Antibiotics for sore throat (Review)

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[Intervention Review]

Antibiotics for sore throat

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ABSTRACT

Background

Sore throat is a common reason for people to present for medical care. Although it remits spontaneously, primary care doctors commonly prescribe antibiotics for it.

Objectives

To assess the benefits of antibiotics for sore throat.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library*, 2008, issue 4) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to November 2008) and EMBASE (January 1990 to November 2008).

Selection criteria

Trials of antibiotic against control with either measures of typical symptoms, or suppurative or non-suppurative complications.

Data collection and analysis

Two review authors independently screened studies for inclusion and extracted data. Differences in opinion were resolved by discussion. Researchers from three studies were contacted for additional information.

Main results

There were 27 studies with 12,835 cases of sore throat.

1. Non-suppurative complications

The trend was antibiotics protecting against acute glomerulonephritis but there were too few cases to be sure. Several studies found antibiotics reduced acute rheumatic fever by more than two thirds (risk ratio (RR) 0.22; 95% CI 0.02 to 2.08).

2. Suppurative complications

Antibiotics reduced the incidence of acute otitis media (RR 0.30; 95% CI 0.15 to 0.58); acute sinusitis (RR 0.48; 95% CI 0.08 to 2.76); and quinsy (RR 0.15; 95% CI 0.05 to 0.47) compared to those taking placebo.

3. Symptoms

Throat soreness and fever were reduced using antibiotics by about half. The greatest difference was seen at Day 3. The number needed to treat (NNT) to prevent one sore throat at Day 3 was less than six; at Week 1 it was 21.

4. Subgroup analyses of symptom reduction

Antibiotics were more effective against symptoms at Day 3 (RR 0.58; 95% CI 0.48 to 0.71) if throat swabs were positive for Streptococcus, compared to RR 0.78; 95% CI 0.63 to 0.97 if negative. Similarly at week 1, RRs 0.29; 95% CI 0.12 to 0.70 for positive, and 0.73; 95% CI 0.50 to 1.07 for negative swabs.

Authors' conclusions

Antibiotics confer relative benefits in the treatment of sore throat. However, the absolute benefits are modest. Protecting sore throat sufferers against suppurative and non-suppurative complications in high-income countries requires treating many with antibiotics for one to benefit. This NNT may be lower in low-income countries. Antibiotics shorten the duration of symptoms by about 16 hours overall.

PLAIN LANGUAGE SUMMARY

Antibiotics for people with sore throats

Sore throats are infections caused by bacteria or viruses. People usually recover quickly (usually after three or four days), although some develop complications. A serious but rare complication is rheumatic fever, which affects the heart and joints. Antibiotics reduce bacterial infections, but they can cause diarrhoea, rash and other adverse effects, and communities build resistance to them. This review of trials found that antibiotics shorten the illness by an average of about one day and can reduce the chance of rheumatic fever in communities where this complication is common.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Outcome	Patients (trials)	Risk of outcome	Relative effect	95% CI	Effect/100 patients	Quality of evidence	Comments
Sore Throat: Day 3	3621 (15)	0.66	0.72	0.68-0.76	19	High	
Sore Throat: Day 7	2974 (13)	0.18	0.65	0.55-0.76	6.4	High	
Rheumatic Fever	10,101 (16)	0.017	0.29	0.18-0.44	1.2	High	Based largely on risk in pre-1960 trials
Glomerulonephritis	5147 (10)	0.001	0.22	0.07-1.32	0.1	Low	Sparse data: 2 cases only
Quinsy	2433 (8)	0.023	0.14	0.05-0.39	2.0	High	
Otitis Media	3760 (11)	0.02	0.28	0.15-0.52	1.4	High	

BACKGROUND

Description of the condition

Sore throat is a very common reason for people to attend for medical care (ABS 1985). Moreover, four to six times as many people suffering sore throat do not seek care (Goslings 1963; Horder 1954). Sore throat is a disease that remits spontaneously, that is, 'cure' is not dependent on treatment (Del Mar 1992c). Nonetheless, primary care doctors commonly prescribe antibiotics for sore throat and other upper respiratory tract infections. There are large differences in clinical practice between countries (Froom 1990) and between primary care doctors (Howie 1971).

Description of the intervention

Traditionally, doctors have attempted to decide whether the cause of the infection is bacterial (when antibiotics might be useful), especially when caused by the Group A Beta-Haemolytic Streptococcus (GABHS) (which can cause acute rheumatic fever and acute glomerulonephritis). But deciding the aetiological agent is difficult (Del Mar 1992b).

Why it is important to do this review

Whether or not to prescribe antibiotics for sore throat is controversial. The issue is important because it is a very common disease, and differences in prescribing result in large cost differences. Moreover, increased prescribing increases patient attendance rates (Howie 1978; Little 1997).

This review is built on an early meta-analysis (Del Mar 1992a), and is an update of previous Cochrane reviews (Del Mar 1997; Del Mar 2000; Del Mar 2004; Del Mar 2006).

OBJECTIVES

To assess the benefits of antibiotics in the management of acute sore throat.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised placebo controlled trials.

Types of participants

Patients presenting for primary care with symptoms of sore throat.

Types of interventions

Antibiotic or placebo control.

Types of outcome measures

At least one of the following:

1. incidence of acute rheumatic fever within two months;
2. acute glomerulonephritis within one month;
3. acute otitis media;
4. acute sinusitis; or
5. quinsy, or measures of the following symptoms: throat soreness, headache or fever.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library,* 2008, issue 4) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to November 2008) and EMBASE (January 1990 to November 2008).

MEDLINE and CENTRAL were searched using the search strategy shown below. We combined the MEDLINE search string with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity maximizing version (2008 revision) (Lefebvre 2008). The search string was adapted for EMBASE, as shown in Appendix 1. Appendix 2 shows the EMBASE search used in previous versions of the review.

MEDLINE (Ovid)

1 explode Pharyngitis/
2 pharyngit$.mp.
3 explode Nasopharyngitis/
4 nasopharyngit$.mp.
5 explode Tonsillitis/
6 tonsillit$.mp.
7 sore throat.mp.
8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9 explode Anti-Bacterial Agents/
10 antibiot$.mp.
11 #9 OR #10
12 #8 AND #11

Searching other resources

References of selected studies and relevant reviews were hand-checked to find additional studies. There were no language or publication restrictions.

Data collection and analysis

Selection of studies

Two review authors independently screened abstracts of potential studies, and full articles were retrieved for those that were trials. Two review authors examined the full articles and either selected for inclusion or rejected to the excluded studies list. Differences in opinion were resolved by discussion.

Data extraction and management

Two review authors independently extracted data from included studies based on patient-relevant outcomes: namely the complications and symptoms listed above. Data extraction involved reading from tables, graphs and in some cases, by contacting trial authors for raw data (Dagnelie 1996; Little 1997; Zwart 2000; Zwart 2003).

Assessment of risk of bias in included studies

Risk of bias was assessed according to the approach indicated for Cochrane reviews (Higgins 2008). We used the following five criteria: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

Measures of treatment effect

All treatment effect outcomes were dichotomous data, reported as risk ratios. For suppurative and non-suppurative complications, these were the reported occurrence of complications during the study period. The presence of symptoms (sore throat, fever, headache) was assessed when possible at Day 3 and Week 1 (days six to eight). We also calculated numbers needed to treat for the primary outcomes.

Dealing with missing data

An intention-to treat analysis was performed for all outcomes.

Assessment of heterogeneity

Heterogeneity was assessed by the chi square test with the significance level set at 0.1. The effect of heterogeneity was determined by the I^2 statistic which indicates the proportion of total variability which can be explained by heterogeneity. In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) values of I^2 greater than 50% were interpreted as indicating substantial heterogeneity.

Data synthesis

Data were combined where possible in order to perform meta-analyses to report RR for all relevant outcomes. A random-effects meta-analytical method was used (Mantel-Haenszel) in order to account for heterogeneity that was detected using the methods described above. Not all studies were able to contribute data to each of the meta-analyses performed.

Subgroup analysis and investigation of heterogeneity

A series of subgroup analyses were performed to assess the differences in outcomes across various subgroups within the participant population:

1. treatment with penicillin (omitting other antibiotics);
2. children compared with adults;
3. positive throat swab versus negative throat swab versus untested / inseparable data for GABHS.

Sensitivity analysis

Sensitivity analyses were performed to assess the degree to which results were influenced by the following criteria:

1. early (pre-1975) versus later (post-1975) studies;
2. blinded versus unblinded studies;
3. antipyretics administered versus no antipyretics administered.

RESULTS

Description of studies

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

Results of the search

A total of 58 studies were considered for the review. Of these, there were 27 controlled studies that met inclusion criteria were included in the review. There were no new trials either excluded or included in this update.

Included studies

The included studies investigated a total of 12,835 cases of sore throat. The majority of studies were conducted in the 1950s, during which time the rates of serious complications (especially acute

rheumatic fever) were much higher than today. Seven recent studies were included (published between 1996 to 2003), perhaps signalling renewed interest in this topic.

The age of participants ranged from less than one year to older than 50 years. The participants of eight early studies were young male recruits from the United States Airforce. Seven of the remaining studies recruited children up to 18 years of age only, three recruited only adults or adolescents aged 15 years or over, and eight studies had no age restrictions.

All studies recruited patients presenting with symptoms of sore throat. Seventeen studies did not distinguish between bacterial and viral aetiology. However, eight studies included Group A Beta Haemolytic Streptococcus (GABHS) positive patients only, whilst two studies excluded patients who were GABHS positive.

Excluded studies

The most common reason for exclusion was lack of appropriate control group (n = 13). Other reasons for exclusion were: irrelevant or non-patient centred outcomes (n = six), main complaint other than acute sore throat (n = six), inappropriate or no randomisation to treatment (n = five), or that the study reported previously published data already included (n = one).

Risk of bias in included studies

The generalisability of studies can be questioned. In five studies subjects were excluded if they did not yield a positive throat swab culture for GABHS. In two studies subjects were excluded if they did yield a positive throat swab culture for GABHS (Petersen 1997; Taylor 1977).

Allocation

In most early studies subjects were randomised to treatment and control groups by methods that could potentially introduce bias (for example, Airforce serial number, drawing a card from a deck, hospital bed number) or not randomised at all. Allocation methods were generally appropriate in the later studies.

Blinding

Eighteen of the studies were double blinded and three were single blinded.

Other potential sources of bias

The use of antipyretic analgesics was not stated in nine studies, administered routinely in five studies, and prohibited in four studies. The prohibition of analgesics might exaggerate any small symptomatic benefit of antibiotics over control if antipyretic analgesics are usually recommended in normal practice.

Effects of interventions

See: **Summary of findings for the main comparison**

1. Non-suppurative complications

Cases of acute glomerulonephritis only occurred in the control group which suggests protection by antibiotics. However, there were only two cases, and only ten studies reported on acute glomerulonephritis as an end point. Therefore, our estimate of the protection has a very wide 95% confidence interval (CI), (RR 0.22; 95% CI 0.02 to 2.08) which precludes us from definitively claiming that antibiotics protect sore throat sufferers from acute glomerulonephritis (Analysis 1.8).

Several studies found benefit from antibiotics for acute rheumatic fever which reduced this complication to about one quarter of that in the placebo group (RR 0.27; 95% CI 0.12 to 0.60) (Analysis 1.1). Few studies examined antibiotics other than penicillin. Confining the analysis to penicillin alone resulted in no difference in estimated protection (RR 0.27; 95% CI 0.14 to 0.50) (Analysis 1.2).

2. Suppurative complications

Antibiotics reduced the incidence of acute otitis media to about one third of that in the placebo group, (Risk Ratio (RR) 0.30; 95% CI 0.15 to 0.58) (Analysis 1.4) and reduced the incidence of acute sinusitis to about one half of that in the placebo group (RR 0.48; 95% CI 0.08 to 2.76) (Analysis 1.6). Data indicate that the incidence of quinsy was also reduced in relation to placebo group (RR 0.15; 95% CI 0.05 to 0.47) (Analysis 1.7).

3. Symptoms

At day 3 of illness, antibiotics reduced symptoms of sore throat (RR 0.68; 95% CI 0.59 to 0.79) (Analysis 2.1), fever (RR 0.71; 95% CI 0.45 to 1.10) (Analysis 3.1), and headache (RR 0.47; 95% CI 0.38 to 0.58) (Analysis 4.1). Day 3 was the greatest time of benefit because the symptoms of only half the patients had settled. At one week (six to eight days) the relative risk of experiencing sore throat was 0.49 (95% CI 0.32 to 0.76), although 82% of controls were better by this time (Analysis 2.5).

A new trial was included in the 2003 update from Thailand (Leelarasamee 2000). It is especially important because it is one of the few trials from a non-Western industrial country. Unfortunately we were unable to enter its data into the meta-analysis because of different ways of collecting the data (in particular no data were collected mid-way through the illness). Nevertheless, the use of antibiotics conferred no benefit (nor harms) on symptoms or complications.

4. Subgroup analysis of symptom reduction

a) Blind versus unblinded studies

There was no significant difference between blinded and unblinded studies for symptoms of sore throat at day 3 (RR 0.65; 95% CI 0.54 to 0.78; and RR 0.79; 95% CI 0.60 to 1.05, respectively) (Analysis 2.2) nor at one week (RR 0.62; 95% CI 0.38 to 1.03 and RR 0.30; 95% CI 0.08 to 1.15, respectively) (Analysis 2.6). Contrary to expectation the trend was for a greater effect of antibiotics for blind studies at day 3.

b) Antipyretics administered versus not administered

Use of antipyretics offered no significant difference between studies in which antipyretics were offered and those in which they were not (RR 0.52; 95% CI 0.33 to 0.81; and RR 0.62; 95% CI 0.55 to 0.70, respectively) (Analysis 2.3).

c) Throat swabs positive for *Streptococcus*, versus negative for *Streptococcus*, versus not tested / inseparable combined data

The probability of still experiencing pain on day 3 is slightly more than a half (RR 0.58; 95% CI 0.48 to 0.71) for those patients who had throat swabs positive for GABHS, compared to three quarters (RR 0.78; 95% CI 0.63 to 0.97) for those with negative swabs (Analysis 2.4). There was a similar effect at one week (RR 0.29; 95% CI 0.12 to 0.70 and RR 0.73; 95% CI 0.50 to 1.07, respectively) (Analysis 2.7). That is, the effectiveness of antibiotics is increased in people with *Streptococci* growing in the throat.

d) Children versus adults

There were few studies that included children (less than 13 years of age): only 61 cases in total for when fever was evaluated at day 3. There was overlap of the RR 95% CI, so that the trend for children to not experience benefits was not significantly different to adults who did (RR 1.27; 95% CI 0.76 to 2.13; and RR 0.29; 95% CI 0.06 to 1.51, respectively) (Analysis 3.3).
Some of these results are summarised (see Figure 1).

Figure 1. Summary of Findings.

Outcome	Patients (trials)	Event Rate	Effect Ratio	95% CI	Effect difference per 100 patients	Quality of Evidence	Comments
Sore Throat: day 3	3621 (15)	0.663	0.72	0.68-0.76	18.6		
Sore Throat: day 7	2974 (13)	0.181	0.65	0.55-0.76	6.4		
Rheumatic Fever	10,101 (16)	0.017	0.29	0.18-0.44	1.2		based largerly on risk on older trials
Glomerulonephritis	5147 (10)	0.001	0	0.07-1.32	0.1		sparse data: 2 cases only
Otitis Media	3760 (11)	0.020	0.28	0.15-0.52	1.4		
Quinsy	2433 (8)	0.023	0.14	0.05-0.39	2.0		

DISCUSSION

Natural history

In the placebo groups, after three days, symptoms of sore throat and fever had disappeared in about 40% and 85%, respectively. Eighty-two percent of patients were symptom free by one week. This natural history was similar in *Streptococcus* positive, negative, and untested patients. About 1.7 per 100 placebo patients developed rheumatic fever. However, this complication occurred only in trials reporting before 1961. The background incidence of acute rheumatic fever has continued to decline in Western societies since then.

Benefits of treatment

The absolute benefit of antibiotics for the duration of symptoms was modest. The reduction of illness time is greatest in the middle of the illness period when the mean absolute reduction is about one day at around day 3. There are not enough data to make conclusions about children. The absolute reduction averaged over the whole illness can only be estimated from these data. The difference in the area under the survival curves of sore throat symptoms for those treated with placebo as opposed to antibiotic is about 16 hours for the first week.

Estimates of the number of people with sore throat who must be treated to resolve the symptoms of one by day 3 the number needed to treat to benefit (NNTB) is about 3.7 for those with positive throat swabs for *Streptococcus*. It is 6.5 of those with a negative swab, and 14.4 for those in whom no swab has been taken. The last result is difficult to understand. Intuitively one would expect the NNTB value to lie between both the swab negative and swab positive results. Perhaps patients with less severe throat infections were recruited into the three studies in which swabs were not taken.

Antibiotics are effective at reducing the relative complication rate of people suffering sore throat. However, the relative benefit exaggerates the absolute benefit because complication rates are low and the illness is short lived. Interpretation of these data is aided by estimating the absolute benefit, which we attempt below.

In these trials, conducted mostly in the 1950s, for every 100 pa-

tients treated with antibiotics rather than placebo, there was one fewer case of acute rheumatic fever, two fewer cases of acute otitis media, and three fewer cases of quinsy. These figures need to be adapted to current circumstances and individuals. For example the complication rate of acute otitis media among those with sore throats before 1975 was 3%. A NNTB of about 50 to prevent one case of acute otitis media can be estimated from the data. After 1975, this complication rate fell to 0.7%, and applying the odds of reducing the complication with antibiotics form the data table yields a NNTB of nearly 200 to prevent one case of acute otitis media. Clinicians will have to exercise judgement in applying these data to their patients.

In particular in the modern times in the West (where absolute rates of complications are lower) the NNTB will rise above a rate at which it might be regarded as worthwhile to treat. In low-income countries where the absolute rate may be much higher, the lower NNTB will mean antibiotics are more likely to be effective.

Adverse effects of treatment

We were unable to present the adverse effects of antibiotic use because of inconsistencies in recording these symptoms. In other studies these were principally diarrhoea, rashes and thrush (Glasziou 1997). Consideration of the side effects of antibiotics would have been useful in further defining their risk-benefits.

Special risk groups

Acute rheumatic fever is common among people living in some parts of the world (Australian Aborigines living in poor socio-economic conditions, for example), and antibiotics may be justified to reduce the complication of acute rheumatic fever in these settings. In other parts of the world the incidence of acute rheumatic fever is so low (one estimate is that it took 12 general practitioners' working lifetimes to encounter one new case of acute rheumatic fever in Western Scotland in the 1980s (Howie 1985) that the risks of serious complication arising from using antibiotics for sore throat might be of the same order as that of acute rheumatic fever.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotics have a beneficial effect on both suppurative and symptom reduction.

The effect on symptoms is small, so that clinicians must judge with individual cases whether it is clinically justifiable to employ antibiotics to produce this effect. In other words their use should be discretionary rather than either prohibited or mandatory. Since 90% of patients are symptom free by one week (whether or not treated with antibiotics), the absolute benefit of antibiotics at this time and beyond is vanishingly small.

Acute rheumatic fever is common among people living in some parts of the world (Australian Aborigines living in poor socio-economic conditions, for example) and antibiotics may be justified to reduce the incidence of this complication in these settings. For other settings where rheumatic fever is rare, there is a balance to be judged between modest symptom reduction and the hazards of antimicrobial therapy.

Implications for research

More trials should be conducted in low-income countries; in socio-economically deprived sections of high-income countries; and also in children. In modern Western societies better prognostic studies which can predict which patients may develop suppurative and non-suppurative complications and may further define which patients benefit from antibiotics.

Studies which use patient-centred outcome measures compatible with those presented here would be greatly beneficial, in terms of easier comparison and analysis of results, and ready inclusion of the authors work in future updates of this meta-analysis.

Few trials have attempted to measure the severity of symptoms. If antibiotics reduce the severity as well as the duration of symptoms, their benefit will have been underestimated in this meta-analysis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bennike 1951

Methods	Open study, quasi-randomised
Participants	669 patients aged from less than one year to greater than 50 years of age. Research was divided into three studies: ordinary tonsillitis, "phlegmonous" tonsillitis and "ulcerative" tonsillitis. Subjects were excluded if they had a complication of tonsillitis on admission or if they had previous antibiotic treatment for the present sore throat
Interventions	Age adjusted intramuscular penicillin twice daily for six days or no treatment as a control condition
Outcomes	Incidence of rheumatic fever, otitis media, quinsy, sinusitis and symptoms of sore throat and headache
Notes	No antipyretics were administered to the control group. The use of antipyretics to subjects in the treatment group was unstated

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Subjects allocated to alternate conditions on alternate days
Allocation concealment?	No	
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	No antipyretics were administered to the control group. The use of antipyretics to subjects in the treatment group was unstated

Brink 1951

Methods	Open study
Participants	395 young adult males recruited into United States Airforce
Interventions	Intramuscular penicillin over four days, chlortetracycline for three days, or no treatment as control group

Brink 1951 (*Continued*)

Outcomes	Incidence of rheumatic fever, otitis media, and symptoms of sore throat, fever and headache
Notes	No antipyretics were administered

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Participants randomised by air force serial number
Allocation concealment?	No	C - Inadequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Brumfitt 1957

Methods	Open study
Participants	121 young adult men, aged eighteen to twenty one years, recruited into United States Airforce. Patients were excluded from study if their temperature was below 99.3 degrees F, if they had sore throat for more than 72 hours prior to presentation, or if they had some other generalised illness
Interventions	Intramuscular penicillin twice daily for four days or no treatment as a control condition
Outcomes	Incidence of rheumatic fever and symptoms of sore throat and fever
Notes	Aspirin gargles were given 6 hourly. Whether subjects were permitted to swallow the aspirin was not documented

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Participants randomised by hospital bed number
Allocation concealment?	No	
Blinding? All outcomes	No	

Brumfitt 1957 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Catanzaro 1954

Methods	Single blind, patients were unaware of treatment type, placebo controlled trial. The outcome of treatment was not determined blind.
Participants	640 young adult males recruited into United States Airforce. Missing data were not explained Data from patients who produced a GABHS negative throat swab were excluded. Subjects were excluded if they presented with a suppurative complication at the time of admission
Interventions	Intramuscular penicillin administered for five days, sulphonamide administered for five days, or no treatment as a control condition
Outcomes	Incidence of rheumatic fever
Notes	Antipyretic use was not documented

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Participants randomised by air force serial number
Allocation concealment?	No	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Chamovitz 1954

Methods	Single blind placebo study.
Participants	366 young adult males recruited into United States Airforce. Patients were excluded if they had previously developed rheumatic fever, had previous penicillin reaction, or if they had a suppurative complication at the time of admission

Chamovitz 1954 (*Continued*)

Interventions	Intramuscular penicillin	
Outcomes	Incidence of rheumatic fever, otitis media, and sinusitis	
Notes	Antipyretic use was not documented	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Participants randomised by air force serial number
Allocation concealment?	No	
Blinding? All outcomes	Unclear	Patients did not know treatment type they were receiving. The outcome of treatment was not determined blind.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Chapple 1956

Methods	Double blind placebo controlled trial	
Participants	308 subjects aged greater than two years old. Data from 283 subjects included in analyses	
Interventions	Age adjusted oral penicillin, sulphadimidine, or barium sulphate (placebo) administered for five days	
Outcomes	Incidence of rheumatic fever, otitis media, and symptom of sore throat	
Notes	All groups received controlled doses of antipyretics twice daily for three days Data from only 200 subjects presenting with sore throat on day 1 included in sore throat analysis	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Participants randomised by random bottle dispensing
Allocation concealment?	Yes	

Chapple 1956 (*Continued*)

Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Dagnelie 1996

Methods	Randomised double-blind placebo controlled trial of penicillin V on the course and bacteriological response in patients with sore throat in general practice
Participants	239 patients aged 4 to 60, presenting with sore-throat to 37 general practices in the Netherlands, who were clinically suspected of GABHS
Interventions	Treatment with either penicillin V, or placebo
Outcomes	Resolution of sore throat, fever, and return to daily activities (assessed by doctor, and by diary for 7 days)
Notes	* Need raw data to make this study comparable to the meta-analysis, however data are available for sore throat on day 3 and quinsy

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

De Meyere 1992

Methods	Double blind placebo trial.
Participants	173 patients aged five to fifty years, from the Gent region of Belgium Data was obtained from 173 subjects on days one and three Data was obtained form 131 subjects on days two, four, five, six and seven

De Meyere 1992 (*Continued*)

	Subjects excluded if they: produced a GABHS negative throat swab, had a sore throat for greater than five days, had a previous history of acute rheumatic fever, had an allergy to beta-lactam antibiotics, had received any antibiotics within the past fourteen days, were in any high risk situation as determined by the physician
Interventions	Oral penicillin or oral placebo three times a day
Outcomes	Symptom of sore throat All data obtained, except from days one and three, were self report from a diary
Notes	Antipyretics were used as required by participants. Use of antipyretics and other symptom relieving methods was documented in a diary

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation method not documented
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Denny 1950

Methods	Single blind study. The outcome was determined blind on follow up by physicians who did not know what treatment type each subject had received.
Participants	1602 young adult males recruited into United States Airforce
Interventions	Intramuscular penicillin for four days or no treatment as a control group
Outcomes	Incidence of rheumatic fever only
Notes	Antipyretic use was not stated

Risk of bias

Item	**Authors' judgement**	**Description**

Denny 1950 (*Continued*)

Adequate sequence generation?	Unclear	Participants randomised by air force serial number
Allocation concealment?	No	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not stated

Denny 1953

Methods	Single blind, randomised placebo controlled trial. Outcome determined blind by physicians who did not know treatment type
Participants	103 young adult males recruited in the United States Airforce. Patients were excluded if they had no exudate on their tonsils or larynx, if they had a leukocyte count of less than 10,000; or if they had experienced symptoms of sore throat for more than 31 hours
Interventions	Intramuscular penicillin daily for five days, oral aureomycin or oral terramycin administered every six hours for 3 days or oral lactose placebo for three days as a control condition
Outcomes	Incidence of acute rheumatic fever, otitis media, quinsy, sinusitis, and symptoms of sore throat and headache
Notes	No antipyretics were administered

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Patients were randomly allocated to treatment groups by drawing a card from a deck.
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

El-Daher 1991

Methods	Double-blinded, randomised controlled trial
Participants	229 children with positive culture for GABHS
Interventions	Early treatment with oral penicillin for 10 days versus oral placebo for 2 days followed by oral penicillin for 8 days
Outcomes	Symptoms of sore throat and headache on day 3
Notes	Examination of patients was done on day 3 before administering penicillin to placebo group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Howe 1997

Methods	22 GPs in one region of the UK recruited
Participants	154 patients aged 16 to 60 years presenting to their GP with sore throat, and for whom the GP would normally prescribe an antibiotic
Interventions	Therapy with either penicillin V (250 mg four times a day), cefixime (200 mg daily), or placebo
Outcomes	Resolution of a composite "symptom score" with time; eradication of GABHS. A diary was kept of symptom resolution over 7 days
Notes	*Symptom results were bundled into a composite "symptom score". The raw data on sore throat, cough and fever resolution has been requested from the authors

Risk of bias

Item	**Authors' judgement**	**Description**

Howe 1997 (*Continued*)

Adequate sequence generation?	Yes	Block randomisation scheme (done in blocks of 6)
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Krober 1985

Methods	Double blind placebo trial.
Participants	Forty-four children presenting to a paediatric clinic. Twenty-six of these subjects yielded GABHS positive throat swabs. Subjects were excluded if: the duration of symptoms was greater than 72 hours; they had received oral antibiotics within the past 72 hours or intramuscular antibiotics within the past 30 days; they had history of penicillin allergy; they had a rash suggestive of scarlet fever; they had a concurrent infection that required antibiotics other than penicillin; or if they had sever illness requiring immediate penicillin treatment. Subjects who produced GABHS negative throat swabs were excluded from the study
Interventions	Oral penicillin or similar looking and tasting oral placebo for the control condition, three times a day for three days
Outcomes	Symptom of fever
Notes	Antipyretic use was not documented

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Subjects were randomised by table of random numbers
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	

Krober 1985 (*Continued*)

Free of selective reporting?	Unclear	Antipyretic use was not documented

Landsman 1951

Methods	Double blind, randomised placebo controlled trial.
Participants	95 patients who presented to general practice complaining of sore throat
Interventions	Oral sulphonamide or similar looking and tasting oral placebo, for the control condition
Outcomes	Incidence of sinusitis or quinsy or symptoms of sore throat or fever
Notes	Antipyretic use was not documented

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised by random numbering of bottles
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Leelarasamee 2000

Methods	Double-blind randomised placebo controlled trial
Participants	1217 patients aged over 5 years presenting to four community -based medical centres with complaints of fever or sore throat of less than ten days duration
Interventions	Patients were randomised to receive either Amoxycillin or placebo for seven days
Outcomes	Duration of sore throat and fever. incidence of complications and adverse reactions
Notes	Antipyretics were given if deemed necessary by physicians

Risk of bias

Leelarasamee 2000 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Little 1997

Methods	Unblinded randomised trial
Participants	716 patients aged 4 years and over, presenting to their GP with a sore throat, with an abnormal physical finding localised to the throat (e.g. inflamed tonsils or pharynx, etc)
Interventions	Patients were randomised to three groups. Patients in the first group were given an antibiotic for 10 days; those in the second group were given no prescription; and in the third group were given an offer of antibiotic prescription if the symptoms were not starting to settle after 3 days
Outcomes	Main outcomes - duration of symptoms, satisfaction and compliance with and perceived efficacy of antibiotics, time off school or work. Patients given a daily diary in which to record symptoms and temperature. Patients who did not return diaries were followed up over the phone
Notes	Patients randomised, but neither patients or doctors blinded to the therapy

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	No	
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	

Free of selective reporting?	Yes	

MacDonald 1951

Methods	Outcome determined blind.
Participants	82 young adult males recruited into the United States Airforce 41 in treatment group; 41 in control group
Interventions	Oral sulphatriad or identical oral lactose placebo, administered to the control condition, taken every four hours
Outcomes	Symptom of sore throat
Notes	Antipyretics were administered to 1 subject in the treatment group and 2 subjects in the control group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Participants randomised by air force serial number
Allocation concealment?	No	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Middleton 1988

Methods	Multi-center, double-blind, randomised, placebo-controlled
Participants	One hundred and seventy-eight patients aged 4 to 29 years with streptococcal pharyngitis. Patients had symptom duration of less than 4 days. Results reported for 57 patients with severe illness only
Interventions	Eight individual doses of penicillin or un medicated placebo
Outcomes	Symptoms of sore throat and fever
Notes	Phone report after 48 hours used to measure outcome at day 3

Middleton 1988 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Nelson 1984

Methods	An oral placebo was used to single blind patients, however outcome was not determined blind
Participants	51 children aged 5 to 11 years. Sixteen subjects were excluded because they did not produce GABHS positive throat swabs, leaving 35 subjects. Children with history of penicillin hypersensitivity were also excluded
Interventions	Intramuscular penicillin or oral syrup placebo as a control group
Outcomes	Symptoms of sore throat and fever
Notes	No antipyretics were administered

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Subject randomised to conditions by hospital number allocation
Allocation concealment?	No	
Blinding? All outcomes	Unclear	An oral placebo was used to single blind patients, however outcome was not determined blind
Incomplete outcome data addressed? All outcomes	Yes	

Nelson 1984 (*Continued*)

Free of selective reporting?	Yes	

Petersen 1997

Methods	Randomised placebo-controlled trial of patients' culture negative to GABHS
Participants	One hundred and eighty-six adults (aged 18 to 50) presenting to an ambulatory setting, whose chief complaint was sore throat, and whose GAS culture was subsequently found to be negative
Interventions	Treatment of either erythromycin (333 mg, 3 times daily), or placebo
Outcomes	Main outcomes - time to improvement in sore throat, cough, activity level, and sense of well being. Patients completed a daily questionnaire on the progress of outcome measures. Follow up visits were arranged 2 to 3 weeks after enrolment for repeat cultures, collect diaries and assess compliance
Notes	It is not clear how many patients kept diaries for the sore throat data in each group. Authors excluded GAS positive patients, (15 out of 212 initially randomised). Authors are being contacted for raw data

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Unclear	It is not clear how many patients kept diaries for the sore throat data in each group. Authors excluded GAS positive patients, (15 out of 212 initially randomised).

Pichichero 1987

Methods	Double blind randomised placebo controlled trial
Participants	One hundred and fourteen GABHS positive children aged 4 to 18 years. Children were excluded from the study if: a throat swab was negative for GABHS; were allergic to penicillin; had received penicillin in past 7 days; had another acute illness within seven days, had a GABHS positive swab in past month, or had another concurrent infection that required antibiotics

Pichichero 1987 (*Continued*)

Interventions	Oral penicillin for forty eight hours or an identical looking and tasting oral placebo used for the control condition
Outcomes	Incidence of otitis media, quinsy, or sinusitis
Notes	Antipyretics administered 4 hourly

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Siegel 1961

Methods	Randomised controlled trial
Participants	One thousand, two hundred and thirteen patients aged three to sixteen years. Suppurative complications occurring in subjects in the control condition were treated with sulphonamides. Subjects were excluded if they had a complication on admission
Interventions	Intramuscular penicillin or no treatment for the controls
Outcomes	Incidence of rheumatic fever
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Subjects randomised by bed chart number
Allocation concealment?	No	
Blinding? All outcomes	No	

Siegel 1961 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Taylor 1977

Methods	Double blind, randomised placebo controlled trial.
Participants	One hundred and twenty-two children aged two to ten years. Children with positive Streptococcus throat swabs were excluded Nine children were excluded during trial because of pre-existing suppurative complications
Interventions	Oral amoxycillin, oral cotrimoxazole, or an oral placebo was administered by parents three times a day for five days
Outcomes	Incidence of otitis media and sinusitis and symptoms of sore throat and fever
Notes	Antipyretic use was not documented

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of randomisation to groups was not documented
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Wannamaker 1951

Methods	Single blind study. The outcome of intervention was determined blind by physicians who did not know treatment type participants were receiving
Participants	One thousand, nine hundred and seventy-four young adult males recruited into the United States Airforce
Interventions	Intramuscular penicillin over one to three days or no treatment for the control condition

Wannamaker 1951 (*Continued*)

Outcomes	Incidence of rheumatic fever	
Notes	Antipyretic use was not documented	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Subjects randomised to groups by air force serial number
Allocation concealment?	No	
Blinding? All outcomes	Yes	Single blind
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Whitfield 1981

Methods	Double blind, randomised placebo controlled trial.	
Participants	Subjects were patients who presented to the general practitioner with sore throat, aged greater than 10 years. Seven hundred and forty-five patients were commenced in study. Only 528 returned questionnaires. Subjects were excluded if the general practitioner thought the subject would demonstrate poor compliance; if they had previous reaction to penicillin; or a previous episode of rheumatic fever or acute nephritis	
Interventions	Oral penicillin four times a day for five days or identical looking and tasting oral lactose placebo four times a day for five days	
Outcomes	Symptom of fever	
Notes	Antipyretic use was not documented	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised by predetermined random order
Allocation concealment?	Yes	

Whitfield 1981 (*Continued*)

Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Antipyretic use was not documented

Zwart 2000

Methods	Double blind, randomised placebo controlled trial
Participants	Five hundred and sixty-one patients aged 15 to 60 years presenting with sore throat of less than seven days duration
Interventions	Penicillin V for seven days, penicillin V for 3 days followed by 4 days of placebo or placebo or 7 days
Outcomes	Resolution of symptoms and recurrence of sore throat
Notes	Author was contacted for data that could be used in the meta-analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Zwart 2003

Methods	Double blind, randomised placebo controlled trial
Participants	One hundred and fifty-six children aged 4 to 15 years presenting with sore throat of less than 7 days duration with at least 2 of 4 Centor criteria
Interventions	Penicillin V for seven days, penicillin V for 3 days followed by 4 days of placebo or placebo or 7 days

Zwart 2003 (*Continued*)

Outcomes	Duration of symptoms of sore throat, occurrence of streptococcal sequelae	
Notes	Author was contacted for data that could be used in the meta-analysis	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

F: Farenheit
GABHS: Group A Beta Haemolytic Streptococcus

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

Barwitz 1999	Patients were randomised to two GPs for subsequent treatment with different management protocols
Bass 1986	Study used a Likert scale to measure severity and duration of symptoms. No raw scores are available for entry into meta-analysis
Bishop 1952	Non-randomised allocation to treatment groups. (Quote) "Where an exceptionally severe case fell in the control group and it was felt unjustifiable to withhold specific treatment, the case was transferred to one of the other groups and the next case was placed in the control group." This bias was not quantified
Catanzaro 1958	Study compared sulphonamides with other antibiotics. No control condition was used
Cruickshank 1960	Study is another report of the data previously published by Brunfitt, 1957
Dowell 2001	Cough was the main complaint for patients, not sore throat
Gerber 1985	Study compared two different regimens of penicillin. No placebo control group was used
Gerber 1989	Assessed two regimes of penicillin. No control group used
Ginsburg 1980	Study compared penicillin V with cefadroxil. No placebo control group was used

(*Continued*)

Guthrie 1988	Study did not use control condition
Haverkorn 1971	Subjects not treated with antibiotics given antipyretics. Subjects receiving antibiotics received no antipyretics. No control condition
Herz 1988	No patient centred outcomes, except return visits for URIs. Poor randomisation - out of a series of 202, the first and last 50 were assigned to antibiotics, with the middle 102 assigned to control
Howie 1970	Illness was "cold or flu-like illness", not acute pharyngitis (exclusively). Soreness of throat not an outcome measure
Jensen 1991	Patients were not randomly allocated to treatment groups and were not blinded to treatment
Marlow 1989	Patient population highly selected (non-pregnant, negative rapid strep. test, negative throat culture, no other infection present, not allergic to erythromycin, aged older than 12), and patient-centred outcomes not compatible with those in this meta-analysis
Massell 1951	Study examined effect of penicillin on hemolytic streptococci infections in rheumatic patients only, without randomisation to control condition. Infections that were not treated with penicillin for 'various reasons' were treated as controls. These reasons were not given
McDonald 1985	No data suitable for this meta-analysis were described although symptoms were recorded. The author was approached for these data, but no reply was received
Merenstein 1974	No data on suppurative or non-suppurative complications. No data on day three for soreness of throat, fever, or headache
Morris 1956	Study observed effect of Sulfadiazine on prevention of rheumatic fever only. No control condition was used
Nasonova 1999	Study in a controlled clinical trial without randomisation of subjects
Pandraud 2002	Investigation of effect of fusafune on chronic conditions of follicular pharyngitis. Not relevant for this review
Randolph 1985	No data on suppurative or non-suppurative complications. No data on day three or seven for soreness of throat, fever, or headache
Schalen 1985	Primary complaint hoarseness, not sore throat. No patient centred outcomes apart from hoarseness
Schalen 1993	Patients presented for laryngitis and hoarseness, not pharyngitis
Schwartz 1981	Study compared seven versus ten days of treatment with penicillin. No control group was used
Shevrygin 2000	Study was a clinical trial without a control condition
Shvartzman 1993	Study compared efficacy of amoxycillin against penicillin, no control condition was used

(*Continued*)

Stillerman 1986	Study compared penicillin with cephalosporins. No control group was used
Stromberg 1988	No placebo control group was used. Study compared different antibiotic regimens
Todd 1984	Primary complaint not sore throat - purulent nasopharyngitis instead
Valkenburg 1971	Study did not involve any control measures. Data only given for subjects not treated with antibiotics

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of acute rheumatic fever within two months. Rheumatic fever defined by clinical diagnosis	16	10101	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.12, 0.60]
2 Incidence of acute rheumatic fever within two months. Penicillin versus placebo	14	8175	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.50]
3 Incidence of acute rheumatic fever within two months: early (pre-1975) versus late studies (post-1975)	16	10101	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.12, 0.60]
3.1 Incidence of acute rheumatic fever within 2 months: early (pre-1975) studies	10	7617	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.12, 0.60]
3.2 Incidence of acute rheumatic fever within 2 months: late (post-1975) studies	6	2484	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis	11	3760	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.15, 0.58]
5 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)	11	3760	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.15, 0.58]
5.1 Incidence of otitis media within 14 days: early (pre-1975) studies	5	1837	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.15, 0.62]
5.2 Incidence of otitis media within 14 days: late (post-1975) studies	6	1923	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.74]
6 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis	8	2387	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.08, 2.76]
7 Incidence of quinsy within two months. Quinsy defined by clinical diagnosis	8	2433	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.05, 0.47]
8 Incidence of acute glomerulonephritis within one month. Acute glomerulonephritis defined by clinical diagnosis	10	5147	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.02, 2.08]

Comparison 2. Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom of sore throat on day three	15	3621	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.59, 0.79]
2 Symptom of sore throat on day three: blind versus unblinded studies	15	3621	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.59, 0.79]
2.1 Symptom of sore throat on day 3: blinded studies.	12	2662	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.54, 0.78]
2.2 Symptom of sore throat on day 3: unblinded studies.	3	959	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.60, 1.05]
3 Symptom of sore throat on day three: antipyretics versus no antipyretics	5	1137	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.48, 0.70]
3.1 Symptom of sore throat on day 3: antipyretics administered.	3	455	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]
3.2 Symptom of sore throat on day 3: no antipyretics administered.	2	682	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.55, 0.70]
4 Symptom of sore throat on day three: Streptococcus positive throat swab, negative swab, untested/ inseparable	15	3600	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.59, 0.78]
4.1 Symptom of sore throat on day 3: Group A Beta Haemolytic Streptococcus positive throat swab	11	1839	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.48, 0.71]
4.2 Symptom of sore throat on day 3: Group A Beta Haemolytic Streptococcus negative throat swab	6	736	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
4.3 Symptom of sore throat on day 3: Untested for GABHS culture or combined inseparable data	3	1025	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 1.00]
5 Symptom of sore throat at one week (six to eight days)	13	2974	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.32, 0.76]
6 Symptom of sore throat at one week (six to eight days): blind versus unblinded studies	13	2944	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.86]
6.1 Symptom of sore throat at 1 week (6-8 days): blinded studies	9	1616	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.38, 1.03]
6.2 Symptom of sore throat at 1 week (6-8 days): unblinded studies	4	1328	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.08, 1.15]

7 Symptom of sore throat at one week (six to eight days): GABHS positive throat swab, GABHS negative swab. Untes	12	2524	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.29, 0.80]
7.1 Symptom of sore throat at 1 week (6-8days): Group A Beta Heamolytic Streptococcus positive throat swab	7	1117	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.12, 0.70]
7.2 Symptom of sore throat at 1 week (6-8days): Group A Beta Heamolytic Streptococcus negative throat swab	5	541	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.07]
7.3 Symptom of sore throat at 1 week (6-8days): Group A Beta Heamolytic Streptococcus untested	3	866	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.03, 4.47]

Comparison 3. Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom of fever on day three	7	1334	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.10]
2 Symptom of fever on day three: blinded versus unblinded studies	7	1334	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.45, 1.10]
2.1 Symptom of fever on day 3: blinded studies.	4	703	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.23]
2.2 Symptom of fever on day 3: unblinded studies.	3	631	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.31, 1.37]
3 Symptom of fever on day three: children compared with adults	4	657	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.18, 1.46]
3.1 Symptom of fever on day 3: children	2	61	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.76, 2.13]
3.2 Symptom of fever on day 3: adults	2	596	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.51]
4 Symptom of fever at one week (six to eight days)	3	777	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 4. Antibiotics versus control for the treatment of sore throat: symptom of headache

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom of headache on day three	3	911	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.27, 0.71]
2 Symptom of headache on day three: blinded versus unblinded studies	3	911	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.27, 0.71]
2.1 Symptom headache on day three: blinded studies	2	436	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.09, 1.20]
2.2 Symptom of headache on day three: unblinded studies	1	475	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.41, 0.72]

Analysis 1.1. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 1 Incidence of acute rheumatic fever within two months. Rheumatic fever defined by clinical diagnosis.

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome: 1 Incidence of acute rheumatic fever within two months. Rheumatic fever defined by clinical diagnosis

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bennike 1951	0/238	0/268		0.0 [0.0, 0.0]
Pichichero 1987	0/59	0/58		0.0 [0.0, 0.0]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Brumfitt 1957	0/62	0/59		0.0 [0.0, 0.0]
Chapple 1956	0/186	0/97		0.0 [0.0, 0.0]
Leelarasamee 2000	0/369	0/386		0.0 [0.0, 0.0]
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
De Meyere 1992	0/87	0/94		0.0 [0.0, 0.0]
Little 1997	0/454	0/216		0.0 [0.0, 0.0]
Chamovitz 1954	0/257	2/109		0.09 [0.00, 1.76]
Denny 1950	2/798	17/804		0.12 [0.03, 0.51]
Wannamaker 1951	5/978	35/996		0.15 [0.06, 0.37]

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Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Siegel 1961	0/605	2/608		0.20 [0.01, 4.18]
Brink 1951	2/277	5/198		0.29 [0.06, 1.46]
Denny 1953	2/157	1/50		0.64 [0.06, 6.88]
Catanzaro 1954	26/650	12/220		0.73 [0.38, 1.43]
Total (95% CI)	**5656**	**4445**		**0.27 [0.12, 0.60]**

Total events: 37 (Antibiotics), 74 (Placebo)

Heterogeneity: Tau² = 0.51; Chi² = 12.20, df = 6 (P = 0.06); I² =51%

Test for overall effect: Z = 3.20 (P = 0.0014)

Analysis 1.2. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 2 Incidence of acute rheumatic fever within two months. Penicillin versus placebo.

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome: 2 Incidence of acute rheumatic fever within two months. Penicillin versus placebo

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bennike 1951	0/238	0/268		0.0 [0.0, 0.0]
Brink 1951	2/197	5/198		0.40 [0.08, 2.05]
Brumfitt 1957	0/62	0/59		0.0 [0.0, 0.0]
Catanzaro 1954	12/420	12/220		0.52 [0.24, 1.15]
Chamovitz 1954	0/257	2/109		0.09 [0.00, 1.76]
Chapple 1956	0/99	0/97		0.0 [0.0, 0.0]
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
De Meyere 1992	0/87	0/94		0.0 [0.0, 0.0]
Denny 1950	2/798	17/804		0.12 [0.03, 0.51]
Denny 1953	1/53	1/50		0.94 [0.06, 14.68]
Pichichero 1987	0/59	0/58		0.0 [0.0, 0.0]

(*Continued* . . .)

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Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Siegel 1961	0/605	2/608		0.20 [0.01, 4.18]
Wannamaker 1951	5/978	35/996		0.15 [0.06, 0.37]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Total (95% CI)	**4332**	**3843**		**0.27 [0.14, 0.50]**

Total events: 22 (Antibiotics), 74 (Placebo)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 7.61$, df = 6 (P = 0.27); $I^2 = 21\%$

Test for overall effect: Z = 4.16 (P = 0.000032)

Analysis 1.3. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 3 Incidence of acute rheumatic fever within two months: early (pre-1975) versus late studies (post-1975).

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome: 3 Incidence of acute rheumatic fever within two months: early (pre-1975) versus late studies (post-1975)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Incidence of acute rheumatic fever within 2 months: early (pre-1975) studies				
Bennike 1951	0/238	0/268		0.0 [0.0, 0.0]
Brink 1951	2/277	5/198		0.29 [0.06, 1.46]
Brumfitt 1957	0/62	0/59		0.0 [0.0, 0.0]
Catanzaro 1954	26/650	12/220		0.73 [0.38, 1.43]
Chamovitz 1954	0/257	2/109		0.09 [0.00, 1.76]
Chapple 1956	0/186	0/97		0.0 [0.0, 0.0]
Denny 1950	2/798	17/804		0.12 [0.03, 0.51]
Denny 1953	2/157	1/50		0.64 [0.06, 6.88]
Siegel 1961	0/605	2/608		0.20 [0.01, 4.18]
Wannamaker 1951	5/978	35/996		0.15 [0.06, 0.37]
Subtotal (95% CI)	**4208**	**3409**		**0.27 [0.12, 0.60]**

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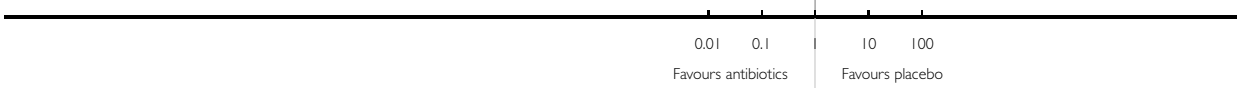
Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total events: 37 (Antibiotics), 74 (Placebo)				
Heterogeneity: Tau^2 = 0.51; Chi^2 = 12.20, df = 6 (P = 0.06); I^2 =51%				
Test for overall effect: Z = 3.20 (P = 0.0014)				
2 Incidence of acute rheumatic fever within 2 months: late (post-1975) studies				
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
De Meyere 1992	0/87	0/94		0.0 [0.0, 0.0]
Leelarasamee 2000	0/369	0/386		0.0 [0.0, 0.0]
Little 1997	0/454	0/216		0.0 [0.0, 0.0]
Pichichero 1987	0/59	0/58		0.0 [0.0, 0.0]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1448**	**1036**		**0.0 [0.0, 0.0]**
Total events: 0 (Antibiotics), 0 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**5656**	**4445**		**0.27 [0.12, 0.60]**
Total events: 37 (Antibiotics), 74 (Placebo)				
Heterogeneity: Tau^2 = 0.51; Chi^2 = 12.20, df = 6 (P = 0.06); I^2 =51%				
Test for overall effect: Z = 3.20 (P = 0.0014)				



Analysis 1.4. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 4 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis.

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome: 4 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bennike 1951	0/238	2/268		0.23 [0.01, 4.67]
Brink 1951	5/277	13/198		0.27 [0.10, 0.76]
Chamovitz 1954	0/257	1/109		0.14 [0.01, 3.46]
Chapple 1956	5/186	5/97		0.52 [0.15, 1.76]
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
De Meyere 1992	0/87	0/94		0.0 [0.0, 0.0]
Denny 1953	0/157	2/50		0.06 [0.00, 1.32]
Little 1997	0/454	1/216		0.16 [0.01, 3.89]
Pichichero 1987	1/59	0/55		2.80 [0.12, 67.32]
Taylor 1977	0/131	4/66		0.06 [0.00, 1.03]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Total (95% CI)	**2325**	**1435**		**0.30 [0.15, 0.58]**

Total events: 11 (Antibiotics), 28 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.41$, df = 7 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 3.59 (P = 0.00033)

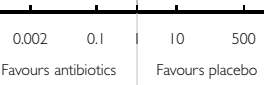
Analysis 1.5. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 5 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975).

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome: 5 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Incidence of otitis media within 14 days: early (pre-1975) studies				
Bennike 1951	0/238	2/268		0.23 [0.01, 4.67]
Brink 1951	5/277	13/198		0.27 [0.10, 0.76]
Chamovitz 1954	0/257	1/109		0.14 [0.01, 3.46]
Chapple 1956	5/186	5/97		0.52 [0.15, 1.76]
Denny 1953	0/157	2/50		0.06 [0.00, 1.32]
Subtotal (95% CI)	**1115**	**722**		**0.30 [0.15, 0.62]**
Total events: 10 (Antibiotics), 23 (Placebo)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.08$, df = 4 (P = 0.72); $I^2 = 0.0\%$				
Test for overall effect: Z = 3.28 (P = 0.0010)				
2 Incidence of otitis media within 14 days: late (post-1975) studies				
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
De Meyere 1992	0/87	0/94		0.0 [0.0, 0.0]
Little 1997	0/454	1/216		0.16 [0.01, 3.89]
Pichichero 1987	1/59	0/55		2.80 [0.12, 67.32]
Taylor 1977	0/131	4/66		0.06 [0.00, 1.03]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1210**	**713**		**0.28 [0.03, 2.74]**
Total events: 1 (Antibiotics), 5 (Placebo)				
Heterogeneity: $Tau^2 = 1.62$; $Chi^2 = 3.30$, df = 2 (P = 0.19); $I^2 = 39\%$				
Test for overall effect: Z = 1.10 (P = 0.27)				
Total (95% CI)	**2325**	**1435**		**0.30 [0.15, 0.58]**
Total events: 11 (Antibiotics), 28 (Placebo)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.41$, df = 7 (P = 0.61); $I^2 = 0.0\%$				
Test for overall effect: Z = 3.59 (P = 0.00033)				



Analysis 1.6. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 6 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis.

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

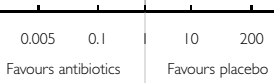
Outcome: 6 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Chamovitz 1954	1/257	3/109		0.14 [0.01, 1.34]
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
De Meyere 1992	0/87	0/84		0.0 [0.0, 0.0]
Denny 1953	0/157	1/50		0.11 [0.00, 2.60]
Landsman 1951	2/52	0/43		4.15 [0.20, 84.21]
Little 1997	1/454	0/216		1.43 [0.06, 34.98]
Pichichero 1987	0/59	0/58		0.0 [0.0, 0.0]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Total (95% CI)	**1545**	**842**		**0.48 [0.08, 2.76]**

Total events: 4 (Antibiotics), 4 (Placebo)

Heterogeneity: $Tau^2 = 1.04$; $Chi^2 = 4.45$, df = 3 (P = 0.22); $I^2 = 33\%$

Test for overall effect: Z = 0.82 (P = 0.41)



Analysis 1.7. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 7 Incidence of quinsy within two months. Quinsy defined by clinical diagnosis.

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

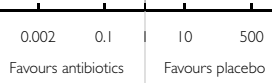
Outcome: 7 Incidence of quinsy within two months. Quinsy defined by clinical diagnosis

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bennike 1951	1/238	15/268		0.08 [0.01, 0.56]
Dagnelie 1996	0/121	2/118		0.20 [0.01, 4.02]
De Meyere 1992	0/87	0/94		0.0 [0.0, 0.0]
Howe 1997	1/69	0/34		1.50 [0.06, 35.88]
Landsman 1951	0/52	2/43		0.17 [0.01, 3.37]
Little 1997	0/454	1/216		0.16 [0.01, 3.89]
Pichichero 1987	0/59	0/58		0.0 [0.0, 0.0]
Zwart 2000	0/358	3/164		0.07 [0.00, 1.26]
Total (95% CI)	**1438**	**995**		**0.15 [0.05, 0.47]**

Total events: 2 (Antibiotics), 23 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.85$, df = 5 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 3.26 (P = 0.00111)



Analysis 1.8. Comparison 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications, Outcome 8 Incidence of acute glomerulonephritis within one month. Acute glomerulonephritis defined by clinical diagnosis.

Review: Antibiotics for sore throat

Comparison: 1 Antibiotics versus placebo for the treatment of sore throat: incidence of complications

Outcome: 8 Incidence of acute glomerulonephritis within one month. Acute glomerulonephritis defined by clinical diagnosis

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bennike 1951	0/238	0/268		0.0 [0.0, 0.0]
Brink 1951	0/277	0/198		0.0 [0.0, 0.0]
Brumfitt 1957	0/62	0/59		0.0 [0.0, 0.0]
Chamovitz 1954	0/257	1/109		0.14 [0.01, 3.46]
Chapple 1956	0/186	0/97		0.0 [0.0, 0.0]
Dagnelie 1996	0/121	0/118		0.0 [0.0, 0.0]
Leelarasamee 2000	0/369	0/386		0.0 [0.0, 0.0]
Little 1997	0/454	0/216		0.0 [0.0, 0.0]
Siegel 1961	0/605	1/605		0.33 [0.01, 8.17]
Zwart 2000	0/358	0/164		0.0 [0.0, 0.0]
Total (95% CI)	**2927**	**2220**		**0.22 [0.02, 2.08]**

Total events: 0 (Antibiotics), 2 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 1.32 (P = 0.19)

Analysis 2.1. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 1 Symptom of sore throat on day three.

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 1 Symptom of sore throat on day three

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brink 1951	119/277	129/198		8.5 %	0.66 [0.56, 0.78]
Brumfitt 1957	21/42	26/40		5.9 %	0.77 [0.53, 1.12]
Chapple 1956	40/135	37/65		6.4 %	0.52 [0.37, 0.73]
Dagnelie 1996	36/117	57/117		6.5 %	0.63 [0.45, 0.88]
De Meyere 1992	18/82	59/91		5.2 %	0.34 [0.22, 0.52]
Denny 1953	89/157	48/50		8.7 %	0.59 [0.51, 0.68]
El-Daher 1991	42/111	106/118		7.6 %	0.42 [0.33, 0.54]
Landsman 1951	6/52	7/43		1.7 %	0.71 [0.26, 1.95]
Little 1997	135/215	122/187		8.8 %	0.96 [0.83, 1.11]
MacDonald 1951	18/41	27/41		5.5 %	0.67 [0.44, 1.00]
Middleton 1988	2/34	5/23		0.8 %	0.27 [0.06, 1.28]
Petersen 1997	60/89	74/90		8.5 %	0.82 [0.69, 0.98]
Whitfield 1981	129/256	165/272		8.7 %	0.83 [0.71, 0.97]
Zwart 2000	215/358	131/164		9.1 %	0.75 [0.67, 0.84]
Zwart 2003	79/100	38/56		8.1 %	1.16 [0.95, 1.43]
Total (95% CI)	**2066**	**1555**		**100.0 %**	**0.68 [0.59, 0.79]**

Total events: 1009 (Antibiotics), 1031 (Placebo)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 85.89$, df = 14 ($P<0.00001$); $I^2 = 84\%$

Test for overall effect: $Z = 5.03$ ($P < 0.00001$)

Analysis 2.2. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 2 Symptom of sore throat on day three: blind versus unblinded studies.

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 2 Symptom of sore throat on day three: blind versus unblinded studies

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Symptom of sore throat on day 3: blinded studies.					
Chapple 1956	40/135	37/65		6.4 %	0.52 [0.37, 0.73]
Dagnelie 1996	36/117	57/117		6.5 %	0.63 [0.45, 0.88]
De Meyere 1992	18/82	59/91		5.2 %	0.34 [0.22, 0.52]
Denny 1953	89/157	48/50		8.7 %	0.59 [0.51, 0.68]
El-Daher 1991	42/111	106/118		7.6 %	0.42 [0.33, 0.54]
Landsman 1951	6/52	7/43		1.7 %	0.71 [0.26, 1.95]
MacDonald 1951	18/41	27/41		5.5 %	0.67 [0.44, 1.00]
Middleton 1988	2/34	5/23		0.8 %	0.27 [0.06, 1.28]
Petersen 1997	60/89	74/90		8.5 %	0.82 [0.69, 0.98]
Whitfield 1981	129/256	165/272		8.7 %	0.83 [0.71, 0.97]
Zwart 2000	215/358	131/164		9.1 %	0.75 [0.67, 0.84]
Zwart 2003	79/100	38/56		8.1 %	1.16 [0.95, 1.43]
Subtotal (95% CI)	**1532**	**1130**		**76.8 %**	**0.65 [0.54, 0.78]**
Total events: 734 (Antibiotics), 754 (Placebo)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 70.93$, df = 11 (P<0.00001); $I^2 = 84\%$					
Test for overall effect: Z = 4.67 (P < 0.00001)					
2 Symptom of sore throat on day 3: unblinded studies.					
Brink 1951	119/277	129/198		8.5 %	0.66 [0.56, 0.78]
Brumfitt 1957	21/42	26/40		5.9 %	0.77 [0.53, 1.12]
Little 1997	135/215	122/187		8.8 %	0.96 [0.83, 1.11]
Subtotal (95% CI)	**534**	**425**		**23.2 %**	**0.79 [0.60, 1.05]**
Total events: 275 (Antibiotics), 277 (Placebo)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 11.17$, df = 2 (P = 0.004); $I^2 = 82\%$					
Test for overall effect: Z = 1.62 (P = 0.11)					
Total (95% CI)	**2066**	**1555**		**100.0 %**	**0.68 [0.59, 0.79]**
Total events: 1009 (Antibiotics), 1031 (Placebo)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 85.89$, df = 14 (P<0.00001); $I^2 = 84\%$					
Test for overall effect: Z = 5.03 (P < 0.00001)					

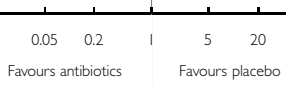
Analysis 2.3. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 3 Symptom of sore throat on day three: antipyretics versus no antipyretics.

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 3 Symptom of sore throat on day three: antipyretics versus no antipyretics

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Symptom of sore throat on day 3: antipyretics administered.					
Brumfitt 1957	21/42	26/40		14.4 %	0.77 [0.53, 1.12]
Chapple 1956	40/135	37/65		16.6 %	0.52 [0.37, 0.73]
De Meyere 1992	18/82	59/91		12.1 %	0.34 [0.22, 0.52]
Subtotal (95% CI)	**259**	**196**		**43.1 %**	**0.52 [0.33, 0.81]**
Total events: 79 (Antibiotics), 122 (Placebo)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.26$, df = 2 (P = 0.02); $I^2 = 76\%$					
Test for overall effect: Z = 2.87 (P = 0.0041)					
2 Symptom of sore throat on day 3: no antipyretics administered.					
Brink 1951	119/277	129/198		27.6 %	0.66 [0.56, 0.78]
Denny 1953	89/157	48/50		29.2 %	0.59 [0.51, 0.68]
Subtotal (95% CI)	**434**	**248**		**56.9 %**	**0.62 [0.55, 0.70]**
Total events: 208 (Antibiotics), 177 (Placebo)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.17$, df = 1 (P = 0.28); $I^2 = 14\%$					
Test for overall effect: Z = 7.76 (P < 0.00001)					
Total (95% CI)	**693**	**444**		**100.0 %**	**0.58 [0.48, 0.70]**
Total events: 287 (Antibiotics), 299 (Placebo)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.52$, df = 4 (P = 0.03); $I^2 = 62\%$					
Test for overall effect: Z = 5.76 (P < 0.00001)					



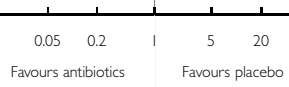
Analysis 2.4. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 4 Symptom of sore throat on day three: Streptococcus positive throat swab, negative swab, untested/ inseparable.

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 4 Symptom of sore throat on day three: Streptococcus positive throat swab, negative swab, untested/ inseparable

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Symptom of sore throat on day 3: Group A Beta Haemolytic Streptococcus positive throat swab					
Brink 1951	119/277	129/198		6.9 %	0.66 [0.56, 0.78]
Brumfitt 1957	21/42	26/40		4.9 %	0.77 [0.53, 1.12]
Chapple 1956	13/68	22/41		3.4 %	0.36 [0.20, 0.63]
Dagnelie 1996	13/55	36/55		3.8 %	0.36 [0.22, 0.60]
De Meyere 1992	18/82	59/91		4.4 %	0.34 [0.22, 0.52]
Denny 1953	89/157	48/50		7.0 %	0.59 [0.51, 0.68]
El-Daher 1991	42/111	106/118		6.2 %	0.42 [0.33, 0.54]
MacDonald 1951	13/26	17/24		4.2 %	0.71 [0.44, 1.12]
Middleton 1988	2/24	5/23		0.8 %	0.38 [0.08, 1.78]
Zwart 2000	102/178	68/83		6.9 %	0.70 [0.59, 0.82]
Zwart 2003	39/53	28/43		5.9 %	1.13 [0.86, 1.48]
Subtotal (95% CI)	**1073**	**766**		**54.5 %**	**0.58 [0.48, 0.71]**
Total events: 471 (Antibiotics), 544 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 51.31, df = 10 (P<0.00001); I^2 =81%					
Test for overall effect: Z = 5.34 (P < 0.00001)					
2 Symptom of sore throat on day 3: Group A Beta Haemolytic Streptococcus negative throat swab					
Chapple 1956	13/67	16/26		3.4 %	0.32 [0.18, 0.56]
Dagnelie 1996	31/60	29/51		5.3 %	0.91 [0.65, 1.28]
MacDonald 1951	5/15	10/17		2.1 %	0.57 [0.25, 1.29]
Petersen 1997	60/89	74/90		6.8 %	0.82 [0.69, 0.98]
Zwart 2000	113/180	63/81		6.9 %	0.81 [0.69, 0.95]
Zwart 2003	40/47	10/13		5.5 %	1.11 [0.80, 1.52]
Subtotal (95% CI)	**458**	**278**		**30.0 %**	**0.78 [0.63, 0.97]**
Total events: 262 (Antibiotics), 202 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 15.65, df = 5 (P = 0.01); I^2 =68%					
Test for overall effect: Z = 2.20 (P = 0.028)					



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Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Symptom of sore throat on day 3: Untested for GABHS culture or combined inseparable data					
Landsman 1951	6/52	7/43		1.5 %	0.71 [0.26, 1.95]
Little 1997	135/215	122/187		7.0 %	0.96 [0.83, 1.11]
Whitfield 1981	129/256	165/272		7.0 %	0.83 [0.71, 0.97]
Subtotal (95% CI)	**523**	**502**		**15.6 %**	**0.89 [0.80, 1.00]**
Total events: 270 (Antibiotics), 294 (Placebo)					
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 2 (P = 0.35); I² =4%					
Test for overall effect: Z = 1.98 (P = 0.048)					
Total (95% CI)	**2054**	**1546**		**100.0 %**	**0.68 [0.59, 0.78]**
Total events: 1003 (Antibiotics), 1040 (Placebo)					
Heterogeneity: Tau² = 0.07; Chi² = 103.16, df = 19 (P<0.00001); I² =82%					
Test for overall effect: Z = 5.46 (P < 0.00001)					

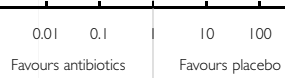
Analysis 2.5. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 5 Symptom of sore throat at one week (six to eight days).

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 5 Symptom of sore throat at one week (six to eight days)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bennike 1951	0/100	7/99		0.07 [0.00, 1.14]
Brink 1951	4/277	15/198		0.19 [0.06, 0.57]
Brumfitt 1957	0/42	2/40		0.19 [0.01, 3.85]
Dagnelie 1996	3/51	15/51		0.20 [0.06, 0.65]
De Meyere 1992	3/61	10/70		0.34 [0.10, 1.19]
Denny 1953	6/157	16/50		0.12 [0.05, 0.29]
Landsman 1951	0/52	0/43		0.0 [0.0, 0.0]
Little 1997	66/388	35/184		0.89 [0.62, 1.30]
MacDonald 1951	0/41	1/41		0.33 [0.01, 7.95]



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Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Petersen 1997	21/89	32/90		0.66 [0.42, 1.06]
Taylor 1977	6/129	3/59		0.91 [0.24, 3.53]
Zwart 2000	117/352	63/154		0.81 [0.64, 1.03]
Zwart 2003	20/100	7/56		1.60 [0.72, 3.55]
Total (95% CI)	**1839**	**1135**		**0.49 [0.32, 0.76]**

Total events: 246 (Antibiotics), 206 (Placebo)

Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = 38.59$, df = 11 (P = 0.00006); $I^2 = 71\%$

Test for overall effect: Z = 3.19 (P = 0.0014)

Analysis 2.6. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 6 Symptom of sore throat at one week (six to eight days): blind versus unblinded studies.

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 6 Symptom of sore throat at one week (six to eight days): blind versus unblinded studies

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Symptom of sore throat at 1 week (6-8 days): blinded studies				
Dagnelie 1996	4/47	3/35		0.99 [0.24, 4.16]
De Meyere 1992	3/51	10/70		0.41 [0.12, 1.42]
Denny 1953	6/157	16/50		0.12 [0.05, 0.29]
Landsman 1951	0/52	0/43		0.0 [0.0, 0.0]
MacDonald 1951	0/41	1/41		0.33 [0.01, 7.95]
Petersen 1997	21/89	32/90		0.66 [0.42, 1.06]
Taylor 1977	6/129	3/59		0.91 [0.24, 3.53]
Zwart 2000	117/352	63/154		0.81 [0.64, 1.03]
Zwart 2003	20/100	7/56		1.60 [0.72, 3.55]
Subtotal (95% CI)	**1018**	**598**		**0.62 [0.38, 1.03]**

Total events: 177 (Antibiotics), 135 (Placebo)

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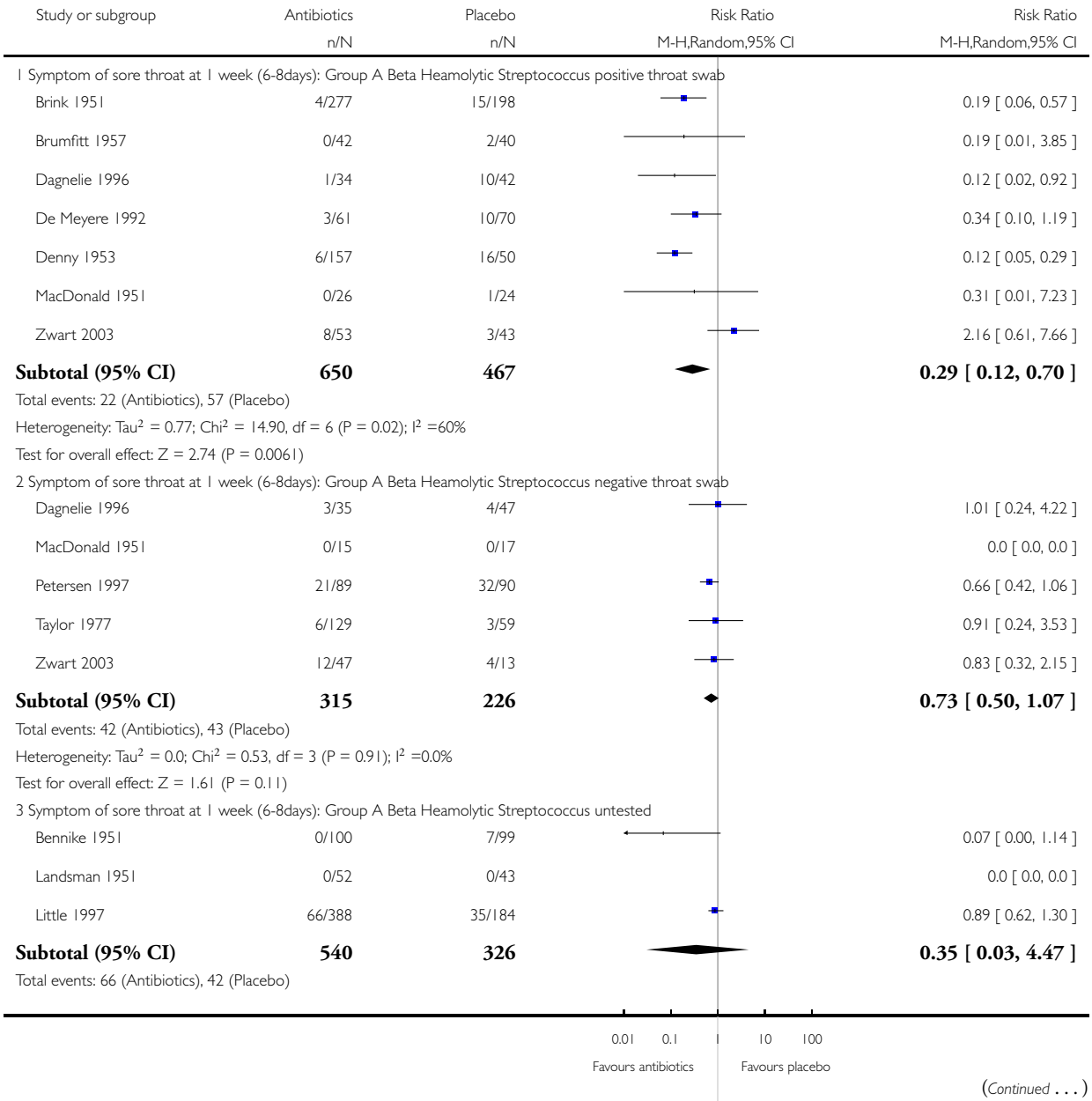
Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.28; Chi^2 = 22.27, df = 7 (P = 0.002); I^2 =69%				
Test for overall effect: Z = 1.83 (P = 0.068)				
2 Symptom of sore throat at 1 week (6-8 days): unblinded studies				
Bennike 1951	0/100	7/99		0.07 [0.00, 1.14]
Brink 1951	4/277	15/198		0.19 [0.06, 0.57]
Brumfitt 1957	0/42	2/40		0.19 [0.01, 3.85]
Little 1997	66/388	35/184		0.89 [0.62, 1.30]
Subtotal (95% CI)	**807**	**521**		**0.30 [0.08, 1.15]**
Total events: 70 (Antibiotics), 59 (Placebo)				
Heterogeneity: Tau^2 = 1.10; Chi^2 = 11.19, df = 3 (P = 0.01); I^2 =73%				
Test for overall effect: Z = 1.76 (P = 0.079)				
Total (95% CI)	**1825**	**1119**		**0.57 [0.38, 0.86]**
Total events: 247 (Antibiotics), 194 (Placebo)				
Heterogeneity: Tau^2 = 0.24; Chi^2 = 33.28, df = 11 (P = 0.00047); I^2 =67%				
Test for overall effect: Z = 2.71 (P = 0.0068)				

Analysis 2.7. Comparison 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat, Outcome 7 Symptom of sore throat at one week (six to eight days): GABHS positive throat swab, GABHS negative swab. Untes.

Review: Antibiotics for sore throat

Comparison: 2 Antibiotics versus placebo for the treatment of sore throats: symptom of sore throat

Outcome: 7 Symptom of sore throat at one week (six to eight days): GABHS positive throat swab, GABHS negative swab. Untes



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 2.58; Chi² = 3.40, df = 1 (P = 0.07); I² =71%				
Test for overall effect: Z = 0.81 (P = 0.42)				
Total (95% CI)	**1505**	**1019**	◆	**0.48 [0.29, 0.80]**
Total events: 130 (Antibiotics), 142 (Placebo)				
Heterogeneity: Tau² = 0.42; Chi² = 33.79, df = 12 (P = 0.00073); I² =64%				
Test for overall effect: Z = 2.84 (P = 0.0045)				

Analysis 3.1. Comparison 3 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 1 Symptom of fever on day three.

Review: Antibiotics for sore throat

Comparison: 3 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 1 Symptom of fever on day three

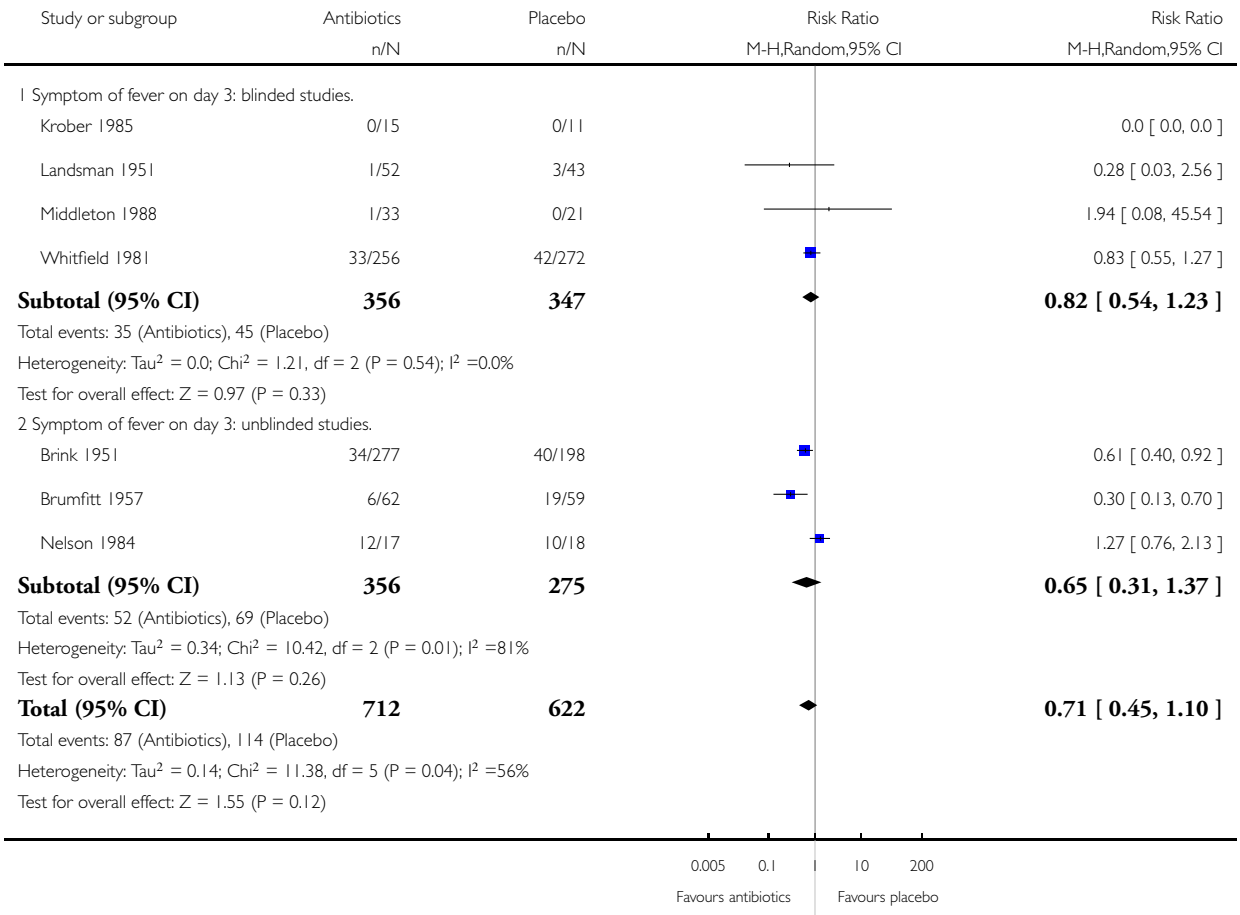
Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Brink 1951	34/277	40/198	■	0.61 [0.40, 0.92]
Brumfitt 1957	6/62	19/59	■	0.30 [0.13, 0.70]
Krober 1985	0/15	0/11		0.0 [0.0, 0.0]
Landsman 1951	1/52	3/43	■	0.28 [0.03, 2.56]
Middleton 1988	1/33	0/21	■	1.94 [0.08, 45.54]
Nelson 1984	12/17	10/18	■	1.27 [0.76, 2.13]
Whitfield 1981	33/256	42/272	■	0.83 [0.55, 1.27]
Total (95% CI)	**712**	**622**	◆	**0.71 [0.45, 1.10]**
Total events: 87 (Antibiotics), 114 (Placebo)				
Heterogeneity: Tau² = 0.14; Chi² = 11.38, df = 5 (P = 0.04); I² =56%				
Test for overall effect: Z = 1.55 (P = 0.12)				

Analysis 3.2. Comparison 3 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 2 Symptom of fever on day three: blinded versus unblinded studies.

Review: Antibiotics for sore throat

Comparison: 3 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 2 Symptom of fever on day three: blinded versus unblinded studies

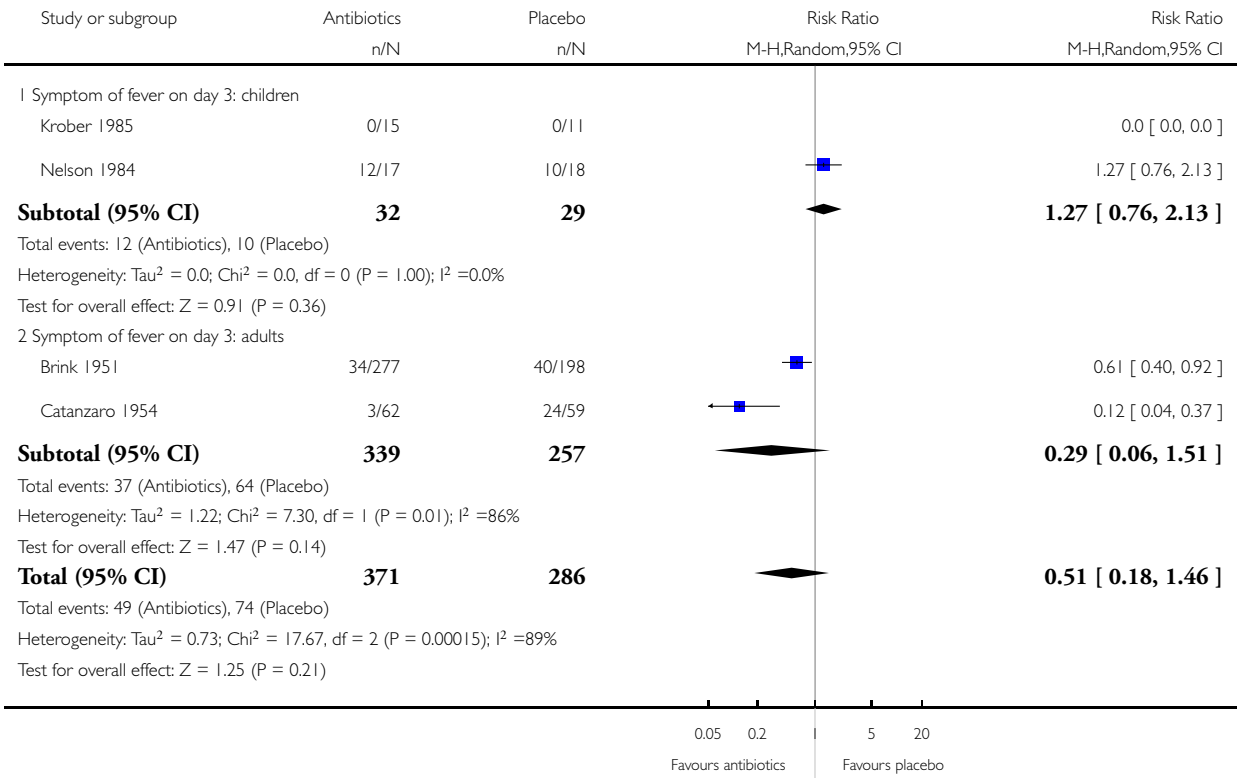


Analysis 3.3. Comparison 3 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 3 Symptom of fever on day three: children compared with adults.

Review: Antibiotics for sore throat

Comparison: 3 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 3 Symptom of fever on day three: children compared with adults



Analysis 3.4. Comparison 3 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 4 Symptom of fever at one week (six to eight days).

Review: Antibiotics for sore throat

Comparison: 3 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 4 Symptom of fever at one week (six to eight days)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Brink 1951	0/277	0/198		0.0 [0.0, 0.0]
Denny 1950	0/157	0/50		0.0 [0.0, 0.0]
Landsman 1951	0/52	0/43		0.0 [0.0, 0.0]
Total (95% CI)	**486**	**291**		**0.0 [0.0, 0.0]**

Total events: 0 (Antibiotics), 0 (Placebo)

Heterogeneity: Tau² = ï½; Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)

Analysis 4.1. Comparison 4 Antibiotics versus control for the treatment of sore throat: symptom of headache, Outcome 1 Symptom of headache on day three.

Review: Antibiotics for sore throat

Comparison: 4 Antibiotics versus control for the treatment of sore throat: symptom of headache

Outcome: 1 Symptom of headache on day three

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brink 1951	61/277	80/198		40.1 %	0.55 [0.41, 0.72]
Denny 1953	54/157	30/50		38.7 %	0.57 [0.42, 0.78]
El-Daher 1991	7/118	37/111		21.1 %	0.18 [0.08, 0.38]
Total (95% CI)	**552**	**359**		**100.0 %**	**0.44 [0.27, 0.71]**

Total events: 122 (Antibiotics), 147 (Placebo)

Heterogeneity: Tau² = 0.13; Chi² = 8.71, df = 2 (P = 0.01); I² =77%

Test for overall effect: Z = 3.39 (P = 0.00069)

Analysis 4.2. Comparison 4 Antibiotics versus control for the treatment of sore throat: symptom of headache, Outcome 2 Symptom of headache on day three: blinded versus unblinded studies.

Review: Antibiotics for sore throat

Comparison: 4 Antibiotics versus control for the treatment of sore throat: symptom of headache

Outcome: 2 Symptom of headache on day three: blinded versus unblinded studies

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Symptom headache on day three: blinded studies					
Denny 1953	54/157	30/50		38.7 %	0.57 [0.42, 0.78]
El-Daher 1991	7/118	37/111		21.1 %	0.18 [0.08, 0.38]
Subtotal (95% CI)	**275**	**161**		**59.9 %**	**0.33 [0.09, 1.20]**
Total events: 61 (Antibiotics), 67 (Placebo)					
Heterogeneity: Tau^2 = 0.77; Chi^2 = 9.71, df = 1 (P = 0.002); I^2 =90%					
Test for overall effect: Z = 1.68 (P = 0.094)					
2 Symptom of headache on day three: unblinded studies					
Brink 1951	61/277	80/198		40.1 %	0.55 [0.41, 0.72]
Subtotal (95% CI)	**277**	**198**		**40.1 %**	**0.55 [0.41, 0.72]**
Total events: 61 (Antibiotics), 80 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.27 (P = 0.000020)					
Total (95% CI)	**552**	**359**		**100.0 %**	**0.44 [0.27, 0.71]**
Total events: 122 (Antibiotics), 147 (Placebo)					
Heterogeneity: Tau^2 = 0.13; Chi^2 = 8.71, df = 2 (P = 0.01); I^2 =77%					
Test for overall effect: Z = 3.39 (P = 0.00069)					

APPENDICES

Appendix 1. Embase.com search strategy

(Embase.com used in most recent update)
#1. 'pharyngitis'/exp AND [embase]/lim
#2. pharyngit*:ti,ab AND [2004-2008]/py
#3. 'rhinopharyngitis'/exp AND [embase]/lim
#4. rhinopharyngit*:ti,ab OR nasopharyngit*:ti,ab [embase]/lim
#5. 'tonsillitis'/exp AND [embase]/lim
#6. tonsillit*:ti,ab AND [embase]/lim
#7. 'sore throat'/exp AND [embase]/lim
#8. 'sore throat':ti,ab OR 'sore throats':ti,ab embase]/lim
#9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10. 'antibiotic agent'/exp AND [embase]/lim
#11. antibiotic*:ti,ab AND [embase]/lim
#12. #10 OR #11 619,306

#13. random*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR 'cross over':ti,ab OR placebo*:ti,ab OR ass ign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab AND [embase]/lim
#14. 'double blind':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab AND [embase]/lim
#15. 'crossover procedure'/exp AND [embase]/lim
#16. 'double blind procedure'/exp AND [embase]/lim
#17. 'single blind procedure'/exp AND [embase]/lim
#18. 'randomized controlled trial'/exp AND [embase]/lim
#19. #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20. #9 AND #12 AND #19

Appendix 2. EMBASE search strategy

EMBASE (WebSPIRS)
#1 explode 'pharyngitis-' / all subheadings in DEM,DER,DRM,DRR
#2 (pharyngit* in ti) or (pharyngit* in ab)
#3 explode 'rhinopharyngitis-' / all subheadings in DEM,DER,DRM,DRR
#4 (nasopharyngit* in ti) or (nasopharyngit* in ab)
#5 explode 'tonsillitis-' / all subheadings in DEM,DER,DRM,DRR
#6 (tonsillit* in ti) or (tonsillit* in ab)
#7 explode 'sore-throat' / all subheadings in DEM,DER,DRM,DRR
#8 (sore throat in ti) or (sore throat in ab)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 'antibiotic-agent' / all subheadings in DEM,DER,DRM,DRR
#11 (antibiotic* in ti) or (antibiotic* in ab)
#12 #10 or #11
#13 #9 and #12
#14 explode 'randomized-controlled-trial' / all subheadings
#15 explode 'controlled-study' / all subheadings
#16 explode 'single-blind-procedure' / all subheadings
#17 explode 'double-blind-procedure' / all subheadings
#18 explode 'crossover-procedure' / all subheadings
#19 explode 'phase-3-clinical-trial' / all subheadings
#20 (randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)
#21 ((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)
#22 (controlled clinical trial* in ti) or (controlled clinical trial* in ab)
#23 (explode 'randomized-controlled-trial' / all subheadings) or (explode 'controlled-study' / all subheadings) or (explode 'single-blind-procedure' / all subheadings) or (explode 'double-blind-procedure' / all subheadings) or (explode 'crossover-procedure' / all subheadings) or (explode 'phase-3-clinical-trial' / all subheadings) or ((randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)) or (((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)) or ((controlled clinical trial* in ti) or (controlled clinical trial* in ab))
#24 (nonhuman in der) not ((human in der)and (nonhuman in der))
#25 ((explode 'randomized-controlled-trial' / all subheadings) or (explode 'controlled-study' / all subheadings) or (explode 'single-blind-procedure' / all subheadings) or (explode 'double-blind-procedure' / all subheadings) or (explode 'crossover-procedure' / all subheadings) or (explode 'phase-3-clinical-trial' / all subheadings) or ((randomi?ed controlled trial in ti) or (randomi?ed controlled trial in ab)) or (((random* or placebo* or double-blind*)in ti) or ((random* or placebo* or double-blind*)in ab)) or ((controlled clinical trial* in ti) or (controlled clinical trial* in ab))) not ((nonhuman in der) not ((human in der)and (nonhuman in der)))
#26 #13 and #25

FEEDBACK

Antibiotics for sore throat

Summary

1. The objectives as they are stated in the abstract include an assessment of the harms associated with the use of antibiotics in the management of sore throat, but the objectives as stated in the text of the review no longer refer to any assessment of harm. Indeed, the review does not address any adverse effects of antibiotics [which are not unimportant] and does not provide a reasonable explanation as to why this is not done other than to state in the discussion that this was not possible because of inconsistencies in the way these data were recorded. In the absence of RCT data on harmful effects the authors might have considered whether usable information could be provided by other study designs.
2. Reviews on this subject should treat adults and children separately, but this review does not attempt to do this.
3. All clinically important outcomes have not been addressed by the review and others such as resource use, re-attendance and time off school or work are probably at least as important as those that were selected. It may have been more helpful to have collected data on all available outcomes provided that they are free from detection bias.
4. The question addressed by the review is not sufficiently well defined to allow the review to be executed systematically. Clear definitions are not given for the key elements of the question.
Most importantly, clear definitions of what is meant by primary care and sore throat are not given, leading to confusion around inclusion and exclusion decisions. Many of the control groups of the included studies do not involve a placebo but instead simply compare treatment with antibiotics to no treatment, so that some excluded studies would be eligible for inclusion, such as Catanzaro 1958 which was excluded because it compared antibiotics with sulfadiazine.
Apparent errors in inclusion and exclusion decisions have arisen probably as a result of the general lack of clarity discussed above. Specifically, the lack of a clear definition of what is meant by primary care appears to have led to the inclusion of an odd assortment of studies. For example, a couple of the included trials studied only people with sore throat who were admitted to hospital (Siegal 1961 and Bennike 1951). In addition, there appears to be an issue around the definition of a sore throat particularly in relation to positive or negative Streptococcus throat swabs. Streptococcal sore throats are a small sub-set of the total population of sore throats and the failure of the reviewers to address this in the inclusion criteria means that the results of pragmatic trials of sore throat are mixed in with those of
streptococcal sore throat.
There is a failure to always faithfully report the detailed results of the included studies, and there are several numerical errors in the data abstracted. For example, in Bennike 1951 the baseline numbers include patients in the "ulcerative tonsillitis" group even though most outcomes are not reported for this group.
5. The search strategy is restricted to a Medline search, a search of the Cochrane Library and citation checking. No attempt appears to have been made to search other databases. The reviewers are not explicit about the details of their searching activities nor about how they used the work of the Cochrane Acute Respiratory Infections Group.
6. References to the included and excluded studies were incomplete. Specifically they were not provided for Dagnelie 1996, Howie 1997, Little 1997 and Peterson 1997 (included) and Herx 1988, Howie 1970, Marlow 1989, McDonald 1985, Schalen 1993 and Todd 1984 (excluded).
7. Given the nature of the data presented, it is possible that a formal meta-analysis was inappropriate. A descriptive analysis may have been more appropriate and more informative.
8. There is considerable uncertainty around the effectiveness of antibiotics on sore throat on the basis of the existing research examined by this review and this is not emphasised by the authors. Particular problems exist around the relevance of the trials to the present day with regard to the outcomes examined (rheumatic fever and glomerulonephritis), the poor quality of the majority of the included trials and the generalisability of the trials with regard to the study populations (e.g. United States air force recruits).

Reply

1. This is valid criticism: we need to describe the inadequacies of the information in the trials (after checking again) in the text.
2. A subgroup analysis on the basis of age is a good idea, and we will attempt this at the next major review.
3. This is a good idea, and we will attempt this at the next major review.
4. Certainly the issue of definitions is particularly difficult in this group of illnesses. One of us has written a paper on these difficulties (Del Mar C. Managing sore throat: a literature review. I. Making the diagnosis. Med J Aust 1992;156:572-5.). There is a particular

difficulty in the fact that primary care doctors use the terms 'sore throat' tonsillitis and pharyngitis in slightly different ways, including interchangeably. Moreover the notion that patients with positive swabs for Streptococcus have a different illness can be challenged. Nevertheless a subgroup analysis for this with swab-positive and swab-negative is a good idea which we will incorporate with our next review.
Thank for pointing numerical errors out to us, and we will check on this. Please could you detail other numerical errors for us?
5. We are explicit about our search method. At the time we undertook the search the Cochrane Acute Respiratory Infections Group had no material to assist us. This will be reviewed at the next major update.
6. Thank you for drawing our attention to this.
7. As is often the case, there is considerable variation in the population groups, treatments, outcomes measures, etc in these trials. This does not make a synthesis inappropriate, but rather allows us to examine whether these factors appear to make a difference. We also felt it important to specifically attempt to calculate the SIZE of the benefits, as this is what clinicians are interested in, and what will persuade them to modify their practice. It is then important to recognise that the size of the effect will vary in different populations: as we point out, in groups at high risk of rheumatic fever - such as Australian aboriginals - the prevention of RF is important; we are also interested in trying to better predict which sub-groups will experience the most or least symptom relief, and plan to detail this in the next update.
8. We think we have discussed this in the Review. However we will reconsider what we have written in the overhaul.

Contributors

Jackie Young (on behalf of an interdepartmental critical appraisal workshop based in the Department of Public Health and Epidemiology, The University of Birmingham, UK) Email: j.m.young.20@bham.ac.uk

Antibiotics for sore throat

Summary

I noticed that trials with no events in either groups are not (cannot) be part of the pooled estimates. Although I see there is a statistical/ technical problem here it does not seem right. It appears to imply that no events is no evidence. I wonder whether it is defensible to add one event in both groups and add the evidence as one would normally do?
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Many thanks for this. We have gone back and checked with statisticians about your point. The issue seems to be:
1. Whether empty cells are a problem. The concern is that because one cannot divide anything by zero, this might represent a problem. We think not, because in no forest plots are there totals with zero--except for acute glomerulonephritis (there were no cases in the intervention arms of any trials, and only two in the control arms).
2. Whether the empty cells represent no evidence or evidence of no effect. We only recoded a zero where the study declared the outcome. Thus we assume that "no events" implies no events, rather than no reporting of events that might have occurred.
We have reported in Peto Odds ratios, the best measure for rare events.
Chris Del Mar

Contributors

Gerben ter Riet

Typographical error in the Abstract, 26 August 2008

Summary

Feedback: There seems to be a printing error in the abstract: the total number of cases according to the full text is 12835, but the number given in the abstract is 2835.

Reply

Many thanks. We will correct the typing error.
Chris Del Mar (Feedback reply submitted 28 August 2008)

Contributors

Martti Teikari (Feedback comment submitted 27 August 2008)

WHAT'S NEW

Last assessed as up-to-date: 24 November 2008.

25 November 2008	New search has been performed	Searches conducted. No new studies were identified and conclusions remain unchanged.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 2, 1997

27 August 2008	Feedback has been incorporated	Typographical error in the Abstract corrected.
12 July 2008	Amended	Converted to new review format.
18 October 2006	Feedback has been incorporated	Feedback added.
9 March 2006	New search has been performed	In this 2006 update there is an addition of data from one new study by Zwart 2003. Additionally, reported statistics were changed from odds ratios to more clinically meaningful relative risks (using a random-effects model). Since the update for this review was submitted to *The Cochrane Library* (Issue 4, 2006), we have been alerted to an error in the data extraction. This error involved switching the number of participants experiencing headache on day 3 between the intervention and placebo groups for the study by El-daher,

(*Continued*)

		1991. We therefore incorrectly concluded that antibiotics conferred no benefit for the symptom of headache, whereas in fact, the meta-analysis does show a significant protective effect (RR 0.47, 95% CI 0.38 - 0.58).
22 May 2003	New search has been performed	Searches conducted.
8 May 2000	New search has been performed	Searches conducted.
30 June 1999	New search has been performed	Searches conducted.
31 March 1996	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Chris Del Mar first conceived the review, presenting it as a meta-analysis in a journal (Del Mar 1992a; Del Mar 1992b). It was subsequently improved and modified for *The Cochrane Library* with Paul Glasziou (who improved the sub-group analyses) and Anneliese Spinks (who updated searches and completed the analyses).

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Bond University (2006 update), Australia.
- University of Oxford, UK.
- Griffith University, Australia.

External sources

- NHS support, UK.

NOTES

The Acute Respiratory Infections Group would like to thank Dr Dilruba Nasrin for reading and commenting on this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Pharyngitis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans