2 trials; 616 participants; low-certainty evidence; Analysis 1.7) (Disney 1992a; Reed 1991).

5. Incidence of complications

In one trial in adults (244 participants), no complications were reported in the cephalosporin group (119 participants) or the penicillin group (125 participants) (Carbon 1995; Analysis 1.8).

6. Adverse events

Three trials in adults reported the incidence of adverse effects (Carbon 1995; Nemeth 1999; Reed 1991). There was significant heterogeneity amongst 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; 3 trials; 1279 participants; very low-certainty evidence; Analysis 1.9; Summary of findings 1).

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 participant with penicillin allergy.

Comparison 2: macrolides 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 certainty of the evidence for the primary outcome, resolution of symptoms, and for the secondary outcomes as low. We downgraded the certainty of the evidence two levels due to unclear randomisation and wide confidence intervals. See Summary of findings 2.

Primary outcome

1. 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 time points post-treatment. In the ITT analysis, there were no differences between the treatment groups (OR 1.11, 95% CI 0.92 to 1.35; 6 trials; 1728 participants; low-certainty evidence; Analysis 2.1; Summary of findings 2). The estimate of effect in adults (OR 1.07, 95% CI 0.86 to 1.34; 5 trials; 1239 participants; low-certainty evidence; Analysis 2.1) was similar to that in children (OR 1.25, 95% CI 0.85 to 1.84; 1 trial; 489 participants; low-certainty evidence; Analysis 2.1). The test for subgroup differences was not significant (P = 0.51). 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; 6 trials; 1159 participants; low-certainty evidence; Analysis 2.2; Summary of findings 2). The estimate for the five trials in adults was OR 0.88 (95% CI 0.59 to 1.31; 5 trials; 801 participants; low-certainty evidence; Analysis 2.2) and for one trial in children was OR 0.64 (95% CI 0.36 to 1.11; 1 trial; 358 participants; low-certainty evidence; Analysis 2.2).

ITT analysis of pharmaceutical industry-sponsored trials versus trials that did not report funding sources did not show significant differences in results: trials with no sponsor reported (OR 1.11, 95% CI 0.84 to 1.48; 3 trials; low-certainty evidence; Analysis 2.3) and sponsored studies (OR 1.12, 95% CI 0.85 to 1.46; 3 trials; low-certainty evidence; Analysis 2.3).

Secondary outcomes

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; 2 trials; 371 participants; low-certainty evidence; Analysis 2.4) (Bachand 1991; Levenstein 1991).

2. Fever

Two trials with 371 adult participants reported resolution of fever at 2 to 10 days post-treatment (Bachand 1991; Levenstein 1991). All participants in both groups were free of fever at the time of evaluation (45 participants in the macrolide group and 39 participants in the penicillin group; OR 1.05, 95% CI 0.69 to 1.59; 2 trials; 371 participants; low-certainty evidence; Analysis 2.5).

3. Duration of illness

Not reported.

4. Incidence of relapse

Six trials (802 participants) evaluated incidence of clinical relapse: 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; 6 trials; 802 participants; low-certainty evidence; Analysis 2.6; Summary of findings 2). In the trials in adults, the OR was 0.90 (95% CI 0.34 to 2.39; 5 trials; 495 participants; low-certainty evidence; Analysis 2.6). In the only trial in children, the OR was 3.10 (95% CI 0.67 to 14.25; very low-certainty evidence; Analysis 2.6).

5. Incidence of complications

Not reported.

6. Adverse events

In the six trials (1727 participants), 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; 6 trials; 1727 participants; low-certainty evidence; 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; 489 participants; NNTH 17.2; low-certainty evidence; Analysis 2.7). However, the test for subgroup differences was not significant.

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 participants taking penicillin (O'Doherty 1996). Most studies did not report any serious adverse events, but Levenstein 1991 reported two serious events: depression and balanitis.

Comparison 3: azithromycin versus amoxicillin

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). We downgraded the certainty of the evidence for all outcomes by three levels due to poor reporting of randomisation, wide confidence intervals (low precision), and potential publication bias. See Summary of findings 3.

Primary outcome

1. Resolution of symptoms post-treatment

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.

Resolution of symptoms was not different between azithromycin and amoxicillin in the ITT analysis (OR 0.76, 95% CI 0.55 to 1.05; 1 trial; 673 participants; very low-certainty evidence; Analysis 3.1; Summary of findings 3). In the bacteriological per-protocol analysis, in the azithromycin group, 239/245 participants achieved clinical cure at the first evaluation point versus 218/237 in the amoxicillin group (OR 0.29, 95% CI 0.11 to 0.73; NNTB 18; 1 trial; 482 participants; very low-certainty evidence; Analysis 3.2). The 'bacteriological per protocol population' 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.

Secondary outcomes

1. Sore throat

Not reported.

2. Fever

Not reported.

3. Duration of illness

Not reported.

4. Incidence of relapse

Between days 38 to 45 after treatment commencement (long-term follow-up), 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; 1 trial; 673 participants; very low-certainty evidence; Analysis 3.3; Summary of findings 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; 1 trial; 422 participants; very low-certainty evidence; Analysis 3.4).

5. Incidence of complications

Not reported.

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; 1 trial; 673 participants; very low-certainty evidence; Analysis 3.5; Summary of findings 3). The most commonly reported adverse events were related to the digestive system (diarrhoea, nausea, vomiting, abdominal pain) and occurred more frequently in participants treated with azithromycin (34.1%) than in 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.

Comparison 4: carbacephem versus penicillin

We included three trials (795 participants) in this comparison: 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). We downgraded the certainty of the evidence for all outcomes by two levels due to poor reporting of randomisation and wide confidence intervals (imprecision). See Summary of findings 4.

Primary outcome

1. 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 the absence of symptom resolution post-treatment 0.70, 95% CI 0.49 to 0.99; ARD 0.07; NNTB 14.3; 3 trials; 795 participants; low-certainty evidence; Analysis 4.1; Summary of findings 4). There was no difference in adults (OR 0.75, 95% CI 0.46 to 1.22; 2 trials; 562 participants; low-certainty evidence; Analysis 4.1). There was a beneficial effect from carbacephem in children (OR 0.57, 95% CI 0.33 to 0.99; ARD 0.12; NNTB 8.3; 1 trial; 233 participants; low-certainty evidence; Analysis 4.1). However, the test for subgroup differences was not significant.

The analysis of evaluable participants showed no differences between treatment groups (OR 0.62, 95% CI 0.38 to 1.01; 3 trials; 602 participants; low-certainty evidence; Analysis 4.2; Summary of findings 4).

Secondary outcomes

1. Sore throat

Not reported.

2. Fever

Not reported.

3. Duration of illness

Not reported.

4. Incidence of relapse

There were no differences in the incidence of clinical relapse between carbacephem and penicillin groups (21 events in 267 participants treated with carbacephem, and 16 events in 256 participants treated with penicillin: OR 1.27, 95% CI 0.64 to 2.50; 3 trials; 523 participants; low-certainty evidence; Analysis 4.3; Summary of findings 4).

5. Incidence of complications

Not reported.

6. Adverse events

There were no differences in reported adverse events between treatments (75 events in 396 participants treated with carbacephem, and 71 events in 399 participants treated with penicillin: OR 1.08, 95% CI 0.75 to 1.55; 3 trials; 795 participants; low-certainty evidence; Analysis 4.4; Summary of findings 4). 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.

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).

Comparison 5: clindamycin versus ampicillin

Jackson 1973 compared treatment with clindamycin to ampicillin (314 participants). The only clinical outcome reported was adverse events. We downgraded the certainty of the evidence by two levels due to poor reporting of randomisation and wide confidence intervals (imprecision).

Primary outcome

1. Resolution of symptoms post-treatment

Not reported.

Secondary outcomes

1. Sore throat

Not reported.

2. Fever

Not reported.

3. Duration of illness

Not reported.

4. Incidence of relapse

Not reported.

5. Incidence of complications

Not reported.

6. Adverse events

Adverse events were reported in 6 of 156 participants in the clindamycin group and 14 of 158 participants in the ampicillin group. The difference was not statistically significant (OR 0.41, 95% CI 0.15 to 1.10; 1 trial; 314 participants; low-certainty evidence; 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.

Comparison 6: sulphonamides versus penicillin

We included one trial in adults (87 participants) in this comparison (Trickett 1973), which reported only on adverse events. We downgraded the certainty of the evidence for this outcome by three levels due to poor reporting of randomisation and allocation concealment and very wide confidence intervals (imprecision).

Primary outcome

1. Resolution of symptoms post-treatment

Not reported.

Secondary outcomes

1. Sore throat

Not reported.

2. Fever

Not reported.

3. Duration of illness

Not reported.

4. Incidence of relapse

Not reported.

5. Incidence of complications

Not reported.

6. Adverse events

Trickett 1973 reported eight events in the sulphonamides group 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; 1 trial; 87 participants; very low-certainty evidence; Analysis 6.1). 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 trials. Carbon 1995 reported one participant with a "severe allergic reaction" in the penicillin group, but provided no further details. Muller 1992 reported that one participant developed a rash and another experienced vomiting, both attributed to use of penicillin (although participants were then successfully switched to amoxicillin/clavulanate). However, in the loracarbef group, one participant discontinued treatment because of a rash. Trickett 1973 reported one participant with a rash in the penicillin group, but two participants reported a rash in the trimethoprim/sulfamethoxazole group. None of the other included trials specifically reported penicillin allergy.

DISCUSSION

Summary of main results

Our meta-analysis found generally low-certainty 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 (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 those treated with penicillin, but the event rate was low (approximately 3.5%), and the NNTB was 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 in children treated with macrolides, who seemed to experience more adverse events than those 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 reported poorly if at all 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% (Bhattacharya 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 2016 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 amongst 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, hence eradication of streptococci in carriers is not a treatment goal. Information on complications was scarcely reported, therefore we could not draw any conclusions regarding this outcome.

Our review included studies involving children and adults, but the age ranges of participants in each study varied widely, and there was significant overlap. It was therefore not always possible to perform subgroup analyses based on age groups. We were unable 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, despite the low risk of bias due to methodology, reporting of findings and transparency of analyses in the trials were often unsatisfactory. Participant characteristics were poorly reported and outcomes reported poorly or not defined at all. Dropout rates in some studies were very high (> 20%).

The overall risk of bias in the 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 an important reason for patients to consult their doctor (van Driel 2006), was only reported as a separate outcome in one study (McCarty 1992a). However, most studies 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 certainty of the pooled evidence assessed using the GRADE approach was low for all outcomes in the comparison of macrolides versus penicillin, and low or very low for the comparison of cephalosporins versus penicillin. We downgraded the certainty of evidence mainly due to 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 amongst studies. Most trials measured clinical outcomes within two weeks of the end of antibiotic treatment and were therefore pooled for the outcome resolution of symptoms post-treatment. We considered the trial that reported symptom resolution within the first 24 hours of treatment separately. Very few trials reported on specific symptoms related to acute GABHS tonsillopharyngitis. Because symptom resolution is a subjective outcome, the interpretation may differ amongst trials, and pooling may therefore be inappropriate. However, differences between comparison groups in the same trial were not affected as 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 postrandomisation 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: 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 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 an 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. However, the interpretation of the NNTBs (how many patients needed to treat is acceptable) is not clear-cut and depends on assessment of benefit and harm, as well as cost-effectiveness.

All included trials 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). Studies performed in low-income and high-prevalence communities are therefore 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 33.3).

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).

An 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% 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 that concluded 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 an 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 was only observed in adults and may be biased by the rather liberal definition of relapse in the study accounting 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 patients that need to be treated with cephalosporins rather than penicillin to prevent one patient 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 of which 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. Costs and antimicrobial resistance patterns are therefore important in making treatment choices.

AUTHORS' CONCLUSIONS

Implications for practice

Our review did not find evidence for clinically important differences in clinical outcomes when different classes of antibiotics were compared with penicillin in adults and children with pharyngitis caused by group A beta-haemolytic streptococci (GABHS). The finding that carbacephems and cephalosporins may have some benefit over penicillin in terms of resolution of symptoms and prevention of relapse was inconsistent across analysis methods (only statistically significant for the evaluable participants analysis), and the number needed to treat for an additional beneficial outcome was substantial. This means our findings support current guideline recommendations for the treatment of patients with GABHS tonsillopharyngitis, which list penicillin as first choice. Moreover, the occurrence of adverse events may not be different between antibiotic groups, and data on the incidence of complications were too few to draw conclusions.

As other reviews have shown, 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, low-certainty evidence supports guidelines recommending penicillin as first choice for both adults and children. This takes into consideration the costs of antibiotics and the favourable antimicrobial resistance pattern of penicillin.

Implications for research

The observed differences in clinical efficacy between adults and children needs further exploration. The currently available studies included different age ranges, which makes it difficult to identify differential effects in various age groups. Individual participant 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 the 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 (e.g. 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

Study characteristics	
Methods	RCT, randomised 1:1 Double-blinded Double-dummy
Participants	Number of randomised participants: 128 (108 *Streptococcus pyogenes* positive) Number of participants evaluated: 90 Number of dropouts: 38 (29.7%) Setting: 17 clinical centres in the USA Age: 12 to 62 years Diagnosis: rapid immunoassay test, throat culture Inclusion criteria: confirmed GABHS pharyngitis Exclusion criteria: risk for pregnancy or lactation, weight < 34 kg, no sore throat with at least 1 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 4 weeks/long-acting injectable penicillin within 6 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**
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).

Bachand 1991 *(Continued)*

		29.7% postrandomisation 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

Study characteristics	
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 years Diagnosis: rapid antigen test, throat culture Inclusion criteria: fever =/> 38 °C, odynophagia, erythema or purulent exudate of pharynx, at least 1 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 3 times a day for 10 days (n = 119); penicillin V (PEV) megaunit (600 mg) 3 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
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 or symptoms, or both), 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 postrandomisation 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

Carbon 1995 *(Continued)*

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

Study characteristics	
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 the USA Age: 4 to 17 years 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, IN, USA 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

Disney 1992a *(Continued)*

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 participants reported ITT analysis for clinical outcome
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, IN, USA

Disney 1992b

Study characteristics	
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 the USA Age: 6 months to 12 years Diagnosis: rapid antigen test, throat culture Inclusion criteria: clinical diagnosis of acute streptococcal pharyngitis/tonsillitis, inflammation and swelling, with or without fever =/> 38 °C or exudate, rapid antigen test or throat culture positive for GABHS, history of compliance Exclusion criteria: history of renal impairment (serum creatinine ≥ 177 µmol/L, 2.0 mg/dL), any condition that could preclude evaluation of response, requirement for systemic 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 (participant > 25 kg) (n = 120); penicillin VK oral suspension 20 mg/kg/day 4 doses, daily maximum 500 mg or 250 mg caps 4 per day (participant > 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 1 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	

Disney 1992b *(Continued)*

Bias	Authors' judgement	Support for judgement
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

Study characteristics	
Methods	Study 1: RCT Double-blinded Study 2: RCT Double-blinded
Participants	Study 1: Number of participants randomised: 214 (47 no *Streptococcus pyogenes*) Number of evaluated participants: 162 (75.7%) Number of dropouts: 3 lost to follow-up from evaluable participants Setting: private paediatric practices in the USA Age: 1 to 16 years 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 the USA 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 units) and procaine penicillin (300,000 units) 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, IN, USA 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, USA 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 Study 2: Reported as "randomised", but no description of randomisation sequence

Henness 1982 *(Continued)*

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% postrandomisation 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 an employee of Mead Johnson Pharmaceutical Division, Evansville, IN, USA.

Jackson 1973

Study characteristics	
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 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

Jackson 1973 *(Continued)*

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 (clindamycin 7 and ampicillin 5). 30% postrandomisation dropout
Selective reporting (reporting bias)	Unclear risk	Only clinical outcome for poststreptococcal sequelae ITT for adverse events
Other bias	High risk	Funding: Upjohn Company

Levenstein 1991

Study characteristics

Methods	RCT Double-blinded Double-dummy
Participants	Number of participants enrolled: 243 (82 *Streptococcus pyogenes* negative) Number of participants evaluated in clinical outcome analysis: 125 (51.4%) Number of dropouts: 28 (12%) Setting: multicentre (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 1 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 of clarithromycin or penicillin VK in this trial, renal impairment or history of glomerulonephritis, history of hepatic disease

Levenstein 1991 *(Continued)*

	or liver enzyme elevation, history of cardiac valvular disease, rash symptomatic of scarlet fever, history of allergies or asthma, or both
Interventions	Groups: clarithromycin, 250 mg capsules every 12 hours (n = 128); penicillin VK, 250 mg capsules 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
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% postrandomisation dropout No ITT for clinical outcomes
Selective reporting (reporting bias)	Unclear risk	Safety analysis on all 243 randomised participants; clinical and bacteriological outcomes on only 125 participants
Other bias	Unclear risk	Funding: not reported

McCarty 1992a

Study characteristics

Methods	RCT Double-blinded Double-dummy

McCarty 1992a *(Continued)*

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 ≥ 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 maximum 375 mg, or 200 mg capsules 2 per day (n = 107); penicillin VK oral suspension 20 mg/kg/day 4 doses daily maximum 500 mg, or 250 mg capsules 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 (loracarbef 12 and penicillin 19), insufficient therapy, incomplete data, use of other antibiotic, non-compliance, lack of post-therapy culture 21.6% postrandomisation dropout No ITT for clinical outcome
Selective reporting (reporting bias)	Unclear risk	ITT for adverse events analysis

McCarty 1992a *(Continued)*

Other bias	High risk	Funding: Eli Lilly and Company

Muller 1992

Study characteristics	
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 years 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 or the patient's parent/guardian, or both. 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 or cephalosporins, or both
Interventions	Groups: 1) loracarbef (n = 169) suspension of 15 mg/kg/day in 2 divided doses up to a maximum daily dose of 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 maximum 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. Paracetamol was used during therapy by 5.5% of the participants.
Outcomes	Clinical outcomes at days 4 to 6: participants' 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 participant 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 participant or parent/guardian wished to withdraw from the study; if the blinding was broken for safety reasons; or if the participant had an elevated pre-therapy serum creatinine. Adverse events: at least 1 adverse event was reported by loracarbef = 22 (13.0%) and penicillin V = 19 (10.9%) participants. 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 V = 5/175 (2.9%) (P = 0.272). Few participants (approximately 5% of the total population) reported adverse events during the 28- to 35-day post-therapy follow-up period.

Muller 1992 *(Continued)*

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	54/169 (31.9%) loracarbef-treated and 51/115 (29.1%) penicillin-treated participants did not qualify for efficacy evaluation. The most common reasons for disqualification in each therapy group were bacteriological (loracarbef = 37, penicillin V = 3); 12 participants in each group received either insufficient therapy, had no follow-up data (lost to follow-up), or had incomplete data; loracarbef = 3 and penicillin V = 1 participants were disqualified from the efficacy analysis due to protocol violations; loracarbef = 1 participant was disqualified for efficacy evaluation due to the use of another antibiotic during the study period, and loracarbef = 1 participant 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

Study characteristics

Methods	RCT non-inferiority trial 15 May 2003 to 22 May 2004
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 the USA), Latin America (3 sites in Costa Rica, 1 in Guatamala), and India (4 sites); paediatric outpatients

NCT00643149 *(Continued)*

	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 Sustained Release 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 48 hours 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.
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 participants treated, 125 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

Study characteristics	
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 the USA 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 4 times a day (n = 305); cefdinir 300 mg twice a day (n = 304); penicillin V 250 mg 4 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, MI, USA (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 non-compliance (not specified in which group) 30% dropout

Nemeth 1999 *(Continued)*

		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, penicillin V = 4); difference between groups is not significant.
Other bias	High risk	Funding: Parke-Davis Pharmaceutical Research, Ann Arbor, MI, USA (first author is employee)

Norrby 2002

Study characteristics	
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, South 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 of 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 preinfection 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"

Norrby 2002 *(Continued)*

	Modified ITT (1 participant with negative GABHS excluded) 2 publications of same study with different outcomes

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 1 randomised participant 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

Study characteristics

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 in 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
Interventions	Groups: azithromycin suspension single oral dose 10 mg/kg (n = 166); azithromycin suspension 1 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

O'Doherty 1996 *(Continued)*

	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% postrandomisation 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.
Other bias	Unclear risk	Funding: not reported

Randolph 1985

Study characteristics

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

Randolph 1985 *(Continued)*

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.
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

Study characteristics

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 the USA Age: > 1 month Diagnosis: rapid test, throat culture Inclusion criteria: sore throat or poor eating, rapid test positive for GABHS Exclusion criteria: allergy to penicillin or cephalosporins, pregnancy, history of renal or hepatic impairment, significant underlying disease or concomitant infection that could preclude evaluation of response to treatment, antibiotic in the previous 3 days

Reed 1991 *(Continued)*

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 Lilly and Company, Indianapolis, IN, USA 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
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% postrandomisation dropout No ITT analysis
Selective reporting (reporting bias)	Unclear risk	Only clinical (and bacteriological) outcomes reported, no specific symptom outcomes reported. Adverse events reported; no ITT analysis.
Other bias	High risk	Funding: Eli Lilly and Company, Indianapolis, IN, USA

Stein 1991

Study characteristics

Methods	RCT Double-blinded Double-dummy
Participants	Number of participants enrolled and randomised: 128 (clarithromycin 65 and penicillin 63) Number of participants with *Streptococcus pyogenes*: 109 Number of participants evaluated: 95 (clarithromycin 47 and penicillin 48) Number of dropouts: 33 (26%)

Stein 1991 *(Continued)*

	Setting: multicentre (not specified) Age: 12 to 58 years Diagnosis: clinical examination, rapid immunoassay test Inclusion criteria: signs and symptoms of streptococcal throat infection, rapid immunoassay test positive for GABHS antigen Exclusion criteria: age < 12 years, pregnancy, lactation, hypersensitivity to erythromycin or penicillin, receiving antibiotics, impaired renal or liver function
Interventions	Groups: clarithromycin 250 mg capsule every 12 hours (n = 65); penicillin V 250 mg capsule every 6 hours (n = 63) Duration of treatment: 10 days Duration of follow-up: 29 to 35 days
Outcomes	Clinical outcomes at day 5 to 7 and at day 14 to 16: cure (complete resolution of signs and symptoms); improved (considerable resolution of presenting signs and symptoms); failure (no improvement) Relapse at day 29 to 35 Adverse effects 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

Study characteristics

Methods	RCT Double-blinded Double-dummy

Trickett 1973 *(Continued)*

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, breastfeeding, antibiotic other than study drugs during the trial period, inadequate folate reserves, malabsorption syndrome, haemolytic anaemia, anticonvulsant therapy (dilantin, primidone), antibiotic 1 week preceding acute streptococcal infection, renal insufficiency, abnormal liver function, low platelets, total white cells, neutrophils, haemoglobin, haematocrit; glucose-6-phosphate dehydrogenase deficiency, systemic lupus erythematosus, history of idiosyncratic or allergic reactions to any of the drugs
Interventions	Groups: sulfamethoxazole (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-La Roche 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
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-La Roche Inc.

Watkins 1997

Study characteristics	
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, breastfeeding; 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**
Random sequence generation (selection bias)	Low risk	Sequence generated by computer program.
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), participant'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% postrandomisation dropout No ITT analysis

Watkins 1997 *(Continued)*

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)

CTM: cefotiam hexetil
GABHS: group A beta-haemolytic streptococcus
ITT: intention-to-treat
lb: pound weight
Penicillin VK: penicillin V potassium
PEV: penicillin V
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
Davies 1995	Not only acute GABHS tonsillopharyngitis
Del Mar 2008	Commentary of an RCT
De Meyere 1992	Not an RCT
Denny 1953	Not double-blinded
Disney 1979	Did not compare 2 different classes of antibiotics
Dykhuizen 1996	Not double-blinded
Eslami 2014	Not double-blinded
Esposito 2002	Not double-blinded
Feder 1999	Not double-blinded

Study	Reason for exclusion
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
Hamill 1993	Not double-blinded
Haverkorn 1971	Not an 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)
Llerena 2011	Meta-analysis
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

Study	Reason for exclusion
Shapera 1973	Not double-blinded
Shvartzman 1993	Not double-blinded
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

DATA AND ANALYSES

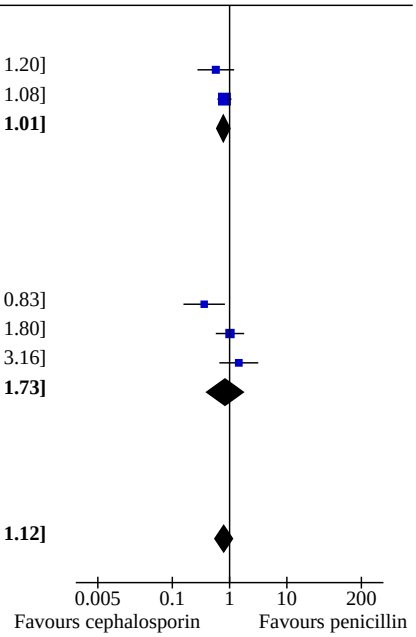
Comparison 1. Cephalosporins versus penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Resolution of symptoms post-treatment (ITT analysis)	5	2018	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.12]
1.1.1 Adults	2	1163	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
1.1.2 Children	3	855	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.40, 1.73]
1.2 Resolution of symptoms post-treatment (evaluable participants)	5	1660	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.27, 0.97]
1.2.1 Adults	2	880	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.24, 1.32]
1.2.2 Children	3	780	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.14, 1.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 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]
1.3.1 Children	1	138	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.34, 2.74]
1.4 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]
1.4.1 Sponsor not reported	2	769	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.27, 0.81]
1.4.2 Sponsored studies	3	1249	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.70, 1.16]
1.5 Sore throat (ITT analysis)	1	138	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.23, 4.04]
1.6 Fever (ITT analysis)	1	138	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.19, 4.98]
1.7 Incidence of relapse (evaluable participants)	4	1386	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.30, 0.99]
1.7.1 Adults	2	770	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.20, 0.88]
1.7.2 Children	2	616	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.45]
1.8 Complications (ITT analysis)	1	244	Odds Ratio (M-H, Random, 95% CI)	Not estimable
1.9 Adverse events (ITT analysis)	3	1279	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.27, 3.25]

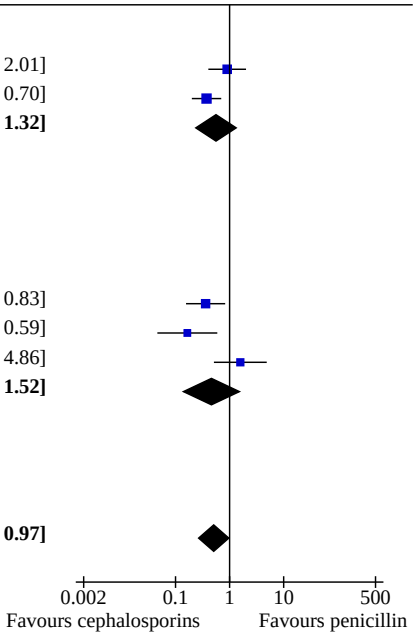
Analysis 1.1. Comparison 1: Cephalosporins versus penicillin, Outcome 1: Resolution of symptoms post-treatment (ITT analysis)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Adults						
Carbon 1995	13	119	22	125	15.5%	0.57 [0.27 , 1.20]
Nemeth 1999	201	609	117	310	36.0%	0.81 [0.61 , 1.08]
Subtotal (95% CI)		**728**		**435**	**51.5%**	**0.78 [0.60 , 1.01]**
Total events:	214		139			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						
1.1.2 Children						
Disney 1992a	8	263	21	262	13.1%	0.36 [0.16 , 0.83]
Henness 1982	38	114	33	100	21.2%	1.02 [0.57 , 1.80]
Reed 1991	22	60	16	56	14.3%	1.45 [0.66 , 3.16]
Subtotal (95% CI)		**437**		**418**	**48.5%**	**0.83 [0.40 , 1.73]**
Total events:	68		70			
Heterogeneity: Tau² = 0.29; Chi² = 6.23, df = 2 (P = 0.04); I² = 68%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Total (95% CI)		**1165**		**853**	**100.0%**	**0.79 [0.55 , 1.12]**
Total events:	282		209			
Heterogeneity: Tau² = 0.07; Chi² = 7.19, df = 4 (P = 0.13); I² = 44%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



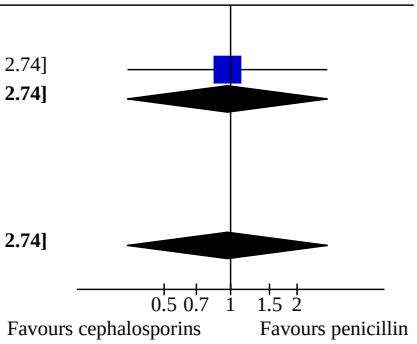
Analysis 1.2. Comparison 1: Cephalosporins versus penicillin, Outcome 2: Resolution of symptoms post-treatment (evaluable participants)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Adults						
Carbon 1995	13	119	14	117	22.0%	0.90 [0.40 , 2.01]
Nemeth 1999	19	427	24	217	25.5%	0.37 [0.20 , 0.70]
Subtotal (95% CI)		**546**		**334**	**47.5%**	**0.56 [0.24 , 1.32]**
Total events:	32		38			
Heterogeneity: Tau² = 0.25; Chi² = 2.87, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.32 (P = 0.19)						
1.2.2 Children						
Disney 1992a	8	263	21	262	21.5%	0.36 [0.16 , 0.83]
Henness 1982	3	79	16	83	14.4%	0.17 [0.05 , 0.59]
Reed 1991	9	47	6	46	16.6%	1.58 [0.51 , 4.86]
Subtotal (95% CI)		**389**		**391**	**52.5%**	**0.46 [0.14 , 1.52]**
Total events:	20		43			
Heterogeneity: Tau² = 0.80; Chi² = 7.45, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 1.27 (P = 0.20)						
Total (95% CI)		**935**		**725**	**100.0%**	**0.51 [0.27 , 0.97]**
Total events:	52		81			
Heterogeneity: Tau² = 0.32; Chi² = 10.42, df = 4 (P = 0.03); I² = 62%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.80), I² = 0%						



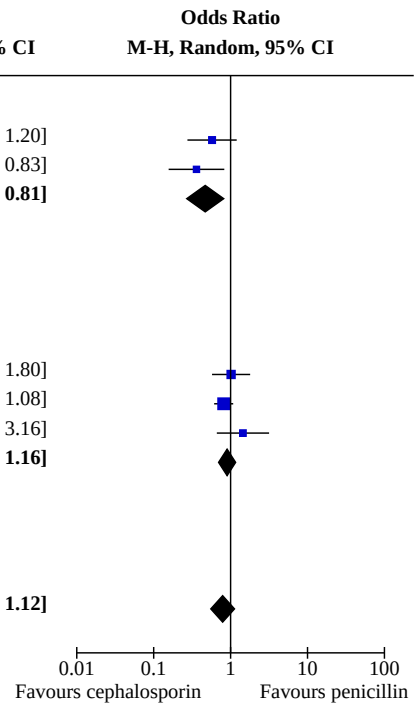
Analysis 1.3. Comparison 1: Cephalosporins versus penicillin, Outcome 3: Resolution of symptoms within 24 hours of treatment (ITT analysis)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Children						
Randolph 1985	8	70	8	68	100.0%	0.97 [0.34 , 2.74]
Subtotal (95% CI)		**70**		**68**	**100.0%**	**0.97 [0.34 , 2.74]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**70**		**68**	**100.0%**	**0.97 [0.34 , 2.74]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Test for subgroup differences: Not applicable						



Analysis 1.4. Comparison 1: Cephalosporins versus penicillin, Outcome 4: Resolution of symptoms ITT (subgroup sponsored versus no sponsor reported)

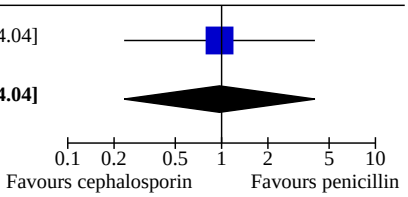
Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Sponsor not reported						
Carbon 1995	13	119	22	125	15.5%	0.57 [0.27 , 1.20]
Disney 1992a	8	263	21	262	13.1%	0.36 [0.16 , 0.83]
Subtotal (95% CI)		**382**		**387**	**28.5%**	**0.47 [0.27 , 0.81]**
Total events:	21		43			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.007)						
1.4.2 Sponsored studies						
Henness 1982	38	114	33	100	21.2%	1.02 [0.57 , 1.80]
Nemeth 1999	201	609	117	310	36.0%	0.81 [0.61 , 1.08]
Reed 1991	22	60	16	56	14.3%	1.45 [0.66 , 3.16]
Subtotal (95% CI)		**783**		**466**	**71.5%**	**0.90 [0.70 , 1.16]**
Total events:	261		166			
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 2 (P = 0.35); I² = 4%						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**1165**		**853**	**100.0%**	**0.79 [0.55 , 1.12]**
Total events:	282		209			
Heterogeneity: Tau² = 0.07; Chi² = 7.19, df = 4 (P = 0.13); I² = 44%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Chi² = 4.46, df = 1 (P = 0.03), I² = 77.6%						



Analysis 1.5. Comparison 1: Cephalosporins versus penicillin, Outcome 5: Sore throat (ITT analysis)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
Randolph 1985	4	70	4	68	100.0%	0.97 [0.23 , 4.04]
Total (95% CI)		**70**		**68**	**100.0%**	**0.97 [0.23 , 4.04]**
Total events:	4		4			

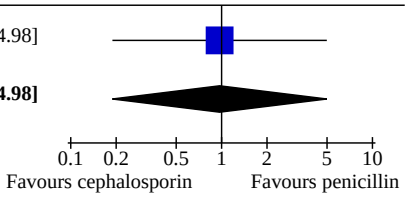
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Cephalosporins versus penicillin, Outcome 6: Fever (ITT analysis)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
Randolph 1985	3	70	3	68	100.0%	0.97 [0.19 , 4.98]
Total (95% CI)		**70**		**68**	**100.0%**	**0.97 [0.19 , 4.98]**
Total events:	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Cephalosporins versus penicillin, Outcome 7: Incidence of relapse (evaluable participants)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 Adults						
Carbon 1995	3	115	7	115	18.3%	0.41 [0.10 , 1.64]
Nemeth 1999	11	374	11	166	47.4%	0.43 [0.18 , 1.01]
Subtotal (95% CI)		**489**		**281**	**65.7%**	**0.42 [0.20 , 0.88]**
Total events:	14		18			

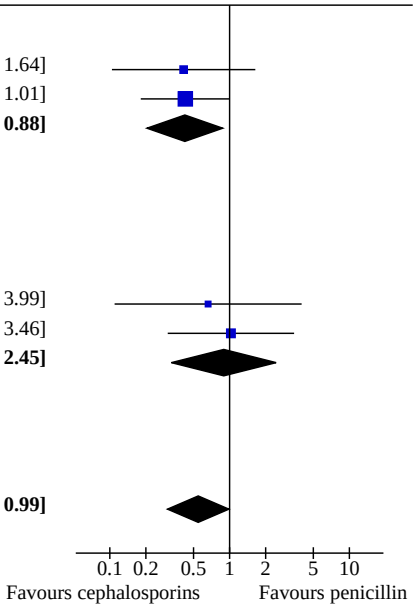
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

1.7.2 Children						
Disney 1992a	2	263	3	262	10.8%	0.66 [0.11 , 3.99]
Reed 1991	6	45	6	46	23.6%	1.03 [0.30 , 3.46]
Subtotal (95% CI)		**308**		**308**	**34.3%**	**0.89 [0.33 , 2.45]**
Total events:	8		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)

Total (95% CI)		**797**		**589**	**100.0%**	**0.55 [0.30 , 0.99]**
Total events:	22		27			

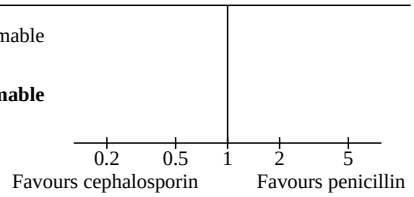
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Chi² = 1.39, df = 1 (P = 0.24), I² = 28.3%



Analysis 1.8. Comparison 1: Cephalosporins versus penicillin, Outcome 8: Complications (ITT analysis)

Study or Subgroup	Cephalosporin Events	Cephalosporin Total	Penicillin Events	Penicillin Total	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		0			

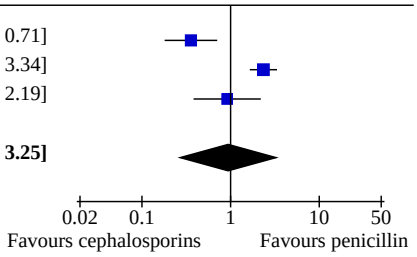
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Cephalosporins versus penicillin, Outcome 9: Adverse events (ITT analysis)

Study or Subgroup	cephalosporin Events	cephalosporin Total	penicillin Events	penicillin Total	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		95			

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



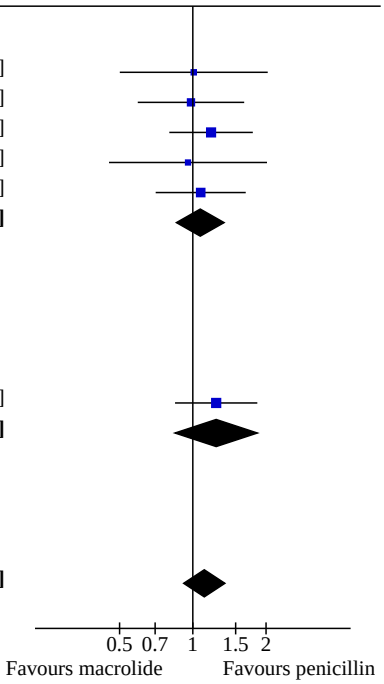
Comparison 2. Macrolides versus penicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Resolution of symptoms post-treatment (ITT analysis)	6	1728	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.92, 1.35]
2.1.1 Adults	5	1239	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.86, 1.34]
2.1.2 Children	1	489	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.84]
2.2 Resolution of symptoms post-treatment (evaluable participants only)	6	1159	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.09]
2.2.1 Adults	5	801	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.31]
2.2.2 Children	1	358	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.36, 1.11]
2.3 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]
2.3.1 Sponsor not reported	3	860	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.84, 1.48]
2.3.2 Sponsored studies	3	868	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.85, 1.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Sore throat post-treatment (ITT analysis)	2	371	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.46]
2.5 Fever post-treatment (ITT analysis)	2	371	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.59]
2.6 Incidence of relapse (evaluable participants)	6	802	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.48, 3.03]
2.6.1 Adults	5	495	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.34, 2.39]
2.6.2 Children	1	307	Odds Ratio (M-H, Random, 95% CI)	3.10 [0.67, 14.25]
2.7 Adverse events (ITT analysis)	6	1727	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.73]
2.7.1 Adults	5	1238	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.50]
2.7.2 Children	1	489	Odds Ratio (M-H, Random, 95% CI)	2.33 [1.06, 5.15]

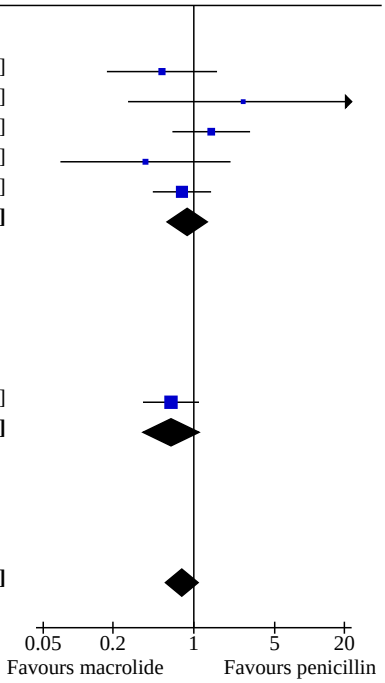
Analysis 2.1. Comparison 2: Macrolides versus penicillin, Outcome 1: Resolution of symptoms post-treatment (ITT analysis)

Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Adults						
Bachand 1991	28	65	27	63	8.1%	1.01 [0.50 , 2.03]
Levenstein 1991	64	128	58	115	15.9%	0.98 [0.59 , 1.63]
Norrby 2002	100	198	91	197	23.5%	1.19 [0.80 , 1.76]
Stein 1991	20	65	20	63	7.3%	0.96 [0.45 , 2.02]
Watkins 1997	75	170	74	175	21.2%	1.08 [0.70 , 1.65]
Subtotal (95% CI)		**626**		**613**	**76.1%**	**1.07 [0.86 , 1.34]**
Total events:	287		270			
Heterogeneity: Chi² = 0.50, df = 4 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.1.2 Children						
O'Doherty 1996	133	326	58	163	23.9%	1.25 [0.85 , 1.84]
Subtotal (95% CI)		**326**		**163**	**23.9%**	**1.25 [0.85 , 1.84]**
Total events:	133		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**952**		**776**	**100.0%**	**1.11 [0.92 , 1.35]**
Total events:	420		328			
Heterogeneity: Chi² = 0.93, df = 5 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.09 (P = 0.27)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



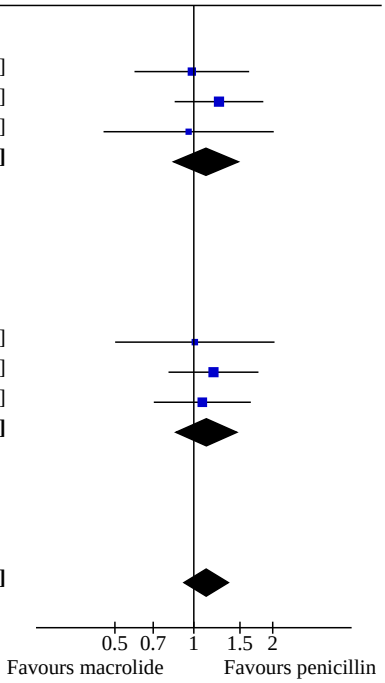
Analysis 2.2. Comparison 2: Macrolides versus penicillin, Outcome 2: Resolution of symptoms post-treatment (evaluable participants only)

Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 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		65			
Heterogeneity: Chi² = 4.24, df = 4 (P = 0.37); I² = 6%						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.2.2 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		28			
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		93			
Heterogeneity: Chi² = 5.07, df = 5 (P = 0.41); I² = 1%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0%						



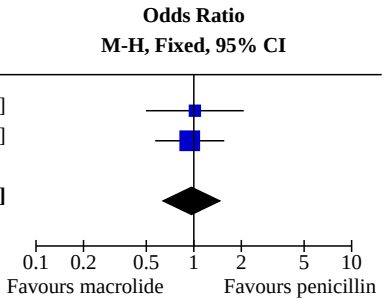
Analysis 2.3. Comparison 2: Macrolides versus penicillin, Outcome 3: Resolution of symptoms ITT (subgroup sponsored versus no sponsor reported)

Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 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		136			
Heterogeneity: Chi² = 0.72, df = 2 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.3.2 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		192			
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.90); I² = 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		328			
Heterogeneity: Chi² = 0.93, df = 5 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.09 (P = 0.27)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



Analysis 2.4. Comparison 2: Macrolides versus penicillin, Outcome 4: Sore throat post-treatment (ITT analysis)

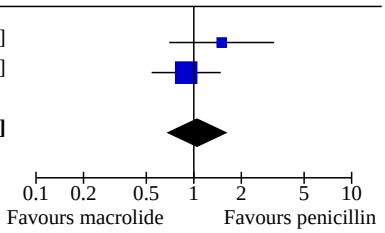
Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bachand 1991	25	65	24	63	32.5%	1.02 [0.50 , 2.07]
Levenstein 1991	66	128	61	115	67.5%	0.94 [0.57 , 1.56]
Total (95% CI)		**193**		**178**	**100.0%**	**0.97 [0.64 , 1.46]**
Total events:	91		85			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Not applicable						



Analysis 2.5. Comparison 2: Macrolides versus penicillin, Outcome 5: Fever post-treatment (ITT analysis)

Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bachand 1991	22	65	16	63	25.2%	1.50 [0.70 , 3.23]
Levenstein 1991	61	128	58	115	74.8%	0.89 [0.54 , 1.48]
Total (95% CI)		**193**		**178**	**100.0%**	**1.05 [0.69 , 1.59]**
Total events:	83		74			

Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Macrolides versus penicillin, Outcome 6: Incidence of relapse (evaluable participants)

Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
2.6.1 Adults						
Bachand 1991	3	13	3	15	18.2%	1.20 [0.20 , 7.31]
Levenstein 1991	1	60	0	1	6.0%	0.08 [0.00 , 2.73]
Norrby 2002	0	1	1	53	6.0%	11.67 [0.32 , 422.14]
Stein 1991	3	47	2	48	17.8%	1.57 [0.25 , 9.84]
Watkins 1997	4	121	8	136	29.2%	0.55 [0.16 , 1.86]
Subtotal (95% CI)		**242**		**253**	**77.2%**	**0.90 [0.34 , 2.39]**
Total events:	11		14			

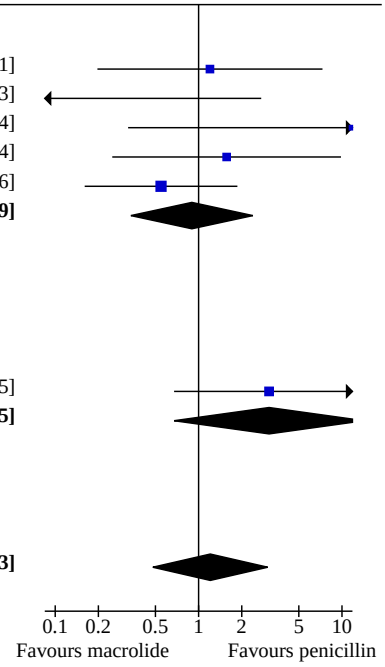
Heterogeneity: Tau² = 0.23; Chi² = 4.86, df = 4 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.22 (P = 0.83)

2.6.2 Children						
O'Doherty 1996	11	199	2	108	22.8%	3.10 [0.67 , 14.25]
Subtotal (95% CI)		**199**		**108**	**22.8%**	**3.10 [0.67 , 14.25]**
Total events:	11		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

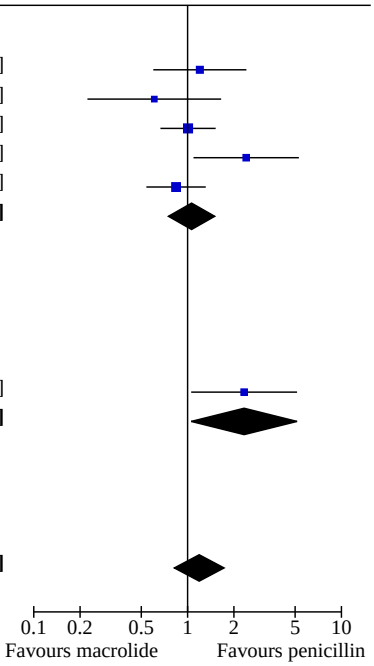
Total (95% CI)		**441**		**361**	**100.0%**	**1.21 [0.48 , 3.03]**
Total events:	22		16			

Heterogeneity: Tau² = 0.37; Chi² = 6.99, df = 5 (P = 0.22); I² = 28%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Chi² = 1.80, df = 1 (P = 0.18), I² = 44.4%



Analysis 2.7. Comparison 2: Macrolides versus penicillin, Outcome 7: Adverse events (ITT analysis)

Study or Subgroup	Macrolide Events	Macrolide Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
2.7.1 Adults						
Bachand 1991	37	65	33	63	15.6%	1.20 [0.60 , 2.41]
Levenstein 1991	7	128	10	115	9.9%	0.61 [0.22 , 1.65]
Norrby 2002	70	198	69	196	24.3%	1.01 [0.67 , 1.52]
Stein 1991	25	65	13	63	13.5%	2.40 [1.09 , 5.29]
Watkins 1997	108	170	118	175	23.2%	0.84 [0.54 , 1.31]
Subtotal (95% CI)		**626**		**612**	**86.5%**	**1.06 [0.75 , 1.50]**
Total events:	247		243			
Heterogeneity: Tau² = 0.06; Chi² = 6.50, df = 4 (P = 0.16); I² = 38%						
Test for overall effect: Z = 0.34 (P = 0.74)						
2.7.2 Children						
O'Doherty 1996	35	326	8	163	13.5%	2.33 [1.06 , 5.15]
Subtotal (95% CI)		**326**		**163**	**13.5%**	**2.33 [1.06 , 5.15]**
Total events:	35		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**952**		**775**	**100.0%**	**1.19 [0.82 , 1.73]**
Total events:	282		251			
Heterogeneity: Tau² = 0.10; Chi² = 10.22, df = 5 (P = 0.07); I² = 51%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 3.18, df = 1 (P = 0.07), I² = 68.5%						



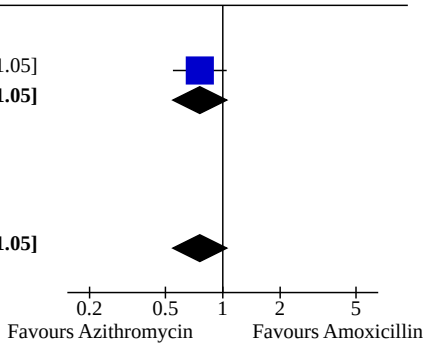
Comparison 3. Azithromycin versus amoxicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Clinical cure at 24 to 28 days (ITT)	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
3.1.1 Children	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
3.2 Clinical cure at 24 to 28 days (bacteriological per protocol population)	1	482	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.73]
3.2.1 Children	1	482	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.73]
3.3 Relapse on day 38 to 45 (ITT)	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.02]
3.3.1 Children	1	673	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.02]
3.4 Relapse on day 38 to 45 (bacteriological per protocol)	1	422	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.82]
3.4.1 Children	1	422	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.82]
3.5 Adverse events (all participants)	1	673	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [1.78, 3.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.1 Children	1	673	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [1.78, 3.99]

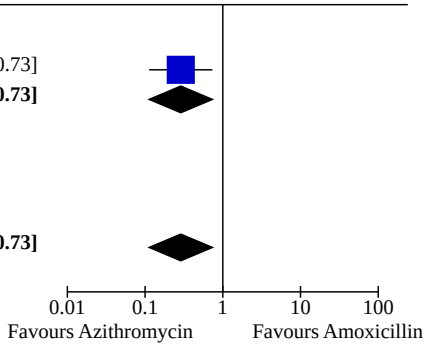
Analysis 3.1. Comparison 3: Azithromycin versus amoxicillin, Outcome 1: Clinical cure at 24 to 28 days (ITT)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Amoxicillin Events	Amoxicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.1.1 Children						
NCT00643149	98	337	118	336	100.0%	0.76 [0.55 , 1.05]
Subtotal (95% CI)		**337**		**336**	**100.0%**	**0.76 [0.55 , 1.05]**
Total events:	98		118			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
Total (95% CI)		**337**		**336**	**100.0%**	**0.76 [0.55 , 1.05]**
Total events:	98		118			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Not applicable						



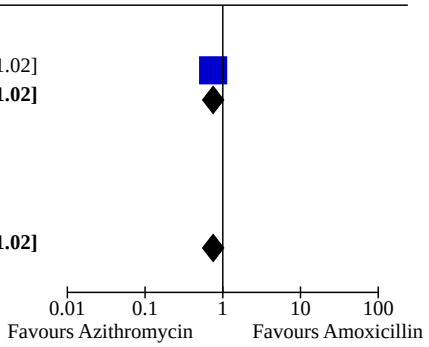
Analysis 3.2. Comparison 3: Azithromycin versus amoxicillin, Outcome 2: Clinical cure at 24 to 28 days (bacteriological per protocol population)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Amoxicillin Events	Amoxicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.2.1 Children						
NCT00643149	6	245	19	237	100.0%	0.29 [0.11 , 0.73]
Subtotal (95% CI)		**245**		**237**	**100.0%**	**0.29 [0.11 , 0.73]**
Total events:	6		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.61 (P = 0.009)						
Total (95% CI)		**245**		**237**	**100.0%**	**0.29 [0.11 , 0.73]**
Total events:	6		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.61 (P = 0.009)						
Test for subgroup differences: Not applicable						



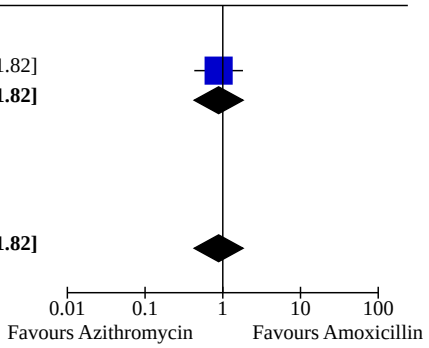
Analysis 3.3. Comparison 3: Azithromycin versus amoxicillin, Outcome 3: Relapse on day 38 to 45 (ITT)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Amoxicillin Events	Amoxicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 Children						
NCT00643149	130	337	153	336	100.0%	0.75 [0.55 , 1.02]
Subtotal (95% CI)		**337**		**336**	**100.0%**	**0.75 [0.55 , 1.02]**
Total events:	130		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
Total (95% CI)		**337**		**336**	**100.0%**	**0.75 [0.55 , 1.02]**
Total events:	130		153			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Not applicable						



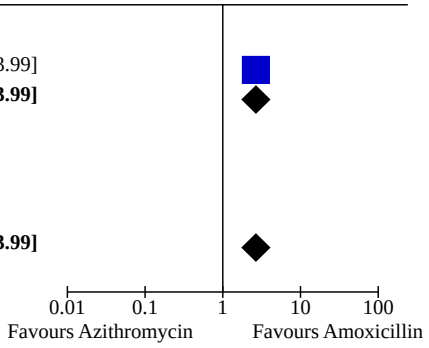
Analysis 3.4. Comparison 3: Azithromycin versus amoxicillin, Outcome 4: Relapse on day 38 to 45 (bacteriological per protocol)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Amoxicillin Events	Amoxicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.4.1 Children						
NCT00643149	16	223	16	199	100.0%	0.88 [0.43 , 1.82]
Subtotal (95% CI)		**223**		**199**	**100.0%**	**0.88 [0.43 , 1.82]**
Total events:	16		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
Total (95% CI)		**223**		**199**	**100.0%**	**0.88 [0.43 , 1.82]**
Total events:	16		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
Test for subgroup differences: Not applicable						



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

Study or Subgroup	Azithromycin Events	Azithromycin Total	Amoxicillin Events	Amoxicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.5.1 Children						
NCT00643149	93	337	42	336	100.0%	2.67 [1.78 , 3.99]
Subtotal (95% CI)		**337**		**336**	**100.0%**	**2.67 [1.78 , 3.99]**
Total events:	93		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.78 (P < 0.00001)						
Total (95% CI)		**337**		**336**	**100.0%**	**2.67 [1.78 , 3.99]**
Total events:	93		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.78 (P < 0.00001)						
Test for subgroup differences: Not applicable						

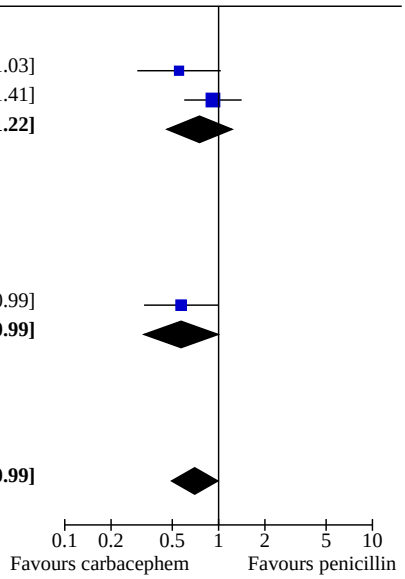


Comparison 4. Carbacephem versus penicillin

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

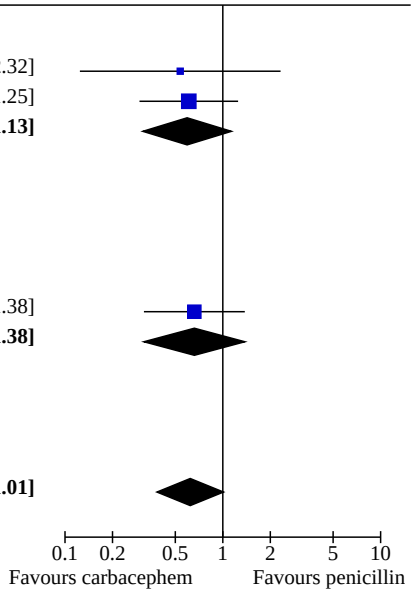
Analysis 4.1. Comparison 4: Carbacephem versus penicillin, Outcome 1: Resolution of symptoms post-treatment (ITT analysis)

Study or Subgroup	Carbacephem Events	Carbacephem Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
4.1.1 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		108			
Heterogeneity: Tau² = 0.05; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 1.15 (P = 0.25)						
4.1.2 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		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Total (95% CI)		**396**		**399**	**100.0%**	**0.70 [0.49 , 0.99]**
Total events:	121		152			
Heterogeneity: Tau² = 0.02; Chi² = 2.60, df = 2 (P = 0.27); I² = 23%						
Test for overall effect: Z = 2.03 (P = 0.04)						
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%						



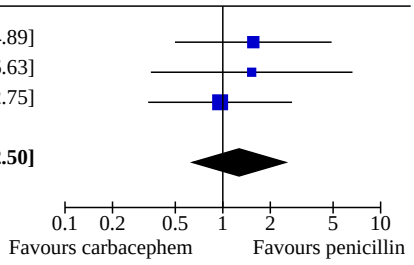
Analysis 4.2. Comparison 4: Carbacephem versus penicillin, Outcome 2: Resolution of symptoms post-treatment (evaluable participants)

Study or Subgroup	Carbacephem Events	Carbacephem Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.2.1 Adults						
McCarty 1992a	3	89	5	82	12.0%	0.54 [0.12 , 2.32]
Muller 1992	14	115	23	124	46.4%	0.61 [0.30 , 1.25]
Subtotal (95% CI)		**204**		**206**	**58.4%**	**0.59 [0.31 , 1.13]**
Total events:	17		28			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
4.2.2 Children						
Disney 1992b	16	104	19	88	41.6%	0.66 [0.32 , 1.38]
Subtotal (95% CI)		**104**		**88**	**41.6%**	**0.66 [0.32 , 1.38]**
Total events:	16		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**308**		**294**	**100.0%**	**0.62 [0.38 , 1.01]**
Total events:	33		47			
Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%						



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

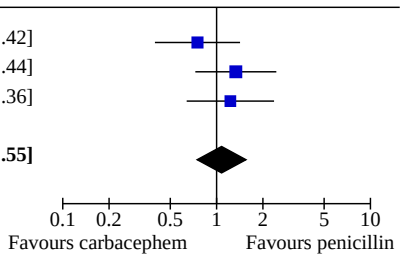
Study or Subgroup	Carbacephem Events	Carbacephem Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Disney 1992b	9	84	5	70	32.6%	1.56 [0.50 , 4.89]
McCarty 1992a	5	75	3	67	19.8%	1.52 [0.35 , 6.63]
Muller 1992	7	108	8	119	47.6%	0.96 [0.34 , 2.75]
Total (95% CI)		**267**		**256**	**100.0%**	**1.27 [0.64 , 2.50]**
Total events:	21		16			
Heterogeneity: Chi² = 0.45, df = 2 (P = 0.80); I² = 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)

Study or Subgroup	Carbacephem Events	Carbacephem Total	Penicillin Events	Penicillin Total	Weight	Odds Ratio M-H, Random, 95% CI
Disney 1992b	22	120	26	113	32.8%	0.75 [0.40 , 1.42]
McCarty 1992a	31	107	26	111	36.2%	1.33 [0.73 , 2.44]
Muller 1992	22	169	19	175	31.1%	1.23 [0.64 , 2.36]
Total (95% CI)		**396**		**399**	**100.0%**	**1.08 [0.75 , 1.55]**
Total events:	75		71			

Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



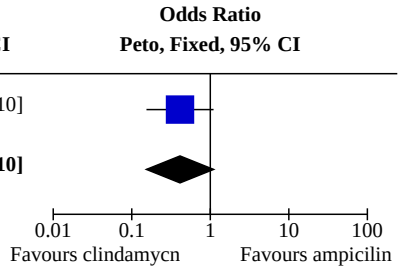
Comparison 5. Clindamycin versus ampicillin

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

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

Study or Subgroup	Clindamycin Events	Clindamycin Total	Ampicillin Events	Ampicillin Total	Weight	Odds Ratio Peto, Fixed, 95% CI
Jackson 1973	6	156	14	158	100.0%	0.41 [0.15 , 1.10]
Total (95% CI)		**156**		**158**	**100.0%**	**0.41 [0.15 , 1.10]**
Total events:	6		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable

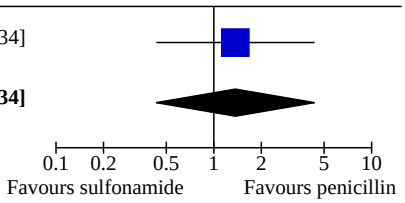


Comparison 6. Sulfonamide versus penicillin

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

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

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



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 streptococ*).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 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*).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**
# 5	**297**
# 4	**1,296,034**
# 3	**1,398**
# 2	**350,460**
# 1	**2,840**

WHAT'S NEW

Date	Event	Description
3 September 2020	New citation required but conclusions have not changed	We did not identify any new trials for inclusion. We excluded one trial previously awaiting classification (Eslami 2014).
3 September 2020	New search has been performed	We updated the searches on 3 September 2020.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 10, 2010

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. This review update includes the Pfizer 2011 study that was identified in the 2012 review publication and had been awaiting classification until data became available. We identified three new trials for exclusion (Kuroki 2013; Stelter 2014; Van Brusselen 2014).
25 March 2016	New citation required but conclusions have not changed	The review conclusions remain unchanged.
19 October 2012	New citation required but conclusions have not changed	Our conclusions remain unchanged.
19 October 2012	New search has been performed	The updated searches identified five new references. We excluded four studies (Bottaro 2012; Llerena 2011; NCT00393744; Rimoin 2011), and requested results from one completed unpublished study (NCT00643149).

CONTRIBUTIONS OF AUTHORS

MVD wrote the protocol. All authors contributed to final editing of the protocol.
ST conducted all searches for this review.
MVD and ADS reviewed the searches for the review updates.
MVD, ADS, and NK independently performed 'Risk of bias' assessment.
MVD, NK and ADS performed data extraction. MVD analysed the data.
MVD wrote the draft review and addressed the peer-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
Sarah Thorning: none known
Thierry Christiaens: none known

SOURCES OF SUPPORT

Internal sources

- None received, Other

  N/A

External sources

- None received, Other

  N/A

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 2013 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 GRADEpro GDT software, and added a description of the GRADE assessment of the overall certainty 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 participants 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.

Hilde Habraken was removed as an author for the 2020 update, as she was no longer able to contribute to this review.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adolescent; Adult; Aged; Aged, 80 and over; Child; Child, Preschool; Humans; Infant; Middle Aged; Young Adult