Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children (Review)

Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 8

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Saleh Altamimi[1], Adli Khalil[2], Khalid A Khalaiwi[3], Ruth A Milner[4], Martin V Pusic[5], Mohammed A Al Othman[2]

[1]Department of Emergency Medicine and Pediatrics, King Fahad Medical City, Riyadh, Saudi Arabia. [2]Department of Emergency Medicine, King Khalid University Hospital, Riyadh, Saudi Arabia. [3]Emergency Medicine Department, George Washington University, Washington, Washington DC, USA. [4]Department of Surgery, University of British Columbia, Vancouver, Canada. [5]Department of Pediatric Emergency Medicine, Columbia University, New York, New York, USA

Contact address: Saleh Altamimi, Department of Emergency Medicine and Pediatrics, King Fahad Medical City, Riyadh, 11563, Saudi Arabia. saltamimi@kfmc.med.sa. salehaltamimi@yahoo.com.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2012.
Review content assessed as up-to-date: 3 April 2012.

Citation: Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al Othman MA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD004872. DOI: 10.1002/14651858.CD004872.pub3.

ABSTRACT

Background

The standard duration of treatment for children with acute group A beta hemolytic streptococcus (GABHS) pharyngitis with oral penicillin is 10 days. Shorter duration antibiotics may have comparable efficacy.

Objectives

To summarize the evidence regarding the efficacy of two to six days of newer oral antibiotics (short duration) compared to 10 days of oral penicillin (standard duration) in treating children with acute GABHS pharyngitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012).

Selection criteria

Randomized controlled trials (RCTs) comparing short duration oral antibiotics to standard duration oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis.

Data collection and analysis

Two review authors scanned the titles and abstracts of retrieved citations and applied the inclusion criteria. We retrieved included studies in full, and extracted data. Two review authors independently assessed trial quality.

Main results

We included 20 studies with 13,102 cases of acute GABHS pharyngitis. The updated search did not identify any new eligible studies; the majority of studies were at high risk of bias. However, the majority of the results were consistent. Compared to standard duration treatment, the short duration treatment studies had shorter periods of fever (mean difference (MD) -0.30 days, 95% confidence interval (CI) -0.45 to -0.14) and throat soreness (MD -0.50 days, 95% CI -0.78 to -0.22); lower risk of early clinical treatment failure (odds ratio (OR) 0.80, 95% CI 0.67 to 0.94); no significant difference in early bacteriological treatment failure (OR 1.08, 95% CI 0.97 to 1.20) or late clinical recurrence (OR 0.95, 95% CI 0.83 to 1.08). However, the overall risk of late bacteriological recurrence was worse in the short duration treatment studies (OR 1.31, 95% CI 1.16 to 1.48), although no significant differences were found when studies of low dose azithromycin (10 mg/kg) were eliminated (OR 1.06, 95% CI 0.92 to 1.22). Three studies reported long duration complications. Out of 8135 cases of acute GABHS pharyngitis, only six cases in the short duration treatment versus eight in the standard duration treatment developed long-term complications in the form of glomerulonephritis and acute rheumatic fever, with no statistically significant difference (OR 0.53, 95% CI 0.17 to 1.64).

Authors' conclusions

Three to six days of oral antibiotics had comparable efficacy compared to the standard duration 10-day course of oral penicillin in treating children with acute GABHS pharyngitis. . In areas where the prevalence of rheumatic heart disease is still high, our results must be interpreted with caution.

PLAIN LANGUAGE SUMMARY

The effect of short duration versus standard duration antibiotic therapy for streptococcal throat infection in children

Streptococcal (strep) throat infection is very common. A 10-day course of penicillin is prescribed mainly to protect against the complication of acute rheumatic fever, which can occur approximately 20 days after streptococcal throat and cause damage to the heart valves. Cases of acute rheumatic fever have dropped dramatically in high-income countries. Newer antibiotics taken for a shorter duration, may have a comparable effect to penicillin taken for 10 days.

We summarized medical literature regarding the effect of two to six days of oral antibiotics (short duration) in treating children with streptococcal throat infection, compared with 10 days of oral penicillin (standard duration). We included 20 studies with 13,102 cases of acute group A beta hemolytic streptococcus (GABHS) pharyngitis. The short duration treatment resulted in better compliance but more side effects. All side effects were self-limiting: mostly mild to moderate diarrhea, vomiting and abdominal pain. Three studies reported the rate of long duration complications with no statistically significant difference.

Our study has several limitations. Firstly, only 3 out of the 20 included studies followed the participants for a sufficient duration to be able to study the prevalence of complications of GABHS pharyngitis. Although these three studies had a total of 8135 participants, results were too under-powered to draw any conclusions on differences in complication rates. This means our conclusion is not applicable in low-income countries where the prevalence of rheumatic heart disease is high. Another limitation is that the primary studies evaluated different antibiotics for variable durations (three to six days). Also, studies were of limited quality. Finally, although the shorter antibiotic duration appeared to be effective and more convenient, it is more expensive than the standard duration 10 days of penicillin. However, one must take into account the reality of patient behavior and the price of unsuccessful or incomplete therapy.

Three to six days of oral antibiotics for children with streptococcal throat infection is a safe treatment with a comparable effect to the standard duration of 10 days of penicillin. However, our results must be interpreted with caution in low-income countries where acute rheumatic fever is still a problem.

BACKGROUND

Description of the condition

Sore throat is one of the most common symptoms that primary

health care physicians have to deal with (Nandi 2001) and group A beta hemolytic streptococcus (GABHS) is the most common bacterial cause. Fifty per cent of cases are in children between the ages of 5 and 15 years (Bisno 1997). Although patients recover without antibiotic therapy, treatment is sometimes advised to hasten clinical resolution, prevent suppurative sequelae and decrease the incidence of rheumatic fever and glomerulonephritis (Bisno 1997). Rheumatic fever is a systemic disease affecting the periarteriolar connective tissue and can occur after an untreated group A streptococcal pharyngeal infection. It is believed to be caused by antibody cross-reactivity and leads to pancarditis (inflammation of the heart layers). Chronic rheumatic heart disease leads to cardinal anatomic changes of the valve including leaflet thickening, commissural fusion and shortening and thickening of the tendinous cords (Kumar 2008).

Description of the intervention

Many antibiotics have been shown to be effective in treating GABHS pharyngitis, including penicillin and its congeners (such as ampicillin, amoxicillin and semi-synthetic penicillins) as well as many cephalosporins, macrolides and clindamycin (Bisno 1997). Penicillin is often chosen because of its proven efficacy, safety, narrow spectrum and low cost. Oral penicillin for 10 days is still recommended as standard of care, because of past concern for maximum protection against acute rheumatic fever (the principal and original reason for using antibiotics for sore throat). However, a shorter duration of newer antibiotics, such as cephalosporins, has been shown to have comparable efficacy and has the advantage of overcoming beta lactamase producing organisms, as well as a longer half life, as with azithromycin. The incorporation of potentially more costly treatments in the era of health care reform must take into account the reality of patient behavior and the price of unsuccessful or incomplete therapy.

How the intervention might work

It is difficult to comply with a 10-day antibiotic course. If we summarize the available evidence and show that a short duration antibiotic course is efficacious in treating GABHS pharyngitis, this will make treatment much more convenient to the patient and will improve compliance.

Why it is important to do this review

A 10-day course of antibiotics has variable patient compliance (Cohen 1996), possibly because symptomatic improvement is often achieved within 24 to 48 hours of starting therapy. Patient (or parent) motivation to complete the recommended 10 day duration of penicillin diminishes rapidly after two to three days. Greater convenience to patients may result in improved compliance (Cohen 1996); and reduced failure rate (Adam 2000a; Tack 1997), complications (Tack 1997) and returns to the physician (Adam 2000a); and overall cost (Adam 2000a; Cohen 1996; Tack 1997).

OBJECTIVES

To summarize the evidence regarding the effect of 2 to 6 days of oral antibiotics in treating children with group A beta hemolytic streptococcus (GABHS) pharyngitis, compared with a 10-day course of oral penicillin, on duration of symptoms (fever and sore throat), eradication of the organism and recurrence and complication rates (acute rheumatic fever and acute poststreptococcal glomerulonephritis). We considered differences in reported side effects, for example diarrhea, yeast infections, gastrointestinal upset and rash.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) only.

Types of participants

Children, 1 to 18 years of age, with documented acute streptococcal pharyngitis, based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, pediatrician or otolaryngologist). We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis.

Types of interventions

Short duration (two to six days) of oral antibiotics versus a control of 10 days of oral penicillin (i.e. the recommended standard duration of treatment). We excluded studies comparing short duration antibiotics with 10 days of antibiotics other than penicillin. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Types of outcome measures

Primary outcomes

1. The number of days to resolution of fever and sore throat.

Secondary outcomes

1. Early clinical treatment failure, defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.
2. Late clinical recurrence, defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of antibiotic treatment.
3. Early bacteriological treatment failure, defined as persistence of the same GABHS strain in the first two weeks after completion of antibiotic treatment.
4. Late bacteriological recurrence, defined as recurrence of the same GABHS strain after initial resolution, beyond the two-week period immediately after completion of antibiotic treatment.
5. Compliance.
6. Acute rheumatic fever.
7. Acute poststreptococcal glomerulonephritis.
8. Suppurative and non-suppurative complications.
9. Differences in reported side effects, for example diarrhea, yeast infections, gastrointestinal upset and rash.

Search methods for identification of studies

Electronic searches

Originally we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4) and the Database of Abstracts of Reviews of Effects (DARE), MEDLINE (1966 to October, Week 5 2007), OLDMEDLINE (1950 to December 1965) and EMBASE (January 1990 to November 2007) (Appendix 1).

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 3; www.thecochranelibrary.com (accessed 3 April 2012), which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 2007 to March week 3, 2012) and EMBASE (January 2007 to April 2012).

We combined the MEDLINE search string shown in Appendix 2 with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search string for EMBASE (Appendix 3).

Searching other resources

We did not impose any language or publication restrictions. We identified any other reviews (systematic and narrative) or meta-analyses on this topic (Thornton 2000) in addition to identifying relevant clinical trials. We checked the bibliography of published RCTs, asked experts for trial information and we contacted pharmaceutical companies. We searched conference abstract proceedings, ISI Web of Science, the System for Information on Grey Literature in Europe (SIGLE) and the British Library Index of Conference Proceedings. We also searched www.clinicaltrials.gov, Computer Retrieval of Information on Scientific Projects (CRISP), META and the Glaxo Wellcome Register of clinical trials for ongoing and/or unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (KK, AK) independently performed the initial scan using titles and abstracts of all retrieved citations and applied the inclusion criteria. Both review authors documented the reasons for study exclusion and retrieved potentially eligible trials in full. We assessed trials fulfilling the review inclusion criteria for quality (Chalmers 1981; Meade 1997). We calculated inter-rater agreement using Kappa statistics. We resolved disagreements by consensus. Two authors (SA, MA) independently performed the updated scan and selection of studies using the same methodology as in the initial review.

Data extraction and management

We divided the study into two or more studies whenever it had more than two treatment arms, each comparing one intervention against the control (for example, Cohen 2002a; Cohen 2002b). Two review authors (KK, AK) independently collected and compared the following data using a standardized data collection form. We resolved differences by consensus.

Characteristics of participants

Number of participants, age, race and gender.

Characteristics of intervention

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

Characteristics of outcome measures

Duration of fever and sore throat, clinical treatment failure, bacteriological treatment failure, recurrence rate, rate of complications,

including glomerulonephritis and acute rheumatic fever and suppurative complications such as acute otitis media, sinusitis and peritonsillar abscess.

Adverse effects

Presence and type.

Assessment of risk of bias in included studies

Two review authors (SA, AK) independently assessed the risk of bias using The Cochrane Collaboration's 'risk of bias' tool (Higgins 2011) which assesses methodological quality according to:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting; and
- other bias.

We resolved disagreement by consensus. We included all eligible studies in the analysis.

Measures of treatment effect

We expressed continuous data as mean differences (MDs) and calculated an overall MD. We expressed dichotomous data as an odds ratio (OR). We reported occurrence of complications during the study period.

Unit of analysis issues

We defined several different outcomes (time to fever resolution, time to sore throat resolution, early clinical treatment failure, late clinical recurrence, early bacteriological treatment failure, late bacteriological recurrence, adverse effects, compliance and complications) based on different periods of follow-up. We performed separate analyses. We analyzed studies that compared more than two intervention groups (if meeting the inclusion criteria) by making multiple pair-wise comparisons. We did not include any participants twice.

Dealing with missing data

We analyzed only the available data. We assumed the data to be missing at random and unlikely to be related to the actual values of the missing data.

Assessment of heterogeneity

We tested for heterogeneity using the Z score, the Chi^2 test and the I^2 statistic with values greater than 50% indicating substantial heterogeneity.

Assessment of reporting biases

We tested for publication bias and small study effects using a funnel plot.

Data synthesis

We conducted a meta-analysis using the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We divided the studies into five subgroups according to the intervention antibiotic: azithromycin 10 mg/kg, azithromycin 20 mg/kg, clarithromycin, cefuroxime and others. We compared its performance against all identified outcomes of interest.

Sensitivity analysis

We did not perform a sensitivity analysis

RESULTS

Description of studies

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

Results of the search

Two review authors (KK, AK) independently searched for relevant trials. (KK's electronic search yielded 915 citations and AK's search yielded 917). After the initial scan of the titles and abstracts, 98 trials were preliminarily eligible on KK's list and 115 on AK's list, scoring a fair inter-observer allocation agreement (kappa = 0.61). After consensus, we agreed upon an initial combined list of 97 eligible studies and we retrieved the studies in full. We identified and retrieved 10 further citations from the reference lists of these studies. We did not find any additional trials in relevant systematic reviews or from our contact with experts and pharmaceutical companies. We found an abstract of one eligible unpublished trial, presented at a scientific meeting. However, data from that study were not available from the principal investigator. Two review authors (SA, AK) independently performed the updated search and found no new eligible studies.

Included studies

We assessed 107 trials for inclusion. Eighty-six trials did not meet our inclusion criteria, which left 21 eligible published clinical trials. We excluded one further study (Adam 2000b) because it was a re-publication of part of the data published in a larger study (Adam 2000a), which is included in the review.

Twenty RCTs met our inclusion criteria and we included them in the review. These trials investigated a total of 13,102 cases of group A beta hemolytic streptococcus (GABHS) throat infections (tonsillitis, pharyngitis, tonsillopharyngitis). The majority of studies were recent (1994 to 2004), during which period the rates of serious complications (especially acute rheumatic fever) were less common than before. The age of participants ranged from 1 to 18 years, with the exception of one study which included participants aged up to 25 years. All studies recruited participants presenting with signs and symptoms of tonsillopharyngitis and positive rapid GABHS antigen test of throat swab. The most common intervention antibiotic was azithromycin (n = 6). Other intervention antibiotics were cefuroxime (n = 3), erythromycin (n = 2), clarithromycin (n = 3), cefixime (n =1), amoxacillin (n = 1), amoxacillin/clavulanate (n = 2), penicillin V (n =1), cefprozil (n = 1), cefpodoxime (n = 1), josamycin (n = 1), cefdinir (n = 1), ceftibuten (n = 1) and loracarbef (n = 1).

Excluded studies

We excluded one study (Adam 2000b), because it was a republication of part of the data that was published in a larger study (Adam 2000a).

Risk of bias in included studies

All studies showed random assignment, per our inclusion criteria. Ranomization was mostly not concealed or unclear. All studies were analyzed by treatment received rather than by an intention-to-treat analysis and all studies mentioned withdrawals. Only three studies were blinded (O'Doherty 1996a; Pichichero 1994; Tack 1997). All studies had a standardized assessment (Figure 1; Figure 2).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

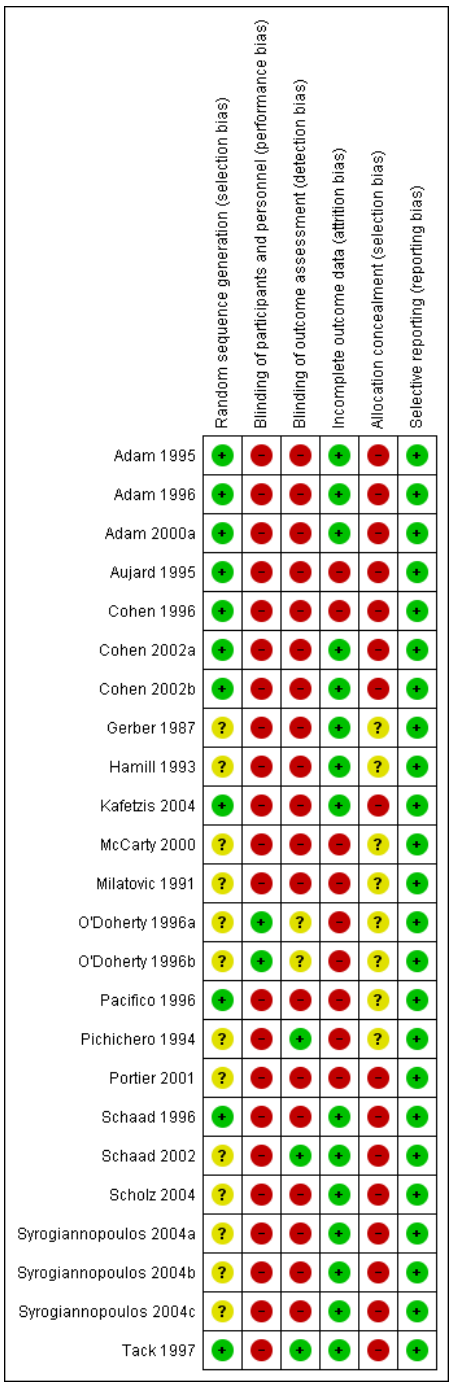
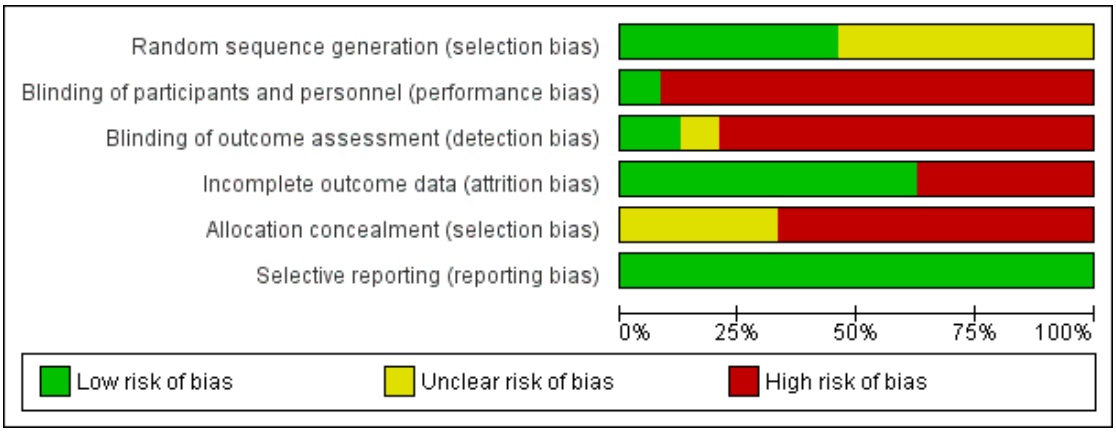


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Thirteen studies used an open, random allocation and seven had insufficient information to permit judgment. Eleven studies used computer generated randomizations, while nine were unclear.

Blinding

Only three studies were blinded (O'Doherty 1996a; Pichichero 1994; Tack 1997). The risk of bias can be significant in assessing outcomes that are subjective in nature like resolution of symptoms and clinical failure, or reporting of side effects and complications.

Incomplete outcome data

Eight out of 20 studies were at high risk for attrition bias, due mostly to significant missing outcome data.

Selective reporting

All studies were at low risk for reporting bias, as study protocols were all available and all prespecified outcomes have been reported.

Other potential sources of bias

None.

Effects of interventions

Primary outcome

Our primary outcome was time to fever resolution as it is the main presenting symptom and the most common symptom of concern for parents. The time to fever resolution was reported in only two studies (Aujard 1995; Kafetzis 2004). Both studies favored the short duration group. In the first study, the short duration group had a mean duration of fever of 2.04 days compared with 2.38 days in the standard duration group, while in the second study the durations were 2.82 days and 3.1 days, respectively (mean difference (MD) -0.30, 95% confidence interval (CI) -0.45 to -0.14) (Analysis 1.1).

Secondary outcomes

Sore throat is a complication of pharyngitis that commonly causes patient discomfort and may cause difficulty in drinking. Time to sore throat resolution was reported in only one study (Aujard 1995). The MD of sore throat was 2.19 days (standard deviation (SD) 0.81) in the short duration treatment group and 2.69 days (SD 1.13) in the standard duration treatment group (MD -0.50, 95% CI -0.78 to -0.22) (Analysis 1.2).

Early clinical treatment failure

All included studies except Milatovic 1991 reported risk of early clinical treatment failure (1 to 10 days after completion of the antibiotic duration) but only two studies (Aujard 1995; Kafetzis 2004) gave details about specific clinical signs and symptoms. The short duration treatment group showed a lower risk of early clinical treatment failure (odds ratio (OR) 0.80, 95% CI 0.67 to 0.94) (Analysis 2.1).

Late clinical recurrence

Thirteen studies assessed the risk of late clinical recurrence. The majority of the studies performed follow-up four weeks after completion of treatment, with a range from two weeks to one year in one study. The risk of late clinical recurrence was not statistically different between short duration and standard duration groups (OR 0.95, 95% CI 0.83 to 1.08) (Analysis 2.2).

Early bacteriological treatment failure

Bacterial eradication is important in order to reduce the chance of recurrence and GABHS complications, especially acute rheumatic fever and glomerulonephritis. All included studies assessed risk of early (1 to 10 days) bacteriological treatment failure. There was no significant difference in the risk of early bacteriological treatment failure between short duration and standard duration groups (OR 1.08, 95% CI 0.97 to 1.20) (Analysis 3.1).

Late bacteriological recurrence

All studies assessed the risk of late (four to six weeks) bacteriological recurrence. The risk of late bacteriological recurrence was significantly worse in the short duration treatment groups (OR 1.31, 95% CI 1.16 to 1.48). However, when eliminating the studies of low dose azithromycin (10 mg/kg), which performed much worse than other short duration regimens (OR 3.62, 95% CI 2.66 to 4.92), the two treatment groups were no longer statistically different (OR 1.06, 95% CI 0.92 to 1.22).

Adverse effects

All but three studies (Adam 2000a; Gerber 1987; Milatovic 1991) reported side effects. More side effects were seen in the short duration treatment group (OR 1.85, 95% CI 1.55 to 2.21) (Analysis 4.1). All side effects were mild to moderate and self-limiting. Most of the events involved the gastrointestinal system (diarrhea, vomiting and abdominal pain) in both treatment groups.

Compliance

Five studies reported patient compliance with the study treatment (Adam 1996; Aujard 1995; Cohen 1996; Cohen 2002a; Cohen 2002b; McCarty 2000). Non-compliance was reduced in the short duration treatment group (OR 0.21, 95% CI 0.16 to 0.29).

Complications

Only three studies reported post-GABHS pharyngitis complications. In the Adam 2000a study, 5 out of 4482 participants with a 12-month follow-up period developed complications. In the short duration treatment group three participants developed acute rheumatic fever and one developed glomerulonephritis. In the standard duration treatment group one patient developed glomerulonephritis.

In the Schaad 2002 study, two participants in the short duration treatment group developed proteinuria or glomerulonephritis and six participants in the standard duration treatment group developed proteinuria and/or glomerulonephritis or reactive arthritis. These findings disappeared without treatment within one to three weeks.

In the Scholz 2004 study, one patient in the standard duration treatment group developed glomerulonephritis.

Overall, there was no statistically significant difference in the risk of complications (OR 0.53, 95% CI 0.17 to 1.64).

Subgroup analysis

Due to the limited number of trials that assessed the same drug for short treatment we focused on the overall effect. However, we have included in the analysis figures that show the effect per drug for four subsets of studies based on the type of short duration antibiotic used: azithromycin 10 mg/kg, azithromycin 20 mg/kg, clarithromycin and cefuroxime.

Small study effect

We used funnel plots to check small study effect and reporting bias (Figure 3; Figure 4). No asymmetry was evident from examining these plots.

Figure 3. Funnel plot of comparison: 2 Clinical efficacy, outcome: 2.1 Clinical treatment failure (early).

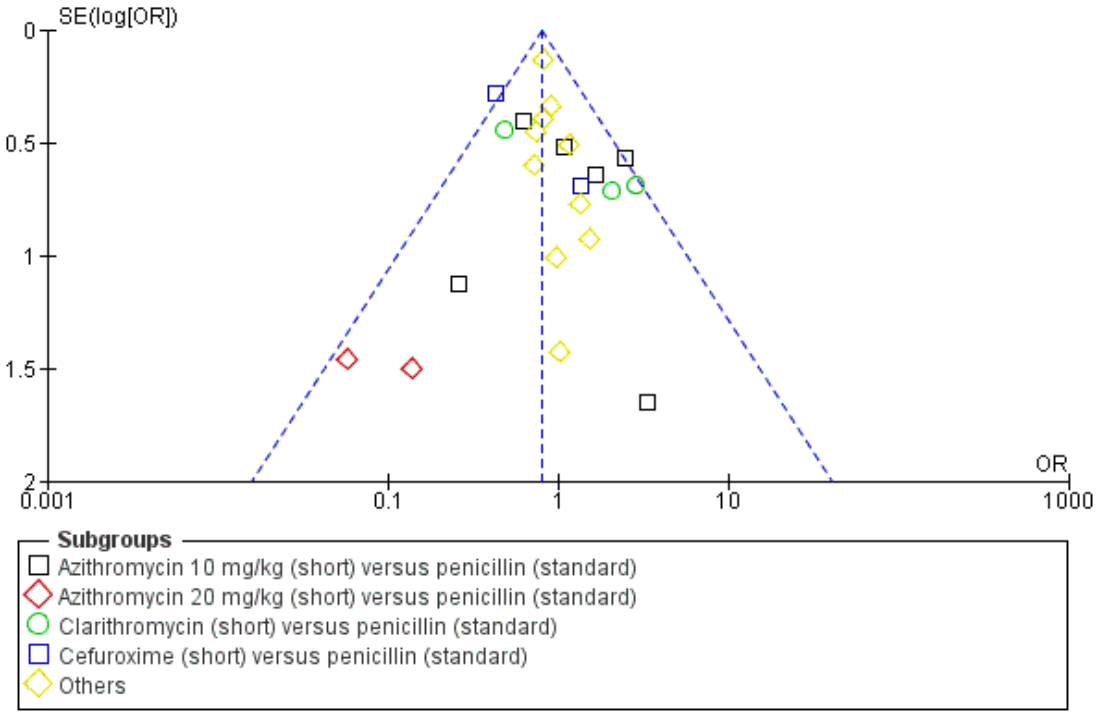
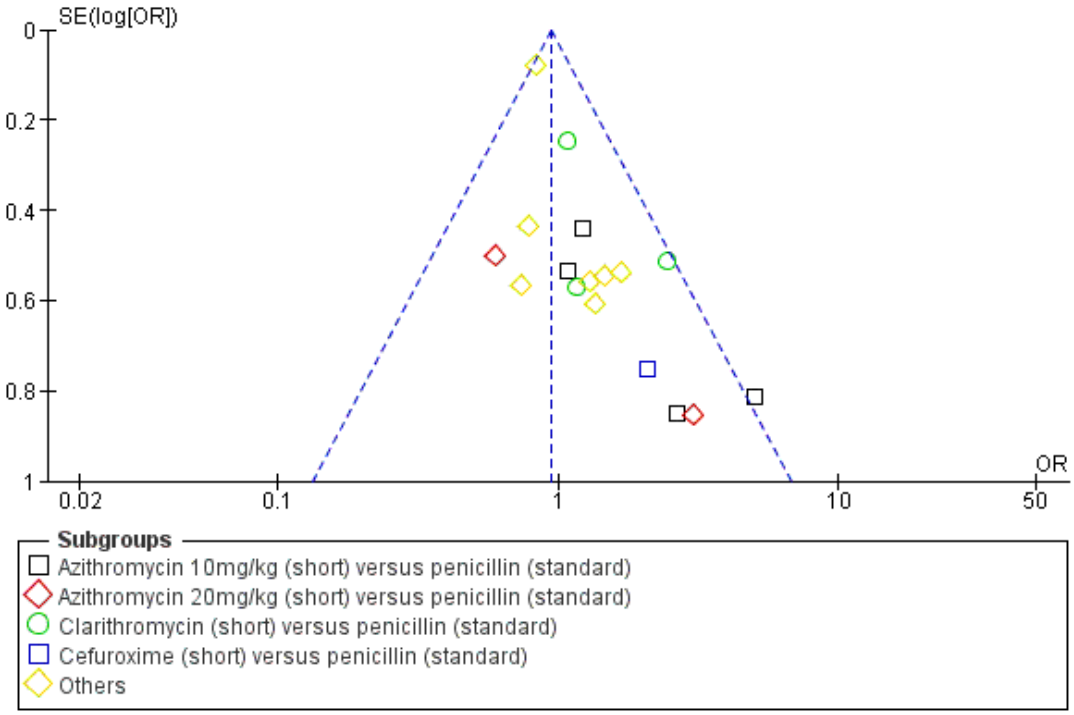


Figure 4. Funnel plot of comparison: 2 Clinical efficacy, outcome: 2.2 Clinical treatment failure (late).



DISCUSSION

On a global scale, group A beta hemolytic streptococcus (GABHS) infection is an important cause of morbidity and mortality. In low-income countries rheumatic fever remains an endemic disease with an annual incidence ranging from 100 to 200 per 100,000 school-aged children and is a major cause of cardiovascular mortality (Olivier 2000). The global burden of disease caused by GABHS is not known. A report by the Centre for International Child Health, University of Melbourne, reviewed recent population-based data in order to estimate the burden of GABHS diseases (Carapetis 2005). The report highlighted deficiencies in the available data and found that there are at least 517,000 deaths annually due to severe GABHS diseases (for example, acute rheumatic fever, rheumatic heart disease, poststreptococcal glomerulonephritis and invasive infections). The prevalence of severe GABHS disease is at least 18.1 million cases, with 1.78 million new cases each year. The greatest burden is due to rheumatic heart disease, with a prevalence of at least 15.6 million cases, with 282,000 new cases and 233,000 deaths each year. The burden of invasive GABHS diseases is unexpectedly high, with at least 663,000 new cases and 163,000 deaths each year. The report states that there are more than 111 million prevalent cases of GABHS pyoderma and over 616 million cases of GABHS pharyngitis per year.

The incidence of rheumatic fever has declined in high-income countries since the 1950s and now has an annual incidence of around 0.5 cases per 100,000 children of school age. The incidence of acute rheumatic fever in the United States, particularly over the past 50 years has decreased substantially. The reason for this is unclear. It has been proposed that certain M types of GABHS include strains that are particularly rheumatogenic and that others are non-rheumatogenic. Shulman 2006 compared the M type distribution of GABHS recovered from children in Chicago, Illinois with acute pharyngitis between 1961 and 1968 to that of GABHS recovered from Chicago children and children from across the United States between 2000 and 2004, with attention to changes in M types that were previously associated with rheumatogenic strains. Shulman found rheumatogenic types comprised 49.7% of 468 pharyngeal isolates between 1961 and 1968 but only 10.6% of 450 Chicago isolates and 17.9% of 3969 isolates nationwide between 2000 and 2004 ($P < 0.001$). These data support the concept of rheumatogenic strains of GABHS and indicate that the marked

decrease in the incidence of acute rheumatic fever in the United States over the past four decades is correlated with the replacement of rheumatogenic types by non-rheumatogenic types in cases of acute GABHS pharyngitis in children. The reasons underlying the observed change in distribution of M types remain to be explained (Shulman 2006).

The standard duration 10 days of penicillin in treating children with acute GABHS pharyngitis is difficult to comply with. We have shown in this systematic review that a short duration (three to six days) of oral antibiotics has comparable efficacy to the standard 10-day duration of oral penicillin. The two regimes showed comparable results, including time to resolution of fever and sore throat, risk of early clinical and bacteriological treatment failure, late clinical and bacteriological recurrence and risk of complications. The short duration treatment was superior with regard to compliance. Low dose azithromycin (10 mg/kg/day) for three days was significantly inferior to standard duration treatment and other short duration treatments with regard to bacteriological eradication. There were more side effects with the short duration treatment, however, all were self-limiting and mainly mild to moderate vomiting, diarrhea or abdominal pain.

We were struck by the wide range of antibiotic regimens studied. Fourteen different antibiotic regimens were tried in the 20 studies that met our inclusion criteria. In addition, short duration treatment included regimens as brief as three days.

Our study has several limitations. Firstly, only 3 out of the 20 included studies followed the participants for a sufficient duration to be able to study the prevalence of complications of acute GABHS pharyngitis (Adam 2000a; Schaad 2002; Scholz 2004). Although these three studies had a total of 8135 participants, results were too under-powered to draw any conclusions on differences in complication rates. This means our conclusion is not applicable in low-income countries where the prevalence of rheumatic heart disease is high. Another limitation is that the primary studies were heterogeneous. They studied different antibiotics for variable durations (three to six days). Also, studies had limited quality. Finally, although the shorter antibiotic duration appeared to be effective and more convenient, it is more expensive than the standard duration 10 days of penicillin. However, one must take into account the reality of patient behavior and the price of unsuccessful or incomplete therapy.

Summary of main results

We included 20 studies with 13,102 cases of acute GABHS pharyngitis. The updated search did not identify any new eligible studies. Compared to standard duration treatment, the short duration treatment had shorter periods of fever and throat soreness and lower risk of early clinical treatment failure. There was no significant difference in early bacteriological treatment failure, or late clinical recurrence, however, the overall risk of late bacteriological recurrence was worse in the short duration treatment group, although no significant differences were found when studies of low dose azithromycin (10mg/kg) were eliminated. Three studies reported long duration complications with no statistically significant difference.

The outstanding uncertainty is in the difference of the risk of late complications. In areas where the risk of rheumatic heart disease is high, the risk may outweigh the benefit of improved convenience and compliance with short duration antibiotics.

Overall completeness and applicability of evidence

We included 20 studies with 13,102 cases of acute GABHS pharyngitis. All included studies were very relevant to the objectives of our review. The studies did not achieve enough power to make any conclusions on the comparison of complication rates of acute rheumatic fever and acute poststreptococcal glomerulonephritis.

Quality of the evidence

A significant number of studies were at high risk for selection bias, performance bias, detection bias and attrition bias. Most studies used unconcealed randomization methods and were not blinded. The majority of the results from one study to the other however, were consistent.

Potential biases in the review process

We attempted to identify every relevant trial using a rigorous search strategy. Two authors independently applied the same search methodology and resolved disagreement by consensus. Publication bias may be considered a potential threat to the validity of results.

Agreements and disagreements with other studies or reviews

In a recent Cochrane review of 27 trials, antibiotics were found to reduce sore throat symptoms by about 16 hours and protect against suppurative and non-suppurative complications (Spinks 2011). In another Cochrane review, the authors found insufficient evidence for clinically meaningful differences between antibiotics for GABHS tonsillopharyngitis (Van Driel 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Three to six days treatment with oral antibiotics has comparable efficacy to the standard duration 10 days of oral penicillin in treating children with acute GABHS pharyngitis. The shorter duration

of antibiotic treatment can be more convenient for the patient, and will improve compliance. If the clinician chooses azithromycin for three days, a dose of 20 mg/kg/day should be used rather than 10 mg/kg/day. No conclusions can be drawn on the comparison of complication rates of acute rheumatic fever and acute poststreptococcal glomerulonephritis. In areas where the prevalence of rheumatic heart disease is still high, our results must be interpreted with caution.

Implications for research

Large, international blinded randomized clinical trials with long-term follow-up for at least 12 months will be very valuable to compare the difference in complication rates between short duration and standard duration antibiotic regimes in treating children with acute GABHS pharyngitis. Evaluating the efficacy of shorter duration oral penicillin will also be very useful. The clinical and bacteriological efficacy of three to six days of newer antibiotic therapy was comparable to that of the standard 10 days of penicillin; a regimen that has a high non-compliance rate.

ACKNOWLEDGEMENTS

Special thanks to Elizabeth Dooley, Managing Editor of the Cochrane Acute Respiratory Infections Group for her support and guidance. We would also like to thank the Contact Editor Abigail Fraser and Peer Referees, Suzanne Cunliffe, Amita Jain, Itzhak Brook and Rob Ware for their valuable comments and guidance on previous drafts of this review.

REFERENCES

References to studies included in this review

Adam 1995 ***{published data only}***
Adam D, Hostalek U, Troster K, Cefixim Study Group. 5-day cefixim therapy for bacterial pharyngitis and/or tonsillitis: comparison with 10 day penicillin V therapy. *Infection* 1995;**23**(Suppl 2):83–6.

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

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

Aujard 1995 ***{published data only}***
Aujard Y, Boucot I, Brahimi N, Chiche D, Bingen E. Comparative efficacy and safety of four-day cefuroxime axetil and ten-day penicillin treatment of group A beta-hemolytic streptococcal pharyngitis in children. *Pediatric Infectious Disease Journal* 1995;**14**(4):295–300.

Cohen 1996 ***{published data only}***
Cohen R, Levy C, Doit C, De La Rocque F, Boucherat M, Fitoussi F, et al.Six-day amoxicillin vs ten-day penicillin V therapy for group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 1996;**15**(8):678–82.

Cohen 2002a ***{published data only}***
Cohen R, Reinert P, De La Rocque F, Levy C, Boucherat M, Robert M, et al.Comparison of two dosages of azithromycin for three days versus penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2002;**21**(4):297–303.

Cohen 2002b ***{published data only}***
Cohen R, Reinert P, De La Rocque F, Levy C, Boucherat M, Robert M, et al.Comparison of two dosages of azithromycin for three days versus penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2002;**21**(4):297–303.

Gerber 1987 ***{published data only}***
Gerber MA, Randolph MF, Chanatry J, Wright LL, De Meo K, Kaplan EL. Five versus ten days of penicillin V therapy for streptococcal pharyngitis. *American Journal of Diseases in Children* 1987;**141**(2):224–7.

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

Kafetzis 2004 ***{published data only}***
Kafetzis D, Liapi G, Tsolia M, Aoudi H, Mathioudakis J, Paraskakis I, et al.Failure to eradicate group A beta-hemolytic streptococci (GABHS) from the upper respiratory tract after antibiotic treatment. *International Journal of Antimicrobial Agents* 2004;**23**(1):67–71.

McCarty 2000 ***{published data only}***
McCarty J, Hedrick J, Gooch W. Clarithromycin suspension versus penicillin V suspension in children with streptococcal pharyngitis. *Advance in Therapy* 2000;**17**(1):14–26.

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

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

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

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

Pichichero 1994 *{published data only}*
Pichichero M, Gooch W, Rodriguez W, Blumer J, Aronoff S, Jacobs R, et al.Effective short-course treatment of acute group A beta hemolytic streptococcal tonsillopharyngitis. *Archives of Pediatrics and Adolesent Medicine* 1994;**148**(10): 1053–60.

Portier 2001 *{published data only}*
Portier H, Bourrillon A, Lucht F, Choutet P, Gehanno P, Meziane L, et al.Treatment of acute group A beta-hemolytic streptococcal tonsillitis in children with 5-day course of josamycine [Treatment des angines aigues a' strptocoque beta he'molytique du groupe A chez I enfant per la josamycine pendant cinq jours]. *Archives de Pediatrie* 2001;**8**:700–6.

Schaad 1996 *{published data only}*
Schaad U, Heynen G, Swiss Tonsillopharyngitis Study Group. Evaluation of the efficacy, safety and toleration of azithromycin vs penicillin V in the treatment of acute streptococcal pharyngitis in children: results of multicenter, open comparative study. *Pediatric Infectious Disease Journal* 1996;**15**(9):791–5.

Schaad 2002 *{published data only}*
Schaad U, Kellerhals P, Altwegg M, Swiss Pharyngitis Study Group. Azithromycin versus penicillin V for treatment of acute group A streptococcal pharyngitis. *Pediatric Infectious Disease Journal* 2002;**21**(4):304–8.

Scholz 2004 *{published data only}*
Scholz H. Streptococcal-A tonsillopharyngitis: a 5-day course of cefuroxime axetil versus a 10-day course of penicillin V. *Chemotherapy* 2004;**50**:51–4.

Syrogiannopoulos 2004a *{published and unpublished data}*
Syrogiannopoulos G, Bozdogan B, Grivea I, Ednie L, Kritikou D, Katopodis G, et al.Hellenic Antibiotic-Resistant Respiratory Pathogens Study Group. Two dosages of clarithromycine for five days, amoxacillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2004;**23**(9):857–65.

Syrogiannopoulos 2004b *{published data only}*
Syrogiannopoulos G. Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2004;**23**(9):857–65.

Syrogiannopoulos 2004c *{published data only}*
Syrogiannopoulos G. Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatric Infectious Disease Journal* 2004;**23**(9):857–65.

Tack 1997 *{published data only}*
Tack K, Hedrick J, Rothstien E, Nemeth MA, Keyserling C, Pichichero M, et al.A study of 5-day cefdinir treatment for streptococcal pharyngitis in children. *Archives of Pediatrics and Adolescent Medicine* 1997;**151**(1):45–9.

References to studies excluded from this review

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

Additional references

Bisno 1997
Bisno AL, Gerber MA, Gawltney JM Jr, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. Infectious Diseases Society of America. *Clinical Infectious Diseases* 1997;**25**:574–83.

Carapetis 2005
Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infectious Diseases* 2005;**5**:685–94.

Chalmers 1981
Chalmers TC, Smith H Jr, Blackburn B, Silverman B, Schroeder B, Rietman D, et al.A method for assessing the quality of a randomized clinical trial. *Controlled Clinical Trials* 1981;**2**:31–49.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kumar 2008
Kumar V, Fausto N, Abbas A. *Robbins and Cotran Pathologic Basis of Disease*. 7th Edition. Philadelphia: Elsevier, 2008.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Meade 1997
Meade MO, Richardson WS. Selecting and appraising studies for a systematic review. *Annals of Internal Medicine* 1997;**127**:531–7.

Nandi 2001
Nandi S, Kumar R, Ray P, Vohra H, Ganguly N. Group A streptococcal sore throat in a periurban population of northern India: a one-year prospective study. *Bulletin of the World Health Organization* 2001;**79**(6):528–33.

Olivier 2000
Olivier C. Rheumatic fever: is it still a problem?. *Journal of Antimicrobial Chemotherapy* 2000;**45**:13–21.

Shulman 2006
Shulman ST, Stollerman G, Beall B, Dale JB, Tanz RR. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. *Clinical Infectious Diseases* 2006;**15**:441–7.

Spinks 2011
Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD000023.pub3]

Thornton 2000
Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *Journal of Clinical Epidemiology* 2000;**53**:207–16.

Van Driel 2010
Van Driel ML, De Sutter AI, Keber N, Habraken H, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD004406.pub2]

References to other published versions of this review

Altamimi 2009
Altamimi S, Khalil A, Khalaiwi KA, Milner R, Pusic MV, Al Othman MA. Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004872.pub2]

Altamimi 2010
Altamimi S, Khalil A, Khalaiwi KA, Milner R, Pusic M, Al Othman MA. Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. *Sao Paulo Medical Journal* 2010;**128**(1):48.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adam 1995

Methods	Open, controlled, randomized, multicenter trial
Participants	160 participants aged from 1 to 12 years; mean age 5.5 years
Interventions	1. Penicillin V 20,000 IU/kg tid for 10 days 2. Cefixime 8 mg/kg od for 5 days
Outcomes	Clinical and bacteriological efficacy of study drugs. Secondary outcome was study medication safety and tolerability
Notes	Early follow-up: 1 to 5 days after the end of therapy Late follow-up: 3 to 4 weeks after end of therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Based on computer-generated number"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Adam 1996

Methods	Multicenter, randomized, open-label, controlled study
Participants	227 participants aged from 1 to 17 years; mean age 7.1 years. 103 males; 98 females
Interventions	1. Penicillin V 50,000 IU/kg (30 mg/kg) max. 2,225,000 IU tid for 10 days 2. Erythromycin estolate 40 mg/kg max. 1800 mg bid for 5 days
Outcomes	Clinical and bacteriological efficacy of study drugs
Notes	Early follow-up: 1 to 3 days after the end of therapy Late follow-up: 6 +/- 2 weeks after the end of therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"according to a computer generated list to receive either"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding or incomplete blinding and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Adam 2000a

Methods	Multicenter, randomized, open-label, controlled study
Participants	4782 participants aged 1 to 18 years; mean 6.1 years. Male/female 50.3%/49.7%. Weight 24.4 kg (9.2 to 79)

Adam 2000a (*Continued*)

Interventions	1. Penicillin V 50,000 IU/kg/day (max. 2,250,000 IU) tid for 10 days 2. One of six antibiotics for 5 days: • Amoxicillin/clavulanate 37.5 mg/kg/day (max. 1875 mg/day) tid • Ceftibuten 9 mg/kg/day (max. 400 mg/day) od • Cefuroxime axetil 20 mg/kg/day (max. 500 mg/day) bid • Loracarbef 15 mg/kg/day (max. 400 mg/day) bid • Clarithromycin 15 mg/kg/day (max. 500 mg/day) bid • Erythromycin estolate 40 mg/kg/day (max. 1600 mg/day) bid
Outcomes	Clinical and bacteriological efficacy of study drugs. And incidence of poststreptococcal sequelae (rheumatic fever, acute glomerulonephritis)
Notes	Early follow-up: 7 to 9 days after end of treatment Late follow-up: 7 to 8 weeks, 6 months, 12 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Referred to a random number table
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Aujard 1995

Methods	Prospective, randomized, multicenter study
Participants	308 children aged 2 to 15 years; mean age 6.9 years. 92 males; 108 females
Interventions	1. Penicillin V 45 mg/kg/day, 3 divided doses for 10 days 2. Cefuroxime axetil 20 mg/kg/dose bid for 4 days
Outcomes	Primary outcome was eradication of GABHS from throat culture obtained at the end of treatment examination. Clinical outcome (success or failure). The time taken for resolution of symptoms and safety analysis (side effects of each medication)
Notes	Early follow-up: 2 to 4 days after completion of therapy Late follow-up: 28 to 32 days after completion of therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"according to computer-generated lists"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Cohen 1996

Methods	Prospective, comparative, open, randomized multicenter trial
Participants	321 patients aged 3 to 15 years; mean age 5.9. 153 males; 165 females
Interventions	1. Penicillin V 15 mg/kg/day tds for 10 days 2. Amoxicillin 25 mg/ kg/dose bid for 6 days
Outcomes	Compare the clinical and bacteriological efficacy and safety of amoxicillin and penicillin V in children with group A streptococcal tonsillopharyngitis
Notes	Early follow-up: 4 days after completion of therapy Late follow-up: 1 month after completion of therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"were assigned by means of a centralized telephonic computer program"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding or incomplete blinding and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers of reasons for missing data across intervention groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Cohen 2002a

Methods	Prospective, comparative, randomized, multicenter trial
Participants	336 children aged 2 to 12 years; mean age 6 years. 181 males; 155 females
Interventions	1. Penicillin 15 mg/kg/dose tds for 10 days 2. Azithromycin 10 mg/kg/day od for 3 days
Outcomes	The efficacy and tolerability of azithromycin compared with penicillin V
Notes	Early follow-up: on day 14 +/- 2 of the study Late follow-up: on day 30 +/- 4 of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"assigned by means of a centralized telephonic computer program"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding or incomplete blinding and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Cohen 2002b

Methods	Prospective, comparative, randomized, multicenter trial
Participants	332 children aged 2 to 12 years. 175 males; 165 females
Interventions	1. Penicillin 15 mg/kg/dose tds for 10 days 2. Azithromycin 20 mg/kg/day od for 3 days

Cohen 2002b (*Continued*)

Outcomes	The efficacy and tolerability of azithromycin compared with penicillin V
Notes	Early follow-up day 14 +/- 2 of the study Late follow-up on day 30 +/- 4 of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"assigned by means of a centralized telephonic computer program"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding or incomplete blinding and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Gerber 1987

Methods	Prospective, randomized, controlled study
Participants	210 children aged 3 to 25 years; mean age 9.8 years
Interventions	1. Penicillin V 250 mg/kg/dose tds for 10 days 2. Penicillin V 250 mg/kg/dose tds for 5 days
Outcomes	Assess the clinical and bacteriological efficacy and compliance
Notes	Early follow-up: 4 to 6 days following the completion of antibiotic therapy Late follow-up: 2 to 3 weeks after completion of antibiotics

Gerber 1987 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Hamill 1993

Methods	Prospective, randomized, multicenter study
Participants	96 children aged 2 to 12 years; mean age 7.4 years. 51 males; 45 females
Interventions	1. Penicillin V 125 or 250 mg qds for 10 days 2. Azithromycin 10 mg/kg once a day for 3 days
Outcomes	Assess clinical and bacteriological efficacy and safety
Notes	Early follow-up: at days 2 to 3 and 9 to 11 of the study Late follow-up: at day 29 to 31 of the study

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not described

Hamill 1993 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Kafetzis 2004

Methods	Prospective, open-label, comparative, randomized study
Participants	179 children aged 3 to 13 years; mean age 6 years. 107 males; 72 females
Interventions	1. Penicillin V 50 mg/kg/day (800,000 IU/kg/day; max 1.2 million units/day) tds for 10 days 2. Cefprozil 30 mg/kg/day; max 500 mg/day bid for 5 days
Outcomes	Assess the difference in clinical and bacteriological efficacy, compliance and safety of study medication
Notes	Early follow-up: at day 12 to 15 of the study Late follow-up: at day 28 to 30 of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"assigned by means of a computer randomized number"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded

Kafetzis 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

McCarty 2000

Methods	Randomized, comparative, multicenter study
Participants	528 children aged 6 months to 12 years; mean age 90 months. 289 males; 239 females
Interventions	1. Penicillin V 13.3 mg/kg tid for 10 days 2. Clarithromycin 7.5 mg bid for 5 days
Outcomes	Evaluate clinical and bacteriological efficacy, compliance and safety
Notes	Early follow-up: at 1 to 4 days after completion of the antibiotic duration Late follow-up: at 28 to 32 days after completion of the antibiotic duration

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

McCarty 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Milatovic 1991

Methods	Randomized study
Participants	209 children
Interventions	1. Penicillin V for 10 days 2. Cefadroxil for 5 days
Outcomes	Bacteriological efficacy only
Notes	Early follow-up: at day 3 to 5 of antibiotic treatment Late follow-up: at days 11 to 15 and 21 to 35 after completion of antibiotic treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of recruited participants not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Milatovic 1991 (*Continued*)

Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

O'Doherty 1996a

Methods	Randomized, double-blind study	
Participants	489 children aged 2 to 13 years; mean age 7.7 years. 236 males; 253 females	
Interventions	1. Penicillin V 125 to 250 mg qds for 10 days 2. Azithromycin 10 mg/kg od for 3 days	
Outcomes	Assess clinical and bacteriological response at the end of therapy (12 to 14 days) and late (28 to 30 days). Assess treatment-related side effects in each treatment group	
Notes	Early follow-up: 2 to 4 days after completion of antibiotics Late follow-up: 28 to 30 days after completion of antibiotics	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk'; or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

O'Doherty 1996b

Methods	Randomized, double-blind study
Participants	489 children aged 2 to 13 years, mean age 7.7 years. 236 males; 253 females
Interventions	1. Penicillin V 125 to 250 mg qds for 10 days 2. Azithromycin 20 mg/kg od for 3 days
Outcomes	Assess clinical and bacteriological response at the end of therapy (12 to 14 days) and late (28 to 30 days). Assess treatment-related side effects in each treatment group
Notes	Early follow-up: 2 to 4 days after completion of antibiotics Late follow-up: 28 to 30 days after completion of antibiotics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk'; or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Pacifico 1996

Methods	Prospective, randomized, open study
Participants	183 children aged 3 to 12 years. 75 males; 79 females
Interventions	1. Penicillin V 50,000 IU in 2 divided doses for 10 days 2. Azithromycin 10 mg/kg/day od for 3 days

Pacifico 1996 (*Continued*)

Outcomes	Assess clinical and microbiological efficacy and safety	
Notes	Follow-up: at baseline, day 4 to 5, day 12 to 14 and day 34 to 36	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"according to computer generated randomised schedule"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Pichichero 1994

Methods	Prospective, randomized, observer-blind, multicenter study
Participants	484 children aged 2 to 17 years; mean age 8 years
Interventions	1. Penicillin V 40 mg/kg/day for 10 days 2. Cefpodoxime proxetil 10 mg/kg/day bid for 5 days 3. Cefpodoxime proxetil 10 mg/kg/day od for 10 days
Outcomes	Assess bacteriological and clinical effect and safety
Notes	Follow-up visit day 3 to 5, day 9 to 12, day 14 to 17, day 32 to 38
Risk of bias	

Pichichero 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"this was an investigation blinded study"
Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Portier 2001

Methods	Randomized, open study
Participants	325 children aged 2 to 15 years
Interventions	1. Penicillin 50,000 to 100,000 IU tid for 10 days 2. Josamycin 50 mg/kg/day bid for 5 days
Outcomes	Clinical and microbiological response and tolerance assessment
Notes	Follow-up visit: at the end of treatment, day 12, day 30

Risk of bias

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

Portier 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Schaad 1996

Methods	Open, comparative, multicenter study
Participants	343 children aged 6 months to 14 years; mean age 7 years. 171 males; 172 females
Interventions	1. Penicillin V 100,000 IU = 56 mg/kg tid for 10 days 2. Azithromycin 10 mg/kg od for 3 days
Outcomes	Clinical and microbiological response and tolerability
Notes	Follow-up 10 to 14 and 20 to 30 days after the start of treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomizations table"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

Schaad 1996 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Not mentioned
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Schaad 2002

Methods	Multicenter, randomized, comparative, open-label study
Participants	292 children aged 2 to 12 years
Interventions	1. Penicillin V 100,000 IU/kg/day tid for 10 days 2. Azithromycin 10 mg/kg/day od for 3 days
Outcomes	Clinical and microbiological efficacy, antibiotic tolerance and adverse events
Notes	Follow-up at study days 14 and 28

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"grading by laboratory personnel who were blinded regarding the patient therapy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results in-

		cluded all expected outcomes, particularly those that were mentioned in the methods section

Scholz 2004

Methods	Multicenter, randomized, open-label, comparative study
Participants	1975 children aged 1 to 17 years
Interventions	1. Penicillin V 50,000 IU/kg/day (30 mg/kg) tid for 10 days 2. Cefuroxime axetil 20 mg/kg/day (max 500 mg) bid for 5 days
Outcomes	Clinical and bacteriological efficacy, safety and tolerance
Notes	Follow-up: Day 7 to 9 and 12 to 14 in short duration group Day 12 to 14 and 17 to 19 in control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Syrogiannopoulos 2004a

Methods	Multicenter, randomized, comparative, open-label study
Participants	316 children aged 2 to 15 years
Interventions	1. Penicillin V 30 mg/kg/day tid for 10 days 2. Clarithromycin 30 mg/kg/day in 2 divided doses (max. 500 mg/dose) for 5 days
Outcomes	Clinical and bacteriological efficacy and safety
Notes	Follow-up: day 4 to 8 and 21 to 28 after completion of therapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Syrogiannopoulos 2004b

Methods	Multicenter, randomized, comparative, open-label study
Participants	313 children aged 1 to 17 years
Interventions	1. Penicillin V 30 mg/kg/day in 3 divided doses for 10 days 2. Clarithromycin 15 mg/kg/day bid (max. 250 mg/bid) for 5 days
Outcomes	Clinical and bacteriological efficacy and safety

Syrogiannopoulos 2004b (*Continued*)

Notes	Follow-up:day 4 to 8 and 21 to 28 after completion of therapy	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Syrogiannopoulos 2004c

Methods	Multicenter, randomized, comparative, open-label study	
Participants	313 children aged 1 to 17 years	
Interventions	1. Penicillin V 30 mg/kg/day tid for 10 days 2. Amoxicillin/clavulanate (43.8/6.2 mg/kg/day) bid (max. 1 g bid) for 5 days	
Outcomes	Clinical and bacteriological efficacy and safety	
Notes	Follow-up: day 4 to 8 and 21 to 28 after completion of therapy	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Syrogiannopoulos 2004c (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

Tack 1997

Methods	Investigator-blinded, RCT
Participants	482 children aged 1 to 12 years; median 7.7 years. 250 males; 232 females
Interventions	1. Penicillin V 10 mg/kg qds for 10 days 2. Cefdinir 7 mg/kg bid for 5 days
Outcomes	Clinical and microbiological efficacy, antibiotic
Notes	Early follow-up: 5 to 10 days after completing the duration of antibiotics Late follow-up: study day 25 to 30

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Referring to a random number table
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded

Tack 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"central lab had no knowledge of assigned prescription"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Allocation concealment (selection bias)	High risk	Open-label
Selective reporting (reporting bias)	Low risk	The study protocol was not available but it was clear that the published results included all expected outcomes, particularly those that were mentioned in the methods section

bid: twice a day
g: gram
GABHS: group A beta hemolytic streptococcus
IU: international unit
kg: kilogram
mg: milligram
od: daily
qds: four times a day
RCT: randomized controlled trial
tid: three times a day
tds: three times a day

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

Study	Reason for exclusion
Adam 2000b	Replication of part of the data published in a larger study (Adam 2000a) which is included in the review

DATA AND ANALYSES

Comparison 1. Duration of clinical symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of fever	2	348	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.45, -0.14]
2 Duration of sore throat	1	188	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-0.78, -0.22]

Comparison 2. Clinical efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early clinical treatment failure	23	11713	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.67, 0.94]
1.1 Azithromycin 10 mg/kg (short) versus penicillin (standard)	6	1366	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.66, 1.66]
1.2 Azithromycin 20 mg/kg (short) versus penicillin (standard)	2	520	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.64]
1.3 Clarithromycin (short) versus penicillin (standard)	3	1024	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.55, 1.86]
1.4 Cefuroxime (short) versus penicillin (standard)	2	2152	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.81]
1.5 Others	10	6651	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.06]
2 Late clinical recurrence	17	8068	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.08]
2.1 Azithromycin 10mg/kg (short) versus penicillin (standard)	4	869	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.93, 2.83]
2.2 Azithromycin 20mg/kg (short) versus penicillin (standard)	2	465	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.42, 2.09]
2.3 Clarithromycin (short) versus penicillin (standard)	3	932	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.84, 1.88]
2.4 Cefuroxime (short) versus penicillin (standard)	1	158	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.48, 8.95]
2.5 Others	7	5644	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.01]

Comparison 3. Bacteriological efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early bacteriological treatment failure	23	11555	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.97, 1.20]
1.1 Azithromycin 10 mg/kg (short) versus penicillin (standard)	6	1354	Odds Ratio (M-H, Fixed, 95% CI)	3.25 [2.47, 4.27]
1.2 Azithromycin 20 mg/kg (short) versus penicillin (standard)	2	520	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.14, 0.61]
1.3 Clarithromycin (short) versus penicillin (standard)	3	1034	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.98, 1.77]
1.4 Cefuroxime (short) versus penicillin (standard)	2	2111	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.87]
1.5 Others	10	6536	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.05]
2 Late bacteriological recurrence	24	10249	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [1.16, 1.48]
2.1 Azithromycin 10 mg/kg (short) versus penicillin (standard)	6	1085	Odds Ratio (M-H, Fixed, 95% CI)	3.62 [2.66, 4.92]
2.2 Azithromycin 20 mg/kg (short) versus penicillin (standard)	2	437	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.55, 1.96]
2.3 Clarithromycin (short) versus penicillin (standard)	3	890	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [1.12, 2.09]
2.4 Cefuroxime (short) versus penicillin (standard)	2	1858	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.57, 1.11]
2.5 Others	11	5979	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.85, 1.23]

Comparison 4. Side effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Side effects	21	7997	Odds Ratio (M-H, Fixed, 95% CI)	1.85 [1.55, 2.21]
1.1 Azithromycin 10 mg/kg (short) versus penicillin (standard)	6	1538	Odds Ratio (M-H, Fixed, 95% CI)	2.20 [1.49, 3.24]
1.2 Azithromycin 20 mg/kg (short) versus penicillin (standard)	2	653	Odds Ratio (M-H, Fixed, 95% CI)	5.13 [2.76, 9.54]
1.3 Clarithromycin (short) versus penicillin (standard)	3	1157	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.22, 2.58]
1.4 Cefuroxime (short) versus penicillin (standard)	2	2331	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.97, 3.62]
1.5 Others	8	2318	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.95, 1.72]

Comparison 5. Compliance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-compliance	6	1909	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.16, 0.29]

Comparison 6. Complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications	3	8135	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.17, 1.64]

Analysis 1.1. Comparison 1 Duration of clinical symptoms, Outcome 1 Duration of fever.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 1 Duration of clinical symptoms

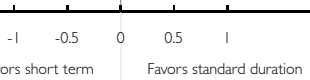
Outcome: 1 Duration of fever

Study or subgroup	Short term N	Mean(SD)	Standard duration N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Aujard 1995	78	2.04 (0.85)	91	2.38 (1.17)		26.5 %	-0.34 [-0.65, -0.03]
Kafetzis 2004	88	2.82 (0.52)	91	3.1 (0.72)		73.5 %	-0.28 [-0.46, -0.10]
Total (95% CI)	**166**		**182**			**100.0 %**	**-0.30 [-0.45, -0.14]**

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² =0.0%

Test for overall effect: Z = 3.69 (P = 0.00023)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Duration of clinical symptoms, Outcome 2 Duration of sore throat.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 1 Duration of clinical symptoms

Outcome: 2 Duration of sore throat

Study or subgroup	Short term N	Mean(SD)	Standard duration N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Aujard 1995	88	2.19 (0.81)	100	2.69 (1.13)		100.0 %	-0.50 [-0.78, -0.22]
Total (95% CI)	**88**		**100**			**100.0 %**	**-0.50 [-0.78, -0.22]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.52 (P = 0.00044)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Clinical efficacy, Outcome 1 Early clinical treatment failure.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 2 Clinical efficacy

Outcome: 1 Early clinical treatment failure

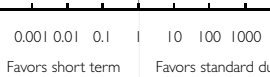
Study or subgroup	Short duration n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Azithromycin 10 mg/kg (short) versus penicillin (standard)					
Cohen 2002a	8/135	8/146		2.4 %	1.09 [0.40, 2.98]
Hamill 1993	1/41	0/44		0.2 %	3.30 [0.13, 83.23]
O'Doherty 1996a	1/123	4/132		1.3 %	0.26 [0.03, 2.38]
Pacifico 1996	11/76	5/78		1.4 %	2.47 [0.82, 7.49]
Schaad 1996	11/160	17/160		5.2 %	0.62 [0.28, 1.37]
Schaad 2002	7/141	4/130		1.3 %	1.65 [0.47, 5.76]
Subtotal (95% CI)	**676**	**690**		**11.6 %**	**1.05 [0.66, 1.66]**

Total events: 39 (Short duration), 38 (Standard duration)

(*Continued* . . .)

(. . . *Continued*)

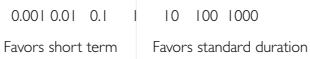
Study or subgroup	Short duration n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 6.48, df = 5 (P = 0.26); I² =23%					
Test for overall effect: Z = 0.19 (P = 0.85)					
2 Azithromycin 20 mg/kg (short) versus penicillin (standard)					
Cohen 2002b	0/139	8/146		2.7 %	0.06 [0.00, 1.02]
O'Doherty 1996b	0/103	4/132		1.3 %	0.14 [0.01, 2.59]
Subtotal (95% CI)	**242**	**278**		**4.0 %**	**0.08 [0.01, 0.64]**
Total events: 0 (Short duration), 12 (Standard duration)					
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² =0.0%					
Test for overall effect: Z = 2.39 (P = 0.017)					
3 Clarithromycin (short) versus penicillin (standard)					
McCarty 2000	8/252	15/235		4.9 %	0.48 [0.20, 1.16]
Syrogiannopoulos 2004a	6/135	3/135		0.9 %	2.05 [0.50, 8.36]
Syrogiannopoulos 2004b	8/132	3/135		0.9 %	2.84 [0.74, 10.94]
Subtotal (95% CI)	**519**	**505**		**6.8 %**	**1.02 [0.55, 1.86]**
Total events: 22 (Short duration), 21 (Standard duration)					
Heterogeneity: Chi² = 5.97, df = 2 (P = 0.05); I² =67%					
Test for overall effect: Z = 0.05 (P = 0.96)					
4 Cefuroxime (short) versus penicillin (standard)					
Aujard 1995	5/97	4/103		1.2 %	1.35 [0.35, 5.16]
Scholz 2004	15/496	99/1456		15.9 %	0.43 [0.25, 0.74]
Subtotal (95% CI)	**593**	**1559**		**17.1 %**	**0.49 [0.30, 0.81]**
Total events: 20 (Short duration), 103 (Standard duration)					
Heterogeneity: Chi² = 2.40, df = 1 (P = 0.12); I² =58%					
Test for overall effect: Z = 2.79 (P = 0.0053)					
5 Others					
Adam 1995	3/75	2/76		0.6 %	1.54 [0.25, 9.50]
Adam 1996	2/102	2/99		0.7 %	0.97 [0.13, 7.02]
Adam 2000a	167/3028	93/1412		39.2 %	0.83 [0.64, 1.08]
Cohen 1996	13/141	15/136		4.5 %	0.82 [0.37, 1.79]
Gerber 1987	6/99	6/73		2.1 %	0.72 [0.22, 2.33]
Kafetzis 2004	1/88	1/91		0.3 %	1.03 [0.06, 16.80]
Pichichero 1994	9/161	12/163		3.7 %	0.75 [0.31, 1.82]
Portier 2001	11/114	7/83		2.4 %	1.16 [0.43, 3.13]
Syrogiannopoulos 2004c	4/135	3/135		1.0 %	1.34 [0.29, 6.12]
Tack 1997	19/224	20/216		6.1 %	0.91 [0.47, 1.75]
Subtotal (95% CI)	**4167**	**2484**		**60.5 %**	**0.86 [0.70, 1.06]**
Total events: 235 (Short duration), 161 (Standard duration)					
Heterogeneity: Chi² = 1.42, df = 9 (P = 1.00); I² =0.0%					



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Short duration n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.43 (P = 0.15)					
Total (95% CI)	**6197**	**5516**		**100.0 %**	**0.80 [0.67, 0.94]**
Total events: 316 (Short duration), 335 (Standard duration)					
Heterogeneity: Chi^2 = 26.06, df = 22 (P = 0.25); I^2 =16%					
Test for overall effect: Z = 2.66 (P = 0.0078)					
Test for subgroup differences: Chi^2 = 10.58, df = 4 (P = 0.03), I^2 =62%					



Analysis 2.2. Comparison 2 Clinical efficacy, Outcome 2 Late clinical recurrence.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 2 Clinical efficacy

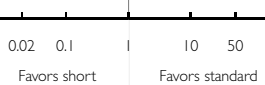
Outcome: 2 Late clinical recurrence

Study or subgroup	Short duration n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Azithromycin 10mg/kg (short) versus penicillin (standard)					
Cohen 2002a	12/118	11/130		2.1 %	1.22 [0.52, 2.89]
O'Doherty 1996a	5/106	2/108		0.4 %	2.62 [0.50, 13.83]
Pacifico 1996	8/65	2/73		0.4 %	4.98 [1.02, 24.39]
Schaad 2002	8/139	7/130		1.5 %	1.07 [0.38, 3.05]
Subtotal (95% CI)	**428**	**441**		**4.3 %**	**1.62 [0.93, 2.83]**
Total events: 33 (Short duration), 22 (Standard duration)					
Heterogeneity: Chi^2 = 3.25, df = 3 (P = 0.35); I^2 =8%					
Test for overall effect: Z = 1.70 (P = 0.090)					
2 Azithromycin 20mg/kg (short) versus penicillin (standard)					
Cohen 2002b	7/134	11/130		2.3 %	0.60 [0.22, 1.59]
O'Doherty 1996b	5/93	2/108		0.4 %	3.01 [0.57, 15.90]
Subtotal (95% CI)	**227**	**238**		**2.7 %**	**0.94 [0.42, 2.09]**
Total events: 12 (Short duration), 13 (Standard duration)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Short duration n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 2.71, df = 1 (P = 0.10); I² =63%					
Test for overall effect: Z = 0.15 (P = 0.88)					
3 Clarithromycin (short) versus penicillin (standard)					
McCarty 2000	43/231	37/211		6.9 %	1.08 [0.66, 1.75]
Syrogiannopoulos 2004a	7/125	6/124		1.2 %	1.17 [0.38, 3.58]
Syrogiannopoulos 2004b	13/117	6/124		1.1 %	2.46 [0.90, 6.70]
Subtotal (95% CI)	**473**	**459**		**9.3 %**	**1.26 [0.84, 1.88]**
Total events: 63 (Short duration), 49 (Standard duration)					
Heterogeneity: Chi² = 2.13, df = 2 (P = 0.34); I² =6%					
Test for overall effect: Z = 1.11 (P = 0.27)					
4 Cefuroxime (short) versus penicillin (standard)					
Aujard 1995	5/72	3/86		0.6 %	2.06 [0.48, 8.95]
Subtotal (95% CI)	**72**	**86**		**0.6 %**	**2.06 [0.48, 8.95]**
Total events: 5 (Short duration), 3 (Standard duration)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
5 Others					
Adam 1995	6/75	8/76		1.6 %	0.74 [0.24, 2.24]
Adam 1996	10/102	6/99		1.2 %	1.68 [0.59, 4.83]
Adam 2000a	565/3052	305/1430		74.2 %	0.84 [0.72, 0.98]
Cohen 1996	9/111	6/105		1.2 %	1.46 [0.50, 4.24]
Kafetzis 2004	11/88	14/91		2.6 %	0.79 [0.34, 1.84]
Portier 2001	7/83	5/78		1.0 %	1.34 [0.41, 4.43]
Syrogiannopoulos 2004c	8/130	6/124		1.3 %	1.29 [0.43, 3.83]
Subtotal (95% CI)	**3641**	**2003**		**83.1 %**	**0.87 [0.75, 1.01]**
Total events: 616 (Short duration), 350 (Standard duration)					
Heterogeneity: Chi² = 3.78, df = 6 (P = 0.71); I² =0.0%					
Test for overall effect: Z = 1.88 (P = 0.060)					
Total (95% CI)	**4841**	**3227**		**100.0 %**	**0.95 [0.83, 1.08]**
Total events: 729 (Short duration), 437 (Standard duration)					
Heterogeneity: Chi² = 18.86, df = 16 (P = 0.28); I² =15%					
Test for overall effect: Z = 0.83 (P = 0.41)					
Test for subgroup differences: Chi² = 7.86, df = 4 (P = 0.10), I² =49%					

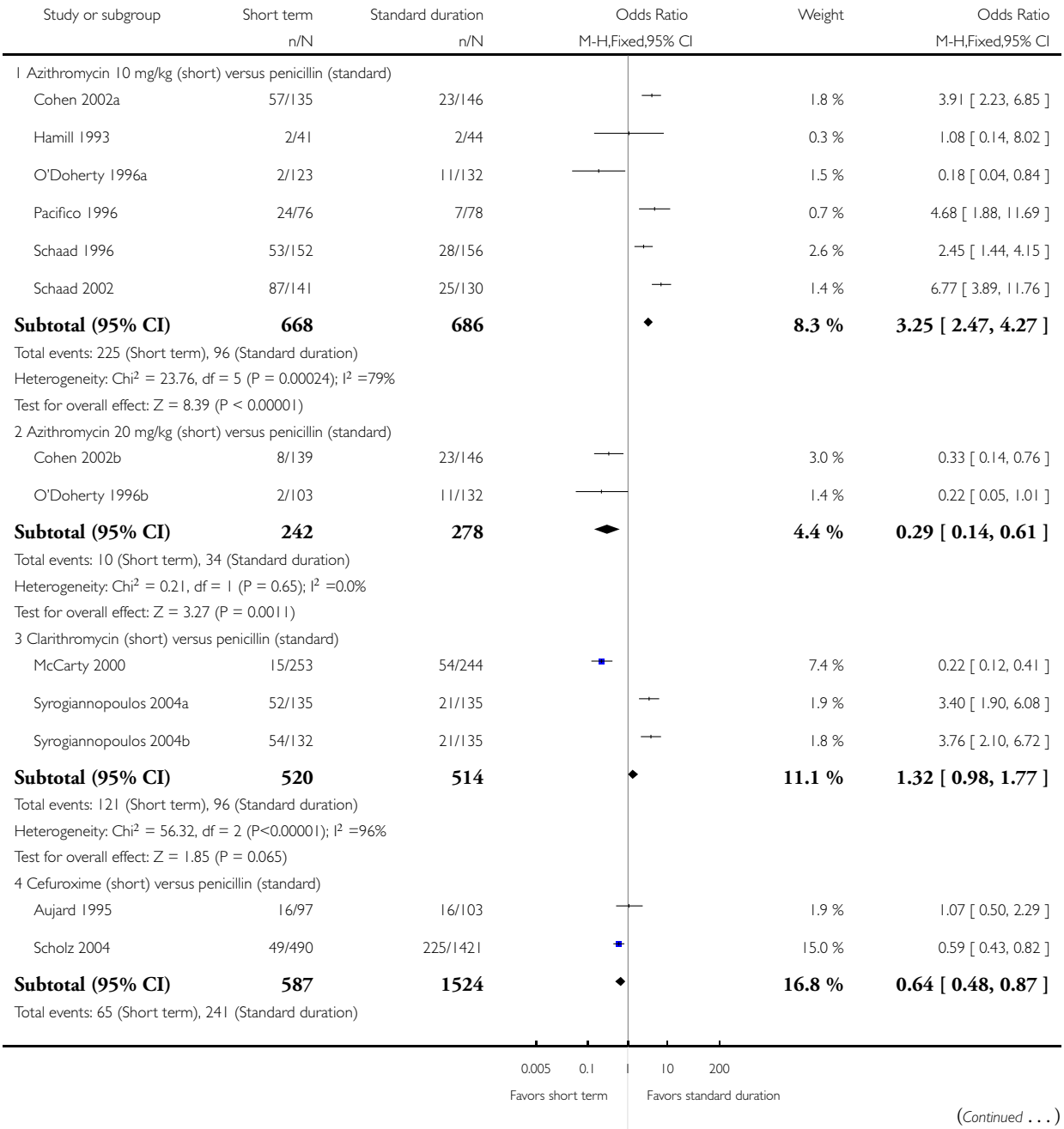


Analysis 3.1. Comparison 3 Bacteriological efficacy, Outcome 1 Early bacteriological treatment failure.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 3 Bacteriological efficacy

Outcome: 1 Early bacteriological treatment failure



(*Continued . . .*)

(. . . *Continued*)

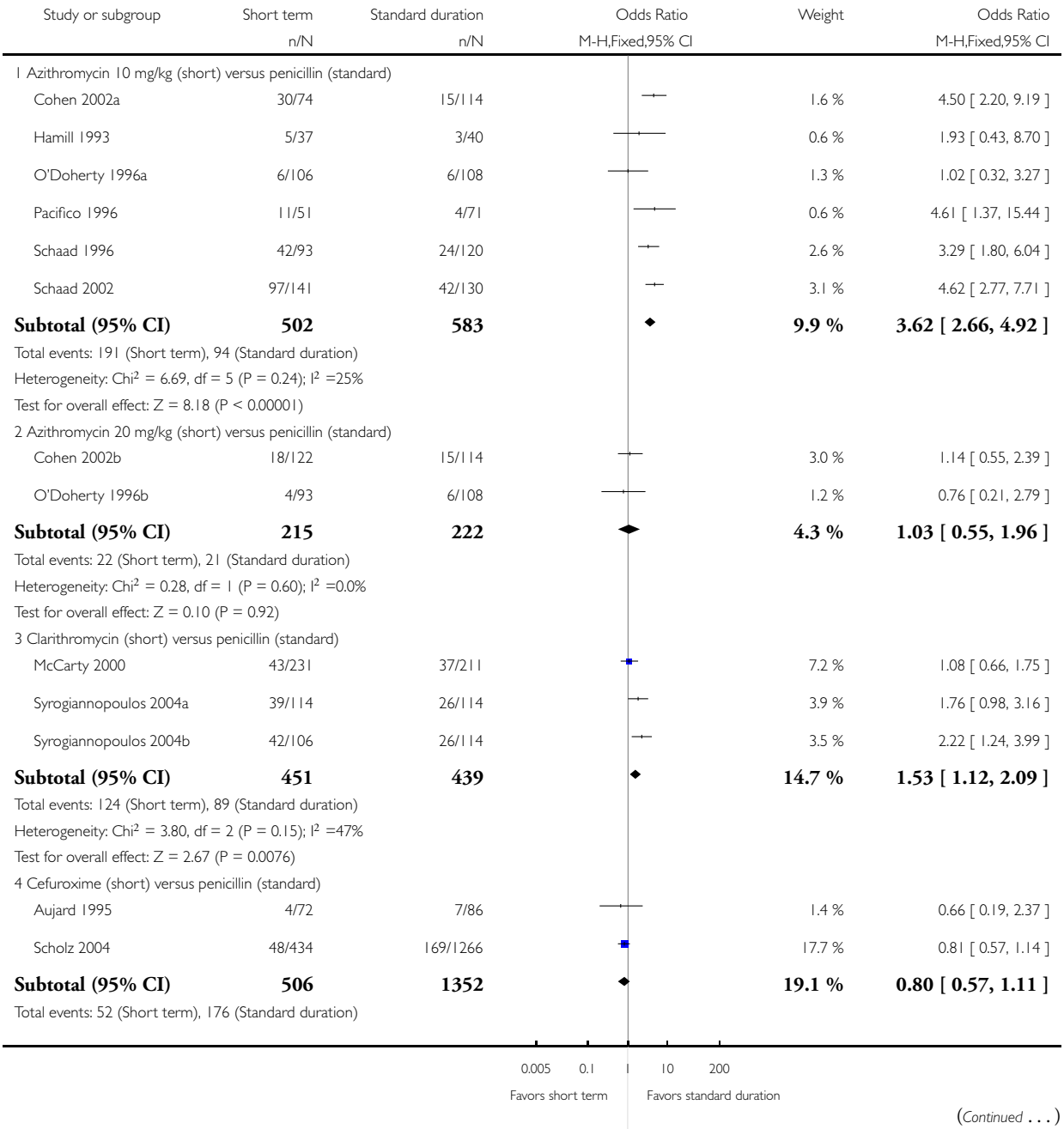
Study or subgroup	Short term n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 2.03, df = 1 (P = 0.15); I² =51%					
Test for overall effect: Z = 2.89 (P = 0.0038)					
5 Others					
Adam 1995	12/69	8/68		1.0 %	1.58 [0.60, 4.15]
Adam 1996	17/102	12/99		1.5 %	1.45 [0.65, 3.22]
Adam 2000a	501/3002	215/1380		35.3 %	1.09 [0.91, 1.29]
Cohen 1996	23/141	20/136		2.5 %	1.13 [0.59, 2.17]
Gerber 1987	6/73	7/99		0.8 %	1.18 [0.38, 3.66]
Kafetzis 2004	2/88	12/91		1.7 %	0.15 [0.03, 0.71]
Pichichero 1994	11/126	27/130		3.5 %	0.36 [0.17, 0.77]
Portier 2001	20/113	22/109		2.7 %	0.85 [0.43, 1.67]
Syrogiannopoulos 2004c	20/135	21/135		2.6 %	0.94 [0.49, 1.84]
Tack 1997	23/224	61/216		8.0 %	0.29 [0.17, 0.49]
Subtotal (95% CI)	**4073**	**2463**		**59.4 %**	**0.91 [0.79, 1.05]**
Total events: 635 (Short term), 405 (Standard duration)					
Heterogeneity: Chi² = 36.33, df = 9 (P = 0.00003); I² =75%					
Test for overall effect: Z = 1.28 (P = 0.20)					
Total (95% CI)	**6090**	**5465**		**100.0 %**	**1.08 [0.97, 1.20]**
Total events: 1056 (Short term), 872 (Standard duration)					
Heterogeneity: Chi² = 211.35, df = 22 (P<0.00001); I² =90%					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: Chi² = 92.55, df = 4 (P = 0.00), I² =96%					

Analysis 3.2. Comparison 3 Bacteriological efficacy, Outcome 2 Late bacteriological recurrence.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 3 Bacteriological efficacy

Outcome: 2 Late bacteriological recurrence



(*Continued . . .*)

(. . . *Continued*)

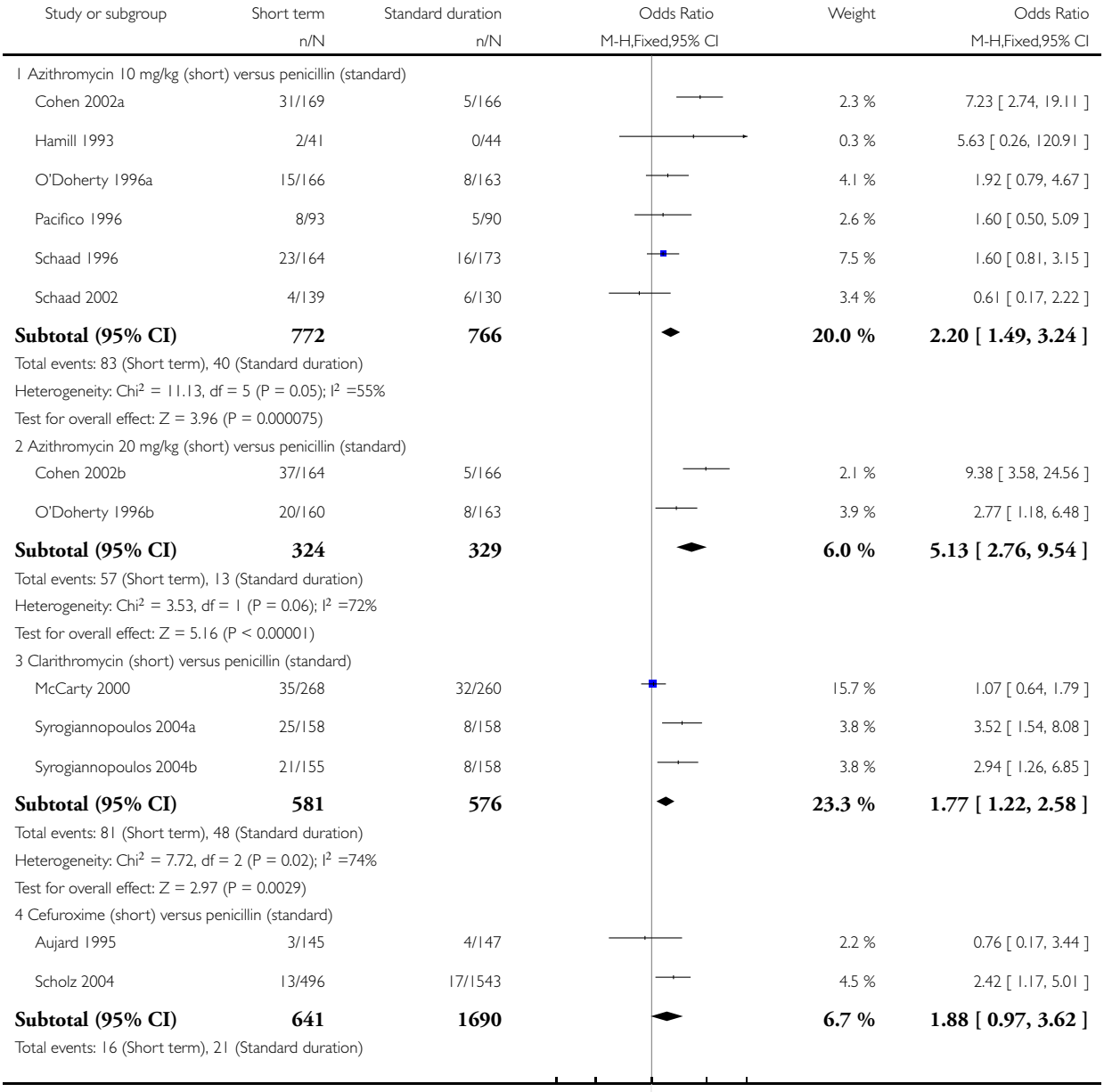
Study or subgroup	Short term n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² =0.0%					
Test for overall effect: Z = 1.35 (P = 0.18)					
5 Others					
Adam 1995	6/75	8/76		1.7 %	0.74 [0.24, 2.24]
Adam 1996	25/102	24/99		4.2 %	1.01 [0.53, 1.93]
Adam 2000a	208/2667	83/1229		24.1 %	1.17 [0.90, 1.52]
Cohen 1996	11/111	6/105		1.3 %	1.82 [0.65, 5.10]
Gerber 1987	14/73	8/99		1.3 %	2.70 [1.07, 6.83]
Kafetzis 2004	7/88	23/91		4.8 %	0.26 [0.10, 0.63]
Milatovic 1991	16/104	16/105		3.1 %	1.01 [0.48, 2.15]
Pichichero 1994	13/126	18/130		3.7 %	0.72 [0.33, 1.53]
Portier 2001	10/83	10/78		2.1 %	0.93 [0.37, 2.38]
Syrogiannopoulos 2004c	21/123	26/114		5.2 %	0.70 [0.37, 1.32]
Tack 1997	7/171	3/130		0.8 %	1.81 [0.46, 7.13]
Subtotal (95% CI)	**3723**	**2256**		**52.1 %**	**1.02 [0.85, 1.23]**
Total events: 338 (Short term), 225 (Standard duration)					
Heterogeneity: Chi² = 18.62, df = 10 (P = 0.05); I² =46%					
Test for overall effect: Z = 0.24 (P = 0.81)					
Total (95% CI)	**5397**	**4852**		**100.0 %**	**1.31 [1.16, 1.48]**
Total events: 727 (Short term), 605 (Standard duration)					
Heterogeneity: Chi² = 87.52, df = 23 (P<0.00001); I² =74%					
Test for overall effect: Z = 4.26 (P = 0.000020)					
Test for subgroup differences: Chi² = 58.98, df = 4 (P = 0.00), I² =93%					

Analysis 4.1. Comparison 4 Side effects, Outcome 1 Side effects.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 4 Side effects

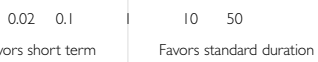
Outcome: 1 Side effects



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Short term n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² =46%					
Test for overall effect: Z = 1.87 (P = 0.061)					
5 Others					
Adam 1995	5/75	6/76		3.1 %	0.83 [0.24, 2.86]
Adam 1996	10/115	8/112		4.1 %	1.24 [0.47, 3.26]
Cohen 1996	4/160	8/158		4.4 %	0.48 [0.14, 1.63]
Kafetzis 2004	4/88	3/91		1.6 %	1.40 [0.30, 6.43]
Pichichero 1994	11/161	6/163		3.1 %	1.92 [0.69, 5.32]
Portier 2001	24/168	16/156		7.9 %	1.46 [0.74, 2.86]
Syrogiannopoulos 2004c	23/155	8/158		3.8 %	3.27 [1.41, 7.55]
Tack 1997	30/240	33/242		16.0 %	0.90 [0.53, 1.54]
Subtotal (95% CI)	**1162**	**1156**		**44.0 %**	**1.28 [0.95, 1.72]**
Total events: 111 (Short term), 88 (Standard duration)					
Heterogeneity: Chi² = 10.15, df = 7 (P = 0.18); I² =31%					
Test for overall effect: Z = 1.64 (P = 0.10)					
Total (95% CI)	**3480**	**4517**		**100.0 %**	**1.85 [1.55, 2.21]**
Total events: 348 (Short term), 210 (Standard duration)					
Heterogeneity: Chi² = 48.95, df = 20 (P = 0.00031); I² =59%					
Test for overall effect: Z = 6.71 (P < 0.00001)					
Test for subgroup differences: Chi² = 17.14, df = 4 (P = 0.00), I² =77%					



Analysis 5.1. Comparison 5 Compliance, Outcome 1 Non-compliance.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 5 Compliance

Outcome: 1 Non-compliance

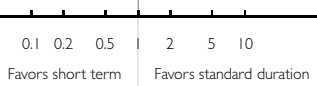
Study or subgroup	Short term n/N	Standard duration n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Adam 1996	3/102	13/99		6.1 %	0.20 [0.06, 0.73]
Aujard 1995	3/97	7/103		3.1 %	0.44 [0.11, 1.74]
Cohen 1996	20/159	50/153		21.2 %	0.30 [0.17, 0.53]
Cohen 2002a	9/169	63/167		28.5 %	0.09 [0.04, 0.19]
Cohen 2002b	10/165	63/167		28.0 %	0.11 [0.05, 0.22]
McCarty 2000	16/268	29/260		13.2 %	0.51 [0.27, 0.96]
Total (95% CI)	**960**	**949**		**100.0 %**	**0.21 [0.16, 0.29]**

Total events: 61 (Short term), 225 (Standard duration)

Heterogeneity: Chi^2 = 17.91, df = 5 (P = 0.003); I^2 =72%

Test for overall effect: Z = 10.13 (P < 0.00001)

Test for subgroup differences: Not applicable

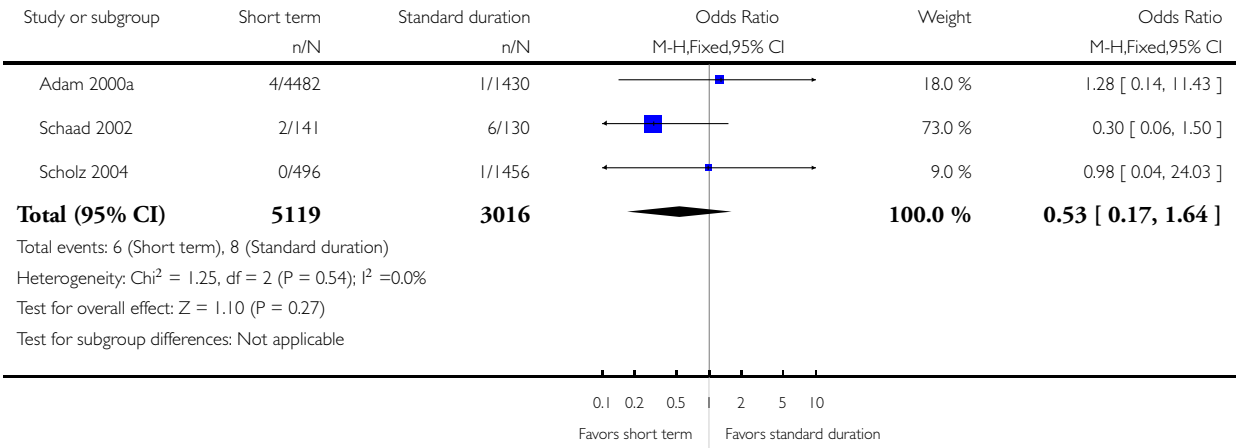


Analysis 6.1. Comparison 6 Complications, Outcome 1 Complications.

Review: Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children

Comparison: 6 Complications

Outcome: 1 Complications



APPENDICES

Appendix 1. Previous MEDLINE and EMBASE search strategies

MEDLINE (Ovid)

1 exp PHARYNGITIS/
2 pharyngitis.mp.
3 exp NASOPHARYNGITIS/
4 nasopharyngitis.mp.
5 TONSILLITIS/
6 tonsillitis.mp.
7 sore throat$.mp.
8 or/1-7
9 exp Streptococcal Infections/
10 Streptococc$.mp.
11 or/9-10
12 exp Anti-Bacterial Agents/
13 antibiotic$.mp.
14 or/12-13
15 8 and 11 and 14

EMBASE (Ovid)

1 exp PHARYNGITIS/
2 pharyngitis.mp.
3 exp NASOPHARYNGITIS/
4 nasopharyngitis.mp.
5 TONSILLITIS/
6 tonsillitis.mp.
7 sore throat$.mp.
8 or/1-7
9 exp Streptococcal Infections/
10 Streptococc$.mp.
11 or/9-10
12 exp Anti-Bacterial Agents/
13 antibiotic$.mp.
14 or/12-13
15 8 and 11 and 14

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Pharyngitis/ (12360)
2 pharyngit*.tw. (3621)
3 Nasopharyngitis/ (236)
4 (nasopharyngit* or rhinopharyngit*).tw. (395)
5 tonsillit*.tw. (3760)
6 tonsillopharyngit*.tw. (224)
7 Respiratory Tract Infections/ (28349)
8 (infection* adj3 upper respiratory).tw. (5356)
9 (throat* adj2 (sore or infect* or inflamm*)).tw. (3240)
10 or/1-9 (46689)
11 Streptococcal Infections/ (25873)
12 Streptococcus/ (18995)
13 Streptococcus pyogenes/ (10494)
14 streptococc*.tw. (66543)
15 gabhs.tw. (315)
16 or/11-15 (82339)
17 10 and 16 (6539)
18 exp Anti-Bacterial Agents/ (1110397)
19 antibiotic*.tw. (188878)
20 18 or 19 (1178879)
21 17 and 20 (3387)

Appendix 3. EMBASE.com search strategy

#28 #27 AND [embase]/lim AND [1-9-2007]/sd NOT [1-9-2011]/sd 43
#27 #23 AND #26 386
#26 #24 OR #25 926167
#25 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEXT/1 blind*):ab,ti AND [embase]/lim 885121
#24 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 255122
#23 #19 AND #22 3231
#22 #20 OR #21 783193

#21 antibiotic*:ab,ti AND [embase]/lim 187075
#20 'antibiotic agent'/exp AND [embase]/lim 739261
#19 #17 OR #18 5126
#18 'streptococcal pharyngitis'/de AND [embase]/lim 299
#17 #11 AND #16 5000
#16 #12 OR #13 OR #14 OR #15 71450
#15 gabhs:ab,ti AND [embase]/lim 350
#14 streptococc*:ab,ti AND [embase]/lim 58052
#13 'streptococcus'/de OR 'streptococcus pyogenes'/de OR 'streptococcus group a'/de AND [embase]/lim 25767
#12 'streptococcus infection'/de OR 'group a streptococcal infection'/de AND [embase]/lim 10886
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 34248
#10 'sore throat'/de AND [embase]/lim OR (throat* NEAR/2 (sore OR infect* OR inflamm*)):ab,ti AND [embase]/lim 3687
#9 (infection* NEAR/3 'upper respiratory'):ab,ti AND [embase]/lim 5944
#8 'upper respiratory tract infection'/de AND [embase]/lim12131
#7 tonsillopharyngit*:ab,ti AND [embase]/lim 272
#6 tonsillit*:ab,ti AND [embase]/lim 3132
#5 'tonsillitis'/exp AND [embase]/lim 6700
#4 nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti AND [embase]/lim 606
#3 'rhinopharyngitis'/de AND [embase]/lim 4118
#2 pharyngit*:ab,ti AND [embase]/lim 3740
#1 'pharyngitis'/exp AND [embase]/lim 14192

WHAT'S NEW

Last assessed as up-to-date: 3 April 2012.

Date	Event	Description
3 April 2012	New citation required but conclusions have not changed	Our conclusions remain unchanged
3 April 2012	New search has been performed	Searches updated. We did not identify any new eligible trials for inclusion or exclusion

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2009

Date	Event	Description
17 February 2008	Amended	Converted to new review format.
12 November 2007	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Khalid A Khlaiwi (KK) and Adli Khalil (AK) were responsible for identification of studies, study selection and data extraction.

Mohammed A Al Othman (MA) and Ruth Milner (RM) were responsible for study quality assessment and data analysis.

Saleh A Altamimi (SA) was responsible for supervising all elements of the review and preparing the text of the review.

Martin V Pusic (MP) and RM were responsible for reviewing data analysis and the text of the review.

For this review update:

SA and AK were responsible for identification of studies, study selection and data extraction.

MA and RM were responsible for study quality assessment and data analysis.

MP and KK were responsible for reviewing data analysis.

SA was responsible for preparing the text of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Emergency Medicine, King Khalid University Hospital, King Saud University, Saudi Arabia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We found most articles using a unified terminology for the late clinical and bacteriological outcomes, which was different to the terminology we initially used in the protocol. We used "late clinical and bacteriological failure", while most studies used "late clinical and bacteriological recurrence", which is a more accurate term, since failure was defined mostly as "persistence after treatment" while recurrence is "return of the initial clinical or bacteriological infection after an initial resolution". We felt that it would be more appropriate to adopt the same late outcome terminology used by most original studies: "late clinical and late bacteriological recurrence". This change of terminology on its own did not lead to a change in the outcome data, however, we removed the "recurrence" outcome, as it is now redundant.

In the protocol we planned to assess heterogeneity using subgroup analyses. However, due to the limited number of trials that assessed the same drug for short treatment we focused on the overall effect. In the Data and analyses section we included the effect per drug for four subsets of studies based on the type of short duration antibiotic used: azithromycin 10 mg/kg, azithromycin 20 mg/kg, clarithromycin and cefuroxime.

INDEX TERMS

Medical Subject Headings (MeSH)

*Streptococcus pyogenes; Acute Disease; Administration, Oral; Anti-Bacterial Agents [*administration & dosage]; Azithromycin [administration & dosage]; Drug Administration Schedule; Penicillins [*administration & dosage]; Pharyngitis [complications; *drug therapy; microbiology]; Randomized Controlled Trials as Topic; Recurrence; Streptococcal Infections [complications; *drug therapy; microbiology]; Tonsillitis [drug therapy; microbiology]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant