Antibiotics for sore throat

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Antibiotics for sore throat (Review)

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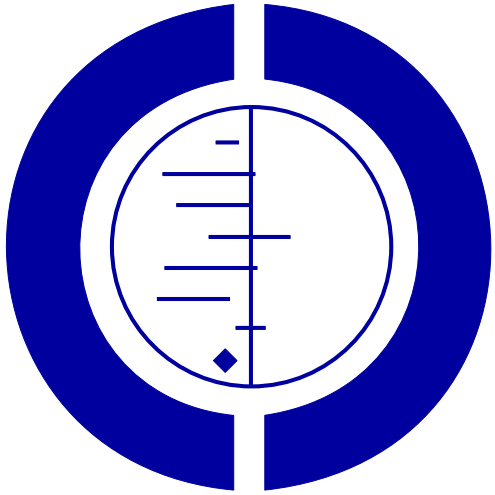

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TABLE OF CONTENTS

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ABSTRACT

Background
Sore throat is a very 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*, Issue 1, 2006), MEDLINE (January 1966 to March 2006) and EMBASE (January 1990 to December 2005).

Selection criteria
Trials of antibiotic against control with either measures of the typical symptoms (throat soreness, headache or fever), or suppurative or non-suppurative complications of sore throat.

Data collection and analysis
Potential studies were screened independently by two authors for inclusion, with differences in opinion resolved by discussion. Data were then independently extracted from studies selected by inclusion by two authors. Researchers from three studies were contacted for additional information.

Main results
There were 27 studies with 2835 cases of sore throat.

1. Non-suppurative complications
There was a trend for antibiotics to protect against acute glomerulonephritis, but there were insufficient cases to be sure. Several studies found antibiotics reduced acute rheumatic fever by more than two thirds (relative risk (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); of acute sinusitis (RR 0.48; 95% CI 0.08 to 2.76); and of quinsy (peritonsillar abscess) compared to those taking placebo (RR 0.15; 95% CI 0.05 to 0.47).

3. Symptoms
Throat soreness and fever were reduced by antibiotics by about one half. The greatest difference was seen at about 3 to 4 days (when the symptoms of about 50% of untreated patients had settled). By one week about 90% of treated and untreated patients were symptom-free. The overall number need to treat to prevent one sore throat at day 3 was just under six (95% CI 4.9 to 7.0); at week 1 it was 21 (95% CI 13.2 to 47.9).

4. Subgroup analyses of symptom reduction

Analysis by: age; blind versus unblinded; or use of antipyretics, found no significant differences.
Analysis of results of throat swabs showed that antibiotics were more effective against symptoms at day 3, RR 0.58 (95% CI 0.48 to 0.71) if the 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 modern Western society can only be achieved by treating many with antibiotics, most of whom will derive no benefit. In emerging economies (where rates of acute rheumatic fever are high, for example), the number needed to treat may be much lower for antibiotics to be considered effective. Antibiotics shorten the duration of symptoms by about sixteen hours overall.

PLAIN LANGUAGE SUMMARY

Antibiotics are of limited use for most people with sore throats

Sore throats are infections caused by bacteria or viruses, affecting mostly children and young adults. People usually recover quickly (usually after three or four days), although some develop complications. A serious but rare one of these 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. They can reduce the chance of rheumatic fever in communities where this complication is common.

BACKGROUND

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 individual primary care doctors (Howie 1971).

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 (which can cause acute rheumatic fever and acute glomerulonephritis). But deciding the etiological agent is difficult (Del Mar 1992b).

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 was built on an early meta-analysis (Del Mar 1992a).

OBJECTIVES

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

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 intervention

Antibiotic or placebo control.

Types of outcome measures

At least one of the following: incidence of acute rheumatic fever within two months; acute glomerulonephritis within one month; acute otitis media; acute sinusitis; or quinsy, or measures of the following symptoms: throat soreness, headache or fever.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Acute Respiratory Infections Group methods used in reviews.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library,* Issue 1, 2006), MEDLINE (January 1966 to March 2006) and EMBASE (January 1990 to December 2005).

The MEDLINE and CENTRAL search strategies are shown below. We combined the MEDLINE search string with the Cochrane highly sensitive search strategy phases one and two as published in Appendix 5b of the Cochrane Reviewers' Handbook (Higgins 2005). The search string was adapted for EMBASE, as shown below.

MEDLINE (WebSPIRS)
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

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

References of selected studies and relevant reviews were hand-checked to find additional studies. No language restrictions were applied. We determined which studies were trials by examining the abstracts of identified articles.

METHODS OF THE REVIEW

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

Data was independently extracted from included studies by two authors and was 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 authors for raw data (Dagnelie 1996; Little 1997; Zwart 2000; Zwart 2003).

DESCRIPTION OF STUDIES

A total of 58 studies were considered for the review. Of these, there were 27 controlled studies that met inclusion criteria and were included in the review. 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).

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 (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 air-force. 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 bacterium (GABHS) positive patients only, whilst two studies excluded patients who were GABHS positive.

METHODOLOGICAL QUALITY

Many of the studies were of poor quality. Only 18 studies were double blinded: three were single blind. In most early studies subjects were randomised to treatment and control groups by methods that could potentially introduce bias (for example, air-force serial number, drawing a card from a deck, hospital bed number) or not randomised at all. The generalisability of studies can be questioned. In five studies subjects were excluded if they did not yield a positive throat-swab culture for Group A Beta-Haemolytic Streptococcus. In two studies subjects were excluded if they did yield a positive throat-swab culture for Group A Beta-Haemolytic Streptococcus (Petersen 1997; Taylor 1977). 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.

RESULTS

1. Non-suppurative complications (see Table 01)
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.

Several studies found benefit from antibiotics for acute rheumatic fever which reduced this complication to about one quarter that in the placebo group (RR 0.27; 95% CI 0.12 to 0.60). 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).

2. Suppurative complications (see Table 01)
Antibiotics reduced the incidence of acute otitis media to about one third of that in the placebo group, (relative risk (RR) 0.30; 95% CI 0.15 to 0.58) 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). 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).

3. Symptoms (see Table 01)
At day 3 of illness, antibiotics reduced symptoms of sore throat (RR 0.68; 95% CI 0.59 to 0.79), fever (RR 0.71; 95% CI 0.45 to 1.10), and headache (RR 0.47; 95% CI 0.38 to 0.58). 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.

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 (see Table 01)
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) 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). Contrary to expectation the trend was for a greater effect of antibiotics for blind studies at day 3.

b) Antipyretics administered versus not administered (see Table 01)

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).

c) Throat swabs positive for Streptococcus, versus negative for Streptococcus, versus not tested / inseparable combined data (see the MetaView Table 01)

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 Group A Beta-Haemolytic Streptococcus, compared to three quarters (RR 0.78; 95% CI 0.63 to 0.97) for those with negative swabs. 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). That is, the effectiveness of antibiotics is increased in people with Streptococci growing in the throat.

d) Children versus adults (see Table 01)

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).

Some of these results are summarised (see Summary of Findings)

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 (NNT) 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 NNT 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 patients 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 NNT 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 NNT 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 NNT will rise above a rate at which it might be regarded as worthwhile to treat. In developing countries where the absolute rate may be much higher, the lower NNT 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 ninety percent 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 developing countries; in socio-economically deprived sections of developed ones; 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.

NOTES

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

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 airforce recruits).

Author's 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 dfficulties (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 pahryngitis in slightly different ways, including interchangably. Moreover the notion that patients with postiive swabs for Streptococcus have a differnet 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 meterial 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.

Author's 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

POTENTIAL CONFLICT OF INTEREST

None

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Thanks to Prof Jim Dickinson for helpful suggestions about dividing the studies into early and late last century to examine the idea that the pathogenesis of this illness, and, or, its sequelae, have changed with time.
Ian Thomas and Michael Thomas for research assistance.
Thanks to Beth Clewer and Katie Farmer who in January 1999 drew our attention to mistakes in the data extraction by their careful checking of original studies as part of their medical student project at the University of Bristol Medical School.
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Internal sources of support

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- University of Oxford UK
- Griffith University AUSTRALIA

REFERENCES

References to studies included in this review

Bennike 1951 *{published data only}*
Bennike TBMK, Kjaer E, Skadhauge K, Trolle E. Penicillin therapy in acute tonsillitis, phlegmonous tonsillitis and ulcerative tonsillitis. *Acta Medica Scandinavica* 1951;**139**:253–74.

Brink 1951 *{published data only}*
Brink WRR, Denny FW, Wannamaker LW. Effect of penicillin and aureomycin on the natural course of streptococcal tonsillitis and pharyngitis. *American Journal of Medicine* 1951;**10**:300–8.

Brumfitt 1957 *{published data only}*
Brumfitt WS, Slater DH. Treatment of acute sore throat with penicillin: a controlled trial among young soldiers. *Lancet* 1957;**272** (6958):8–11.

Catanzaro 1954 *{published data only}*
Catanzaro FJ, Morris AJ, Chamovitz R, Rammelkamp CH, Stolzer B, Perry WD. The role of Streptococcus in the pathogenesis of rheumatic fever. *American Journal of Medicine* 1954;**17**(6):749–56.

Chamovitz 1954 *{published data only}*
Chamovitz R, Stetson CA, Rammelkamp CH. Prevention of

rheumatic fever by treatment of previous streptococcal infections. *New England Journal of Medicine* 1954;**251**(12):466–71.

Chapple 1956 *{published data only}*
Chapple LM, Paulett JD, Tuckman E, Woodall JT, Tomlinson AJH, McDonald JC. Treatment of acute sore throat in general practice. *British Medical Journal* 1956;**March**(4969):705–8.

Dagnelie 1996 *{published and unpublished data}*
Dagnelie CF, van-der-Graaf Y, De Melker RA. Do patients with sore throat benefit from penicillin? A randomised double-blind placebo-controlled clinical trial with penicillin V in general practice. *British Journal of General Practice* 1996;**46**(411):589–93.

De Meyere 1992 *{published data only}*
De Meyere M, Mervielde Y, Verschraegen G, Bogaert M. Effect of penicillin on the clinical course of streptococcal pharyngitis in general practice. *European Journal of Clinical Pharmacology* 1992;**43**(6):581–5.

Denny 1950 *{published data only}*
Denny LW, Brink WR, Rammelkamp CH, Custer EA. Prevention of rheumatic fever: treatment of the preceding streptococcal infection. *Journal of the American Medical Association* 1950;**143**(2):151–3.

Denny 1953 *{published data only}*
Denny LW, Hahn EO. Comparative effects of penicillin, aureomycin and terramycin on streptococcal tonsillitis and pharygitis. *Pediatrics* 1953;**11**(1):7–14.

El-Daher 1991 *{published data only}*
El-Daher NT, Hijazi SS, Rawashdeh NM, Al-Khalil IA, Abu-Ektaish FM, Abdel-Latif DI. Immediate vs. delayed treatment of Group A beta-hemolytic streptococcal pharyngitis with penicillin V. *Pediatric Infectious Diseases Journal* 1991;**10**(2):126–30.

Howe 1997 *{published and unpublished data}*
Howe RW, Millar MR, Coast J, Whitfield M, Peters TJ, Brookes S. A randomized controlled trial of antibiotics on symptom resolution in patients presenting to their general practitioner with a sore throat. *British Journal of General Practice* 1997;**47**(418):280–4.

Krober 1985 *{published data only}*
Krober JW, Michels GN. Streptococcal pharyngitis: Placebo controlled double blind evaluation of clinical response to penicillin therapy. *Journal of the American Medical Association* 1985;**253**(9):1271–4.

Landsman 1951 *{published data only}*
Landsman JB, Grist NR, Black R, McFarlane D, Blair W. Sore throat in general practice. *British Medical Journal* 1951;**1**:326–9.

Leelarasamee 2000 *{published data only}*
Leelarasamee A, Leowattana W, Tobunluepop P, Chub-upakarn S, Artavetakan W, Jarupoonphol V, et al. Amoxycillin for fever and sore throat due to non-exudative pharyngotonsillitis: beneficial or harmful?. *International Journal of Infectious Diseases* 2000;**4**(2):70–4.

Little 1997 *{published and unpublished data}*
Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997;**315**(7104):350–2.

Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997;**314**:722–7.

MacDonald 1951 *{published data only}*
MacDonald TC, Watson IH. Sulphonamides and acute tonsillitis: a controlled experiment in a Royal Airforce community. *British Medical Journal* 1951;**1**:323–6.

Middleton 1988 *{published data only}*
Middleton DB, D'Amico F, Merenstein JH. Standardized symptomatic treatment versus penicillin as initial therapy for streptococcal pharyngitis. *The Journal of Pediatrics* 1988;**113**(6):1089–94.

Nelson 1984 *{published data only}*
Nelson JD. The effect of penicillin therapy on the symptoms and signs of streptococcal pharyngitis. *Pediatric Infectious Disease* 1984;**3**(1):10–3.

Petersen 1997 *{published data only}*
Peterson K, Phillips RS, Soukup J, Komaroff AL, Aronson M. The effect of Erythromycin on resolution of symptoms among adults with pharyngitis not caused by Group A Streptococcus. *Journal of General Internal Medicine* 1997;**12**(2):95–101.

Pichichero 1987 *{published data only}*
Pichichero FA, Talpey WB, Green JL, Francis AB, Roghmann KJ, Hoekelman RA. Adverse and beneficial effects of immediate treatment of Group A Beta Haemolytic Streptococcal pharyngitis with penicillin. *Pediatric Infectious Disease* 1987;**6**(7):635–43.

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

Taylor 1977 *{published data only}*
Taylor B, Abbott GD, McKerr M, Fergusson DM. Amoxycillin and co- trimoxazole in presumed viral respiratory infections of childhood: placebo controlled trial. *British Medical Journal* 1977;**2**(6086):552–4.

Wannamaker 1951 *{published data only}*
Wannamaker LW, Rammelkamp CH, Denny FW, Brink WR, Houser HB, Hahn EO. Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin. *American Journal of Medicine* 1951;**10**:673–94.

Whitfield 1981 *{published data only}*
Whitfield MJ, Hughes AO. Penicillin in sore throat. *Practitioner* 1981;**225**(1352):234–9.

Zwart 2000 *{published and unpublished data}*
Zwart S, Sachs AP, Rujis GJ, Gubbels JW, Hoes AW, de Melker RA. Penicillin for acute sore thoat: randomised double blind trial seven days versus three days treatment or placebo in adults. *BMJ* 2000;**320**(7228):150–4.

Zwart 2003 *{published data only}*
Zwart S, Rovers MM, de Melker RA, Hoes AW. Penicillin for acute sore throat in children: randomised, double blind trial. *BMJ* 2003;**327**(7427):1324–8.

References to studies excluded from this review

Barwitz 1999
Barwitz HJK. Common cold - trial to rationalize management in general practice by recommendation [Erkaltung: eine Handlungsempfehlung]. *Zeitschrift fur Allgemeinmedizin* 1999;**75**:932–8.

Bass 1986

Bass J. Treatment of streptococcal pharyngitis revisited. *Journal of the American Medical Association* 1986;**256**:740–3.

Bishop 1952

Bishop JM, Peden AS, Prankerd TAJ, Cawley RH. Acute sore throat. Clinical features, aetiology and treatment. *Lancet* 1952;**1**:1183–7.

Catanzaro 1958

Catanzaro FJ, Chamovitz R. Prevention of rheumatic fever by treatment of streptococcal infections: factors responsible for failures. *New England Journal of Medicine* 1958;**259**:51–7.

Cruickshank 1960

Cruickshank R. Sore throat: a controlled therapeutic trial in young adults. Controlled Clinical Trials: paper delivered at the conference convened by the Council for International Organisation of Medical Sciences. Oxford: Blackwell, 1960:38–44.

Dowell 2001

Dowell J, Pitkethly M, Bain J, Martin S. A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. *British Journal of General Practice* 2001;**51**:200–5.

Gerber 1985

Gerber MA, Spadaccini LJ, Wright LL, Deutsch L, Kaplan EL. Twice-daily penicillin in the treatment of streptococcal pharyngitis. *American Journal of Diseases of Children* 1985;**139**:1145–8.

Gerber 1989

Gerber MA, Randolph MF. Failure of once-daily penicillin V therapy for streptococcal pharyngitis. *American Journal of Diseases of Children* 1989;**143**:153–5.

Ginsburg 1980

Ginsburg CM, McCracken GH, Crow SD, Steinberg JB, Cope F. A controlled comparative study of penicillin V and cefadroxil therapy on Group A streprococal tonsillopharyngitis. *Journal of International Medical Research* 1980;**8**(Suppl 1):82–6.

Guthrie 1988

Guthrie RM, Ruoff GE, Rofman BA, Ginsberg D, Karp RR, Brown SM, et al. Aetiology of acute pharyngitis and clinical response to empirical therapy with erythromycin versus amoxicillin. *Family Practice* 1988;**5**:29–35.

Haverkorn 1971

Haverkorn MV, Goslings WRO. Streptococcal pharyngitis in the general population. A controlled study of streptococcal pharyngitis and its complications in the Netherlands. *Journal of Infectious Diseases* 1971;**124**:339–47.

Herz 1988

Herz MJ. Antibiotics and the adult sore throat - an unnecessary ceremony. *Family Practice* 1988;**5**:196–9.

Howie 1970

Howie JGR, Clark GA. Double-blind trial of early demethylchlortetracycline in minor respiratory illness in general practice. *Lancet* 1970; **Nov 28**:1099–102.

Jensen 1991

Jensen JH, Larsen SB. Treatment of recurrent acute tonsillitis with clindamycin. An alternative to tonsillectomy?. *Clinical Otolaryngology* 1991;**16**:498–500.

Marlow 1989

Marlow RA, Torrez AJ, Haxby D. The treatment of non streptococcal pharyngitis with erythromycin: a preliminary study. *Family Medicine* 1989;**21**:425–7.

Massell 1951

Massell BF, Sturgis GP, Knobloch JD, Streeper RB, Hall TN, Norcross P. Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcic respiratory infections. *Journal of the American Medical Association* 1951;**146**(16):1469–74.

McDonald 1985

McDonald CJ, Tierny WM, Hui SL, French MLV, Leland DS, Jones RB. A controlled trial of erythromycin in adults with nonstreptococcal pharyngitis. *Journal of Infectious Diseases* 1985;**152**:1093–4.

Merenstein 1974

Merenstein JH, Rogers KD. Early treatment and management by nurse practiotioners. *Journal of the American Medical Association* 1974;**227**:1278–82.

Morris 1956

Morris AJ, Chamovitz R, Catanzaro FJ, Rammelkamp CH. Prevention of rheumatic fever by treatment of previous streptococcic infections; effect of sulfadiazine. *Journal of the American Medical Association* 1956;**160**(2):114–6.

Nasonova 1999

* Nasonova VA, Belov BS, Strachunsky LS, Sudilovskaya EI, Bogdanovich TM, Krechikova OI, et al. Antibacterial therapy of Streptococcus tonsilitis (quinsy and pharyngitis). *Antibiotiki i Khimioterapiia* 1999;**44**:19–23.

Pandraud 2002

Pandraud L. Therapeutic efficacy and clinical acceptability of fusafungine in follicular pharyngitis. *Current Medical Research and Opinion* 2002;**18**:381–8.

Randolph 1985

Randolph MF, Gerber MA, DeMeo KK, Wright L. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *The Journal of Pediatrics* 1985;**106**:870–5.

Schalen 1985

Schalen L, Christenses P, Elisson I, Fex S, Kamme S, Schalen C. Inefficacy of penicillin V in acute laryngitis in adults. Evaluation from results of double-blind study. *Annals of Otology Rhinology and Laryngology* 1985;**94**:14–7.

Schalen 1993

Schalen L, Eliasson I, Kamme C, Schalen C. Erythromycin in acute laryngitis in adults. *Annals of Otology Rhinology and Laryngology* 1993; **102**:209–14.

Schwartz 1981

Schwartz R, Wientzen RL, Pedeira F. Penicillin V for Group A Streptococcal pharyngotonsillitis. A randomised trial of seven vs ten days therapy. *Journal of the American Medical Association* 1981;**246**:1790–5.

Shevrygin 2000

Shevrygin BV, Manuilov BM. Therapeutic efficacy of new drug Pharingal at acute inflammatory diseases of pharynx and tonsils in pediatrics [Terapevticheskaia effektivnost' novogo perparata Faringal pri ostrykh vospalitel'nykh zabolevaniiakh glotki i mindalin u detei]. *Antibiotiki i Khimioterapiia* 2000;**45**:34–6.

Shvartzman 1993
Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. *BMJ* 1993; **306**:1170–2.

Stillerman 1986
Stillerman M. Comparison of oral cephalosporins with penicillin for Group A streptococcal pharyngitis. *Pediatric Infectious Diseases Journal* 1986;**5**:648–54.

Stromberg 1988
Stromberg A, Schwan A, Cars O. Five versus ten days treatment of Group A Streptococcal Pharyngotonsillitis: a randomised controlled clinical trial with phenoxymethylpenicillin and cefadroxil. *Scandinavian Journal of Infectious Disease* 1988;**20**:36–46.

Todd 1984
Todd JK, Todd N, Damato J, Todd WA. Bacteriology and treatment of purulent nasopharyngitis: a double blind, placebo-controlled evaluation. *Pediatric Infectious Disease* 1984;**3**:226–31.

Valkenburg 1971
Valkenburg HHMJ, Goslings WRO. Streptococcal pharyngitis in the general population. The attack rate if not treated with penicillin. *Journal of Infectious Diseases* 1971;**124**:783–6.

Additional references

ABS 1985
Australian Bureau of Statistics. Australian Health Survey. *Canberra: AGPS: (Cat No 4311.0)* 1985:11–52.

Del Mar 1992a
Del Mar C. Managing sore throat: a literature review. I. Making the diagnosis. *Medical Journal of Australia* 1992;**156**:572–5.

Del Mar 1992b
Del Mar C. Managing sore throats: a literature review. II. Do antibiotics confer benefit?. *Medical Journal of Australia* 1992;**156**:644–9.

Del Mar 1992c
Del Mar C. Spontaneously remitting disease, principles of management. *Medical Journal of Australia* 1992;**157**:101–7.

Froom 1990
Froom J, Culpepper L, Grob P, Bartelds A, Bowers P, Bridges-Webb C, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. *BMJ* 1990;**300**: 582–6.

Glasziou 1997
Glasziou P, Hayman M, Del Mar C. Antibiotics versus placebo for acute otitis media in children. In: *Cochrane Database of Systematic Reviews*, 1, 1997.

Goslings 1963
Goslings WRO, Valkenberg HA, Bots AW, Lorrier JC. Attack rates of streptococcal pharyngitis, rheumatic fever and glomerulnephritis in the general population. A controlled pilot study of controlled streptococcal pharyngitis in one village. *New England Journal of Medicine* 1963;**268**:687–94.

Higgins 2005
Higgins JPT, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]; APPENDIX 5b. *The Cochrane Library*. Chichester, UK: John Wiley & Sons, Ltd, 2005.

Horder 1954
Horder J, Horder E. Illness in general practice. *Practitioner* 1954; **173**:177–87.

Howie 1971
Howie JGR, Gill G, Durno D. Respiratory illness and antibiotic use in general practice. *Journal of the Royal College of General Practitioners* 1971;**21**:657–61.

Howie 1978
Howie JGR. Antibiotics and respiratory illness in general practice: prescribing policy and workload. *British Medical Journal* 1978;**2**: 1342–6.

Howie 1985
Howie JGR, Foggo B. Antibiotics, sore throats and rheumatic fever. *Journal of the Royal College of General Practitioners* 1985;**35**:223–4.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Bennike 1951
Methods	Open study, non-randomised. Subjects allocated to alternate conditions on alternate days
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

Characteristics of included studies (*Continued*)

Notes	No antipyretics were administered to the control group. The use of antipyretics to subjects in the treatment group was unstated
Allocation concealment	C – Inadequate

Study	**Brink 1951**
Methods	Open study, randomised by airforce serial number
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
Outcomes	Incidence of rheumatic fever, otitis media, and symptoms of sore throat, fever and headache
Notes	No antipyretics were administered
Allocation concealment	C – Inadequate

Study	**Brumfitt 1957**
Methods	Open study, randomised by bed number
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
Allocation concealment	C – Inadequate

Study	**Catanzaro 1954**
Methods	Single blind, patients were unaware of treatment type, placebo controlled trial. The outcome of treatment was not determined blind. Patients were randomly allocated by airforce serial number
Participants	640 young adult males recruited into United States Airforce. Missing data were not explained Data from patients who produced a Group A Beta Haemolytic Streptococcus 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
Allocation concealment	C – Inadequate

Study	**Chamovitz 1954**
Methods	Single blind placebo study. Patients did not know treatment type they were receiving. The outcome of treatment was not determined blind. Subjects were randomised by airforce serial number
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
Interventions	Intramuscular penicillin
Outcomes	Incidence of rheumatic fever, otitis media, and sinusitis
Notes	Antipyretic use was not documented

Characteristics of included studies (*Continued*)

Allocation concealment	C – Inadequate

Study	**Chapple 1956**
Methods	Double blind placebo trial, randomised by random bottle dispensing
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
Allocation concealment	A – Adequate

Study	**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
Allocation concealment	A – Adequate

Study	**De Meyere 1992**
Methods	Double blind placebo trial. Method of randomisation to treatment groups was not documented
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 Subjects excluded if they: produced a Group A Beta Haemolytic Streptococcus 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
Allocation concealment	A – Adequate

Study	**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. Subject were randomised to groups by airforce serial number
Participants	1602 young adult males recruited into United States Airforce
Interventions	Intramuscular penicillin for four days or no treatment as a control group

Characteristics of included studies (*Continued*)

Outcomes	Incidence of rheumatic fever only
Notes	Antipyretic use was not stated
Allocation concealment	C – Inadequate

Study	**Denny 1953**
Methods	Single blind trial. Oral placebo used. Patients were randomly allocated to treatment groups by drawing a card from a deck. 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
Allocation concealment	B – Unclear

Study	**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
Allocation concealment	A – Adequate

Study	**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	Unusual randomisation scheme (done in blocks of 6) *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
Allocation concealment	A – Adequate

Study	**Krober 1985**
Methods	Double blind placebo trial. Subjects were randomised by table of random numbers
Participants	Forty-four children presenting to a paediatric clinic. Twenty-six of these subjects yielded group A beta haemolytic streptococcus 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 Group A Beta Haemolytic Streptococcus 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
Allocation concealment	A – Adequate

Study	**Landsman 1951**
Methods	Double blind placebo. Randomised by random numbering of bottles
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
Allocation concealment	A – Adequate

Study	**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
Allocation concealment	A – Adequate

Study	**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
Allocation concealment	C – Inadequate

Study	**MacDonald 1951**
Methods	Outcome determined blind. Randomised by airforce serial number
Participants	82 young adult males recruited into the United States Airforce

Characteristics of included studies (*Continued*)

	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
Allocation concealment	C – Inadequate

Study	**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 unmedicated placebo
Outcomes	Symptoms of sore throat and fever
Notes	Phone report after 48 hours used to measure outcome at day 3
Allocation concealment	D – Not used

Study	**Nelson 1984**
Methods	Subject randomised to conditions by hospital number allocation. 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 Group A Beta Haemolytic Streptococcus 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
Allocation concealment	C – Inadequate

Study	**Petersen 1997**
Methods	Randomised placebo-controlled trial of patients' culture negative to Group A Streptococcus
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
Allocation concealment	A – Adequate

Study	**Pichichero 1987**
Methods	Double blind placebo trial, randomised by a table of random numbers
Participants	One hundred and fourteen Group A Beta Haemolytic Streptococcus positive children aged 4 to 18 years. Children were excluded from the study if: a throat swab was negative for Group A Beta Haemolytic Streptococcus; were allergic to penicillin; had received penicillin in past 7 days; had another acute illness within

	seven days, had a Group A Beta Haemolytic Streptococcus positive swab in past month, or had another concurrent infection that required antibiotics
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
Allocation concealment	A – Adequate

Study	**Siegel 1961**
Methods	Open study, randomised by bed chart number
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	Antipyretic use was not documented
Allocation concealment	C – Inadequate

Study	**Taylor 1977**
Methods	Double blind placebo trial. The method of randomisation to groups was not documented
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
Allocation concealment	A – Adequate

Study	**Wannamaker 1951**
Methods	Single blind study. The outcome of intervention was determined blind by physicians who did not know treatment type participants were receiving Randomised to groups by airforce serial number
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
Outcomes	Incidence of rheumatic fever
Notes	Antipyretic use was not documented
Allocation concealment	C – Inadequate

Study	**Whitfield 1981**
Methods	Double blind placebo trial. Randomised by predetermined random order
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
Allocation concealment	A – Adequate

Study	**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
Allocation concealment	A – Adequate

Study	**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
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
Allocation concealment	A – Adequate

F = fareheit

Characteristics of excluded studies

Study	**Reason for exclusion**
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
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

Characteristics of excluded studies (*Continued*)

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 streptococcic 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
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

ADDITIONAL TABLES

Table 01. Summary of findings

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	A	
Sore Throat: Day 7	2974 (13)	0.18	0.65	0.55-0.76	6.4	A	
Rheumatic Fever	10,101 (16)	0.017	0.29	0.18-0.44	1.2	A	Based largely on risk in

Table 01. Summary of findings (*Continued*)

Outcome	Patients (trials)	Risk of outcome	Relative effect	95% CI	Effect/100 patients	Quality of evidence	Comments
							pre-1960 trials
Glomerulonephritis	5147 (10)	0.001	0.22	0.07-1.32	0.1	B	Sparse data
Quinsy	2433 (8)	0.023	0.14	0.05-0.39	2.0	A	
Otitis Media	3760 (11)	0.02	0.28	0.15-0.52	1.4	A	

ANALYSES

Comparison 01. Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Incidence of acute rheumatic fever within two months. Rheumatic fever defined by clinical diagnosis	16	10101	Peto Odds Ratio 95% CI	0.30 [0.20, 0.45]
02 Incidence of acute rheumatic fever within two months. Penicillin versus control	14	8175	Peto Odds Ratio 95% CI	0.27 [0.18, 0.41]
03 Incidence of acute rheumatic fever within two months: early (pre-1975) versus late studies (post-1975)	16	10101	Peto Odds Ratio 95% CI	0.30 [0.20, 0.45]
04 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis	11	3760	Peto Odds Ratio 95% CI	0.23 [0.12, 0.44]
05 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)	11	3760	Peto Odds Ratio 95% CI	0.23 [0.12, 0.44]
06 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis	8	2387	Peto Odds Ratio 95% CI	0.46 [0.10, 2.05]
07 Incidence of quinsy within two months. Quinsy defined by clinical diagnosis	8	2433	Peto Odds Ratio 95% CI	0.16 [0.07, 0.35]
08 Incidence of acute glomerulonephritis within one month. Acute glomerulonephritis defined by clinical diagnosis	10	5147	Peto Odds Ratio 95% CI	0.07 [0.00, 1.32]

Comparison 02. Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Symptom of sore throat on day three	15	3621	Peto Odds Ratio 95% CI	0.44 [0.38, 0.50]
02 Symptom of sore throat on day three: blind versus unblinded studies	15	3621	Peto Odds Ratio 95% CI	0.44 [0.38, 0.50]
03 Symptom of sore throat on day three: antipyretics versus no antipyretics	5	1137	Peto Odds Ratio 95% CI	0.31 [0.24, 0.40]
04 Symptom of sore throat on day three: Streptococcus positive throat swab, negative swab, untested/ inseparable	20	3600	Peto Odds Ratio 95% CI	0.42 [0.36, 0.48]
05 Symptom of sore throat at one week (six to eight days)	13	2974	Peto Odds Ratio 95% CI	0.55 [0.44, 0.69]
06 Symptom of sore throat at one week (six to eight days): blind versus unblinded studies	13	2944	Peto Odds Ratio 95% CI	0.59 [0.47, 0.74]
07 Symptom of sore throat at one week (six to eight days): GABHS positive throat swab, GABHS negative swab. Untes	15	2524	Peto Odds Ratio 95% CI	0.49 [0.37, 0.65]

Comparison 03. Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
03 Symptom of fever on day three	7	1334	Peto Odds Ratio 95% CI	0.62 [0.46, 0.85]
04 Symptom of fever on day three: blinded versus unblinded studies	7	1334	Peto Odds Ratio 95% CI	0.62 [0.46, 0.85]
05 Symptom of fever on day three: children compared with adults	4	657	Peto Odds Ratio 95% CI	0.44 [0.29, 0.66]
06 Symptom of fever at one week (six to eight days)	3	777	Peto Odds Ratio 95% CI	Not estimable

Comparison 04. Antibiotics versus control for the treatment of sore throat: symptom of headache

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
03 Symptom of headache on day three	3	911	Peto Odds Ratio 95% CI	0.33 [0.25, 0.45]
04 Symptom of headache on day three: blinded versus unblinded studies	3	911	Peto Odds Ratio 95% CI	0.33 [0.25, 0.45]

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

COVER SHEET

Title	Antibiotics for sore throat
Authors	Del Mar CB, Glasziou PP, Spinks AB
Contribution of author(s)	Chris Del Mar first conceived the review, presenting it as a meta-analysis in a journal (Del Mar 1992a and 1992b). It was subsequently improved and modified for The Cochrane Library with Paul Glasziou (who has improved the sub-group analyses) and Anneliese Spinks (who updated searches and completed the analyses).
Issue protocol first published	1997/1
Review first published	1997/2
Date of most recent amendment	13 November 2006
Date of most recent SUBSTANTIVE amendment	03 August 2006
What's New	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 reivew 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, 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).
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	10 March 2006
Date authors' conclusions section amended	Information not supplied by author
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Editorial group Cochrane Acute Respiratory Infections Group

Editorial group code HM-ARI

GRAPHS AND OTHER TABLES

Figure 01.

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		

Analysis 01.01. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 01 Incidence of acute rheumatic fever within two months. Rheumatic fever defined by clinical diagnosis

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome: 01 Incidence of acute rheumatic fever within two months. Rheumatic fever defined by clinical diagnosis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Bennike 1951	0/238	0/268		0.0	Not estimable
Brink 1951	2/277	5/198		6.9	0.29 [0.06, 1.31]
× Brumfitt 1957	0/62	0/59		0.0	Not estimable
Catanzaro 1954	26/650	12/220		28.0	0.71 [0.33, 1.49]
Chamovitz 1954	0/257	2/109		1.7	0.03 [0.00, 0.72]
× Chapple 1956	0/186	0/97		0.0	Not estimable
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× De Meyere 1992	0/87	0/94		0.0	Not estimable
Denny 1950	2/798	17/804		19.2	0.20 [0.08, 0.50]
Denny 1953	2/157	1/50		2.2	0.60 [0.04, 8.59]
× Leelarasamee 2000	0/369	0/386		0.0	Not estimable
× Little 1997	0/454	0/216		0.0	Not estimable
× Pichichero 1987	0/59	0/58		0.0	Not estimable
Siegel 1961	0/605	2/608		2.0	0.14 [0.01, 2.17]
Wannamaker 1951	5/978	35/996		40.0	0.22 [0.12, 0.41]
× Zwart 2000	0/358	0/164		0.0	Not estimable
Total (95% CI)	5656	4445		100.0	0.30 [0.20, 0.45]

Total events: 37 (Treatment), 74 (Control)

Test for heterogeneity chi-square=9.20 df=6 p=0.16 I^2 =34.8%

Test for overall effect z=5.94 p<0.00001

Analysis 01.02. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 02 Incidence of acute rheumatic fever within two months. Penicillin versus control

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

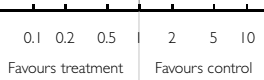
Outcome: 02 Incidence of acute rheumatic fever within two months. Penicillin versus control

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Bennike 1951	0/238	0/268		0.0	Not estimable
Brink 1951	2/197	5/198		7.5	0.42 [0.09, 1.87]
× Brumfitt 1957	0/62	0/59		0.0	Not estimable
Catanzaro 1954	12/420	12/220		22.8	0.49 [0.21, 1.15]
Chamovitz 1954	0/257	2/109		1.8	0.03 [0.00, 0.72]
× Chapple 1956	0/99	0/97		0.0	Not estimable
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× De Meyere 1992	0/87	0/94		0.0	Not estimable
Denny 1950	2/798	17/804		20.6	0.20 [0.08, 0.50]
Denny 1953	1/53	1/50		2.2	0.94 [0.06, 15.30]
× Pichichero 1987	0/59	0/58		0.0	Not estimable
Siegel 1961	0/605	2/608		2.2	0.14 [0.01, 2.17]
Wannamaker 1951	5/978	35/996		42.9	0.22 [0.12, 0.41]
× Zwart 2000	0/358	0/164		0.0	Not estimable
Total (95% CI)	4332	3843		100.0	0.27 [0.18, 0.41]

Total events: 22 (Treatment), 74 (Control)

Test for heterogeneity chi-square=5.71 df=6 p=0.46 I^2 =0.0%

Test for overall effect z=6.27 p<0.00001



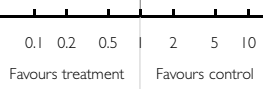
Analysis 01.03. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 03 Incidence of acute rheumatic fever within two months: early (pre-1975) versus late studies (post-1975)

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome: 03 Incidence of acute rheumatic fever within two months: early (pre-1975) versus late studies (post-1975)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Incidence of acute rheumatic fever within 2 months: early (pre-1975) studies					
× Bennike 1951	0/238	0/268		0.0	Not estimable
Brink 1951	2/277	5/198		6.9	0.29 [0.06, 1.31]
× Brumfitt 1957	0/62	0/59		0.0	Not estimable
Catanzaro 1954	26/650	12/220		28.0	0.71 [0.33, 1.49]
Chamovitz 1954	0/257	2/109		1.7	0.03 [0.00, 0.72]
× Chapple 1956	0/186	0/97		0.0	Not estimable
Denny 1950	2/798	17/804		19.2	0.20 [0.08, 0.50]
Denny 1953	2/157	1/50		2.2	0.60 [0.04, 8.59]
Siegel 1961	0/605	2/608		2.0	0.14 [0.01, 2.17]
Wannamaker 1951	5/978	35/996		40.0	0.22 [0.12, 0.41]
Subtotal (95% CI)	4208	3409		100.0	0.30 [0.20, 0.45]
Total events: 37 (Treatment), 74 (Control)					
Test for heterogeneity chi-square=9.20 df=6 p=0.16 I^2 =34.8%					
Test for overall effect z=5.94 p<0.00001					
02 Incidence of actue rheumatic fever within 2 months: late (post-1975) studies					
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× De Meyere 1992	0/87	0/94		0.0	Not estimable
× Leelarasamee 2000	0/369	0/386		0.0	Not estimable
× Little 1997	0/454	0/216		0.0	Not estimable
× Pichichero 1987	0/59	0/58		0.0	Not estimable
× Zwart 2000	0/358	0/164		0.0	Not estimable
Subtotal (95% CI)	1448	1036		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	5656	4445		100.0	0.30 [0.20, 0.45]
Total events: 37 (Treatment), 74 (Control)					
Test for heterogeneity chi-square=9.20 df=6 p=0.16 I^2 =34.8%					
Test for overall effect z=5.94 p<0.00001					



Analysis 01.04. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 04 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

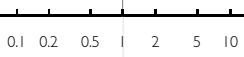
Outcome: 04 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Bennike 1951	0/238	2/268		5.6	0.15 [0.01, 2.43]
Brink 1951	5/277	13/198		47.9	0.27 [0.10, 0.71]
Chamovitz 1954	0/257	1/109		2.4	0.03 [0.00, 2.53]
Chapple 1956	5/186	5/97		24.7	0.49 [0.13, 1.83]
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× De Meyere 1992	0/87	0/94		0.0	Not estimable
Denny 1953	0/157	2/50		4.1	0.02 [0.00, 0.40]
Little 1997	0/454	1/216		2.5	0.04 [0.00, 2.98]
Pichichero 1987	1/59	0/55		2.8	6.90 [0.14, 348.82]
Taylor 1977	0/131	4/66		10.0	0.05 [0.01, 0.39]
× Zwart 2000	0/358	0/164		0.0	Not estimable
Total (95% CI)	2325	1435		100.0	0.23 [0.12, 0.44]

Total events: 11 (Treatment), 28 (Control)

Test for heterogeneity chi-square=10.42 df=7 p=0.17 I^2 =32.8%

Test for overall effect z=4.41 p=0.00001



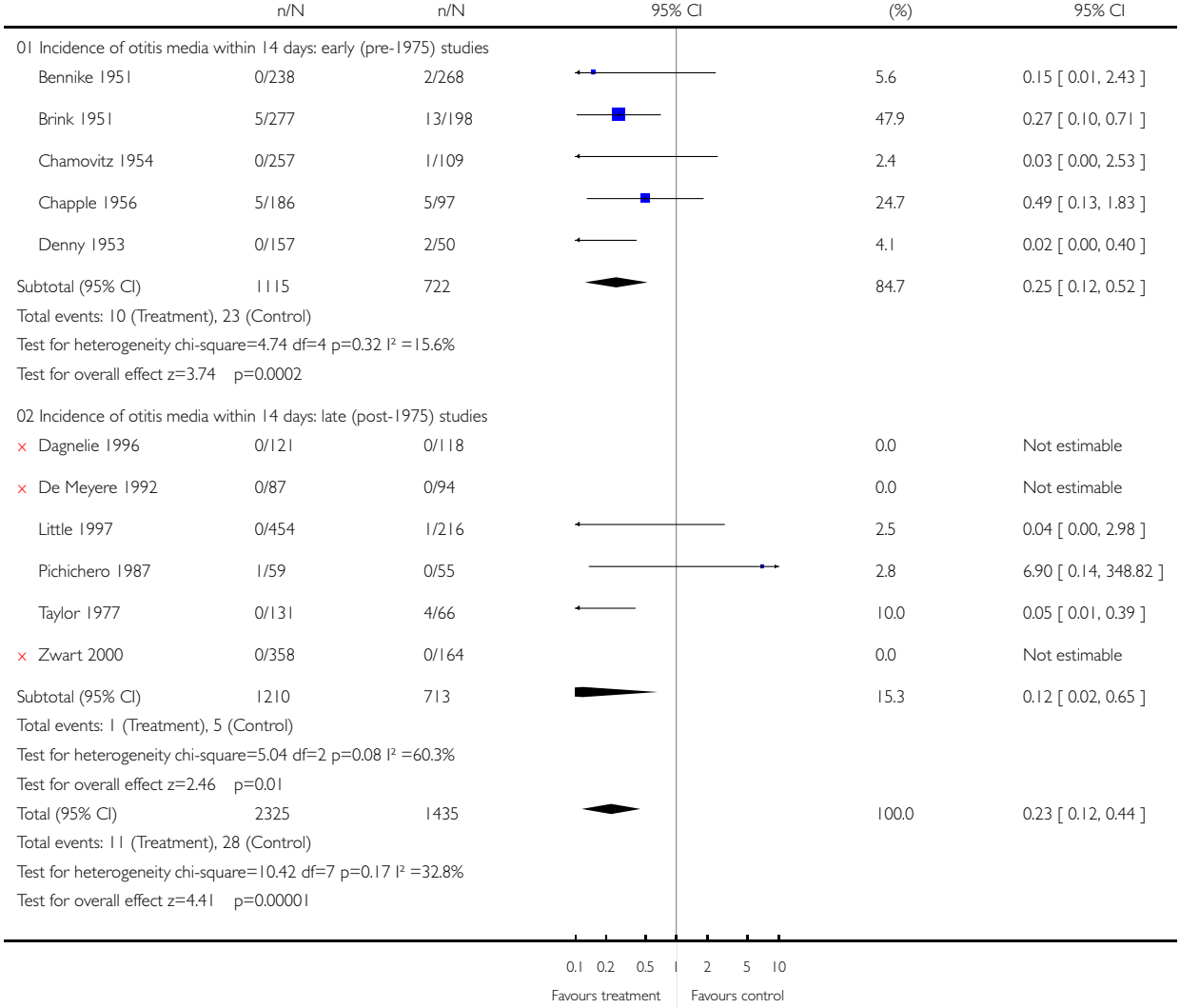
Analysis 01.05. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 05 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome: 05 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Incidence of otitis media within 14 days: early (pre-1975) studies					
Bennike 1951	0/238	2/268		5.6	0.15 [0.01, 2.43]
Brink 1951	5/277	13/198		47.9	0.27 [0.10, 0.71]
Chamovitz 1954	0/257	1/109		2.4	0.03 [0.00, 2.53]
Chapple 1956	5/186	5/97		24.7	0.49 [0.13, 1.83]
Denny 1953	0/157	2/50		4.1	0.02 [0.00, 0.40]
Subtotal (95% CI)	1115	722		84.7	0.25 [0.12, 0.52]
Total events: 10 (Treatment), 23 (Control)					
Test for heterogeneity chi-square=4.74 df=4 p=0.32 I^2 =15.6%					
Test for overall effect z=3.74 p=0.0002					
02 Incidence of otitis media within 14 days: late (post-1975) studies					
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× De Meyere 1992	0/87	0/94		0.0	Not estimable
Little 1997	0/454	1/216		2.5	0.04 [0.00, 2.98]
Pichichero 1987	1/59	0/55		2.8	6.90 [0.14, 348.82]
Taylor 1977	0/131	4/66		10.0	0.05 [0.01, 0.39]
× Zwart 2000	0/358	0/164		0.0	Not estimable
Subtotal (95% CI)	1210	713		15.3	0.12 [0.02, 0.65]
Total events: 1 (Treatment), 5 (Control)					
Test for heterogeneity chi-square=5.04 df=2 p=0.08 I^2 =60.3%					
Test for overall effect z=2.46 p=0.01					
Total (95% CI)	2325	1435		100.0	0.23 [0.12, 0.44]
Total events: 11 (Treatment), 28 (Control)					
Test for heterogeneity chi-square=10.42 df=7 p=0.17 I^2 =32.8%					
Test for overall effect z=4.41 p=0.00001					



Analysis 01.06. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 06 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

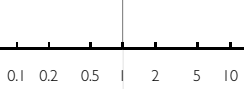
Outcome: 06 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Chamovitz 1954	1/257	3/109		48.2	0.11 [0.01, 0.97]
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× De Meyere 1992	0/87	0/84		0.0	Not estimable
Denny 1953	0/157	1/50		10.6	0.02 [0.00, 1.55]
Landsman 1951	2/52	0/43		28.5	6.34 [0.39, 104.15]
Little 1997	1/454	0/216		12.7	4.37 [0.07, 289.80]
× Pichichero 1987	0/59	0/58		0.0	Not estimable
× Zwart 2000	0/358	0/164		0.0	Not estimable
Total (95% CI)	1545	842		100.0	0.46 [0.10, 2.05]

Total events: 4 (Treatment), 4 (Control)

Test for heterogeneity chi-square=8.19 df=3 p=0.04 I^2 =63.4%

Test for overall effect z=1.02 p=0.3



Analysis 01.07. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 07 Incidence of quinsy within two months. Quinsy defined by clinical diagnosis

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome: 07 Incidence of quinsy within two months. Quinsy defined by clinical diagnosis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Bennike 1951	1/238	15/268		65.1	0.19 [0.07, 0.50]
Dagnelie 1996	0/121	2/118		8.4	0.13 [0.01, 2.10]
× De Meyere 1992	0/87	0/94		0.0	Not estimable
Howe 1997	1/69	0/34		3.7	4.45 [0.07, 287.35]
Landsman 1951	0/52	2/43		8.3	0.11 [0.01, 1.76]
Little 1997	0/454	1/216		3.7	0.04 [0.00, 2.98]
× Pichichero 1987	0/59	0/58		0.0	Not estimable
Zwart 2000	0/358	3/164		10.8	0.04 [0.00, 0.47]

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Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	1438	995		100.0	0.16 [0.07, 0.35]
Total events: 2 (Treatment), 23 (Control)					
Test for heterogeneity chi-square=4.17 df=5 p=0.53 I^2 =0.0%					
Test for overall effect z=4.53 p<0.00001					

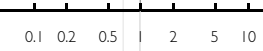
Analysis 01.08. Comparison 01 Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 08 Incidence of acute glomerulonephritis within one month. Acute glomerulonephritis defined by clinical diagnosis

Review: Antibiotics for sore throat

Comparison: 01 Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome: 08 Incidence of acute glomerulonephritis within one month. Acute glomerulonephritis defined by clinical diagnosis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Bennike 1951	0/238	0/268		0.0	Not estimable
× Brink 1951	0/277	0/198		0.0	Not estimable
× Brumfitt 1957	0/62	0/59		0.0	Not estimable
Chamovitz 1954	0/257	1/109		45.5	0.03 [0.00, 2.53]
× Chapple 1956	0/186	0/97		0.0	Not estimable
× Dagnelie 1996	0/121	0/118		0.0	Not estimable
× Leelarasamee 2000	0/369	0/386		0.0	Not estimable
× Little 1997	0/454	0/216		0.0	Not estimable
Siegel 1961	0/605	1/605		54.5	0.14 [0.00, 6.82]
× Zwart 2000	0/358	0/164		0.0	Not estimable
Total (95% CI)	2927	2220		100.0	0.07 [0.00, 1.32]
Total events: 0 (Treatment), 2 (Control)					
Test for heterogeneity chi-square=0.21 df=1 p=0.65 I^2 =0.0%					
Test for overall effect z=1.77 p=0.08					



Analysis 02.01. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 01 Symptom of sore throat on day three

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 01 Symptom of sore throat on day three

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Brink 1951	119/277	129/198		14.7	0.41 [0.29, 0.59]
Brumfitt 1957	21/42	26/40		2.6	0.55 [0.23, 1.30]
Chapple 1956	40/135	37/65		5.3	0.32 [0.17, 0.58]
Dagnelie 1996	36/117	57/117		7.2	0.47 [0.28, 0.80]
De Meyere 1992	18/82	59/91		5.5	0.18 [0.10, 0.32]
Denny 1953	89/157	48/50		4.3	0.17 [0.09, 0.34]
El-Daher 1991	42/111	106/118		6.7	0.10 [0.06, 0.18]
Landsman 1951	6/52	7/43		1.4	0.67 [0.21, 2.16]
Little 1997	135/215	122/187		11.8	0.90 [0.60, 1.35]
MacDonald 1951	18/41	27/41		2.6	0.42 [0.18, 0.99]
Middleton 1988	2/34	5/23		0.8	0.24 [0.05, 1.16]
Petersen 1997	60/89	74/90		4.3	0.46 [0.23, 0.90]
Whitfield 1981	129/256	165/272		16.6	0.66 [0.47, 0.93]
Zwart 2000	215/358	131/164		12.8	0.41 [0.28, 0.61]
Zwart 2003	79/100	38/56		3.4	1.80 [0.85, 3.83]
Total (95% CI)	2066	1555		100.0	0.44 [0.38, 0.50]

Total events: 1009 (Treatment), 1031 (Control)

Test for heterogeneity chi-square=76.91 df=14 p=<0.0001 I^2 =81.8%

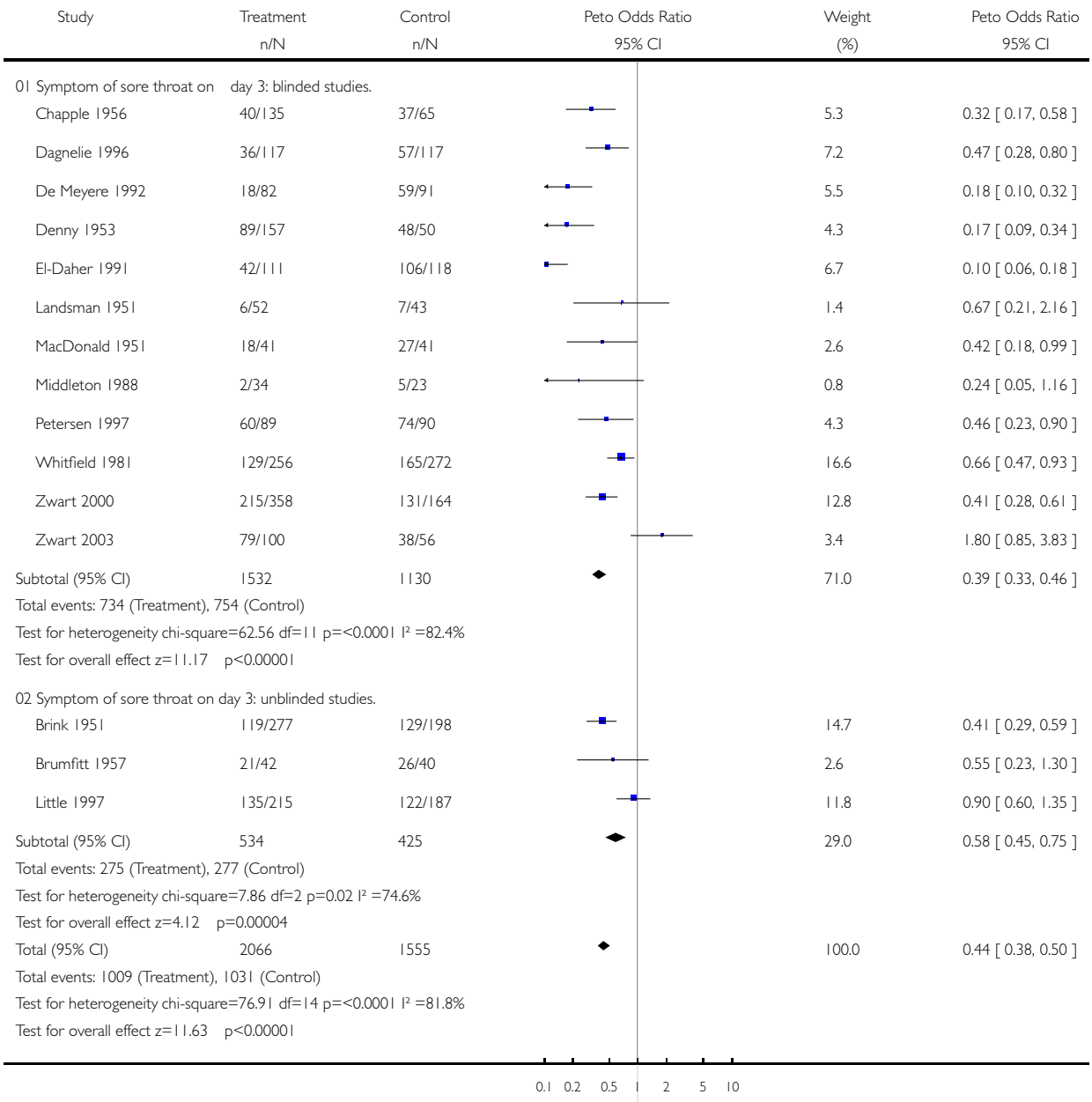
Test for overall effect z=11.63 p<0.00001

Analysis 02.02. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 02 Symptom of sore throat on day three: blind versus unblinded studies

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 02 Symptom of sore throat on day three: blind versus unblinded studies



Analysis 02.03. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 03 Symptom of sore throat on day three: antipyretics versus no antipyretics

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 03 Symptom of sore throat on day three: antipyretics versus no antipyretics

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Symptom of sore throat on day 3: antipyretics administered.					
Brumfitt 1957	21/42	26/40		8.0	0.55 [0.23, 1.30]
Chapple 1956	40/135	37/65		16.4	0.32 [0.17, 0.58]
De Meyere 1992	18/82	59/91		16.8	0.18 [0.10, 0.32]
Subtotal (95% CI)	259	196		41.2	0.28 [0.19, 0.41]
Total events: 79 (Treatment), 122 (Control)					
Test for heterogeneity chi-square=4.63 df=2 p=0.10 I^2 =56.8%					
Test for overall effect z=6.55 p<0.00001					
03 Symptom of sore throat on day 3: no antipyretics administered.					
Brink 1951	119/277	129/198		45.4	0.41 [0.29, 0.59]
Denny 1953	89/157	48/50		13.4	0.17 [0.09, 0.34]
Subtotal (95% CI)	434	248		58.8	0.34 [0.25, 0.47]
Total events: 208 (Treatment), 177 (Control)					
Test for heterogeneity chi-square=4.88 df=1 p=0.03 I^2 =79.5%					
Test for overall effect z=6.63 p<0.00001					
Total (95% CI)	693	444		100.0	0.31 [0.24, 0.40]
Total events: 287 (Treatment), 299 (Control)					
Test for heterogeneity chi-square=10.09 df=4 p=0.04 I^2 =60.4%					
Test for overall effect z=9.29 p<0.00001					

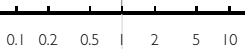
Analysis 02.04. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 04 Symptom of sore throat on day three: Streptococcus positive throat swab, negative swab, untested/ inseparable

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 04 Symptom of sore throat on day three: Streptococcus positive throat swab, negative swab, untested/ inseparable

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Symptom of sore throat on day 3: Group A Beta Haemolytic Streptococcus positive throat swab					
Brink 1951	119/277	129/198		14.8	0.41 [0.29, 0.59]
Brumfitt 1957	21/42	26/40		2.6	0.55 [0.23, 1.30]
Chapple 1956	13/68	22/41		2.9	0.21 [0.09, 0.48]
Dagnelie 1996	13/55	36/55		3.5	0.19 [0.09, 0.39]
De Meyere 1992	18/82	59/91		5.5	0.18 [0.10, 0.32]
Denny 1953	89/157	48/50		4.4	0.17 [0.09, 0.34]
El-Daher 1991	42/111	106/118		6.7	0.10 [0.06, 0.18]
MacDonald 1951	13/26	17/24		1.6	0.43 [0.14, 1.31]
Middleton 1988	2/24	5/23		0.8	0.36 [0.07, 1.74]
Zwart 2000	102/178	68/83		6.6	0.34 [0.20, 0.59]
Zwart 2003	39/53	28/43		2.6	1.49 [0.62, 3.56]
Subtotal (95% CI)	1073	766		51.9	0.28 [0.23, 0.34]
Total events: 471 (Treatment), 544 (Control)					
Test for heterogeneity chi-square=40.42 df=10 p=<0.0001 I^2 =75.3%					
Test for overall effect z=12.74 p<0.00001					
02 Symptom of sore throat on day 3: Group A Beta Haemolytic Streptococcus negative throat swab					
Chapple 1956	13/67	16/26		2.1	0.14 [0.05, 0.38]
Dagnelie 1996	31/60	29/51		3.5	0.81 [0.39, 1.71]
MacDonald 1951	5/15	10/17		1.0	0.37 [0.09, 1.46]
Petersen 1997	60/89	74/90		4.3	0.46 [0.23, 0.90]
Zwart 2000	113/180	63/81		6.3	0.51 [0.29, 0.89]
Zwart 2003	40/47	10/13		0.7	1.78 [0.35, 9.15]
Subtotal (95% CI)	458	278		18.1	0.48 [0.35, 0.67]
Total events: 262 (Treatment), 202 (Control)					
Test for heterogeneity chi-square=10.52 df=5 p=0.06 I^2 =52.5%					
Test for overall effect z=4.30 p=0.00002					
03 Symptom of sore throat on day 3: Untested for GABHS culture or combined inseperable data					
Landsman 1951	6/52	7/43		1.4	0.67 [0.21, 2.16]



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Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Little 1997	135/215	122/187		11.8	0.90 [0.60, 1.35]
Whitfield 1981	129/256	165/272		16.7	0.66 [0.47, 0.93]
Subtotal (95% CI)	523	502		30.0	0.75 [0.58, 0.96]
Total events: 270 (Treatment), 294 (Control)					
Test for heterogeneity chi-square=1.33 df=2 p=0.51 I^2 =0.0%					
Test for overall effect z=2.24 p=0.03					
Total (95% CI)	2054	1546		100.0	0.42 [0.36, 0.48]
Total events: 1003 (Treatment), 1040 (Control)					
Test for heterogeneity chi-square=88.42 df=19 p=<0.0001 I^2 =78.5%					
Test for overall effect z=12.24 p<0.00001					

Analysis 02.05. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 05 Symptom of sore throat at one week (six to eight days)

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 05 Symptom of sore throat at one week (six to eight days)

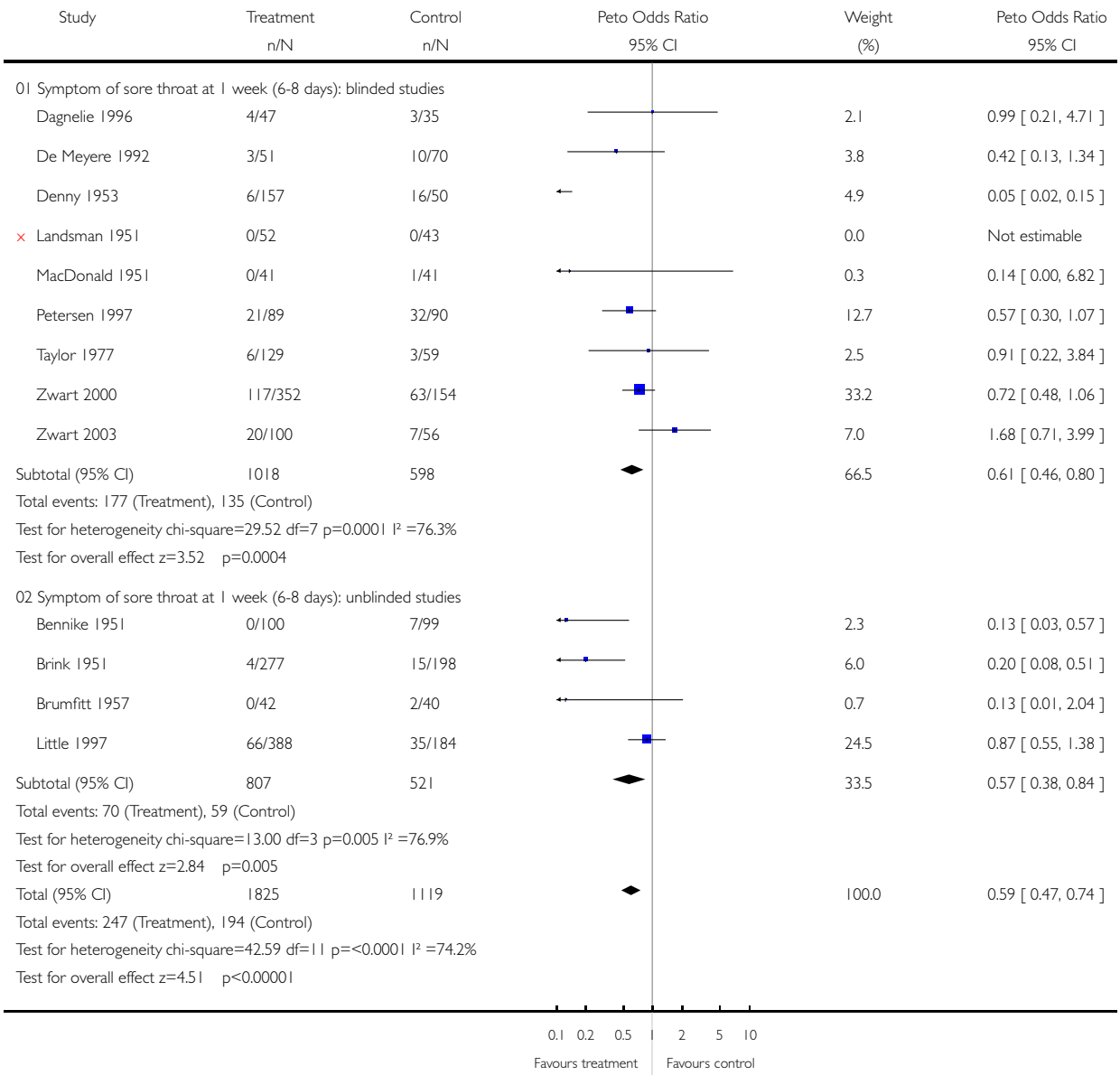
Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Bennike 1951	0/100	7/99		2.2	0.13 [0.03, 0.57]
Brink 1951	4/277	15/198		5.8	0.20 [0.08, 0.51]
Brumfitt 1957	0/42	2/40		0.6	0.13 [0.01, 2.04]
Dagnelie 1996	3/51	15/51		4.9	0.20 [0.07, 0.55]
De Meyere 1992	3/61	10/70		3.8	0.35 [0.11, 1.11]
Denny 1953	6/157	16/50		4.7	0.05 [0.02, 0.15]
× Landsman 1951	0/52	0/43		0.0	Not estimable
Little 1997	66/388	35/184		23.8	0.87 [0.55, 1.38]
MacDonald 1951	0/41	1/41		0.3	0.14 [0.00, 6.82]
Petersen 1997	21/89	32/90		12.3	0.57 [0.30, 1.07]
Taylor 1977	6/129	3/59		2.4	0.91 [0.22, 3.84]
Zwart 2000	117/352	63/154		32.2	0.72 [0.48, 1.06]
Zwart 2003	20/100	7/56		6.8	1.68 [0.71, 3.99]
Total (95% CI)	1839	1135		100.0	0.55 [0.44, 0.69]
Total events: 246 (Treatment), 206 (Control)					
Test for heterogeneity chi-square=46.59 df=11 p=<0.0001 I^2 =76.4%					
Test for overall effect z=5.20 p<0.00001					

Analysis 02.06. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 06 Symptom of sore throat at one week (six to eight days): blind versus unblinded studies

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 06 Symptom of sore throat at one week (six to eight days): blind versus unblinded studies



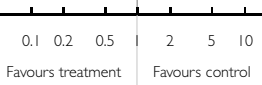
Analysis 02.07. Comparison 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, Outcome 07 Symptom of sore throat at one week (six to eight days): GABHS positive throat swab, GABHS negative swab. Untes

Review: Antibiotics for sore throat

Comparison: 02 Antibiotics versus control for the treatment of sore throats: symptom of sore throat

Outcome: 07 Symptom of sore throat at one week (six to eight days): GABHS positive throat swab, GABHS negative swab. Untes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Symptom of sore throat at 1 week (6-8days): Group A Beta Heamolytic Streptococcus positive throat swab					
Brink 1951	4/277	15/198		8.7	0.20 [0.08, 0.51]
Brumfitt 1957	0/42	2/40		1.0	0.13 [0.01, 2.04]
Dagnelie 1996	1/34	10/42		4.6	0.19 [0.05, 0.68]
De Meyere 1992	3/61	10/70		5.7	0.35 [0.11, 1.11]
Denny 1953	6/157	16/50		7.1	0.05 [0.02, 0.15]
MacDonald 1951	0/26	1/24		0.5	0.12 [0.00, 6.29]
Zwart 2003	8/53	3/43		4.7	2.21 [0.63, 7.75]
Subtotal (95% CI)	650	467		32.3	0.23 [0.14, 0.37]
Total events: 22 (Treatment), 57 (Control)					
Test for heterogeneity chi-square=21.38 df=6 p=0.002 I^2 =71.9%					
Test for overall effect z=5.99 p<0.00001					
02 Symptom of sore throat at 1 week (6-8days): Group A Beta Heamolytic Streptococcus negative throat swab					
Dagnelie 1996	3/35	4/47		3.1	1.01 [0.21, 4.78]
× MacDonald 1951	0/15	0/17		0.0	Not estimable
Petersen 1997	21/89	32/90		18.3	0.57 [0.30, 1.07]
Taylor 1977	6/129	3/59		3.6	0.91 [0.22, 3.84]
Zwart 2003	12/47	4/13		4.0	0.77 [0.19, 3.05]
Subtotal (95% CI)	315	226		29.0	0.67 [0.40, 1.11]
Total events: 42 (Treatment), 43 (Control)					
Test for heterogeneity chi-square=0.75 df=3 p=0.86 I^2 =0.0%					
Test for overall effect z=1.57 p=0.1					
03 Symptom of sore throat at 1 week (6-8days): Group A Beta Heamolytic Streptococcus untested					
Bennike 1951	0/100	7/99		3.3	0.13 [0.03, 0.57]
× Landsman 1951	0/52	0/43		0.0	Not estimable
Little 1997	66/388	35/184		35.5	0.87 [0.55, 1.38]
Subtotal (95% CI)	540	326		38.8	0.74 [0.48, 1.15]
Total events: 66 (Treatment), 42 (Control)					
Test for heterogeneity chi-square=5.81 df=1 p=0.02 I^2 =82.8%					



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Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Test for overall effect z=1.35 p=0.2					
Total (95% CI)	1505	1019		100.0	0.49 [0.37, 0.65]
Total events: 130 (Treatment), 142 (Control)					
Test for heterogeneity chi-square=42.21 df=12 p=<0.0001 I^2 =71.6%					
Test for overall effect z=5.09 p<0.00001					

Analysis 03.03. Comparison 03 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 03 Symptom of fever on day three

Review: Antibiotics for sore throat

Comparison: 03 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 03 Symptom of fever on day three

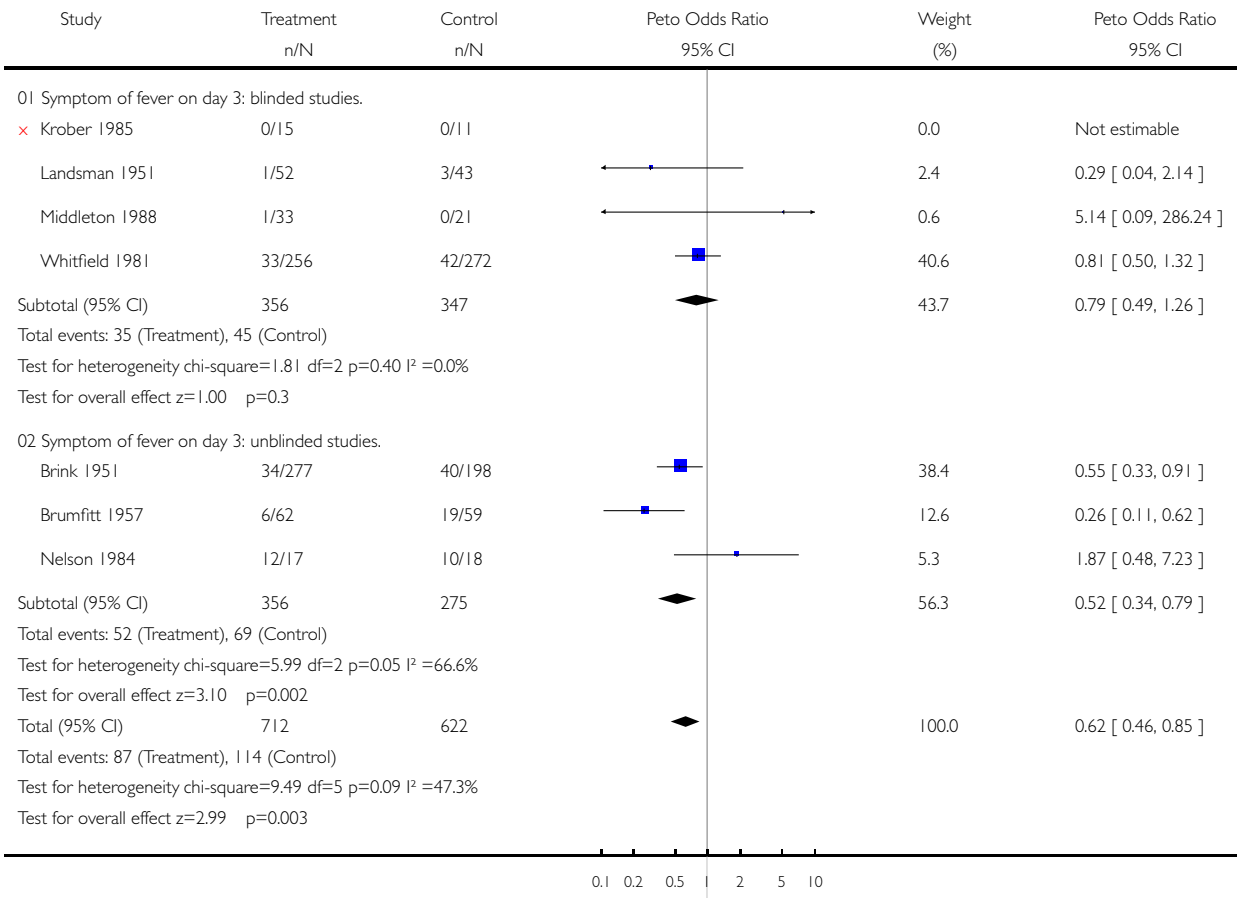
Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Brink 1951	34/277	40/198		38.4	0.55 [0.33, 0.91]
Brumfitt 1957	6/62	19/59		12.6	0.26 [0.11, 0.62]
× Krober 1985	0/15	0/11		0.0	Not estimable
Landsman 1951	1/52	3/43		2.4	0.29 [0.04, 2.14]
Middleton 1988	1/33	0/21		0.6	5.14 [0.09, 286.24]
Nelson 1984	12/17	10/18		5.3	1.87 [0.48, 7.23]
Whitfield 1981	33/256	42/272		40.6	0.81 [0.50, 1.32]
Total (95% CI)	712	622		100.0	0.62 [0.46, 0.85]
Total events: 87 (Treatment), 114 (Control)					
Test for heterogeneity chi-square=9.49 df=5 p=0.09 I^2 =47.3%					
Test for overall effect z=2.99 p=0.003					

Analysis 03.04. Comparison 03 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 04 Symptom of fever on day three: blinded versus unblinded studies

Review: Antibiotics for sore throat

Comparison: 03 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 04 Symptom of fever on day three: blinded versus unblinded studies



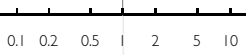
Analysis 03.05. Comparison 03 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 05 Symptom of fever on day three: children compared with adults

Review: Antibiotics for sore throat

Comparison: 03 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 05 Symptom of fever on day three: children compared with adults

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Symptom of fever on day 3: children					
× Krober 1985	0/15	0/11		0.0	Not estimable
Nelson 1984	12/17	10/18		9.3	1.87 [0.48, 7.23]
Subtotal (95% CI)	32	29		9.3	1.87 [0.48, 7.23]
Total events: 12 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.91 p=0.4					
02 Symptom of fever on day 3: adults					
Brink 1951	34/277	40/198		67.3	0.55 [0.33, 0.91]
Catanzaro 1954	3/62	24/59		23.4	0.13 [0.05, 0.30]
Subtotal (95% CI)	339	257		90.7	0.38 [0.24, 0.58]
Total events: 37 (Treatment), 64 (Control)					
Test for heterogeneity chi-square=8.23 df=1 p=0.004 I^2 =87.9%					
Test for overall effect z=4.41 p=0.00001					
Total (95% CI)	371	286		100.0	0.44 [0.29, 0.66]
Total events: 49 (Treatment), 74 (Control)					
Test for heterogeneity chi-square=13.12 df=2 p=0.001 I^2 =84.8%					
Test for overall effect z=3.93 p=0.00009					



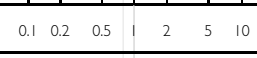
Analysis 03.06. Comparison 03 Antibiotics versus control for the treatment of sore throat: symptom of fever, Outcome 06 Symptom of fever at one week (six to eight days)

Review: Antibiotics for sore throat

Comparison: 03 Antibiotics versus control for the treatment of sore throat: symptom of fever

Outcome: 06 Symptom of fever at one week (six to eight days)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Brink 1951	0/277	0/198		0.0	Not estimable
× Denny 1950	0/157	0/50		0.0	Not estimable
× Landsman 1951	0/52	0/43		0.0	Not estimable
Total (95% CI)	486	291		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 04.03. Comparison 04 Antibiotics versus control for the treatment of sore throat: symptom of headache, Outcome 03 Symptom of headache on day three

Review: Antibiotics for sore throat

Comparison: 04 Antibiotics versus control for the treatment of sore throat: symptom of headache

Outcome: 03 Symptom of headache on day three

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Brink 1951	61/277	80/198		57.2	0.42 [0.28, 0.62]
Denny 1953	54/157	30/50		21.7	0.35 [0.18, 0.66]
El-Daher 1991	7/118	37/111		21.1	0.17 [0.09, 0.33]
Total (95% CI)	552	359		100.0	0.33 [0.25, 0.45]
Total events: 122 (Treatment), 147 (Control)					
Test for heterogeneity chi-square=5.05 df=2 p=0.08 I^2 =60.4%					
Test for overall effect z=7.17 p<0.00001					

Analysis 04.04. Comparison 04 Antibiotics versus control for the treatment of sore throat: symptom of headache, Outcome 04 Symptom of headache on day three: blinded versus unblinded studies

Review: Antibiotics for sore throat

Comparison: 04 Antibiotics versus control for the treatment of sore throat: symptom of headache

Outcome: 04 Symptom of headache on day three: blinded versus unblinded studies

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Symptom headache on day three: blinded studies					
Denny 1953	54/157	30/50		21.7	0.35 [0.18, 0.66]
El-Daher 1991	7/118	37/111		21.1	0.17 [0.09, 0.33]
Subtotal (95% CI)	275	161		42.8	0.25 [0.16, 0.39]
Total events: 61 (Treatment), 67 (Control)					
Test for heterogeneity chi-square=2.22 df=1 p=0.14 I^2 =55.0%					
Test for overall effect z=5.97 p<0.00001					
03 Symptom of headache on day three: unblinded studies					
Brink 1951	61/277	80/198		57.2	0.42 [0.28, 0.62]
Subtotal (95% CI)	277	198		57.2	0.42 [0.28, 0.62]
Total events: 61 (Treatment), 80 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.32 p=0.00002					
Total (95% CI)	552	359		100.0	0.33 [0.25, 0.45]
Total events: 122 (Treatment), 147 (Control)					
Test for heterogeneity chi-square=5.05 df=2 p=0.08 I^2 =60.4%					
Test for overall effect z=7.17 p<0.00001