Antibiotics for treatment of sore throat in children and adults

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[Intervention Review]

Antibiotics for treatment of sore throat in children and adults

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ABSTRACT

Background

Sore throat is a common reason for people to present for medical care and to be prescribed antibiotics. Overuse of antibiotics in primary medicine is a concern, hence it is important to establish their efficacy in treating sore throat and preventing secondary complications.

Objectives

To assess the effects of antibiotics for reducing symptoms of sore throat for child and adult patients.

Search methods

We searched CENTRAL 2021, Issue 2, MEDLINE (January 1966 to April week 1, 2021), Embase (January 1990 to April 2021), and two trial registries (searched 6 April 2021).

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs of antibiotics versus control assessing typical sore throat symptoms or complications amongst children and adults seeking medical care for sore throat symptoms.

Data collection and analysis

We used standard methodological procedures as recommended by Cochrane. Two review authors independently screened studies for inclusion and extracted data, resolving any differences in opinion by discussion. We contacted the trial authors from three studies for additional information. We used GRADE to assess the certainty of the evidence for the efficacy of antibiotics on our primary outcomes (sore throat at day three and one week) and secondary outcomes (fever and headache symptoms and incidence of acute rheumatic fever, acute glomerulonephritis, acute otitis media, acute sinusitis, and quinsy).

Main results

We included 29 trials with 15,337 cases of sore throat. The majority of included studies were conducted in the 1950s, during which time the rates of serious complications (especially acute rheumatic fever) were much higher than today. Although clinical antibiotic trials for sore throat and respiratory symptoms are still being conducted, it is unusual for them to include placebo or 'no treatment' control arms, which is a requirement for inclusion in the review.

The age of participants ranged from younger than one year to older than 50 years, but most participants across all studies were adults. Although all studies recruited patients presenting with symptoms of sore throat, few of them distinguished between bacterial and viral aetiology. Bias may have been introduced through non-clarity in treatment allocation procedures and lack of blinding in some studies. Harms from antibiotics were poorly or inconsistently reported, and were thus not quantified for this review.

1. Symptoms

Throat soreness and headache at day three were reduced by using antibiotics, although 82% of participants in the placebo or no treatment group were symptom-free by one week. The reduction in sore throat symptoms at day three (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.60 to 0.80; 16 studies, 3730 participants; moderate-certainty evidence) was greater than at one week in absolute numbers (RR 0.50, 95% CI 0.34 to 0.75; 14 studies, 3083 participants; moderate-certainty evidence) due to many cases in both treatment groups having resolved by this time. The number needed to treat for an additional beneficial outcome (NNTB) to prevent one sore throat at day three was less than six; at week one it was 18. Compared with placebo or no treatment, antibiotics did not significantly reduce fever at day three (RR 0.75, 95% CI 0.53 to 1.07; 8 studies, 1443 participants; high-certainty evidence), but did reduce headache at day three (RR 0.49, 95% CI 0.34 to 0.70; 4 studies, 1020 participants; high-certainty evidence).

2. Suppurative complications

Whilst the prevalence of suppurative complications was low, antibiotics reduced the incidence of acute otitis media within 14 days (Peto odds ratio (OR) 0.21, 95% CI 0.11 to 0.40; 10 studies, 3646 participants; high-certainty evidence) and quinsy within two months (Peto OR 0.16, 95% CI 0.07 to 0.35; 8 studies, 2433 participants; high-certainty evidence) compared to those receiving placebo or no treatment, but not acute sinusitis within 14 days (Peto OR 0.46, 95% CI 0.10 to 2.05; 8 studies, 2387 participants; high-certainty evidence).

3. Non-suppurative complications

There were too few cases of acute glomerulonephritis to determine whether there was a protective effect of antibiotics compared with placebo against this complication (Peto OR 0.07, 95% CI 0.00 to 1.32; 10 studies, 5147 participants; low-certainty evidence). Antibiotics reduced acute rheumatic fever within two months when compared to the control group (Peto OR 0.36, 95% CI 0.26 to 0.50; 18 studies, 12,249 participants; moderate-certainty evidence). It should be noted that the overall prevalence of acute rheumatic fever was very low, particularly in the later studies.

Authors' conclusions

Antibiotics probably reduce the number of people experiencing sore throat, and reduce the likelihood of headache, and some sore throat complications. As the effect on symptoms can be small, clinicians must judge on an individual basis whether it is clinically justifiable to use antibiotics to produce this effect, and whether the underlying cause of the sore throat is likely to be of bacterial origin. Furthermore, the balance between modest symptom reduction and the potential hazards of antimicrobial resistance must be recognised. Few trials have attempted to measure symptom severity. If antibiotics reduce the severity as well as the duration of symptoms, their benefit will have been underestimated in this meta-analysis. Additionally, more trials are needed in low-income countries, in socio-economically deprived sections of high-income countries, as well as in children.

PLAIN LANGUAGE SUMMARY

Antibiotics for adults and children with sore throats

Review question

Are antibiotics effective in treating the symptoms and reducing the potential complications associated with sore throats?

Background

Sore throats are infections caused by bacteria or viruses. Pain or discomfort is the most distinguishing feature. However, fever and headache are also common accompanying symptoms. People usually recover quickly (after three or four days), although some develop complications. A serious but rare complication is rheumatic fever, which affects the heart and joints. Other complications include acute infection of the sinuses, middle ear, tonsils, and kidney. Antibiotics reduce infections caused by bacteria, but not those caused by viruses, and they can cause diarrhoea, rash, and other adverse effects. In addition, communities build resistance to them.

Search date

The evidence is current to April 2021.

Study characteristics

The 2021 update includes 29 trials with 15,337 cases of sore throat. All of the included studies were randomised controlled trials (a type of study where participants are randomly assigned to one of two or more treatment groups) that sought to determine if antibiotics helped reduce symptoms of sore throat, fever, or headache or the occurrence of more serious complications. The included studies were conducted in both children and adults seeking medical care for their symptoms.

Study funding sources

Many of the early studies were funded by the United States Armed Forces and recruited young, adult male military personnel. Later studies were mostly supported by governmental research grants, with a small number funded by private pharmaceutical companies.

Key results

We found that antibiotics reduced the number of people still experiencing headache on the third day of illness. Antibiotics probably reduced the number of people with sore throat after three days and one week, as well as rheumatic fever within two months in communities where this complication is common. Our confidence in the evidence for antibiotic use varied from low to high for other types of complications associated with sore throat.

Certainty of evidence

Overall, the certainty of the evidence from the included studies was low to high. However, there were very few recent trials included in the review, hence it is unclear if changes in bacterial resistance in the community may have affected the effectiveness of antibiotics.

SUMMARY OF FINDINGS

Summary of findings 1. Antibiotics compared with control for sore throat

Antibiotics compared with control for sore throat

Patient or population: adults and children presenting with sore throat

Settings: community

Intervention: antibiotics

Comparison: control (placebo or no treatment)

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with antibiotics				
Sore throat: day 3	660	462 (396 to 528)	RR 0.70 (0.60 to 0.80)	3730 (16 studies)	⊕⊕⊕⊖ Moderate[a]	
Sore throat: 1 week	190	95 (65 to 143)	RR 0.50 (0.34 to 0.75)	3083 (14 studies)	⊕⊕⊕⊖ Moderate[a]	
Fever: day 3	197	148 (104 to 211)	RR 0.75 (0.53 to 1.07)	1443 (8 studies)	⊕⊕⊕⊕ High	
Headache: day 3	421	206 (143 to 295)	RR 0.49 (0.34 to 0.70)	1020 (4 studies)	⊕⊕⊕⊕ High	
Rheumatic fever (within 2 months, clinical diagnosis)	190	61 (34 to 110)	Peto OR 0.32 (0.18 to 0.58)	12,132 (17 studies)	⊕⊕⊕⊖ Moderate[a]	Based largely on risk in pre-1960 trials
Glomerulonephritis (within 1 month, clinical diagnosis)	1	0 (0 to 2)	Peto OR 0.07 (0.00 to 1.32)	5147 (10 studies)	⊕⊖⊖⊖ Low[b]	Sparse data: 2 cases only in the placebo group

Quinsy (within 2 months, clinical diagnosis)	23	3 (1 to 11)	Peto OR 0.16 (0.07 to 0.35)	2367 (7 studies)	⊕⊕⊕⊕ High
Otitis media (within 14 days, clinical diagnosis)	20	5 (3 to 11)	Peto OR 0.21 (0.11 to 0.40)	3646 (10 studies)	⊕⊕⊕⊕ High

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

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

[a]Downgraded one level for high level of heterogeneity.
[b]Downgraded two levels for serious imprecision relating to very small number of reported cases.

BACKGROUND

Description of the condition

Sore throat is a very common reason for people to attend primary care settings (Finley 2018). Sore throat is a disease that resolves 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; Tyrstrup 2017, and between primary care doctors (Howie 1971).

Description of the intervention

The administration of antibiotics is likely to shorten the time to the remittance of symptoms and reduce the likelihood of complications in patients whose sore throat has a bacteriological aetiology (van Driel 2016). However, their benefits may be limited in the treatment of sore throat more generally (Reveiz 2013). Doctors have traditionally attempted to determine whether the cause of the infection is bacterial, especially when caused by the group A beta-haemolytic *Streptococcus* (GABHS), which can cause acute rheumatic fever and acute glomerulonephritis. However, determining the aetiological agent is difficult (Del Mar 1992b).

How the intervention might work

Antibiotics target bacteria which are potentially responsible for sore throat symptoms and possible subsequent suppurative (pus producing) and non-suppurative sequelae or complications. Successful eradication of bacteria may promote faster healing and the prevention of secondary complications. However, not all sore throat cases are of bacteriologic origin, and bacteria may resist antibiotic treatment, which could limit the overall effectiveness of the intervention.

Why it is important to do this review

Whether or not to prescribe antibiotics for sore throat is controversial, and it has been estimated that antibiotic prescription rates for sore throat exceed appropriate levels (Smith 2018). The issue is important for several reasons. Sore throat is a very common disease, and differences in prescribing result in large cost differences. In addition, increased prescribing increases patient attendance rates (Howie 1978; Little 1997) which may result in unnecessary visits to primary care for mild illness that does not require medical intervention. Furthermore, antibiotic resistance from overuse is an issue of great concern (Ciorba 2015). This 2021 update was built on an early meta-analysis, Del Mar 1992a, and is an update of previous Cochrane Reviews (Del Mar 1997; Del Mar 2004; Del Mar 2006; Spinks 2013).

OBJECTIVES

To assess the effects of antibiotics for reducing symptoms of sore throat for child and adult patients.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

Adults and children seeking medical care for symptoms of sore throat.

Types of interventions

Antibiotics or control consisting of either no treatment or placebo.

Types of outcome measures

Primary outcomes

1. Symptoms of sore throat on day three.
2. Symptoms of sore throat at one week (days six to eight).

Secondary outcomes

1. Symptoms of fever at day three.
2. Symptoms of headache at day three.
3. Incidence of suppurative (pus-producing) complications:
   a. quinsy (peritonsillar abscess);
   b. acute otitis media (middle ear infection);
   c. acute sinusitis.
4. Incidence of non-suppurative complications:
   a. acute rheumatic fever within two months;
   b. acute glomerulonephritis (inflammation of the kidney) within one month.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2021, Issue 2, part of the Cochrane Library (www.thecochranelibrary.com) (accessed 6 April 2021), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to April week 1, 2021), and Embase (January 1990 to April 2021). See Appendix 1 and Appendix 2 for details of the search strategy and Appendix 3 for details of previous searches.

Searching other resources

We searched ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform) on 6 April 2021 for completed and ongoing trials. We hand checked references of selected studies and relevant reviews to find additional studies.

Data collection and analysis

Selection of studies

Two review authors (AS, CDM) independently screened the abstracts of studies identified by the search and retrieved the full-text articles for those deemed potentially relevant. Two review authors (AS, CDM) examined the full-text articles and either included studies or excluded studies, providing reasons for exclusion of the latter studies.

Data extraction and management

Two review authors (AS, CDM) independently extracted data from the included studies based on patient-relevant outcomes, namely the complications and symptoms listed above. We performed data extraction from tables, graphs, and in some cases through contact

with the trial authors for raw data (Dagnelie 1996; de la Poza Abad 2016; Little 1997; Zwart 2000; Zwart 2003).

Assessment of risk of bias in included studies

We assessed risk of bias according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the following six criteria to judge risk of bias: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias.

Measures of treatment effect

All treatment effect outcomes were dichotomous data, reported as risk ratios (RR). We reported the occurrence of complications during the study period for suppurative and non-suppurative complications. We assessed the presence of symptoms (sore throat, fever, headache) when possible at day three and week one (days six to eight). We also calculated the number needed to treat for an additional beneficial outcome (NNTB) for the primary outcomes.

Unit of analysis issues

The unit of analysis was the individual participant, and all included studies performed randomisation at the participant level, therefore no adjustments were necessary for the effect of clustering.

Dealing with missing data

We performed an intention-to treat analysis for all outcomes.

Assessment of heterogeneity

We assessed heterogeneity using the Chi^2 test, with the significance level set at 0.1. We determined the effect of heterogeneity by the I^2 statistic, which indicates the proportion of total variability that can be explained by heterogeneity. We interpreted values of the I^2 statistic greater than 50% as indicating substantial heterogeneity, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

Where possible, we used funnel plots to investigate the possibility of reporting bias. We produced funnel plots when there were sufficient data (10 or more studies).

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

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

1. treatment with penicillin (omitting other antibiotics);
2. children compared with adults; and
3. positive throat swab versus negative throat swab versus untested and/or inseparable data for group A beta-haemolytic *Streptococcus* (GABHS).

Sensitivity analysis

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

1. early (pre-1975) versus later (post-1975) studies; and
2. blinded versus unblinded studies.

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table for the following outcomes: symptoms of sore throat on day three, symptoms of sore throat at one week, incidence of rheumatic fever, incidence of acute glomerulonephritis, incidence of quinsy, and incidence of otitis media (see Summary of findings 1). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of evidence as it relates to the studies contributing data to the meta-analyses (Atkins 2004). We used the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT). We justified all decisions to down- or upgrade the certainty of the evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

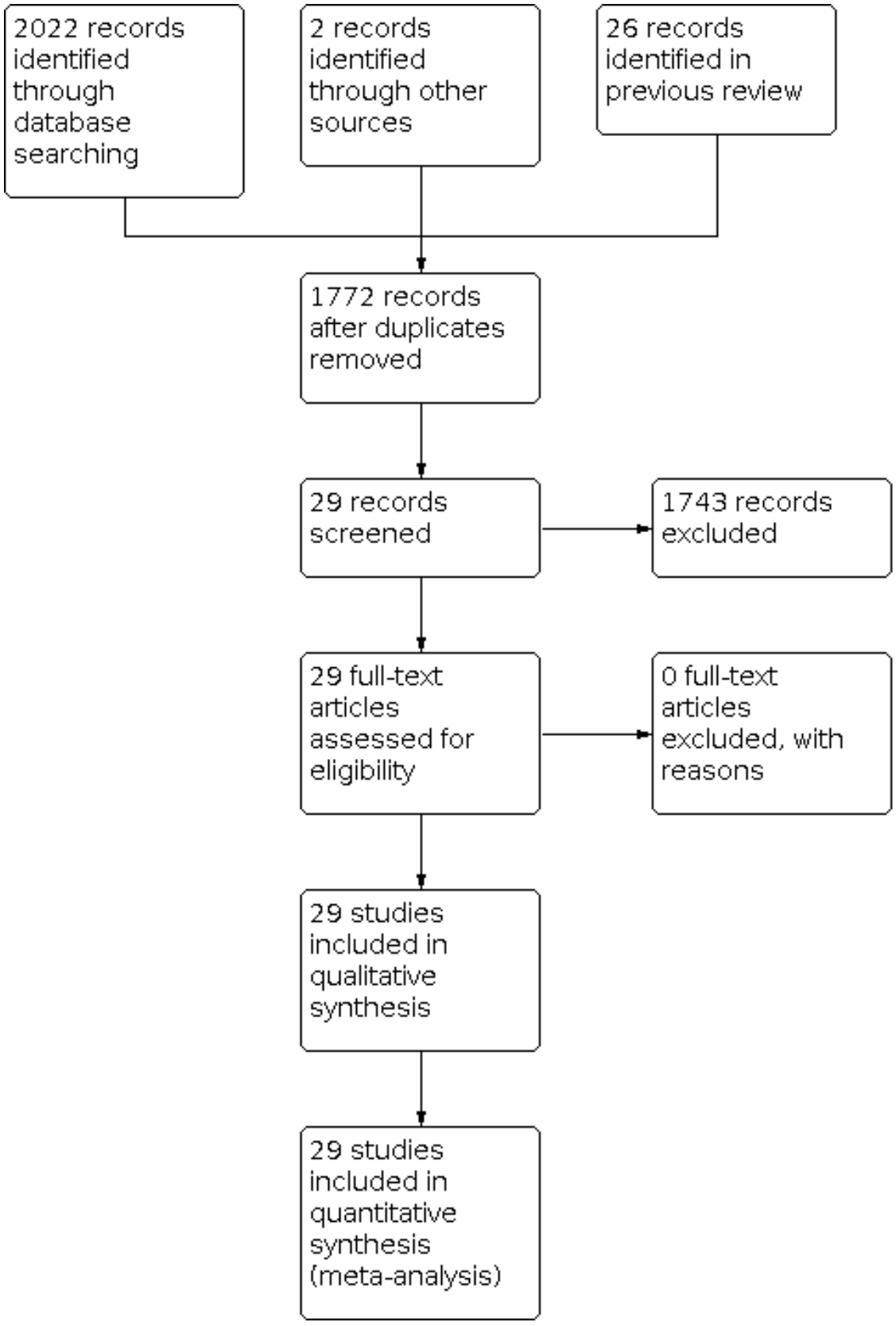
Description of studies

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

Results of the search

We considered a total of 64 studies for the review. The PRISMA flow diagram for studies considered in the 2021 update is shown in Figure 1. PRISMA is an evidence-based minimum set of items for reporting in systematic reviews. Twenty-nine randomised studies met the inclusion criteria of the review, three of which were added in this 2021 update. Of these, two were historic trials that contributed data to the effect of antibiotics on rheumatic fever incidence (Brock 1953; Houser 1953), and one was a recent trial of various antibiotic prescribing regimens for adults with acute respiratory infections (de la Poza Abad 2016). Not all participants in this trial presented with sore throat at the time of enrolment, hence the authors were contacted to provide a subset of trial data that met the inclusion criteria for the review.

Figure 1. Study flow diagram for the 2021 review update.



Included studies

The included studies investigated a total of 15,337 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 they are today. Eight studies have been published since 1996, with only four studies occurring since 2000. Although clinical antibiotic trials for sore throat and respiratory symptoms are still being conducted, it is unusual for them to include placebo or 'no treatment' control arms, which was a requirement for inclusion in the review.

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 (Brink 1951; Brock 1953; Brumfitt 1957; Catanzaro 1954; Chamovitz 1954; Denny 1950; Denny 1953; Houser 1953; MacDonald 1951; Wannamaker 1951). Six of the remaining studies recruited children up to 18 years of age only (El-Daher 1991; Krober 1985; Nelson 1984; Siegel 1961; Taylor 1977; Zwart 2000); four recruited only adults or adolescents aged 15 years or over (de la Poza Abad 2016; Howe 1997; Petersen 1997; Zwart 2003); and nine studies recruited both adults and children (Bennike 1951; Chapple 1956; Dagnelie 1996; De Meyere 1992; Landsman 1951; Leelarasamee 2000; Little 1997; Middleton 1988; Whitfield 1981).

All studies recruited patients presenting with symptoms of sore throat. The majority of studies did not distinguish between bacterial and viral aetiology. However, seven studies included or analysed results for GABHS-positive patients only (Catanzaro 1954; De Meyere 1992; El-Daher 1991; Krober 1985; Middleton 1988; Nelson 1984); one study distinguished differences in outcomes between GABHS-positive and -negative patients (Dagnelie 1996); and two studies specifically excluded patients who were GABHS-positive (Petersen 1997; Taylor 1977).

Excluded studies

The most common reason for exclusion was lack of an appropriate control group (n = 15). Other reasons for exclusion were: irrelevant or non-patient-centred outcomes (n = 6), main complaint other than acute sore throat (n = 5), inappropriate or no randomisation to treatment (n = 5), an intervention other than antibiotics was being tested (n = 2), the study tracked natural course of illness only (n = 1), or the study reported previously published data already included (n = 1).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 2 and summarised in Figure 3.

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

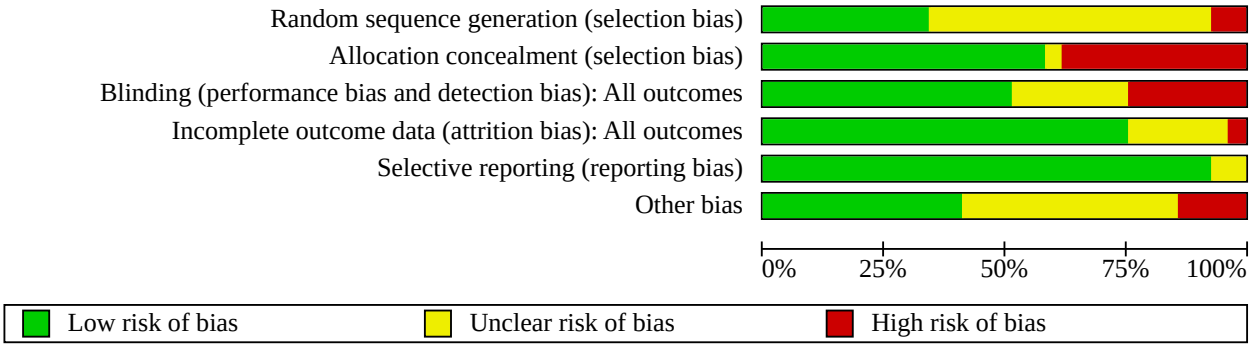


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

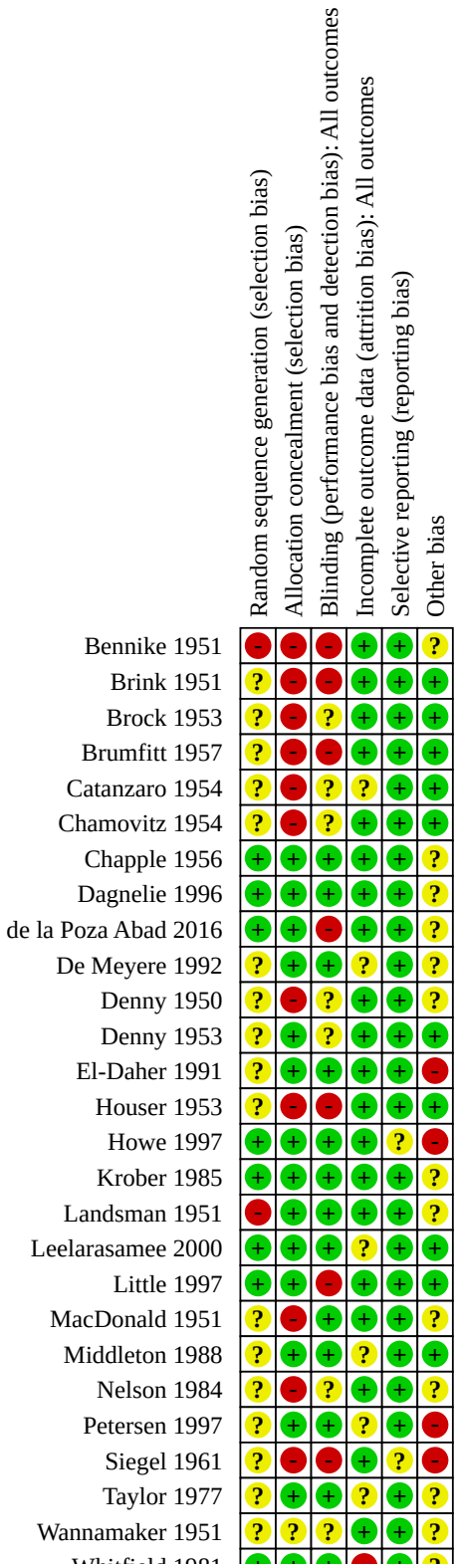
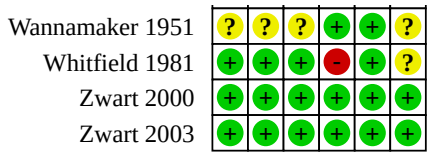


Figure 3. (Continued)



We could produce funnel plots to assess the potential for reporting bias for four outcomes, which are shown in Figure 4 (Symptom of sore throat on day three); Figure 5 (Symptom of sore throat at one week); Figure 6 (Incidence of acute rheumatic fever); and Figure 7 (Incidence of otitis media). Visual inspection of the plots indicated the potential for publication bias related to studies reporting the incidence of sore throat complications.

Figure 4. Funnel plot of comparison: 1 Antibiotics versus control for the treatment of sore throats: symptom of sore throat, outcome: 1.1 Symptom of sore throat on day 3.

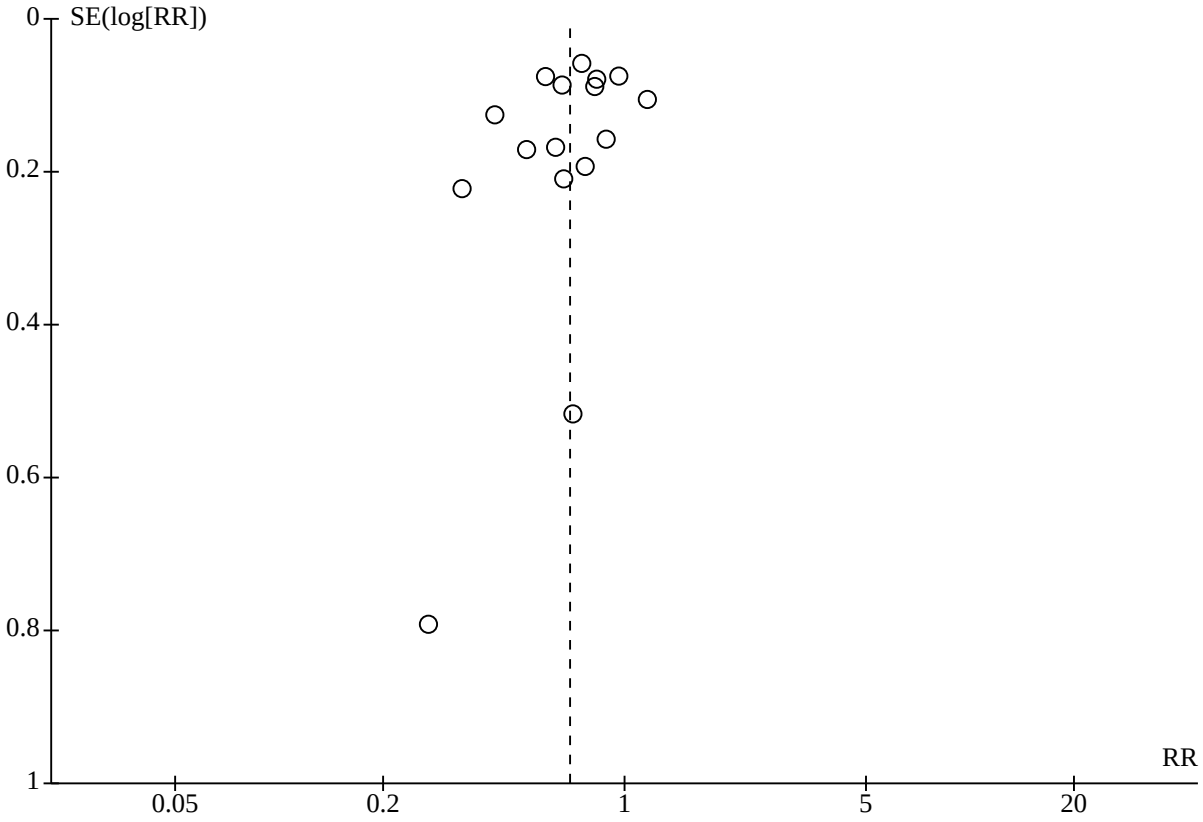


Figure 5. Funnel plot of comparison: 1 Antibiotics versus control for the treatment of sore throat: symptom of sore throat, outcome: 1.6 Symptom of sore throat at 1 week (6 to 8 days).

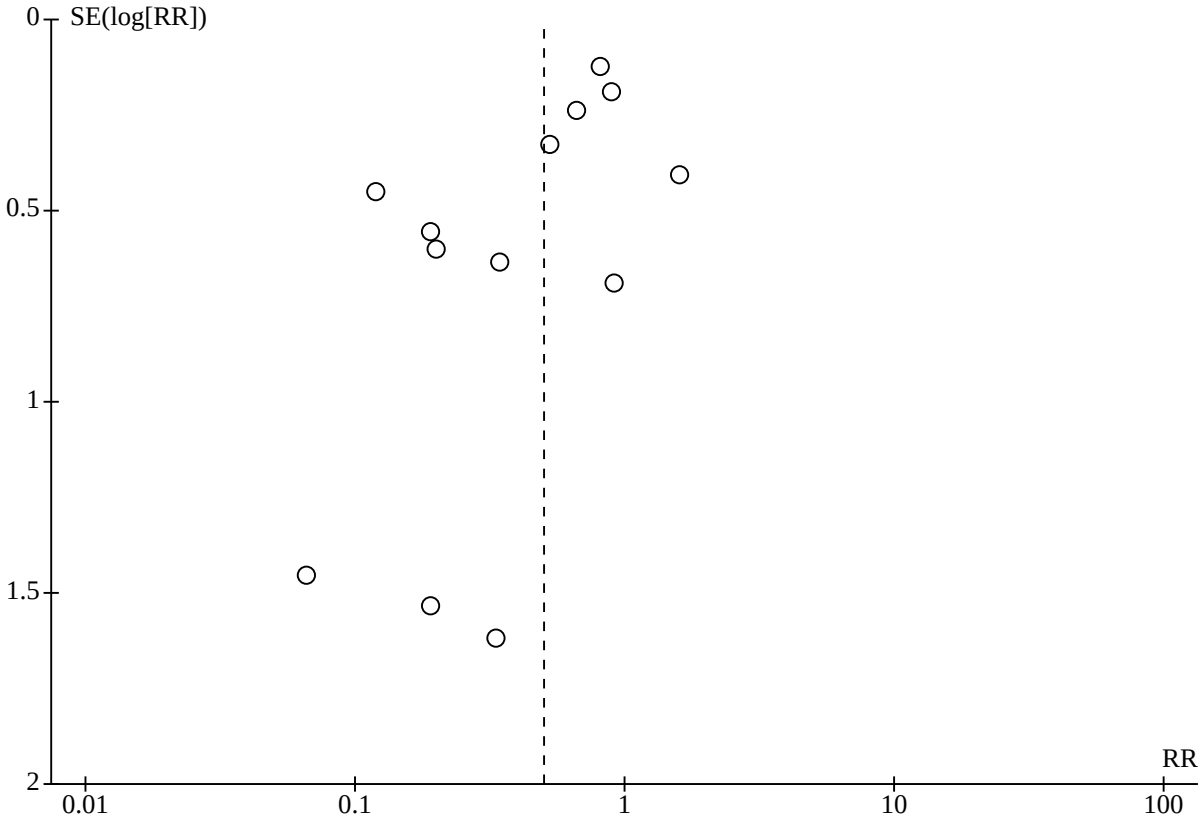


Figure 6. Funnel plot of comparison: 4 Antibiotics versus control for the treatment of sore throat: incidence of complications, outcome: 4.1 Incidence of acute rheumatic fever within 2 months. Rheumatic fever defined by clinical diagnosis.

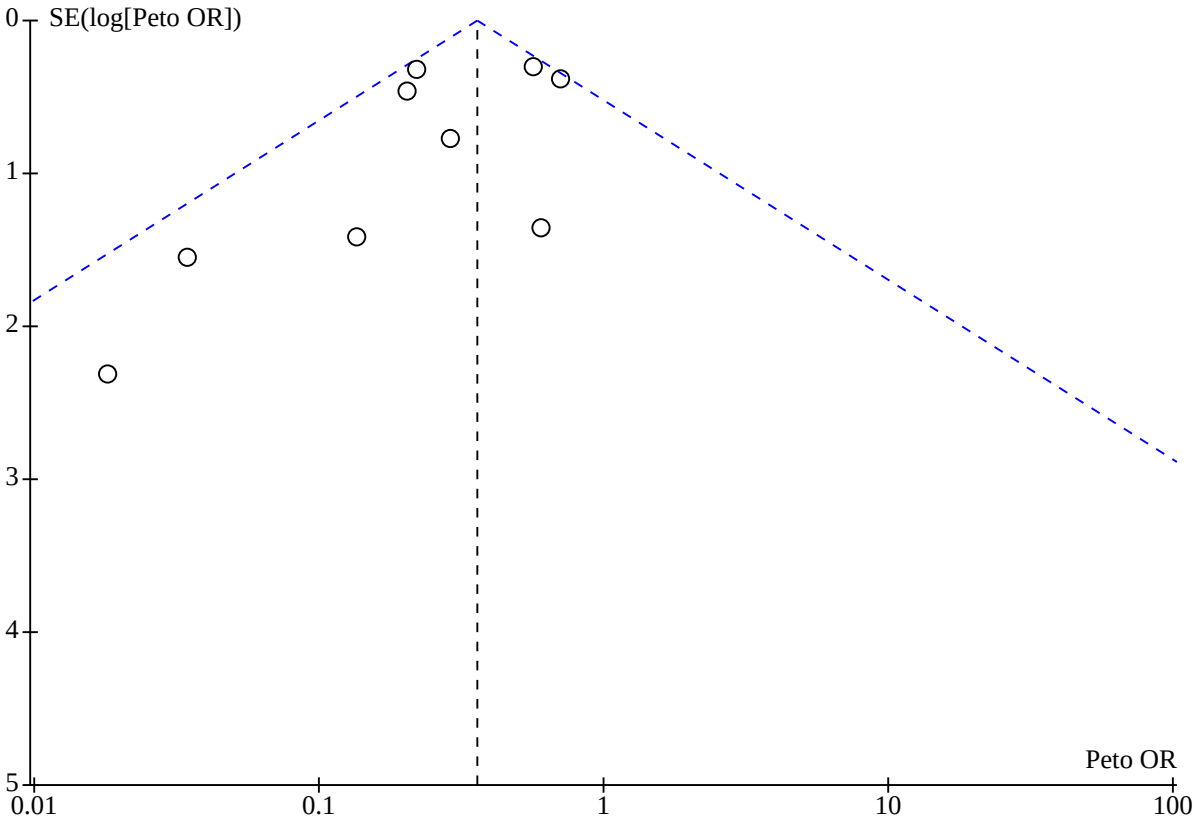
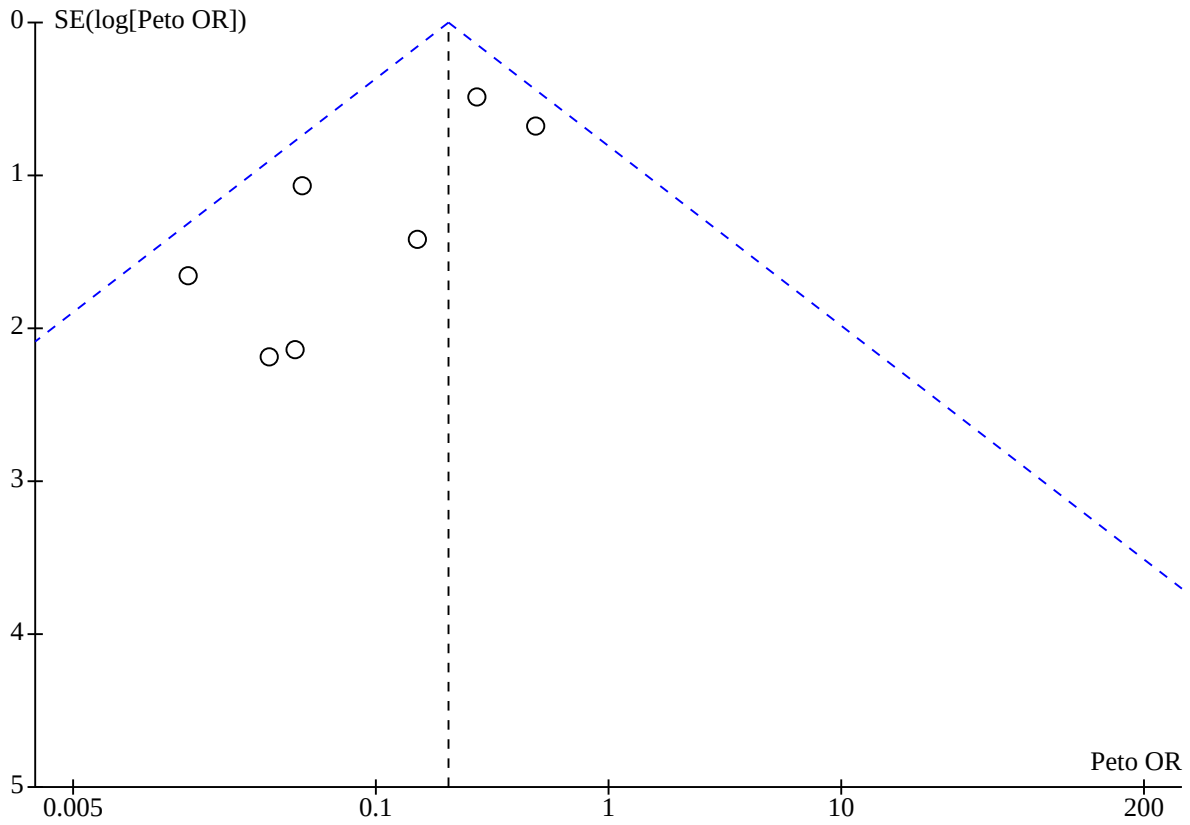


Figure 7. Funnel plot of comparison: 4 Antibiotics versus control for the treatment of sore throat: incidence of complications, outcome: 4.4 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis.



Allocation

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

Blinding

Fifteen studies were double-blinded and seven were single-blinded, whilst seven studies involved no blinding of participants or study personnel.

Incomplete outcome data

Outcome data were complete for nearly all of the included studies. It was not clear in one study how many participants maintained pain score diaries, and some participants who were initially randomised were excluded due to being GABHS-positive (Petersen 1997).

Selective reporting

Nearly all of the studies had a low risk of bias related to selective reporting of outcomes.

Other potential sources of bias

The use of antipyretic analgesics was not stated in nine studies, administered routinely in five studies, and prohibited in four studies. The prohibition of analgesics might exaggerate any small symptomatic benefit of antibiotics over control if antipyretic analgesics are usually recommended in normal practice. Funding arrangements contributed another potential source of bias to four studies that were supported by pharmaceutical companies; this may have influenced outcomes for these studies.

Effects of interventions

See: **Summary of findings 1** Antibiotics compared with control for sore throat

Primary outcomes

1. Symptoms of sore throat on day three

At day three of the illness, antibiotics reduced symptoms of sore throat (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.60 to 0.80; 16 studies, 3730 participants; moderate-certainty evidence; Analysis 1.1).

2. Symptoms of sore throat at one week (days six to eight)

At one week (six to eight days), the RR of experiencing sore throat was 0.50 (95% CI 0.34 to 0.75; 14 studies, 3083 participants; moderate-certainty evidence; Analysis 1.6), although 82% of controls were better by this time.

Secondary outcomes

1. Symptoms of fever at day three

At day three of the illness, antibiotics did not significantly reduce symptoms of fever (RR 0.75, 95% CI 0.53 to 1.07; 8 studies, 1443 participants; high-certainty evidence; Analysis 2.1).

2. Symptoms of headache at day three

At day three of the illness, antibiotics reduced symptoms of headache (RR 0.49, 95% CI 0.34 to 0.70; 4 studies, 1020 participants; high-certainty evidence; Analysis 3.1).

3. Incidence of suppurative complications

The incidence of acute otitis media within 14 days was lower in participants receiving antibiotics compared with those in the control group (Peto odds ratio (OR) 0.21, 95% CI 0.11 to 0.40; 10 studies, 3646 participants; high-certainty evidence; Analysis 4.4). However, antibiotic use made little or no difference to the incidence of acute sinusitis within 14 days (Peto OR 0.46, 95% CI 0.10 to 2.05; 7 studies, 2270 participants; high-certainty evidence; Analysis 4.6). Data indicated that the incidence of quinsy within two months was also reduced in relation to the control group (Peto OR 0.16, 95% CI 0.07 to 0.35; 7 studies, 2367 participants; high-certainty evidence; Analysis 4.7).

4. Incidence of non-suppurative complications

Only 10 studies reported on acute glomerulonephritis as an endpoint, and only two cases occurred, both in the control group. Our estimate of the protection has a very wide 95% CI, including the possibility of no difference between treatment and control groups (Peto OR 0.07, 95% CI 0.00 to 1.32; 10 studies, 5147 participants; low-certainty evidence; Analysis 4.8), which precludes us from definitively claiming that antibiotics protect sore throat sufferers from acute glomerulonephritis.

Several studies found a benefit of antibiotics for acute rheumatic fever within two months. The incidence of this complication was lower in people treated with antibiotics versus those in the control group (Peto OR 0.36, 95% CI 0.26 to 0.50; 17 studies, 12,132 participants; moderate-certainty evidence; Analysis 4.1). Few studies examined antibiotics other than penicillin.

A selection of these results is summarised in Summary of findings 1.

A trial from Thailand was included in the 2003 update (Leelarasamee 2000). This trial is especially important because it is one of the few trials from a non-Western industrial country. Unfortunately, we were unable to enter data from this study into the meta-analysis due to the different ways in which data were collected (in particular no data were collected mid-way through the illness). Nevertheless, the use of antibiotics conferred no benefit (or harm) on symptoms or complications.

Subgroup analysis of symptom reduction and prevention of complications

1. Treatment with penicillin (omitting other antibiotics) for preventing rheumatic fever

Most studies (15 out of 18) assessing the efficacy of antibiotics on preventing rheumatic fever within two months used penicillin. Confining the analysis to these studies alone resulted in less heterogeneity as indicated by the I^2 statistic (1%) and a slightly higher estimated protection (Peto OR 0.26, 95% CI 0.18 to 0.40; 14 studies, 8407 participants; moderate-certainly evidence; Analysis 4.2) than the main analysis for the effect of antibiotics in preventing rheumatic fever (Peto OR 0.36, 95% CI 0.26 to 0.50; 17 studies, 12,132 participants; moderate-certainty evidence; Analysis 4.1).

2. Children versus adults

Few of the included studies involved children (younger than 13 years of age): only 61 cases in total for when fever was evaluated at day three. 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; 2 studies, 61 participants; moderate-certainty evidence, and RR 0.48, 95% CI 0.21 to 1.10; 3 studies, 705 participants; moderate-certainty evidence, respectively; Analysis 2.3).

3. Throat swabs positive for Streptococcus versus negative for Streptococcus versus not tested and/or inseparable combined data

The probability of still experiencing pain on day three was slightly more than one-half (RR 0.58, 95% CI 0.48 to 0.71; 11 studies, 1839 participants; moderate-certainty evidence) for those participants who had positive throat swabs for GABHS, compared to three-quarters (RR 0.78, 95% CI 0.63 to 0.97; 6 studies, 736 participants; moderate-certainty evidence; Analysis 1.5) for those with negative swabs. At one week the efficacy of antibiotics was similarly higher for participants with positive GABHS swabs (RR 0.29, 95% CI 0.12 to 0.70; 7 studies, 1117 participants; moderate-certainty evidence) compared with negative swabs (RR 0.73, 95% CI 0.50 to 1.07; 5 studies, 541 participants; moderate-certainty evidence; Analysis 1.9).

Sensitivity analysis of symptom reduction and prevention of complications

1. Early (pre-1975) versus later (post-1975) studies

We performed analyses to compare the effect of early (pre-1975) versus late (post-1975) studies on symptoms of sore throat at day three (Analysis 1.2) and one week (Analysis 1.7). Although there was a trend for earlier studies to have a greater effect on reducing sore throat symptoms as day three (RR 0.62, 95% CI 0.56 to 0.69; 6 studies, 1141 participants; moderate-certainty evidence) than later studies (RR 0.72, 95% CI 0.60 to 0.88; 10 studies, 2589 participants; moderate-certainty evidence), the confidence intervals for the two time periods overlapped, meaning this trend was not significant. In contrast, earlier studies found a greater effect on reducing sore throat symptoms at one week (RR 0.14, 95% CI 0.08 to 0.27; 6 studies, 1140 participants; moderate-certainty evidence) than later studies (RR 0.73, 95% CI 0.55 to 0.97; 8 studies, 1943 participants; moderate-certainty evidence).

We performed analyses to compare the effect of early (pre-1975) versus late (post-1975) studies on the incidence of rheumatic fever within two months (Analysis 4.3), and otitis media within 14 days (Analysis 4.5). Whilst early studies showed that antibiotics probably reduced incidence of rheumatic fever (Peto OR 0.30, 95% CI 0.20 to 0.45; 10 studies, 7617 participants; moderate-certainty evidence), the effect of antibiotics in later studies could not be calculated due to the absence of cases amongst either antibiotic-treated or control

participants (Peto OR not estimable; 5 studies, 2367 participants; low-certainty evidence).

There was a subgroup difference between the effectiveness of antibiotics in reducing the incidence of otitis media for early studies (Peto OR 0.25, 95% CI 0.12 to 0.52; 5 studies, 1837 participants; high-certainty evidence) versus late studies (Peto OR 0.05, 95% CI 0.01 to 0.31; 6 studies, 1923 participants; moderate-certainty evidence). The certainty of the evidence was lower for later studies due to the wider confidence interval.

2. Blind versus unblinded studies

There was probably little or no difference between blinded and unblinded studies for symptoms of sore throat at day three (RR 0.65, 95% CI 0.54 to 0.78; 12 studies, 2662 participants; moderate-certainty evidence, and RR 0.81, 95% CI 0.65 to 1.01; 4 studies, 1068 participants; moderate-certainty evidence, respectively; Analysis 1.3) or at one week (RR 0.62, 95% CI 0.38 to 1.03; 9 studies, 1616 participants; moderate-certainty evidence, and RR 0.43, 95% CI 0.20 to 0.91; 5 studies, 1437 participants; moderate-certainty evidence, respectively; Analysis 1.8).

DISCUSSION

Summary of main results

Antibiotics reduce symptoms and the likelihood of complications in the treatment of sore throat. However, the absolute benefits are modest.

Symptoms

Headache symptoms on the third day of treatment were reduced when using antibiotics; throat soreness was probably also reduced with antibiotics. The NNTB to prevent one sore throat was less than six at day three and 18 at one week. Antibiotics were more effective against symptoms at day three and one week if throat swabs were positive for GABHS compared to negative throat swabs.

In the control (placebo and no treatment) groups, after three days symptoms of sore throat and fever had disappeared in about 40% and 85% of participants respectively. Eighty-two per cent of participants were symptom-free by one week. This natural history was similar in *Streptococcus*-positive, -negative, and untested participants. Regarding estimates of the number of people with sore throat who must be treated to resolve the symptoms of one person by day three, the NNTB was about 3.7 for those with positive throat swabs for *Streptococcus*; 6.5 for those with a negative swab; and 14.4 for those in whom no swab was taken. The last result is difficult to understand, as intuitively one would expect the NNTB value to lie between both the swab-negative and swab-positive results. Perhaps participants with less severe throat infections were recruited into the three studies in which swabs were not taken.

Non-suppurative and suppurative complications

There were too few cases of acute glomerulonephritis to permit a determination as to whether antibiotics protected against this complication. Moderate-certainty evidence showed that antibiotics probably reduce acute rheumatic fever within two months. However, few recent trials reported this outcome. About 1.7 per 100 placebo participants developed rheumatic fever in trials reporting before 1961. The background incidence of acute rheumatic fever has continued to decline in high-income countries since then.

Antibiotics reduced the number of people experiencing acute otitis media and quinsy compared to the control group. However, antibiotic use made little or no difference compared to control for protecting against acute sinusitis.

In the included trials, conducted mostly in the 1950s, for every 100 participants treated with antibiotics, there was one fewer case of acute rheumatic fever, two fewer cases of acute otitis media, and three fewer cases of quinsy than in the control group. These figures need to be adapted to current circumstances and individuals. For example, the complication rate of acute otitis media amongst those with sore throats before 1975 was 3%. An NNTB of about 50 to prevent one case of acute otitis media can be estimated from the data. After 1975, this complication rate fell to 0.7%, and applying the odds of reducing the complication with antibiotics from the data table yields an NNTB of nearly 200 to prevent one case of acute otitis media. Clinicians will have to exercise judgement in applying these data to treatment decisions.

Adverse effects of treatment

We were unable to present the adverse effects of antibiotic use because of inconsistencies in the recording of these symptoms. In other studies these were principally diarrhoea, rashes, and thrush (Venekamp 2015). Consideration of the side effects of antibiotics would have been useful in further defining their risk-benefits.

Overall completeness and applicability of evidence

The majority of trials included in this 2021 review update were conducted prior to 1975, with only four trials published since 2000. The main reason for this is that very few antibiotic trials conducted recently include a placebo control arm. It is therefore unknown whether changes in bacterial resistance and population immunity over time may have altered the applicability of results.

Special risk groups

Acute rheumatic fever is common amongst people living in some parts of the world (Australian Indigenous populations living in low 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 complications arising from the use of antibiotics for sore throat might be of the same order as that of acute rheumatic fever.

Quality of the evidence

We assessed the certainty of the evidence as low to high. The greatest compromise to the certainty of the evidence arose from non-clarity in treatment allocation procedures and lack of blinding in some studies. Heterogeneity also played a role in downgrading the certainty of evidence for the effect of antibiotics on sore throat symptoms.

Potential biases in the review process

Non-reporting of antipyretic use in a high number of studies may have constituted a source of bias in the results. Publication bias may also be considered a potential threat to the validity of results, particularly for the earlier studies.

Agreements and disagreements with other studies or reviews

A recent review analysing the risk-benefit profile of antimicrobial prescribing for children concluded that antibiotics show little benefit in preventing quinsy following sore throat (Keith 2010). A clinical evidence review of antibiotic treatment for streptococcal pharyngitis concluded that amongst patients with signs and symptoms of positive bacterial infection, a specific diagnosis should be determined by performing either a throat culture or rapid antigen-detection test, especially in children (Wessels 2011). Antibiotic treatment with penicillin or a first-generation cephalosporin is then recommended in the case of positive bacteriologic assessment.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotics have a modest beneficial effect in reducing the likelihood of suppurative and non-suppurative complications (except for acute sinusitis and acute glomerulonephritis) as well as in reducing the duration of symptoms of sore throat. However, the effect on symptoms is small, so that clinicians must base their judgement on individual cases as to whether it is clinically justifiable to employ antibiotics to produce this effect. This decision should be driven by whether the underlying cause of the sore throat is of bacterial or viral origin, although this is not always possible to determine.

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

Implications for research

More trials are needed in low-income countries, socio-economically deprived sections of high-income countries, and in children. In high-income countries, better prognostic studies are called for that can predict which patients might develop suppurative and non-suppurative complications. This will help to further define which patients will benefit from antibiotics.

Studies that 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 into future updates of this review.

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

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bennike 1951

Study characteristics		
Methods	Randomised controlled trial	
Participants	669 participants aged from less than 1 year to older than 50 years of age. Research was divided into 3 studies: ordinary tonsillitis, "phlegmonous" tonsillitis, and "ulcerative" tonsillitis. Patients were excluded if they had a complication of tonsillitis on admission or if they had received previous antibiotic treatment for the current sore throat.	
Interventions	Age-adjusted intramuscular penicillin twice daily for 6 days or no treatment as a control condition	
Outcomes	Incidence of rheumatic fever, otitis media, quinsy, sinusitis, and symptoms of sore throat and headache	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Participants allocated to alternate conditions on alternate days.
Allocation concealment (selection bias)	High risk	No concealment of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.

Bennike 1951 *(Continued)*

Other bias	Unclear risk	No antipyretics were administered to the control group. The use of antipyretics to participants in the treatment group was unstated. Funding source for the study was not stated.

Brink 1951

Study characteristics	
Methods	Randomised controlled trial with 3 intervention arms (2 intervention and 1 control) conducted between 8 March 8 and 30 April 1949
Participants	395 United States Air Force recruits (intervention: n = 119; control: n = 129) admitted to Wyoming base hospital with respiratory symptoms or fever with exudate of the tonsils or pharynx
Interventions	Intervention 1: intramuscular penicillin over 4 days. The dosage was 300,000 units on admission, 300,000 units at 48 hours, and 600,000 units at 96 hours. Intervention 2: aureomycin (0.5 g) administered immediately, then 0.5 g every 4 hours for 24 hours and 0.25 g every 4 hours for the next 3 days Control: no treatment
Outcomes	Symptoms of sore throat at day 3 and 1 week, fever at day 3 and 1 week, and headache at day 3. Incidence of rheumatic fever and otitis media
Notes	This investigation was supported through the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of The Surgeon General, Washington, DC.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants randomised by Air Force serial number.
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Low risk	The study was funded by a government department.

Brock 1953

Study characteristics	
Methods	Randomised controlled trial with 4 intervention arms (3 intervention and 1 control)
Participants	349 adult males (intervention: n = 262; control: n = 87) admitted to US military hospital within 31 hours of onset of exudative pharyngitis and isolation of group A streptococcal from throat culture. Age of participants was not reported.
Interventions	Intervention: 3 injections of intramuscular penicillin (600,000 units) administered at 3-day intervals. Intervention arms consisted of a) immediate treatment, b) 3-day treatment delay, and c) 5-day treatment delay; control consisted of intramuscular saline injection administered on day 1 and day 5.
Outcomes	Incidence of rheumatic fever within 1 month of study enrolment
Notes	The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed by shuffling a deck of cards.
Allocation concealment (selection bias)	High risk	No concealment of treatment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding is not mentioned; however, participants in the control group did receive a placebo saline injection. The schedule for saline injections differed from the schedule for those receiving penicillin.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Low risk	The study was funded by a government department.

Brumfitt 1957

Study characteristics	
Methods	Randomised controlled trial
Participants	121 young adult males, aged 18 to 21 years (intervention: n = 62; control: n = 59), recruited into United States Air Force. Patients were excluded from study if their temperature was below 99.3 °F, if they had sore throat for more than 72 hours prior to presentation, or if they had some other generalised illness.
Interventions	Intervention: intramuscular penicillin twice daily for 4 days; control: no treatment
Outcomes	Incidence of rheumatic fever and symptoms of sore throat and fever at day 3

Brumfitt 1957 *(Continued)*

Notes	Aspirin gargles were given 6-hourly. Whether participants were permitted to swallow the aspirin was not documented. The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised by hospital bed number.
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Low risk	The study was funded by a government department.

Catanzaro 1954

Study characteristics

Methods	Randomised controlled trial with 3 treatment arms; we included data from 2 of the treatment arms in the review
Participants	640 United States Air Force recruits (intervention n = 420; control n = 220) admitted to hospital with exudative tonsillitis or pharyngitis who tested positive for GABHS. Patients were excluded if they presented with a suppurative complication at the time of admission, had a family history of rheumatic fever, or exhibited a previous reaction to penicillin. Age of participants was not reported; however, they are described as "young adult males".
Interventions	Intervention: intramuscular penicillin (900,000 units) administered on day 9, 11, and 13 after onset of illness; control: placebo. A third treatment arm (not included in this review) involved administration of sulphonamide.
Outcomes	Incidence of rheumatic fever within 45 days
Notes	The study was conducted in 2 "halves" which were combined for this review. The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias

Catanzaro 1954 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised by Air Force serial number.
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants were blinded; however, there was no mention of investigator blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data were not explained.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Low risk	The study was funded by a government department.

Chamovitz 1954

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms (2 intervention and 1 control). Study was conducted between 4 January and 9 July 1953.
Participants	366 United States Air Force recruits (intervention 1: n = 129; intervention 2: n = 119; control: n = 89) admitted to hospital with exudative tonsillitis or pharyngitis. 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. Age of participants was not reported. However, they are described as "young adult males".
Interventions	Intervention 1: intramuscular penicillin (1,200,000 units); intervention 2: intramuscular penicillin (600,000 units); control: placebo injection
Outcomes	Incidence of rheumatic fever, otitis media, and acute glomerulonephritis
Notes	Antipyretic use was not documented. The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants randomised by Air Force serial number.
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias)	Unclear risk	Participants were blinded to the treatment they received; however, investigators were not blinded.

Chamovitz 1954 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Relevant outcomes are reported.
Other bias	Low risk	The study was funded by a government department.

Chapple 1956

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms; we included data from 2 treatment arms in the review. Participants were recruited between February 1954 and September 1955.
Participants	Data included in this review correspond to 283 participants older than 2 years (intervention: n = 186; control: n = 97) presenting to general practice in the United Kingdom with acute infection of the throat or middle ear. Patients were excluded if their illness had already lasted longer than 48 hours. Of the 308 participants enrolled in the full study, 69 were aged 2 to 4 years; 120 were aged 5 to 9 years; and 119 were aged 10 or more years.
Interventions	Intervention: age-adjusted oral penicillin administered 4 times per day for 5 days; control: placebo (barium sulphate) administered solution for the same frequency and duration as the intervention. A third treatment arm (not included in this review) consisted of an oral sulfadimidine solution.
Outcomes	Incidence of rheumatic fever, otitis media, and symptom of sore throat on the third day as reported by the participant or estimated by the participant's mother
Notes	All groups received controlled doses of antipyretics twice daily for 3 days. Data from only 200 participants presenting with sore throat on day 1 included in sore throat analysis. Specific funding details for the study were not provided; however, the investigators acknowledge Glaxo Laboratories for supplying the 3 preparations used in the trial, and the Medical Department, Imperial Chemical (Pharmaceuticals) Limited, for providing sulfadimidine.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised by random bottle dispensing.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded to the treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete data were distributed evenly across treatment arms.

Chapple 1956 *(Continued)*

Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Unclear risk	Funding source not described.

Dagnelie 1996

Study characteristics

Methods	Randomised controlled trial conducted between 1990 and 1992
Participants	239 patients (intervention: n = 121; control: n = 118) aged 4 to 60 years, presenting with sore throat to 37 general practices in the Netherlands, who were clinically suspected of GABHS. Patients were excluded if they had imminent quinsy, concomitant disease, allergy to penicillin, previous use of antimicrobials within the preceding 4 weeks, or sore throat for greater than 14 days. Intervention participant characteristics: mean age = 26.6 years, 36% male; control participant characteristics: mean age = 24.6 years; 42% male
Interventions	Intervention: treatment with oral penicillin V (250 mg for ages 4 to 9, 500 mg for ages 10 and over; 3 times per day for 10 days); control: placebo oral tablets for identical duration and frequency
Outcomes	Presence of sore throat and fever on day 3 (assessed by treating medical practitioner), incidence of quinsy
Notes	Raw data would be required to include 1-week symptoms in the meta-analysis. Funding sources for the study were not provided in the published article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and investigators were blind to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Funding sources were not reported for the study.

de la Poza Abad 2016

Study characteristics

de la Poza Abad 2016 *(Continued)*

Methods	Randomised controlled trial with 4 intervention arms. We included a subset of data from 2 of the intervention arms in the review.
Participants	109 adult patients (intervention: n = 57; control: n = 52) presenting with uncomplicated acute sore throat to primary healthcare centres in Spain for whom the choice to use antibiotics for treatment was in doubt. Only data from participants who reported sore throat at baseline were included in the review - the full study cohort in the published article includes participants who did not have sore throat at baseline.
Interventions	Intervention: treatment with immediate antibiotics; antibiotic type and dosage were selected by the treating medical practitioner. Control: no treatment. 2 additional intervention arms not included in this review involved delayed antibiotic prescriptions.
Outcomes	Duration and severity of sore throat, headache and fever symptoms as recorded by participants in a daily diary. We included data on the presence of sore throat and fever at day 3 and 1 week, and headache at day 3 in the review.
Notes	We contacted the authors to provide the subset of data included in the review. The study was sponsored through a governmental grant of the Instituto de Salud Carlos III, Spanish Ministry of Health (grant no. EC08/00095), which is co-funded by the European Regional Development Fund (FEDER; "A way of making Europe").

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using permutated block sizes of 4 which were stratified according to type of infection.
Allocation concealment (selection bias)	Low risk	A centralised electronic database was used to allocate participants to the study intervention arms.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or healthcare professionals delivering the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Antibiotic choice was by the treating physician. Individuals were only eligible for inclusion in the trial if the benefit of antibiotics for treating their illness was in doubt. The study was funded by a government grant.

De Meyere 1992

Study characteristics

Methods	Randomised controlled trial conducted from January to December 1989

De Meyere 1992 *(Continued)*

Participants	173 participants aged 5 to 50 years (intervention: n = 82; control: n = 91), presenting to general practice in the Gent region of Belgium with acute sore throat who tested positive for GABHS. Participants were excluded if they: produced a GABHS-negative throat swab, had a sore throat for greater than 5 days, had a previous history of acute rheumatic fever, had an allergy to beta-lactam antibiotics, had received any antibiotics within the past 14 days, or were in any high-risk situation as determined by the physician. Intervention participant characteristics: mean age = 23.18 years, 36.5% male; control participant characteristics: mean age = 24.08 years; 43% male
Interventions	Intervention: oral penicillin tablets (phenoxymethylcillin 250 mg for adults, 125 mg for children aged up to 10 years) administered 3 times per day for 10 days Control: identical oral placebo tablets administered with the same frequency schedule as the intervention
Outcomes	Symptom of sore throat at day 3 as assessed by the treating physician and at 1 week as self reported in a daily symptom diary. The daily symptom diary was completed by a subset of participants (131/173).
Notes	Participants used antipyretics as required. Use of antipyretics and other symptom-relieving methods was documented in the daily diary. Funding sources for the study were not provided in the published article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not documented.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and study investigators were blind to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 participants (5 from the intervention group and 3 from the control group) who were initially randomised into the study dropped out and were not included in the analysis. Data for sore throat at 1 week were only available for a subset of the initial study cohort (131/173).
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Funding sources for the study were not reported.

Denny 1950

Study characteristics

Methods	Randomised controlled trial conducted between 24 January and 1 July 1949

Denny 1950 *(Continued)*

Participants	1602 United States Air Force recruits (intervention: n = 798; control: n = 804) admitted to hospital with exudative pharyngitis or tonsillitis. Age information was not provided; however, participants are described as "young, adult males".
Interventions	Intervention: intramuscular penicillin (prior to 3 March 1949: 300,000 units of procaine penicillin G administered at time of admission and then repeated after 72 hours; after 3 March 1949: 300,000 units of procaine penicillin G administered at time of admission and then repeated after 48 hours followed by 600,000 units after 96 hours) Control: no treatment
Outcomes	Incidence of rheumatic fever as diagnosed using a modification of the Jones classification
Notes	The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of the Surgeon General, Washington, DC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised by Air Force serial number (odd versus even last digit)
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind study - assessment was conducted by physicians who were unaware of treatment condition. Participants were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Antipyretic use was not stated. The study was funded by a government department.

Denny 1953

Study characteristics

Methods	Randomised controlled trial
Participants	103 young, adult males recruited in the United States Air Force. 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 5 days, oral chlortetracycline (Aureomycin) or oral tetracycline (Terramycin) administered every 6 hours for 3 days or oral lactose placebo for 3 days as a control condition
Outcomes	Incidence of acute rheumatic fever, otitis media, quinsy, and symptoms of sore throat and headache

Denny 1953 *(Continued)*

Notes	The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to treatment groups by drawing a card from a deck.
Allocation concealment (selection bias)	Low risk	The study investigators were unaware to which treatment participants had been allocated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind study - assessment was conducted by physicians who were unaware of the treatment condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Low risk	No antipyretics were administered. The study was funded by a government department.

El-Daher 1991

Study characteristics

Methods	Randomised controlled trial conducted between September 1988 and November 1989
Participants	229 children aged 4 to 14 years (intervention: n = 111; control: n = 118) presenting to paediatric clinics in Jordan who tested positive for GABHS. Patients were excluded if they had an allergy to penicillin, had received antibiotics in the previous 7 days, had an acute illness of any kind in preceding 7 days, GABHS infection in preceding month, or recurrent infection requiring treatment other than penicillin. Intervention participant characteristics: mean age = 7.79 years, 54% male; control participant characteristics: mean age = 8.26 years; 56% male
Interventions	Intervention: immediate treatment with oral penicillin V (liquid suspension of 50,000 IU/kg/day) administered over 3 doses daily for 10 days; control: identical oral placebo for 2 days followed by oral penicillin for 8 days
Outcomes	Symptoms of sore throat and headache on day 3 as assessed by the treating physician
Notes	Examination of participants was performed on day 3 before administering penicillin to the control group. The study was supported by the Deanship of Research, Jordan University of Science and Technology, Grant 87/59, and by Biochemie GmbH.

Risk of bias

El-Daher 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - both participants and study investigators were blind to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	High risk	The funding source for the study included a biotechnology company.

Houser 1953

Study characteristics	
Methods	Randomised controlled trial with 4 treatment arms recruiting participants between 23 February 23 and 14 November 1950. 3 intervention arms involved antibiotic treatment.
Participants	2044 United States Air Force recruits (intervention (3 arms combined): n = 1009; control: n = 1035) admitted to US hospitals with exudative lesions on their tonsils or pharynx. All participants were males aged 17 to 21 years.
Interventions	Intervention arm 1: chlortetracycline (Aureomycin) (total 11 g) administered over 6 days of treatment Intervention arm 2: chlortetracycline (Aureomycin) (total 10.5 g) administered over 5 days of treatment Intervention arm 3: chlortetracycline (Aureomycin) (total 8 g) administered over 4 days of treatment Control: no treatment
Outcomes	Incidence of rheumatic fever diagnosed using modified Jones classification.
Notes	Individuals who would have been eligible for inclusion during intervention arm 1 and for part of intervention arm 3 were not recruited into the study due to being included in a separate study being conducted simultaneously. The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed using Air Force serial numbers.

Houser 1953 *(Continued)*

Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or healthcare workers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Low risk	The study was funded by a government department.

Howe 1997

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms (2 intervention and 1 control) conducted from October 1993 to May 1994
Participants	154 participants aged 16 to 60 years (intervention: n = 100; control: n = 54) presenting to general practice in the United Kingdom with sore throat and for whom the GP would normally prescribe an antibiotic. Patients were excluded if they had received antibiotics in the previous 14 days, had a history of rheumatic fever or nephritis, or allergy to penicillin or cephalosporins.
Interventions	Intervention arm 1: penicillin V (250 mg 4 times daily) for 5 days Intervention arm 2: cefixime (200 mg daily) for 5 days Control: placebo for 5 days (dosage frequency not reported)
Outcomes	Incidence of quinsy as diagnosed by medical practitioner
Notes	Symptom results recorded in participant diary (including sore throat and fever) were bundled into a composite "symptom score". We requested the raw data on sore throat and fever resolution from the authors but did not receive this information, hence it could not be included in the meta-analyses for symptom reduction. The trial was terminated earlier than expected due to local concerns about necrotising fascitis associated with GABHS. The trial was funded by Lederle.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A block randomisation scheme was used (performed in blocks of 6).
Allocation concealment (selection bias)	Low risk	Medical practitioners were blinded to allocation.

Howe 1997 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Both participant and medical practitioners were blinded to the intervention received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A high number of participants did not complete the symptom diaries; however, there is low risk of incomplete data for the outcome of quinsy, which is the only outcome included for the study in our review.
Selective reporting (reporting bias)	Unclear risk	Other relevant outcomes (e.g. the incidence of other complications) were not reported in the published article, and symptoms of sore throat and fever could not be separated from the published data.
Other bias	High risk	A high number of eligible patients who were very ill declined to participate or were deemed too ill by their practitioner, which may have influenced the outcomes. The study was funded by a pharmaceutical company.

Krober 1985

Study characteristics	
Methods	Randomised controlled trial conducted over 2 periods: January 1982 to March 1983 (Hawaii) and November 1983 to Jannuary 1984 (Washington state)
Participants	26 children (intervention: n = 15; control: n = 11) presenting to a paediatric clinic with sore throat in the United States (Hawaii and Washington state) who yielded GABHS-positive throat swabs. Patients 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 severe illness requiring immediate penicillin treatment. Participant characteristics: intervention mean age = 9.3 years, males = 36%; control: mean age = 7.8 years, males = 47%
Interventions	Intervention: oral penicillin V (250 mg) 3 times daily for 3 days Control: oral placebo with a similar look and taste for the same frequency and duration as the intervention
Outcomes	Symptom of fever at day 3 as assessed by the medical practitioner
Notes	Participants agreed not to use antipyretics during the course of the study. The funding source for the study was not reported in the published article.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised using a random numbers table.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.

Krober 1985 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - study investigators and participants were blind to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	The funding source for the study was not reported.

Landsman 1951

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms (2 intervention and 1 control). Study duration was not stated.
Participants	95 children and adult patients (intervention: n = 42; control: n = 43) who presented to a general practice in Scotland complaining of sore throat. The participant group included children and adults; however, the age and sex distribution across treatment arms was not reported.
Interventions	Intervention arm 1: oral sulfanilamide (0.5 g) Intervention arm 2: oral sulphatriad (0.5 g) Control: similar looking and tasting oral lactose placebo (0.5 g) The duration and frequency of medication for each treatment arm was not stated.
Outcomes	Symptom of sore throat and fever at day 3 and 1 week; incidence of sinusitis and quinsy
Notes	Antipyretic use was not documented. The research was supported by a grant from the (UK) Medical Research Council.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The randomisation method changed during the trial; initially each participating GP was intended to prescribe the same medication to all participants for a full month; however, due to criticism of the methods this was changed to randomisation by numbering of bottles.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators responsible for participant recruitment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind - participants and study investigators were blinded to treatment received

Landsman 1951 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	5 cases were lost to follow-up and not included in the analysis. 4 of the cases involved loss of the treating card, so the treatment was not known; 1 case did not adhere to the treatment.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Antipyretic use was not documented.

Leelarasamee 2000

Study characteristics	
Methods	Double-blind, randomised, placebo-controlled trial
Participants	1217 participants aged over 5 years presenting to 4 community-based medical centres with complaints of fever or sore throat of less than 10 days duration
Interventions	Participants were randomised to receive either amoxicillin or placebo for 7 days.
Outcomes	Duration of sore throat and fever. Incidence of complications and adverse reactions
Notes	Antipyretics were given if deemed necessary by the physician. The study was funded by the World Health Organization, Ministry of Public Health, Siriraj-China Medical Board, and Inclen Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some loss to follow-up occurred.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Low risk	The study was funded by international and government grants and industry funding.

Little 1997

Study characteristics

Little 1997 *(Continued)*

Methods	Randomised controlled trial with 3 intervention arms conducted between September 1994 and May 1996
Participants	716 participants aged 4 years and over (intervention: n = 454; control: n = 216) presenting to 11 GPs in the UK with a sore throat. Patients were excluded if there were other explanations for sore throat (drugs, aphthous ulcers, candida, etc.), were very ill (in which case not giving antibiotics could be considered unethical), had a history of rheumatic fever, recurrent tonsillitis, or quinsy, or were pregnant.
Interventions	Intervention 1: 10-day prescription of penicillin V: 250 mg 4 times daily (125 mg for children under 5 years old) Intervention 2: antibiotic prescription offered after 3 days if symptoms were not resolving Control: no treatment
Outcomes	Symptoms of sore throat at day 3 and 1 week as recorded in a daily symptom diary. Incidence of rheumatic fever, otitis media, quinsy, and sinusitis. Participants who did not return diaries were followed up over the phone.
Notes	The study was supported by a Wessex National Health Service regional research and development fund.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised envelopes were used to allocate participants to treatment arms.
Allocation concealment (selection bias)	Low risk	Treating GPs were unaware of the allocation sequence.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants or assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition of participants (outcomes recorded for 94%)
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Low risk	The study was funded by a government grant.

MacDonald 1951

Study characteristics

Methods	Randomised controlled trial
Participants	82 young, adult males recruited into the United States Air Force (41 in treatment group, 41 in control group)

MacDonald 1951 *(Continued)*

Interventions	Intervention: oral sulphatriad, taken every 4 hours Control: identical oral lactose placebo, taken every 4 hours
Outcomes	Symptom of sore throat
Notes	Antipyretics were administered to 1 participant in the treatment group and 2 participants in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised by Air Force serial number.
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - outcomes were determined blind, and participants were unaware of treatment received
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	The funding source for the study was not reported.

Middleton 1988

Study characteristics

Methods	Randomised controlled trial conducted from January 1982 to April 1985
Participants	178 participants aged 4 to 29 years (intervention: n = 91; control: n = 97) presenting to primary care facilities in the United States with streptococcal pharyngitis. Results reported for participants with severe illness or positive GABHS throat swab, or both, only. Patients were excluded if they had taken antibiotics during previous 4 days, had symptoms for more than 4 days, or had an allergy to penicillin.
Interventions	Intervention: 8 individual doses of penicillin (250 mg, 4 times daily for 4 days) Control: identical placebo taken for same duration and frequency as intervention
Outcomes	Symptoms of sore throat and fever on day 3 as self reported by telephone interview
Notes	Aspirin or paracetamol was provided to participants in age-adjusted doses. The study was supported in part by a grant (AA-3) from the Health Research and Services Foundation, an agency of the Allegheny County United Way.

Middleton 1988 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation method was not stated.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to study investigators.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - both participants and investigators were blinded to treatment received
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results were only reported for participants who tested positive for GABHS or had severe illness, or both.
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Low risk	The study was funded by a government grant.

Nelson 1984

Study characteristics	
Methods	Randomised controlled trial conducted during the winter months of 1958 to 1959
Participants	35 children aged 5 to 11 years (intervention: n = 17; control: n = 18) admitted to hospital in the United Staes with acute respiratory illness who tested positive for GABHS. 16 participants initially enrolled in the study were excluded from the analysis because they did not produce GABHS-positive throat swabs, leaving 35 participants included in the study. Children with history of penicillin hypersensitivity were also excluded. Participant age and sex distribution were not reported; however, it was stated that they were comparable across the treatment arms.
Interventions	Intervention: intramuscular penicillin G (300,000 units) for 48 hours Placebo: oral syrup placebo
Outcomes	Symptoms of fever on day 3
Notes	No antipyretics were administered. The study was published more than 20 years after being conducted. The funding source for the study was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised to conditions by hospital number allocation.
Allocation concealment (selection bias)	High risk	No allocation concealment

Nelson 1984 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was single-blind - an oral placebo was used to blind participants, but study outcomes were not determined blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	The funding source for the study was not reported.

Petersen 1997

Study characteristics	
Methods	Randomised controlled trial conducted from January 1983 to December 1984
Participants	186 adults aged 18 to 50 years (intervention: n = 93, control: n = 93) presenting to an ambulatory setting in Massachusetts, United States, with sore throat who tested negative for GABHS culture. Patients were excluded if the had been ill for more than 6 days, had a temperature exceeding 40 °C, current otitis media or pneumonia, symptoms of vaginitis or urinary tract infection, were pregnant or breastfeeding, had a history of rheumatic fever, had significant medical illness other than hypertension, had taken antibiotics within previous 10 days, had allergy to erythromycin, were illiterate in English, or were considered to potentially be non-compliant. Intervention participant characteristics: mean age = 25 years; male = 39% Control participant characteristics: mean age = 26 years; male = 32%
Interventions	Intervention: erythromycin (333 mg, 3 times daily) Control: placebo
Outcomes	Symptom of sore throat on day 3 and at 1 week as self reported by participants in a daily symptom diary collected at a 3-week follow-up visit
Notes	The study was supported by the Henry J. Kaiser Foundation and by a grant from the Upjohn Company.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed to practitioners responsible for recruiting participants.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and treating practitioners were blinded to the treatment received

Petersen 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear how many participants in each group kept diaries for the sore throat data. The study authors excluded GABHS-positive participants (15 out of 212 initially randomised into treatment).
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	High risk	The study was funded in part by a pharmaceutical company.

Siegel 1961

Study characteristics	
Methods	Randomised controlled trial
Participants	1213 children aged 3 to 16 years (intervention: n = 605; control: n = 608) with uncomplicated acute respiratory illness who returned a positive GAS test. Suppurative complications occurring in participants in the control condition were treated with sulphonamides. Patients were excluded if they had a complication on admission.
Interventions	Intervention: intramuscular penicillin (600,000 units) Control: no treatment
Outcomes	Incidence of rheumatic fever
Notes	The study was supported by grants from the American Heart Association, the United States Public Health Service (Grant H-4164-C2), and Wyeth Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were allocated to treatment according to their bed chart number.
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	There was no blinding of participants or treating medical personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	All relevant outcomes reported.
Other bias	High risk	Antipyretic use was not documented. The study was funded in part by a pharmaceutical company.

Taylor 1977

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms (2 intervention and 1 control)
Participants	Children aged 2 to 10 years (intervention; n = 129; control: n = 59) presenting with presumed viral respiratory infections in New Zealand. Children with positive *Streptococcus* throat swabs or clinically diagnosed with otitis media or pneumonia were excluded.
Interventions	Intervention arm 1: oral amoxicillin (Amoxil) 3 times a day for 5 days Intervention arm 2: oral cotrimoxazole (trimethoprim 40 mg, sulfamethoxazole 200 mg, Bactrim, Roche) 3 times a day for 5 days Control: oral placebo 3 times a day for 5 days
Outcomes	Incidence of acute otitis media and sinusitis and symptoms of sore throat and fever at 1 week
Notes	The funding source for the study was not documented.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomisation to treatment arm was not documented.
Allocation concealment (selection bias)	Low risk	The allocation sequence was not revealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and study investigators were blinded to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A higher number of participants in the control arm were withdrawn during the study and not included in the analysis.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Antipyretic use was not documented. The funding source for the study was not reported.

Wannamaker 1951

Study characteristics	
Methods	Randomised controlled trial conducted between March 1949 and February 1950. The study was conducted in 3 separate phases which involved differing treatment dosage in each phase. Hence there were 6 separate treatment arms (3 intervention and 3 control).
Participants	1974 United States Air Force recruits (intervention: total n = 978; control: total n = 996) admitted to hospital with either exudative pharyngitis or tonsillitis. All participants were young, adult males (further age characteristics were not provided).
Interventions	Intervention arm 1: intramuscular penicillin (120,000 units) in 3 doses over 96 hours

Wannamaker 1951 *(Continued)*

	Intervention arm 2: intramuscular penicillin (600,000 units) in 2 doses over 72 hours Intervention arm 3: intramuscular penicillin (600,000 units) in 1 dose Control (3 separate arms): no treatment
Outcomes	Incidence of rheumatic fever within 2 months as diagnosed by study investigator
Notes	Antipyretic use was not documented. The study was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, DC.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised according to Air Force serial number.
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blind study design - participants were not blinded to the treatment received, but study investigators were
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	The study was government funded. Antipyretic use was not documented.

Whitfield 1981

Study characteristics

Methods	Randomised controlled trial conducted from October 1978 to June 1989
Participants	Participants were aged over 10 years (intervention: n = 256; control: n = 272) presenting to 48 GPs in Avon, United Kingdom with sore throat. Patients were excluded if the GP thought the participant would demonstrate poor compliance or if they had previous reaction to penicillin or a previous episode of rheumatic fever or acute nephritis. Participant age and sex characteristics were not reported.
Interventions	Intervention: oral penicillin V (250 mg) 4 times a day for 5 days Control: identical-looking and -tasting oral lactose placebo 4 times a day for 5 days
Outcomes	Symptoms of sore throat and fever at day 3 as reported by the participants in a study questionnaire
Notes	The study was financially supported by the Scientific Foundation Board of the Royal College of General Practitioners.

Whitfield 1981 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised according to a predetermined random order.
Allocation concealment (selection bias)	Low risk	GPs were blinded to the allocation sequence.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and treating GPs were blinded to the treatment received
Incomplete outcome data (attrition bias) All outcomes	High risk	A large number of participants recruited into the study did not complete the study questionnaire (only 528 out of 745 questionnaires were returned), and analysis was only performed on those returned. Participants not returning questionnaires were more likely than those who did return questionnaires to be smokers, of a lower social class, and aged between 15 and 34 years.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	The study was government funded. Antipyretic use was not documented.

Zwart 2000

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms (2 intervention and 1 control) conducted between 1994 and 1996
Participants	561 participants aged 15 to 60 years (intervention: n = 358; control, n = 164) presenting to 43 general practices in the Netherlands with sore throat of less than 7 days duration. Participants exhibited at least 2 of 4 Centor criteria (history of fever, absence of cough, swollen and tender lymph nodes, tonsillar exudate). Patients were excluded for medical reasons (imminent quinsy, suspected scarlet fever, recurrent illness requiring antibiotics) and intolerance to penicillin. Intervention arm 1 participant characteristics: mean age = 28 years, male = 39% Intervention arm 2 participant characteristics: mean age = 28 years, male = 36% Control participant characteristics: mean age = 28 years, male = 39%
Interventions	Intervention arm 1: penicillin V (500 mg, 3 times daily) for 7 days Intervention arm 2: penicillin V (500 mg, 3 times daily) for 3 days, followed by 4 days of placebo Control: placebo for 7 days (oral tablet taken 3 times daily)
Outcomes	Symptoms of sore throat at day 3 and 1 week. Incidence of acute otitis media, acute sinusitis, quinsy, and acute glomerulonephritis
Notes	We contacted the authors for data that could be used in the meta-analysis, which they provided. This study was funded by Groene Land Achmea Health Insurances and the Stichting Gezondheidszorgonderzoek Ysselmond in Zwolle.

Zwart 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	GPs were blinded to the allocation sequence.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and treating GPs were blind to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was performed.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Low risk	The study was supported by government grants.

Zwart 2003

Study characteristics	
Methods	Randomised controlled trial with 3 treatment arms (2 intervention and 1 control) conducted between 1994 and 1996
Participants	156 children (intervention n = 100; control: n = 56) aged 4 to 15 years presenting to 43 family practices in the Netherlands with sore throat. Inclusion criteria were sore throat of less than 7 days duration exhibiting at least 2 of 4 Centor criteria (history of fever, absence of cough, swollen and tender lymph nodes, tonsillar exudate). Children were excluded for medical reasons (imminent quinsy, suspected scarlet fever, recurrent illness requiring antibiotics) and intolerance to penicillin. Intervention arm 1 participant characteristics: mean age = 9.9 years, male = 44% Intervention arm 2 participant characteristics: mean age = 10.5 years, male = 37% Control participant characteristics: mean age = 10.1 years, male = 54%
Interventions	Intervention arm 1: penicillin V (250 mg, 3 times daily for children aged 4 to 10 years; 500 mg, 3 times daily for children aged 11 to 15 years) for 7 days Intervention arm 2: penicillin V (250 mg, 3 times daily for children aged 4 to 10 years; 500 mg, 3 times daily for children aged 11 to 15 years) for 3 days followed by 4 days of placebo Control: placebo for 7 days (oral tablet taken 3 times daily)
Outcomes	Duration of symptoms of sore throat, occurrence of streptococcal sequelae
Notes	We contacted the authors for data that could be used in the meta-analysis, which they provided. This study was funded by Groene Land Achmea Health Insurances and the Stichting Gezondheidszorgonderzoek Ysselmond in Zwolle.
Risk of bias	

Zwart 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by computer-generated random sequence.
Allocation concealment (selection bias)	Low risk	GPs were blinded to allocation sequence.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study design - participants and treating physicians were blinded to the treatment received
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was performed.
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	Low risk	The study was supported by government grants.

GABHS: group A beta haemolytic *Streptococcus*
GAS: group A streptococcal
GP: general practitioner
IU: international units

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

Study	Reason for exclusion
Barwitz 1999	Participants were randomised to 2 general practitioners for subsequent treatment with different management protocols.
Bass 1986	Study used a Likert scale to measure severity and duration of symptoms. No raw scores were available for entry into meta-analysis.
Bishop 1952	Non-randomised allocation to treatment groups. "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 data previously published by Brumfitt 1957.
Dowell 2001	Cough was the main patient complaint, not sore throat.
Gerber 1985	Study compared 2 different regimens of penicillin. No placebo control group was used.
Gerber 1989	Assessed 2 regimens 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 a control condition.

Study	Reason for exclusion
Haverkorn 1971	Participants not treated with antibiotics were given antipyretics. Participants receiving antibiotics received no antipyretics. No control condition
Herz 1988	No participant-centred outcomes, except return visits for upper respiratory infections 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 exclusively acute pharyngitis. Soreness of throat was not an outcome measure.
Jensen 1991	Participants were not randomly allocated to treatment groups and were not blinded to treatment.
Kapur 2011	No intervention was provided to participants. Study tracked natural course of illness only.
Kolobukhina 2011	Study investigated the combination of Ingavirin (antiviral medication) with an antibacterial agent in adults with viral respiratory infections. No comparison of antibiotics alone against placebo
Marlow 1989	Participant 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 participant-centred outcomes not compatible with those in our meta-analysis.
Massell 1951	Study examined effect of penicillin on haemolytic streptococci infections in rheumatic patients only, without randomisation to control condition. Infections that were not treated with penicillin for "various reasons" were treated as controls. These reasons were not provided.
McDonald 1985	No data suitable for our meta-analysis were described, although symptoms were recorded. We approached the author for these data, but received no reply.
Merenstein 1974	No data on suppurative or non-suppurative complications No data on day 3 for soreness of throat, fever, or headache
Morris 1956	Study observed the effect of sulfadiazine on prevention of rheumatic fever only. No control condition was used.
Nasonova 1999	Study was a controlled clinical trial without participant randomisation.
Pandraud 2002	Investigation of the effect of fusafungine on chronic conditions of follicular pharyngitis. Not relevant to this review
Pichichero 1987	All participants were treated with antibiotics, and there was no placebo group for assessing long-term complications. The methodological design did include a delayed antibiotic group; however, outcomes were not reported in such a way that could be included in the review.
Randolph 1985	No data on suppurative or non-suppurative complications No data on day 3 or 7 for soreness of throat, fever, or headache
Schalen 1985	Primary complaint was hoarseness, not sore throat. No patient-centred outcomes apart from hoarseness
Schalen 1993	Participants presented for laryngitis and hoarseness, not pharyngitis.
Schwartz 1981	Study compared 7 versus 10 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 the efficacy of amoxicillin against penicillin, no control condition was used.

Study	Reason for exclusion
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.
Supajatura 2012	Antibiotics were not offered as an intervention. Study investigated the efficacy of mangosteen spray against placebo only.
Todd 1984	Primary complaint was not sore throat, but purulent nasopharyngitis instead.
Valkenburg 1971	Study did not involve any control measures. Data provided only for participants not treated with antibiotics.

DATA AND ANALYSES

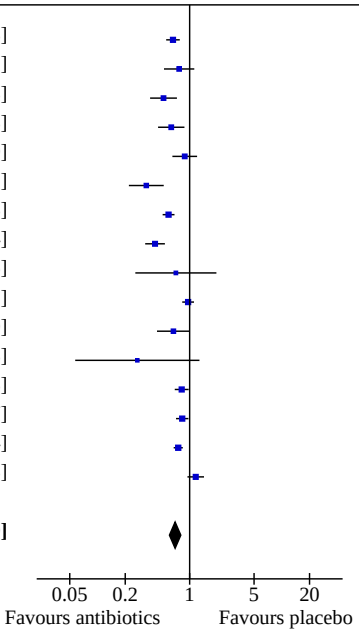
Comparison 1. Antibiotics versus control for the treatment of sore throat: symptoms of sore throat

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Symptom of sore throat on day 3	16	3730	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.80]
1.2 Symptom of sore throat on day 3: early (pre-1975) versus late studies (post-1975)	16	3730	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.80]
1.2.1 Symptom of sore throat on day 3: early (pre-1975) studies	6	1141	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.56, 0.69]
1.2.2 Symptom of sore throat on day 3: late (post-1975) studies	10	2589	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.60, 0.88]
1.3 Symptom of sore throat on day 3: blind versus unblinded studies	16	3730	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.60, 0.80]
1.3.1 Symptom of sore throat on day 3: blinded studies	12	2662	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.54, 0.78]
1.3.2 Symptom of sore throat on day 3: unblinded studies	4	1068	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.01]
1.4 Symptom of sore throat on day 3: antipyretics versus no antipyretics	5	1137	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.48, 0.70]
1.4.1 Symptom of sore throat on day 3: antipyretics administered	3	455	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]
1.4.2 Symptom of sore throat on day 3: no antipyretics administered	2	682	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.55, 0.70]
1.5 Symptom of sore throat on day 3: GABHS-positive throat swab, negative swab, untested/inseparable	15	3600	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.59, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.1 Symptom of sore throat on day 3: GABHS-positive throat swab	11	1839	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.48, 0.71]
1.5.2 Symptom of sore throat on day 3: GABHS-negative throat swab	6	736	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
1.5.3 Symptom of sore throat on day 3: untested for GABHS culture or combined, inseparable data	3	1025	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 1.00]
1.6 Symptom of sore throat at 1 week (6 to 8 days)	14	3083	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.34, 0.75]
1.7 Symptom of sore throat at 1 week (6 to 8 days): early (pre-1975) versus late (post-1975)	14	3083	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.34, 0.75]
1.7.1 Symptom of sore throat at 1 week (6 to 8 days): early (pre-1975) studies	6	1140	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.08, 0.27]
1.7.2 Symptom of sore throat at 1 week (6 to 8 days): late (post-1975) studies	8	1943	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.97]
1.8 Symptom of sore throat at 1 week (6 to 8 days): blind versus unblinded studies	14	3053	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.39, 0.82]
1.8.1 Symptom of sore throat at 1 week (6 to 8 days): blinded studies	9	1616	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.38, 1.03]
1.8.2 Symptom of sore throat at 1 week (6 to 8 days): unblinded studies	5	1437	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.20, 0.91]
1.9 Symptom of sore throat at 1 week (6 to 8 days): GABHS-positive throat swab, GABHS-negative swab	12	2524	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.29, 0.80]
1.9.1 Symptom of sore throat at 1 week (6 to 8 days): GABHS-positive throat swab	7	1117	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.12, 0.70]
1.9.2 Symptom of sore throat at 1 week (6 to 8 days): GABHS-negative throat swab	5	541	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.07]
1.9.3 Symptom of sore throat at 1 week (6 to 8 days): GABHS untested	3	866	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.03, 4.47]

Analysis 1.1. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 1: Symptom of sore throat on day 3

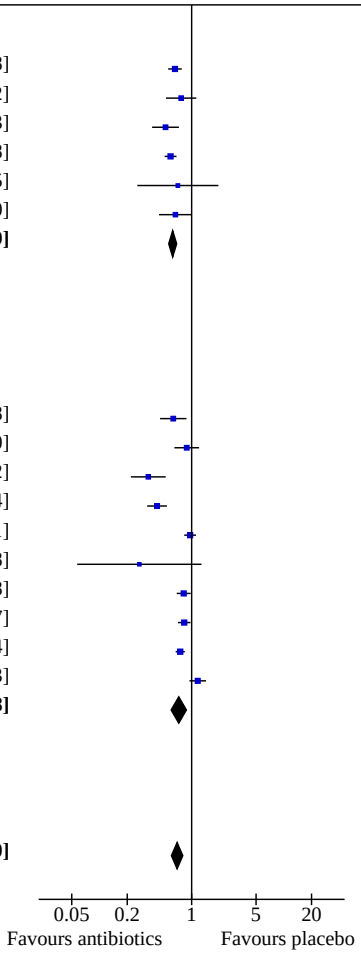
	Antibiotics		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Brink 1951	119	277	129	198	8.0%	0.66 [0.56 , 0.78]	
Brumfitt 1957	21	42	26	40	5.5%	0.77 [0.53 , 1.12]	
Chapple 1956	40	135	37	65	6.0%	0.52 [0.37 , 0.73]	
Dagnelie 1996	36	117	57	117	6.1%	0.63 [0.45 , 0.88]	
de la Poza Abad 2016	32	57	33	52	6.3%	0.88 [0.65 , 1.20]	
De Meyere 1992	18	82	59	91	4.9%	0.34 [0.22 , 0.52]	
Denny 1953	89	157	48	50	8.2%	0.59 [0.51 , 0.68]	
El-Daher 1991	42	111	106	118	7.1%	0.42 [0.33 , 0.54]	
Landsman 1951	6	52	7	43	1.6%	0.71 [0.26 , 1.95]	
Little 1997	135	215	122	187	8.2%	0.96 [0.83 , 1.11]	
MacDonald 1951	18	41	27	41	5.1%	0.67 [0.44 , 1.00]	
Middleton 1988	2	34	5	23	0.8%	0.27 [0.06 , 1.28]	
Petersen 1997	60	89	74	90	8.0%	0.82 [0.69 , 0.98]	
Whitfield 1981	129	256	165	272	8.2%	0.83 [0.71 , 0.97]	
Zwart 2000	215	358	131	164	8.5%	0.75 [0.67 , 0.84]	
Zwart 2003	79	100	38	56	7.6%	1.16 [0.95 , 1.43]	
Total (95% CI)		**2123**		**1607**	**100.0%**	**0.70 [0.60 , 0.80]**	
Total events:	1041		1064				



Heterogeneity: Tau² = 0.06; Chi² = 87.08, df = 15 (P < 0.00001); I² = 83%
Test for overall effect: Z = 5.03 (P < 0.00001)
Test for subgroup differences: Not applicable

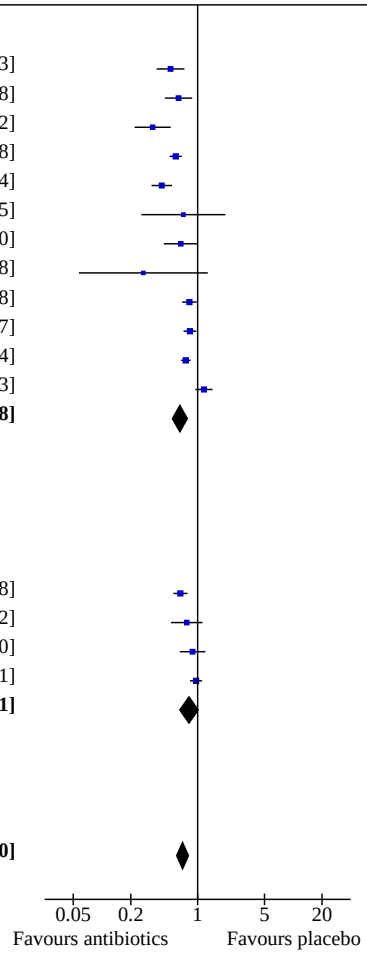
Analysis 1.2. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 2: Symptom of sore throat on day 3: early (pre-1975) versus late studies (post-1975)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Symptom of sore throat on day 3: early (pre-1975) studies						
Brink 1951	119	277	129	198	8.0%	0.66 [0.56 , 0.78]
Brumfitt 1957	21	42	26	40	5.5%	0.77 [0.53 , 1.12]
Chapple 1956	40	135	37	65	6.0%	0.52 [0.37 , 0.73]
Denny 1953	89	157	48	50	8.2%	0.59 [0.51 , 0.68]
Landsman 1951	6	52	7	43	1.6%	0.71 [0.26 , 1.95]
MacDonald 1951	18	41	27	41	5.1%	0.67 [0.44 , 1.00]
Subtotal (95% CI)		**704**		**437**	**34.4%**	**0.62 [0.56 , 0.69]**
Total events:	293		274			
Heterogeneity: Tau² = 0.00; Chi² = 3.53, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 9.44 (P < 0.00001)						
1.2.2 Symptom of sore throat on day 3: late (post-1975) studies						
Dagnelie 1996	36	117	57	117	6.1%	0.63 [0.45 , 0.88]
de la Poza Abad 2016	32	57	33	52	6.3%	0.88 [0.65 , 1.20]
De Meyere 1992	18	82	59	91	4.9%	0.34 [0.22 , 0.52]
El-Daher 1991	42	111	106	118	7.1%	0.42 [0.33 , 0.54]
Little 1997	135	215	122	187	8.2%	0.96 [0.83 , 1.11]
Middleton 1988	2	34	5	23	0.8%	0.27 [0.06 , 1.28]
Petersen 1997	60	89	74	90	8.0%	0.82 [0.69 , 0.98]
Whitfield 1981	129	256	165	272	8.2%	0.83 [0.71 , 0.97]
Zwart 2000	215	358	131	164	8.5%	0.75 [0.67 , 0.84]
Zwart 2003	79	100	38	56	7.6%	1.16 [0.95 , 1.43]
Subtotal (95% CI)		**1419**		**1170**	**65.6%**	**0.72 [0.60 , 0.88]**
Total events:	748		790			
Heterogeneity: Tau² = 0.07; Chi² = 68.15, df = 9 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
Total (95% CI)		**2123**		**1607**	**100.0%**	**0.70 [0.60 , 0.80]**
Total events:	1041		1064			
Heterogeneity: Tau² = 0.06; Chi² = 87.08, df = 15 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 5.03 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.95, df = 1 (P = 0.16), I² = 48.7%						



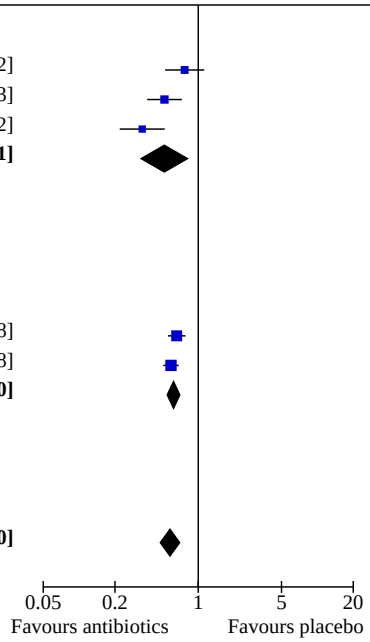
Analysis 1.3. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 3: Symptom of sore throat on day 3: blind versus unblinded studies

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Symptom of sore throat on day 3: blinded studies						
Chapple 1956	40	135	37	65	6.0%	0.52 [0.37 , 0.73]
Dagnelie 1996	36	117	57	117	6.1%	0.63 [0.45 , 0.88]
De Meyere 1992	18	82	59	91	4.9%	0.34 [0.22 , 0.52]
Denny 1953	89	157	48	50	8.2%	0.59 [0.51 , 0.68]
El-Daher 1991	42	111	106	118	7.1%	0.42 [0.33 , 0.54]
Landsman 1951	6	52	7	43	1.6%	0.71 [0.26 , 1.95]
MacDonald 1951	18	41	27	41	5.1%	0.67 [0.44 , 1.00]
Middleton 1988	2	34	5	23	0.8%	0.27 [0.06 , 1.28]
Petersen 1997	60	89	74	90	8.0%	0.82 [0.69 , 0.98]
Whitfield 1981	129	256	165	272	8.2%	0.83 [0.71 , 0.97]
Zwart 2000	215	358	131	164	8.5%	0.75 [0.67 , 0.84]
Zwart 2003	79	100	38	56	7.6%	1.16 [0.95 , 1.43]
Subtotal (95% CI)		**1532**		**1130**	**72.0%**	**0.65 [0.54 , 0.78]**
Total events:	734		754			
Heterogeneity: Tau² = 0.07; Chi² = 70.93, df = 11 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.67 (P < 0.00001)						
1.3.2 Symptom of sore throat on day 3: unblinded studies						
Brink 1951	119	277	129	198	8.0%	0.66 [0.56 , 0.78]
Brumfitt 1957	21	42	26	40	5.5%	0.77 [0.53 , 1.12]
de la Poza Abad 2016	32	57	33	52	6.3%	0.88 [0.65 , 1.20]
Little 1997	135	215	122	187	8.2%	0.96 [0.83 , 1.11]
Subtotal (95% CI)		**591**		**477**	**28.0%**	**0.81 [0.65 , 1.01]**
Total events:	307		310			
Heterogeneity: Tau² = 0.03; Chi² = 11.40, df = 3 (P = 0.010); I² = 74%						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		**2123**		**1607**	**100.0%**	**0.70 [0.60 , 0.80]**
Total events:	1041		1064			
Heterogeneity: Tau² = 0.06; Chi² = 87.08, df = 15 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 5.03 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.30, df = 1 (P = 0.13), I² = 56.5%						



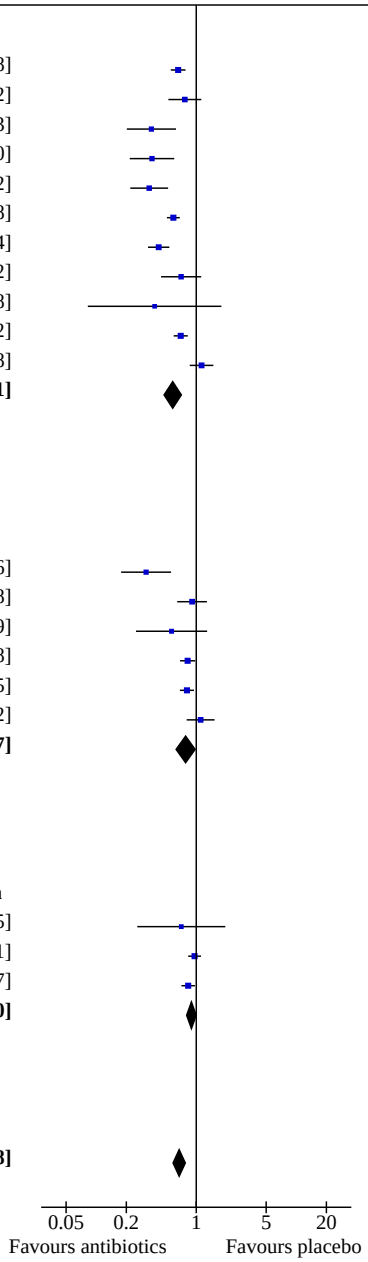
Analysis 1.4. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 4: Symptom of sore throat on day 3: antipyretics versus no antipyretics

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Symptom of sore throat on day 3: antipyretics administered						
Brumfitt 1957	21	42	26	40	14.4%	0.77 [0.53 , 1.12]
Chapple 1956	40	135	37	65	16.6%	0.52 [0.37 , 0.73]
De Meyere 1992	18	82	59	91	12.1%	0.34 [0.22 , 0.52]
Subtotal (95% CI)		**259**		**196**	**43.1%**	**0.52 [0.33 , 0.81]**
Total events:	79		122			
Heterogeneity: Tau² = 0.12; Chi² = 8.26, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 2.87 (P = 0.004)						
1.4.2 Symptom of sore throat on day 3: no antipyretics administered						
Brink 1951	119	277	129	198	27.6%	0.66 [0.56 , 0.78]
Denny 1953	89	157	48	50	29.2%	0.59 [0.51 , 0.68]
Subtotal (95% CI)		**434**		**248**	**56.9%**	**0.62 [0.55 , 0.70]**
Total events:	208		177			
Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 7.76 (P < 0.00001)						
Total (95% CI)		**693**		**444**	**100.0%**	**0.58 [0.48 , 0.70]**
Total events:	287		299			
Heterogeneity: Tau² = 0.03; Chi² = 10.52, df = 4 (P = 0.03); I² = 62%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						



Analysis 1.5. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 5: Symptom of sore throat on day 3: GABHS-positive throat swab, negative swab, untested/inseparable

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Symptom of sore throat on day 3: GABHS-positive throat swab						
Brink 1951	119	277	129	198	6.9%	0.66 [0.56 , 0.78]
Brumfitt 1957	21	42	26	40	4.9%	0.77 [0.53 , 1.12]
Chapple 1956	13	68	22	41	3.4%	0.36 [0.20 , 0.63]
Dagnelie 1996	13	55	36	55	3.8%	0.36 [0.22 , 0.60]
De Meyere 1992	18	82	59	91	4.4%	0.34 [0.22 , 0.52]
Denny 1953	89	157	48	50	7.0%	0.59 [0.51 , 0.68]
El-Daher 1991	42	111	106	118	6.2%	0.42 [0.33 , 0.54]
MacDonald 1951	13	26	17	24	4.2%	0.71 [0.44 , 1.12]
Middleton 1988	2	24	5	23	0.8%	0.38 [0.08 , 1.78]
Zwart 2000	102	178	68	83	6.9%	0.70 [0.59 , 0.82]
Zwart 2003	39	53	28	43	5.9%	1.13 [0.86 , 1.48]
Subtotal (95% CI)		**1073**		**766**	**54.5%**	**0.58 [0.48 , 0.71]**
Total events:	471		544			
Heterogeneity: Tau² = 0.08; Chi² = 51.31, df = 10 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 5.34 (P < 0.00001)						
1.5.2 Symptom of sore throat on day 3: GABHS-negative throat swab						
Chapple 1956	13	67	16	26	3.4%	0.32 [0.18 , 0.56]
Dagnelie 1996	31	60	29	51	5.3%	0.91 [0.65 , 1.28]
MacDonald 1951	5	15	10	17	2.1%	0.57 [0.25 , 1.29]
Petersen 1997	60	89	74	90	6.8%	0.82 [0.69 , 0.98]
Zwart 2000	113	180	63	81	6.9%	0.81 [0.69 , 0.95]
Zwart 2003	40	47	10	13	5.5%	1.11 [0.80 , 1.52]
Subtotal (95% CI)		**458**		**278**	**30.0%**	**0.78 [0.63 , 0.97]**
Total events:	262		202			
Heterogeneity: Tau² = 0.04; Chi² = 15.65, df = 5 (P = 0.008); I² = 68%						
Test for overall effect: Z = 2.20 (P = 0.03)						
1.5.3 Symptom of sore throat on day 3: untested for GABHS culture or combined, inseparable data						
Landsman 1951	6	52	7	43	1.5%	0.71 [0.26 , 1.95]
Little 1997	135	215	122	187	7.0%	0.96 [0.83 , 1.11]
Whitfield 1981	129	256	165	272	7.0%	0.83 [0.71 , 0.97]
Subtotal (95% CI)		**523**		**502**	**15.6%**	**0.89 [0.80 , 1.00]**
Total events:	270		294			
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 2 (P = 0.35); I² = 4%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Total (95% CI)		**2054**		**1546**	**100.0%**	**0.68 [0.59 , 0.78]**
Total events:	1003		1040			
Heterogeneity: Tau² = 0.07; Chi² = 103.16, df = 19 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 5.46 (P < 0.00001)						
Test for subgroup differences: Chi² = 13.85, df = 2 (P = 0.0010), I² = 85.6%						



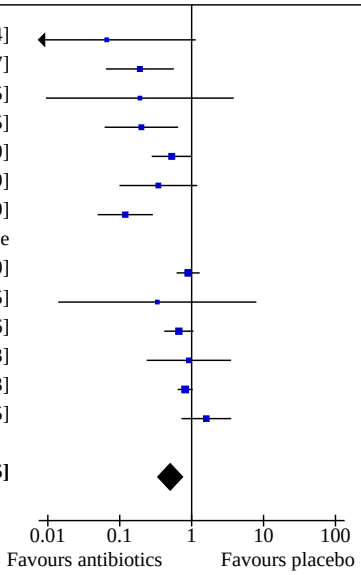
Analysis 1.6. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 6: Symptom of sore throat at 1 week (6 to 8 days)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bennike 1951	0	100	7	99	1.7%	0.07 [0.00 , 1.14]
Brink 1951	4	277	15	198	7.1%	0.19 [0.06 , 0.57]
Brumfitt 1957	0	42	2	40	1.5%	0.19 [0.01 , 3.85]
Dagnelie 1996	3	51	15	51	6.5%	0.20 [0.06 , 0.65]
de la Poza Abad 2016	11	57	19	52	11.0%	0.53 [0.28 , 1.00]
De Meyere 1992	3	61	10	70	6.1%	0.34 [0.10 , 1.19]
Denny 1953	6	157	16	50	8.7%	0.12 [0.05 , 0.29]
Landsman 1951	0	52	0	43		Not estimable
Little 1997	66	388	35	184	13.6%	0.89 [0.62 , 1.30]
MacDonald 1951	0	41	1	41	1.4%	0.33 [0.01 , 7.95]
Petersen 1997	21	89	32	90	12.7%	0.66 [0.42 , 1.06]
Taylor 1977	6	129	3	59	5.5%	0.91 [0.24 , 3.53]
Zwart 2000	117	352	63	154	14.7%	0.81 [0.64 , 1.03]
Zwart 2003	20	100	7	56	9.5%	1.60 [0.72 , 3.55]
Total (95% CI)		**1896**		**1187**	**100.0%**	**0.50 [0.34 , 0.75]**
Total events:	257		225			

Heterogeneity: Tau² = 0.26; Chi² = 39.27, df = 12 (P < 0.0001); I² = 69%

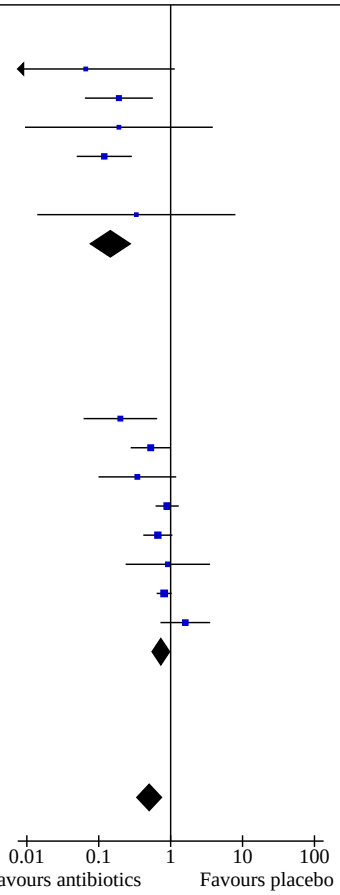
Test for overall effect: Z = 3.42 (P = 0.0006)

Test for subgroup differences: Not applicable



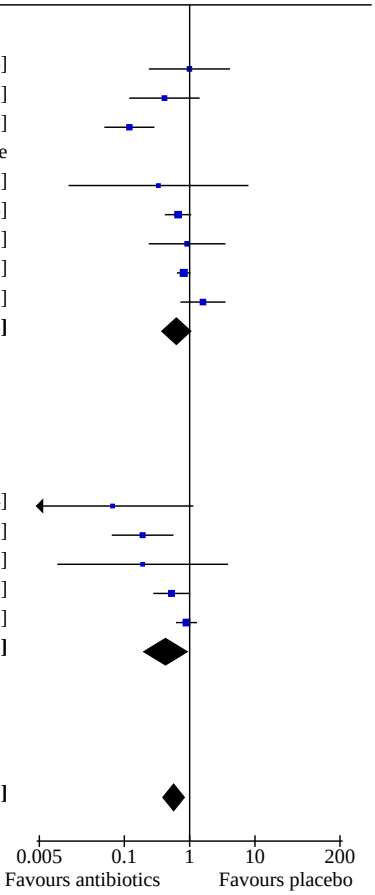
Analysis 1.7. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 7: Symptom of sore throat at 1 week (6 to 8 days): early (pre-1975) versus late (post-1975)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Symptom of sore throat at 1 week (6 to 8 days): early (pre-1975) studies						
Bennike 1951	0	100	7	99	1.7%	0.07 [0.00 , 1.14]
Brink 1951	4	277	15	198	7.1%	0.19 [0.06 , 0.57]
Brumfitt 1957	0	42	2	40	1.5%	0.19 [0.01 , 3.85]
Denny 1953	6	157	16	50	8.7%	0.12 [0.05 , 0.29]
Landsman 1951	0	52	0	43		Not estimable
MacDonald 1951	0	41	1	41	1.4%	0.33 [0.01 , 7.95]
Subtotal (95% CI)		**669**		**471**	**20.4%**	**0.14 [0.08 , 0.27]**
Total events:	10		41			
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 4 (P = 0.91); I² = 0%						
Test for overall effect: Z = 5.94 (P < 0.00001)						
1.7.2 Symptom of sore throat at 1 week (6 to 8 days): late (post-1975) studies						
Dagnelie 1996	3	51	15	51	6.5%	0.20 [0.06 , 0.65]
de la Poza Abad 2016	11	57	19	52	11.0%	0.53 [0.28 , 1.00]
De Meyere 1992	3	61	10	70	6.1%	0.34 [0.10 , 1.19]
Little 1997	66	388	35	184	13.6%	0.89 [0.62 , 1.30]
Petersen 1997	21	89	32	90	12.7%	0.66 [0.42 , 1.06]
Taylor 1977	6	129	3	59	5.5%	0.91 [0.24 , 3.53]
Zwart 2000	117	352	63	154	14.7%	0.81 [0.64 , 1.03]
Zwart 2003	20	100	7	56	9.5%	1.60 [0.72 , 3.55]
Subtotal (95% CI)		**1227**		**716**	**79.6%**	**0.73 [0.55 , 0.97]**
Total events:	247		184			
Heterogeneity: Tau² = 0.06; Chi² = 12.56, df = 7 (P = 0.08); I² = 44%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Total (95% CI)		**1896**		**1187**	**100.0%**	**0.50 [0.34 , 0.75]**
Total events:	257		225			
Heterogeneity: Tau² = 0.26; Chi² = 39.27, df = 12 (P < 0.0001); I² = 69%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
Test for subgroup differences: Chi² = 20.75, df = 1 (P < 0.00001), I² = 95.2%						

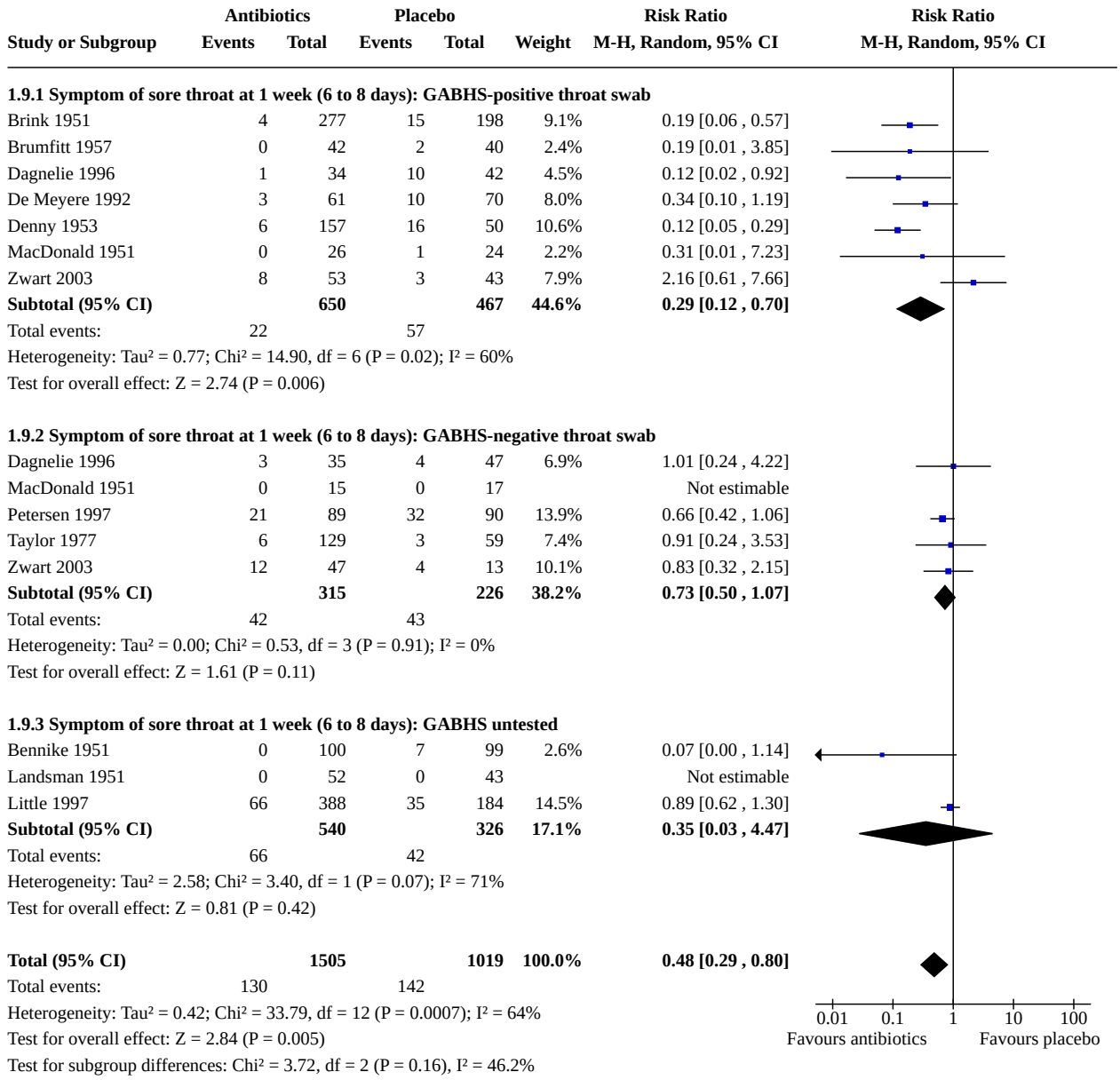


Analysis 1.8. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 8: Symptom of sore throat at 1 week (6 to 8 days): blind versus unblinded studies

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Symptom of sore throat at 1 week (6 to 8 days): blinded studies						
Dagnelie 1996	4	47	3	35	4.8%	0.99 [0.24 , 4.16]
De Meyere 1992	3	51	10	70	5.9%	0.41 [0.12 , 1.42]
Denny 1953	6	157	16	50	8.7%	0.12 [0.05 , 0.29]
Landsman 1951	0	52	0	43		Not estimable
MacDonald 1951	0	41	1	41	1.3%	0.33 [0.01 , 7.95]
Petersen 1997	21	89	32	90	13.3%	0.66 [0.42 , 1.06]
Taylor 1977	6	129	3	59	5.2%	0.91 [0.24 , 3.53]
Zwart 2000	117	352	63	154	15.8%	0.81 [0.64 , 1.03]
Zwart 2003	20	100	7	56	9.5%	1.60 [0.72 , 3.55]
Subtotal (95% CI)		**1018**		**598**	**64.4%**	**0.62 [0.38 , 1.03]**
Total events:	177		135			
Heterogeneity: Tau² = 0.28; Chi² = 22.27, df = 7 (P = 0.002); I² = 69%						
Test for overall effect: Z = 1.83 (P = 0.07)						
1.8.2 Symptom of sore throat at 1 week (6 to 8 days): unblinded studies						
Bennike 1951	0	100	7	99	1.5%	0.07 [0.00 , 1.14]
Brink 1951	4	277	15	198	6.9%	0.19 [0.06 , 0.57]
Brumfitt 1957	0	42	2	40	1.4%	0.19 [0.01 , 3.85]
de la Poza Abad 2016	11	57	19	52	11.2%	0.53 [0.28 , 1.00]
Little 1997	66	388	35	184	14.5%	0.89 [0.62 , 1.30]
Subtotal (95% CI)		**864**		**573**	**35.6%**	**0.43 [0.20 , 0.91]**
Total events:	81		78			
Heterogeneity: Tau² = 0.38; Chi² = 11.69, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)		**1882**		**1171**	**100.0%**	**0.57 [0.39 , 0.82]**
Total events:	258		213			
Heterogeneity: Tau² = 0.21; Chi² = 34.17, df = 12 (P = 0.0006); I² = 65%						
Test for overall effect: Z = 2.98 (P = 0.003)						
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%						



Analysis 1.9. Comparison 1: Antibiotics versus control for the treatment of sore throat: symptoms of sore throat, Outcome 9: Symptom of sore throat at 1 week (6 to 8 days): GABHS-positive throat swab, GABHS-negative swab



Comparison 2. Antibiotics versus control for the treatment of sore throat: symptoms of fever

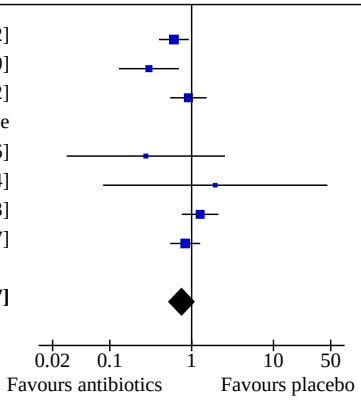
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Symptom of fever on day 3	8	1443	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.07]
2.2 Symptom of fever on day 3: blinded versus unblinded studies	8	1443	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 Symptom of fever on day 3: blinded studies	4	703	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.23]
2.2.2 Symptom of fever on day 3: unblinded studies	4	740	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.21]
2.3 Symptom of fever on day 3: children compared with adults	5	766	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.31, 1.26]
2.3.1 Symptom of fever on day 3: children	2	61	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.76, 2.13]
2.3.2 Symptom of fever on day 3: adults	3	705	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.21, 1.10]
2.4 Symptom of fever at 1 week (6 to 8 days)	4	886	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.55, 1.52]

Analysis 2.1. Comparison 2: Antibiotics versus control for the treatment of sore throat: symptoms of fever, Outcome 1: Symptom of fever on day 3

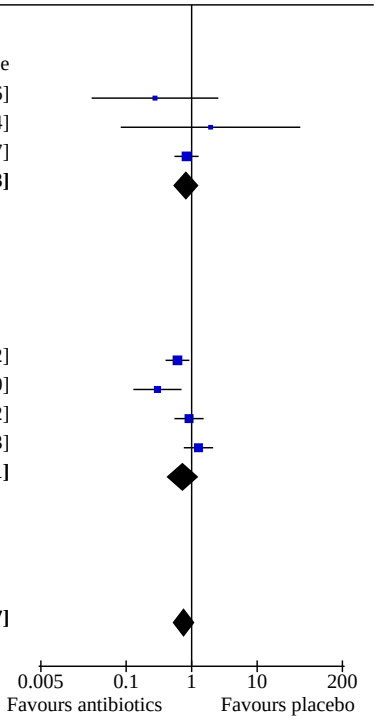
Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brink 1951	34	277	40	198	22.9%	0.61 [0.40 , 0.92]
Brumfitt 1957	6	62	19	59	11.5%	0.30 [0.13 , 0.70]
de la Poza Abad 2016	19	57	19	52	19.7%	0.91 [0.55 , 1.52]
Krober 1985	0	15	0	11		Not estimable
Landsman 1951	1	52	3	43	2.3%	0.28 [0.03 , 2.56]
Middleton 1988	1	33	0	21	1.2%	1.94 [0.08 , 45.54]
Nelson 1984	12	17	10	18	19.7%	1.27 [0.76 , 2.13]
Whitfield 1981	33	256	42	272	22.8%	0.83 [0.55 , 1.27]
Total (95% CI)		**769**		**674**	**100.0%**	**0.75 [0.53 , 1.07]**
Total events:	106		133			

Heterogeneity: Tau² = 0.09; Chi² = 11.83, df = 6 (P = 0.07); I² = 49%
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable



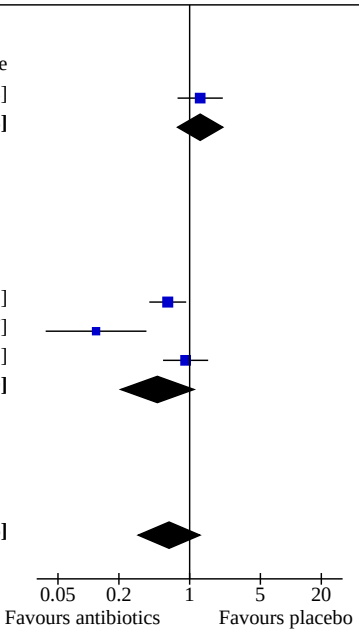
Analysis 2.2. Comparison 2: Antibiotics versus control for the treatment of sore throat: symptoms of fever, Outcome 2: Symptom of fever on day 3: blinded versus unblinded studies

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Symptom of fever on day 3: blinded studies						
Krober 1985	0	15	0	11		Not estimable
Landsman 1951	1	52	3	43	2.3%	0.28 [0.03 , 2.56]
Middleton 1988	1	33	0	21	1.2%	1.94 [0.08 , 45.54]
Whitfield 1981	33	256	42	272	22.8%	0.83 [0.55 , 1.27]
Subtotal (95% CI)		**356**		**347**	**26.3%**	**0.82 [0.54 , 1.23]**
Total events:	35		45			
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
2.2.2 Symptom of fever on day 3: unblinded studies						
Brink 1951	34	277	40	198	22.9%	0.61 [0.40 , 0.92]
Brumfitt 1957	6	62	19	59	11.5%	0.30 [0.13 , 0.70]
de la Poza Abad 2016	19	57	19	52	19.7%	0.91 [0.55 , 1.52]
Nelson 1984	12	17	10	18	19.7%	1.27 [0.76 , 2.13]
Subtotal (95% CI)		**413**		**327**	**73.7%**	**0.72 [0.43 , 1.21]**
Total events:	71		88			
Heterogeneity: Tau² = 0.20; Chi² = 10.87, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 1.23 (P = 0.22)						
Total (95% CI)		**769**		**674**	**100.0%**	**0.75 [0.53 , 1.07]**
Total events:	106		133			
Heterogeneity: Tau² = 0.09; Chi² = 11.83, df = 6 (P = 0.07); I² = 49%						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						



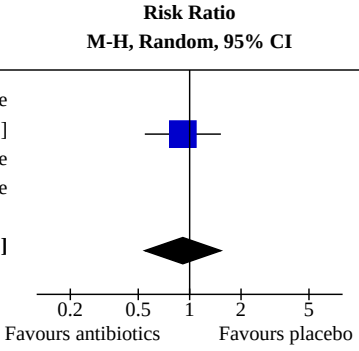
Analysis 2.3. Comparison 2: Antibiotics versus control for the treatment of sore throat: symptoms of fever, Outcome 3: Symptom of fever on day 3: children compared with adults

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Symptom of fever on day 3: children						
Krober 1985	0	15	0	11		Not estimable
Nelson 1984	12	17	10	18	27.1%	1.27 [0.76 , 2.13]
Subtotal (95% CI)		**32**		**29**	**27.1%**	**1.27 [0.76 , 2.13]**
Total events:	12		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
2.3.2 Symptom of fever on day 3: adults						
Brink 1951	34	277	40	198	28.5%	0.61 [0.40 , 0.92]
Catanzaro 1954	3	62	24	59	17.2%	0.12 [0.04 , 0.37]
de la Poza Abad 2016	19	57	19	52	27.2%	0.91 [0.55 , 1.52]
Subtotal (95% CI)		**396**		**309**	**72.9%**	**0.48 [0.21 , 1.10]**
Total events:	56		83			
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 10.97$, df = 2 (P = 0.004); $I^2 = 82\%$						
Test for overall effect: Z = 1.73 (P = 0.08)						
Total (95% CI)		**428**		**338**	**100.0%**	**0.63 [0.31 , 1.26]**
Total events:	68		93			
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 17.90$, df = 3 (P = 0.0005); $I^2 = 83\%$						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: $Chi^2 = 3.81$, df = 1 (P = 0.05), $I^2 = 73.8\%$						



Analysis 2.4. Comparison 2: Antibiotics versus control for the treatment of sore throat: symptoms of fever, Outcome 4: Symptom of fever at 1 week (6 to 8 days)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brink 1951	0	277	0	198		Not estimable
de la Poza Abad 2016	19	57	19	52	100.0%	0.91 [0.55 , 1.52]
Denny 1950	0	157	0	50		Not estimable
Landsman 1951	0	52	0	43		Not estimable
Total (95% CI)		**543**		**343**	**100.0%**	**0.91 [0.55 , 1.52]**
Total events:	19		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
Test for subgroup differences: Not applicable						



Comparison 3. Antibiotics versus control for the treatment of sore throat: symptoms of headache

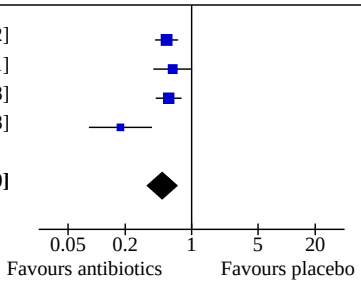
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptom of headache on day 3	4	1020	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.34, 0.70]
3.2 Symptom of headache on day 3: blinded versus unblinded studies	4	1020	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.34, 0.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.1 Symptom of headache on day 3: blinded studies	2	436	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.09, 1.20]
3.2.2 Symptom of headache on day 3: unblinded studies	2	584	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.45, 0.72]

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

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brink 1951	61	277	80	198	31.9%	0.55 [0.41 , 0.72]
de la Poza Abad 2016	18	57	26	52	23.6%	0.63 [0.40 , 1.01]
Denny 1953	54	157	30	50	30.4%	0.57 [0.42 , 0.78]
El-Daher 1991	7	118	37	111	14.1%	0.18 [0.08 , 0.38]
Total (95% CI)		**609**		**411**	**100.0%**	**0.49 [0.34 , 0.70]**
Total events:	140		173			

Heterogeneity: Tau² = 0.08; Chi² = 9.23, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable



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

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Symptom of headache on day 3: blinded studies						
Denny 1953	54	157	30	50	30.4%	0.57 [0.42 , 0.78]
El-Daher 1991	7	118	37	111	14.1%	0.18 [0.08 , 0.38]
Subtotal (95% CI)		**275**		**161**	**44.5%**	**0.33 [0.09 , 1.20]**
Total events:	61		67			

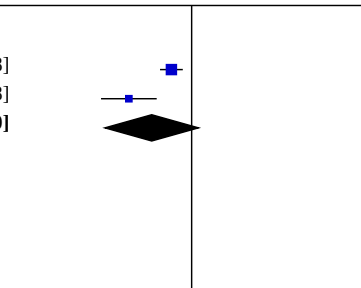
Heterogeneity: Tau² = 0.77; Chi² = 9.71, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 1.68 (P = 0.09)

3.2.2 Symptom of headache on day 3: unblinded studies						
Brink 1951	61	277	80	198	31.9%	0.55 [0.41 , 0.72]
de la Poza Abad 2016	18	57	26	52	23.6%	0.63 [0.40 , 1.01]
Subtotal (95% CI)		**334**		**250**	**55.5%**	**0.57 [0.45 , 0.72]**
Total events:	79		106			

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 4.65 (P < 0.00001)

Total (95% CI)		**609**		**411**	**100.0%**	**0.49 [0.34 , 0.70]**
Total events:	140		173			

Heterogeneity: Tau² = 0.08; Chi² = 9.23, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%



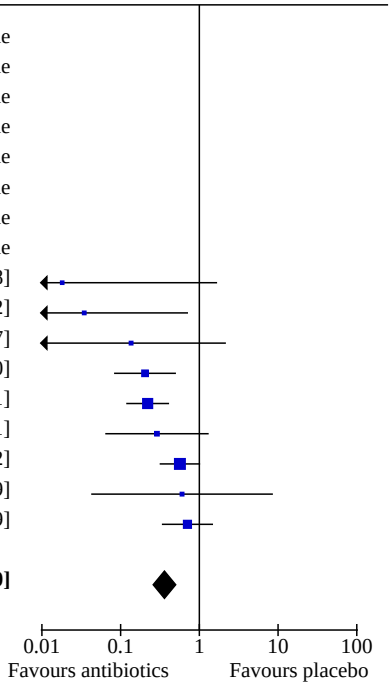
Comparison 4. Antibiotics versus control for the treatment of sore throat: incidence of complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Incidence of acute rheumatic fever within 2 months. Rheumatic fever defined by clinical diagnosis	17	12132	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.26, 0.50]
4.2 Incidence of acute rheumatic fever within 2 months. Penicillin versus placebo	14	8407	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.18, 0.40]
4.3 Incidence of acute rheumatic fever within 2 months: early (pre-1975) versus late studies (post-1975)	15	9984	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.20, 0.45]
4.3.1 Incidence of acute rheumatic fever within 2 months: early (pre-1975) studies	10	7617	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.20, 0.45]
4.3.2 Incidence of acute rheumatic fever within 2 months: late (post-1975) studies	5	2367	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.4 Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis	10	3646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.11, 0.40]
4.5 Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)	10	3646	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.11, 0.40]
4.5.1 Incidence of otitis media within 14 days: early (pre-1975) studies	5	1837	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.12, 0.52]
4.5.2 Incidence of otitis media within 14 days: late (post-1975) studies	5	1809	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.05 [0.01, 0.31]
4.6 Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis	7	2270	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.10, 2.05]
4.7 Incidence of quinsy within 2 months. Quinsy defined by clinical diagnosis	7	2367	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.07, 0.35]
4.8 Incidence of acute glomerulonephritis within 1 month. Acute glomerulonephritis defined by clinical diagnosis	10	5147	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.07 [0.00, 1.32]

Analysis 4.1. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 1: Incidence of acute rheumatic fever within 2 months. Rheumatic fever defined by clinical diagnosis

	Antibiotics		Placebo			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bennike 1951	0	238	0	268		Not estimable	
Zwart 2000	0	358	0	164		Not estimable	
Little 1997	0	454	0	216		Not estimable	
Leelarasamee 2000	0	369	0	386		Not estimable	
De Meyere 1992	0	87	0	94		Not estimable	
Dagnelie 1996	0	121	0	118		Not estimable	
Brumfitt 1957	0	62	0	59		Not estimable	
Chapple 1956	0	186	0	97		Not estimable	
Brock 1953	0	262	1	87	0.5%	0.02 [0.00 , 1.68]	
Chamovitz 1954	0	257	2	109	1.2%	0.03 [0.00 , 0.72]	
Siegel 1961	0	605	2	608	1.4%	0.14 [0.01 , 2.17]	
Denny 1950	2	798	17	804	13.2%	0.20 [0.08 , 0.50]	
Wannamaker 1951	5	978	35	996	27.5%	0.22 [0.12 , 0.41]	
Brink 1951	2	277	5	198	4.7%	0.29 [0.06 , 1.31]	
Houser 1953	16	889	29	910	30.8%	0.57 [0.31 , 1.02]	
Denny 1953	2	157	1	50	1.5%	0.60 [0.04 , 8.59]	
Catanzaro 1954	26	650	12	220	19.3%	0.71 [0.33 , 1.49]	
Total (95% CI)		**6748**		**5384**	**100.0%**	**0.36 [0.26 , 0.50]**	
Total events:	53		104				

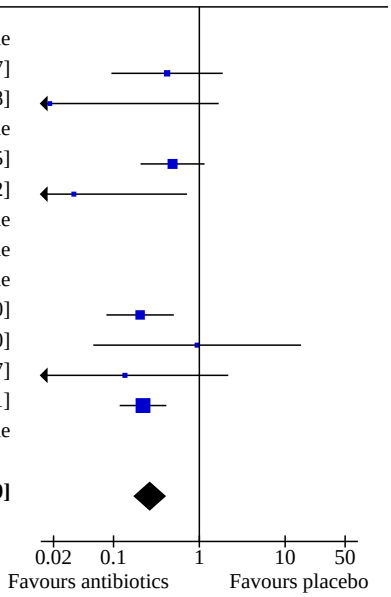
Heterogeneity: Chi² = 13.91, df = 8 (P = 0.08); I² = 42%
Test for overall effect: Z = 6.10 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 2: Incidence of acute rheumatic fever within 2 months. Penicillin versus placebo

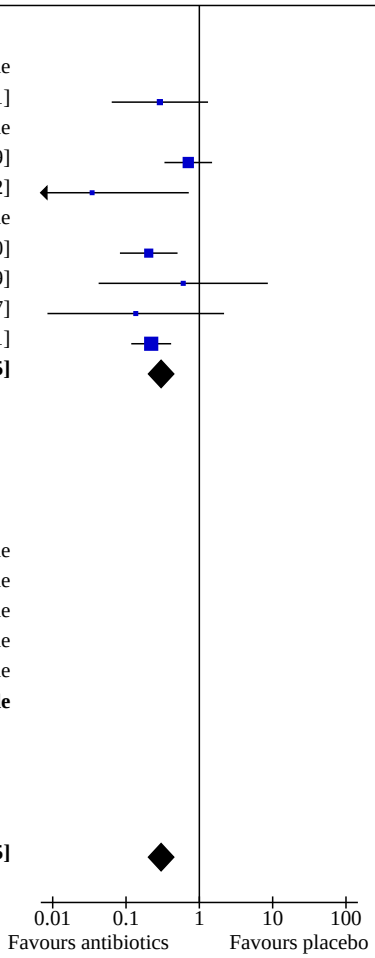
	Antibiotics		Placebo			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bennike 1951	0	238	0	268		Not estimable	
Brink 1951	2	197	5	198	7.5%	0.42 [0.09 , 1.87]	
Brock 1953	0	262	1	87	0.8%	0.02 [0.00 , 1.68]	
Brumfitt 1957	0	62	0	59		Not estimable	
Catanzaro 1954	12	420	12	220	22.7%	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		Not estimable	
Dagnelie 1996	0	121	0	118		Not estimable	
De Meyere 1992	0	87	0	94		Not estimable	
Denny 1950	2	798	17	804	20.4%	0.20 [0.08 , 0.50]	
Denny 1953	1	53	1	50	2.1%	0.94 [0.06 , 15.30]	
Siegel 1961	0	605	2	608	2.2%	0.14 [0.01 , 2.17]	
Wannamaker 1951	5	978	35	996	42.5%	0.22 [0.12 , 0.41]	
Zwart 2000	0	358	0	164		Not estimable	
Total (95% CI)		**4535**		**3872**	**100.0%**	**0.26 [0.18 , 0.40]**	
Total events:	22		75				

Heterogeneity: Chi² = 7.06, df = 7 (P = 0.42); I² = 1%
Test for overall effect: Z = 6.40 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 3: Incidence of acute rheumatic fever within 2 months: early (pre-1975) versus late studies (post-1975)

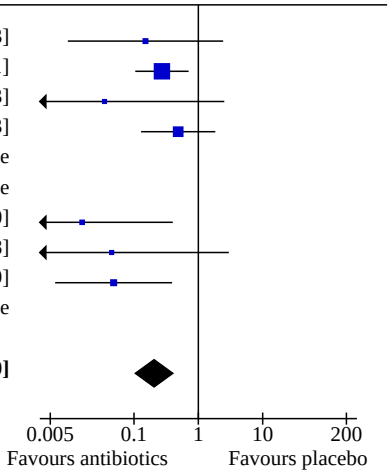
Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.3.1 Incidence of acute rheumatic fever within 2 months: early (pre-1975) studies						
Bennike 1951	0	238	0	268		Not estimable
Brink 1951	2	277	5	198	6.9%	0.29 [0.06 , 1.31]
Brumfitt 1957	0	62	0	59		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		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		74			
Heterogeneity: Chi² = 9.20, df = 6 (P = 0.16); I² = 35%						
Test for overall effect: Z = 5.94 (P < 0.00001)						
4.3.2 Incidence of acute rheumatic fever within 2 months: late (post-1975) studies						
Dagnelie 1996	0	121	0	118		Not estimable
De Meyere 1992	0	87	0	94		Not estimable
Leelarasamee 2000	0	369	0	386		Not estimable
Little 1997	0	454	0	216		Not estimable
Zwart 2000	0	358	0	164		Not estimable
Subtotal (95% CI)		**1389**		**978**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**5597**		**4387**	**100.0%**	**0.30 [0.20 , 0.45]**
Total events:	37		74			
Heterogeneity: Chi² = 9.20, df = 6 (P = 0.16); I² = 35%						
Test for overall effect: Z = 5.94 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 4.4. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 4: Incidence of otitis media within 14 days. Otitis media defined by clinical diagnosis

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bennike 1951	0	238	2	268	5.8%	0.15 [0.01 , 2.43]
Brink 1951	5	277	13	198	49.2%	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	25.5%	0.49 [0.13 , 1.83]
Dagnelie 1996	0	121	0	118		Not estimable
De Meyere 1992	0	87	0	94		Not estimable
Denny 1953	0	157	2	50	4.3%	0.02 [0.00 , 0.40]
Little 1997	0	454	1	216	2.6%	0.04 [0.00 , 2.98]
Taylor 1977	0	131	4	66	10.2%	0.05 [0.01 , 0.39]
Zwart 2000	0	358	0	164		Not estimable
Total (95% CI)		**2266**		**1380**	**100.0%**	**0.21 [0.11 , 0.40]**
Total events:	10		28			

Heterogeneity: Chi² = 7.42, df = 6 (P = 0.28); I² = 19%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 5: Incidence of otitis media within 14 days: early (pre-1975) versus late studies (post-1975)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.5.1 Incidence of otitis media within 14 days: early (pre-1975) studies						
Bennike 1951	0	238	2	268	5.8%	0.15 [0.01 , 2.43]
Brink 1951	5	277	13	198	49.2%	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	25.5%	0.49 [0.13 , 1.83]
Denny 1953	0	157	2	50	4.3%	0.02 [0.00 , 0.40]
Subtotal (95% CI)		**1115**		**722**	**87.2%**	**0.25 [0.12 , 0.52]**
Total events:	10		23			

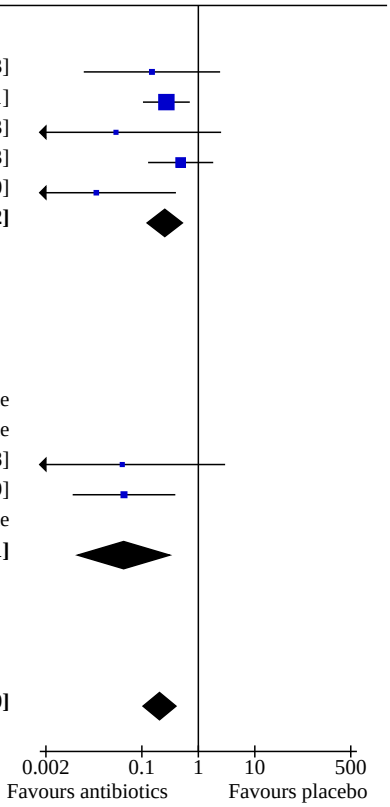
Heterogeneity: Chi² = 4.74, df = 4 (P = 0.32); I² = 16%
Test for overall effect: Z = 3.74 (P = 0.0002)

4.5.2 Incidence of otitis media within 14 days: late (post-1975) studies						
Dagnelie 1996	0	121	0	118		Not estimable
De Meyere 1992	0	87	0	94		Not estimable
Little 1997	0	454	1	216	2.6%	0.04 [0.00 , 2.98]
Taylor 1977	0	131	4	66	10.2%	0.05 [0.01 , 0.39]
Zwart 2000	0	358	0	164		Not estimable
Subtotal (95% CI)		**1151**		**658**	**12.8%**	**0.05 [0.01 , 0.31]**
Total events:	0		5			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)

Total (95% CI)		**2266**		**1380**	**100.0%**	**0.21 [0.11 , 0.40]**
Total events:	10		28			

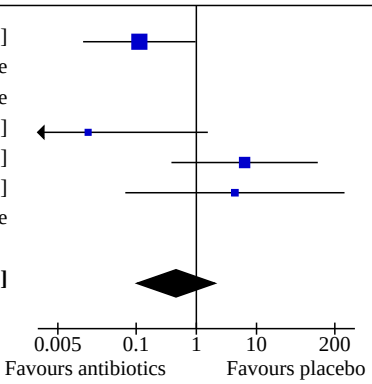
Heterogeneity: Chi² = 7.42, df = 6 (P = 0.28); I² = 19%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Chi² = 2.68, df = 1 (P = 0.10), I² = 62.8%



Analysis 4.6. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 6: Incidence of sinusitis within 14 days. Sinusitis defined by clinical diagnosis

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chamovitz 1954	1	257	3	109	48.2%	0.11 [0.01 , 0.97]
Dagnelie 1996	0	121	0	118		Not estimable
De Meyere 1992	0	87	0	84		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]
Zwart 2000	0	358	0	164		Not estimable
Total (95% CI)		**1486**		**784**	**100.0%**	**0.46 [0.10 , 2.05]**
Total events:	4		4			

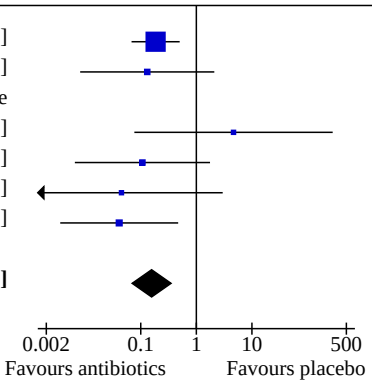
Heterogeneity: Chi² = 8.19, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 7: Incidence of quinsy within 2 months. Quinsy defined by clinical diagnosis

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bennike 1951	1	238	15	268	65.0%	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		Not estimable
Howe 1997	1	100	0	54	3.8%	4.66 [0.08 , 283.57]
Landsman 1951	0	52	2	43	8.2%	0.11 [0.01 , 1.76]
Little 1997	0	454	1	216	3.7%	0.04 [0.00 , 2.98]
Zwart 2000	0	358	3	164	10.8%	0.04 [0.00 , 0.47]
Total (95% CI)		**1410**		**957**	**100.0%**	**0.16 [0.07 , 0.35]**
Total events:	2		23			

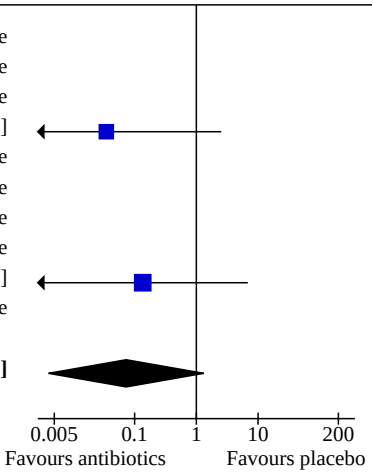
Heterogeneity: Chi² = 4.32, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 4.52 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4: Antibiotics versus control for the treatment of sore throat: incidence of complications, Outcome 8: Incidence of acute glomerulonephritis within 1 month. Acute glomerulonephritis defined by clinical diagnosis

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bennike 1951	0	238	0	268		Not estimable
Brink 1951	0	277	0	198		Not estimable
Brumfitt 1957	0	62	0	59		Not estimable
Chamovitz 1954	0	257	1	109	45.5%	0.03 [0.00 , 2.53]
Chapple 1956	0	186	0	97		Not estimable
Dagnelie 1996	0	121	0	118		Not estimable
Leelarasamee 2000	0	369	0	386		Not estimable
Little 1997	0	454	0	216		Not estimable
Siegel 1961	0	605	1	605	54.5%	0.14 [0.00 , 6.82]
Zwart 2000	0	358	0	164		Not estimable
Total (95% CI)		**2927**		**2220**	**100.0%**	**0.07 [0.00 , 1.32]**
Total events:	0		2			

Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy for the 2021 update

MEDLINE and CENTRAL were searched using the search strategy shown below. We combined the MEDLINE search string with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We adapted the search string for Embase (Appendix 2). There were no language or publication restrictions.

MEDLINE (Ovid)

1 exp Pharyngitis/
2 pharyngit*.tw.
3 exp Nasopharyngitis/
4 (nasopharyngit* or rhinopharyngit*).tw.
5 exp Tonsillitis/
6 tonsillit*.tw.
7 (tonsil* adj2 (inflam* or infect*)).tw.
8 ((throat* or pharyn*) adj3 (infect* or inflam* or strep*)).tw.
9 (sore* adj2 throat*).tw.
10 or/1-9
11 exp Anti-Bacterial Agents/
12 antibiot*.tw,nm.
13 (azithromycin* or clarithromycin* or erythromycin* or roxithromycin* or macrolide* or cefamandole* or cefoperazone* or cefazolin* or cefonicid* or cefsulodin* or cephacetrile* or cefotaxime* or cephalothin* or cephapirin* or cephalexin* or cephaclor* or cephadroxil* or cephaloglycin* or cephradine* or cephaloridine* or ceftazidime* or cephamycin* or cefmetazole* or cefotetan* or cefoxitin* or cephalosporin* or cefpodoxime* or cefuroxime* or cefixime* or amoxicillin* or amoxycillin* or ampicillin* or sulbactum* or tetracyclin* or clindamycin* or lincomycin* or doxycyclin* or fluoroquinolone* or ciprofloxacin* or fleroxacin* or enoxacin* or norfloxacin* or ofloxacin* or pefloxacin* or moxifloxacin* or esparfloxacin* or clindamicin* or penicillin* or ticarcillin* or beta-lactam* or levofloxacin* or trimethoprim* or co-trimoxazole).tw,nm.
14 or/11-13
15 10 and 14

[Enter text here]

Appendix 2. Embase (Elsevier) search strategy

#16 #11 AND #15
#15 #12 OR #13 OR #14
#14 azithromycin*:ab,ti OR clarithromycin*:ab,ti OR erythromycin*:ab,ti OR roxithromycin*:ab,ti OR macrolide*:ab,ti OR cefamandole*:ab,ti OR cefoperazone*:ab,ti OR cefazolin*:ab,ti OR cefonicid*:ab,ti OR
cefsulodin*:ab,ti OR cephacetrile*:ab,ti OR cefotaxime*:ab,ti OR cephalothin*:ab,ti OR cephapirin*:ab,ti OR cephalexin*:ab,ti OR cephaclor*:ab,ti OR cephadroxil*:ab,ti OR cephaloglycin*:ab,ti OR
cephradine*:ab,ti OR cephaloridine*:ab,ti OR ceftazidime*:ab,ti OR cephamycin*:ab,ti OR cefmetazole*:ab,ti OR cefotetan*:ab,ti OR cefoxitin*:ab,ti OR cephalosporin*:ab,ti OR cefpodoxime*:ab,ti OR
cefuroxime*:ab,ti OR cefixime*:ab,ti OR amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR ampicillin*:ab,ti OR sulbactum*:ab,ti OR tetracyclin*:ab,ti OR clindamycin*:ab,ti OR lincomycin*:ab,ti OR doxycyclin*:ab,ti OR fluoroquinolone*:ab,ti OR ciprofloxacin*:ab,ti OR fleroxacin*:ab,ti OR enoxacin*:ab,ti OR norfloxacin*:ab,ti OR ofloxacin*:ab,ti OR pefloxacin*:ab,ti OR moxifloxacin*:ab,ti OR esparfloxacin*:ab,ti OR clindamicin*:ab,ti OR penicillin*:ab,ti OR ticarcillin*:ab,ti OR 'beta-lactam':ab,ti OR 'beta-lactams':ab,ti OR levofloxacin*:ab,ti OR trimethoprim*:ab,ti OR 'co-trimoxazole':ab,ti
#13 antibiot*:ab,ti
#12 'antibiotic agent'/exp
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#10 (sore* NEAR/2 throat*):ab,ti
#9 ((throat* OR pharyn*) NEAR/3 (infect* OR inflam* OR strep*)):ab,ti
#8 'sore throat'/de
#7 (tonsil* NEAR/2 (infect* OR inflam*)):ab,ti
#6 tonsillit*:ab,ti
#5 'tonsillitis'/exp
#4 rhinopharyngit*:ab,ti OR nasopharyngit*:ab,ti
#3 'rhinopharyngitis'/de
#2 pharyngit*:ab,ti
#1 'pharyngitis'/exp

Appendix 3. Details of previous searches

For the 2011 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 2, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 18 May 2011), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (November 2008 to May week 1, 2011) and EMBASE (November 2008 to May 2011).

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

MEDLINE and CENTRAL were searched using the search strategy shown below. We combined the MEDLINE search string with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We adapted the search string for EMBASE.

MEDLINE (Ovid)

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

(Embase.com used in 2011 update)
#1. 'pharyngitis'/exp AND [embase]/lim
#2. pharyngit*:ti,ab AND [2004-2008]/py
#3. 'rhinopharyngitis'/exp AND [embase]/lim
#4. rhinopharyngit*:ti,ab OR nasopharyngit*:ti,ab [embase]/lim
#5. 'tonsillitis'/exp AND [embase]/lim

#6. tonsillit*:ti,ab AND [embase]/lim
#7. 'sore throat'/exp AND [embase]/lim
#8. 'sore throat':ti,ab OR 'sore throats':ti,ab embase]/lim
#9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10. 'antibiotic agent'/exp AND [embase]/lim
#11. antibiotic*:ti,ab AND [embase]/lim
#12. #10 OR #11 619,306
#13. random*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR 'cross over':ti,ab OR placebo*:ti,ab OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab AND [embase]/lim
#14. 'double blind':ti,ab OR 'double blinded':ti,ab OR 'single blind':ti,ab OR 'single blinded':ti,ab AND [embase]/lim
#15. 'crossover procedure'/exp AND [embase]/lim
#16. 'double blind procedure'/exp AND [embase]/lim
#17. 'single blind procedure'/exp AND [embase]/lim
#18. 'randomized controlled trial'/exp AND [embase]/lim
#19. #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20. #9 AND #12 AND #19

(EMBASE search used in earlier versions of the review)
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

F E E D B A C K

Antibiotics for sore throat,

Summary

1. The objectives as they are stated in the abstract include an assessment of the harms associated with the use of antibiotics in the management of sore throat, but the objectives as stated in the text of the review no longer refer to any assessment of harm. Indeed, the review does not address any adverse effects of antibiotics [which are not unimportant] and does not provide a reasonable explanation as

to why this is not done other than to state in the discussion that this was not possible because of inconsistencies in the way these data were recorded. In the absence of RCT data on harmful effects the authors might have considered whether usable information could be provided by other study designs.

2. Reviews on this subject should treat adults and children separately, but this review does not attempt to do this.

3. All clinically important outcomes have not been addressed by the review and others such as resource use, re-attendance and time off school or work are probably at least as important as those that were selected. It may have been more helpful to have collected data on all available outcomes provided that they are free from detection bias.

4. The question addressed by the review is not sufficiently well defined to allow the review to be executed systematically. Clear definitions are not given for the key elements of the question.

Most importantly, clear definitions of what is meant by primary care and sore throat are not given, leading to confusion around inclusion and exclusion decisions. Many of the control groups of the included studies do not involve a placebo but instead simply compare treatment with antibiotics to no treatment, so that some excluded studies would be eligible for inclusion, such as Catanzaro 1958 which was excluded because it compared antibiotics with sulfadiazine.

Apparent errors in inclusion and exclusion decisions have arisen probably as a result of the general lack of clarity discussed above. Specifically, the lack of a clear definition of what is meant by primary care appears to have led to the inclusion of an odd assortment of studies. For example, a couple of the included trials studied only people with sore throat who were admitted to hospital (Siegal 1961 and Bennike 1951). In addition, there appears to be an issue around the definition of a sore throat particularly in relation to positive or negative Streptococcus throat swabs. Streptococcal sore throats are a small sub-set of the total population of sore throats and the failure of the reviewers to address this in the inclusion criteria means that the results of pragmatic trials of sore throat are mixed in with those of streptococcal sore throat.

There is a failure to always faithfully report the detailed results of the included studies, and there are several numerical errors in the data abstracted. For example, in Bennike 1951 the baseline numbers include patients in the "ulcerative tonsillitis" group even though most outcomes are not reported for this group.

5. The search strategy is restricted to a Medline search, a search of the Cochrane Library and citation checking. No attempt appears to have been made to search other databases. The reviewers are not explicit about the details of their searching activities nor about how they used the work of the Cochrane Acute Respiratory Infections Group.

6. References to the included and excluded studies were incomplete. Specifically they were not provided for Dagnelie 1996, Howie 1997, Little 1997 and Peterson 1997 (included) and Herx 1988, Howie 1970, Marlow 1989, McDonald 1985, Schalen 1993 and Todd 1984 (excluded).

7. Given the nature of the data presented, it is possible that a formal meta-analysis was inappropriate. A descriptive analysis may have been more appropriate and more informative.

8. There is considerable uncertainty around the effectiveness of antibiotics on sore throat on the basis of the existing research examined by this review and this is not emphasised by the authors. Particular problems exist around the relevance of the trials to the present day with regard to the outcomes examined (rheumatic fever and glomerulonephritis), the poor quality of the majority of the included trials and the generalisability of the trials with regard to the study populations (e.g. United States air force recruits).

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

Reply

1. This is valid criticism: we need to describe the inadequacies of the information in the trials (after checking again) in the text.

2. A subgroup analysis on the basis of age is a good idea, and we will attempt this at the next major review.

3. This is a good idea, and we will attempt this at the next major review.

4. Certainly the issue of definitions is particularly difficult in this group of illnesses. One of us has written a paper on these difficulties (Del Mar C. Managing sore throat: a literature review. I. Making the diagnosis. Med J Aust 1992;156:572-5.). There is a particular difficulty in the fact that primary care doctors use the terms 'sore throat' tonsillitis and pharyngitis in slightly different ways, including interchangeably. Moreover the notion that patients with positive swabs for Streptococcus have a different illness can be challenged. Nevertheless a subgroup analysis for this with swab-positive and swab-negative is a good idea which we will incorporate with our next review.

Thank for pointing numerical errors out to us, and we will check on this. Please could you detail other numerical errors for us?

5. We are explicit about our search method. At the time we undertook the search the Cochrane Acute Respiratory Infections Group had no material to assist us. This will be reviewed at the next major update.

6. Thank you for drawing our attention to this.

7. As is often the case, there is considerable variation in the population groups, treatments, outcomes measures, etc in these trials. This does not make a synthesis inappropriate, but rather allows us to examine whether these factors appear to make a difference. We also felt it important to specifically attempt to calculate the SIZE of the benefits, as this is what clinicians are interested in, and what will persuade them to modify their practice. It is then important to recognise that the size of the effect will vary in different populations: as we point out, in groups at high risk of rheumatic fever - such as Australian aboriginals - the prevention of RF is important; we are also interested in trying to better predict which sub-groups will experience the most or least symptom relief, and plan to detail this in the next update.

8. We think we have discussed this in the Review. However we will reconsider what we have written in the overhaul.

Contributors

The review team.

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?

Gerben ter Riet

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Many thanks for this. We have gone back and checked with statisticians about your point. The issue seems to be:

1. Whether empty cells are a problem. The concern is that because one cannot divide anything by zero, this might represent a problem. We think not, because in no forest plots are there totals with zero--except for acute glomerulonephritis (there were no cases in the intervention arms of any trials, and only two in the control arms).

2. Whether the empty cells represent no evidence or evidence of no effect. We only recoded a zero where the study declared the outcome. Thus we assume that "no events" implies no events, rather than no reporting of events that might have occurred.

We have reported in Peto Odds ratios, the best measure for rare events.

Contributors

Chris Del Mar

Typographical error in the Abstract, 26 August 2008

Summary

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

Martti Teikari (Feedback comment submitted 27 August 2008)

Reply

Many thanks. We will correct the typing error.

Contributors

Chris Del Mar

Antibiotics for sore throat, 30 December 2013

Summary

Comment: This work is important and useful. I have 2 concerns. First is a value judgment about the size of the treatment effect, especially concerning quinsy. Second, is the exclusion of other causes of adolescent and young adult pharyngitis - group C (see Zwart 2000) strep and Fusobacterium necrophorum. Adolescents and young adults have a significant risk of suppurative complications, and most are not due to group A strep. A complete review in 2014 should acknowledge that sore throat in those age groups include other bacterial causes.

I agree with the conflict of interest statement below:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Robert Centor
Professor Internal Medicine
University of Alabama at Birmingham

Reply

We thank Dr Centor for commenting on the review with his thoughtful points.

1. Our comment on the size of the reduction of the complication of quinsy

The comments we made in the review are these:

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

In other words we think that it is important to keep in mind the incidence of complications (and the absolute risk reduction we can expect from antibiotics) rather than simply focus on the relative risk reduction. In clinical settings (such as low-income countries, and in Australia for example among indigenous communities) where complications are much more common, then clinicians will interpret the finding of this review by increasing the threshold for using antibiotics.

We also, incidentally, mention under “Agreements and disagreements with other studies or reviews” that “A recent review analysing the risk-benefit profile of antimicrobial prescribing for children concluded that antibiotics show little benefit in preventing quinsy following sore throat (Keith 2010).”

2. Exclusion of the other aetiological agents of sore throat such as Group C Streptococcus and Fusobacterium necrophorum.

It is certainly true that there are many aetiological agents other than Group A beta haemolytic Streptococcus (GABHS), including a huge range of viruses and bacteria, and even non-infective causes. However two factors influence the review:

a) The enormous focus on acute rheumatic fever as a complication, which for decades was the over-riding indication, and the single reason proposed by researchers and clinicians for using penicillin for sore throat. This was the motivation for an enormous search to find the best way of identifying GABHS, (and incidentally the reason why your own work on predictors of GABHS was so important).

b) The availability of randomised controlled trials that addressed these agents.

In future updates, any new RCTs that address other aetiological agents will be eligible for inclusion, as can be seen from our inclusion and exclusion criteria.

Contributors

Anneliese Spinks (Feedback reply submitted 24 January 2014)

Antibiotics for sore throat, 26 September 2016

Summary

Thank you for your informative review. A previous review on, generally, the same topic was conducted by Robertson et al. (1) which included n = 10 trials. Would you comment on why the following two citations included in Robertson et al. do not appear either as included or excluded references in your review?

- Brock LL, Siegel AC. Studies on the prevention of rheumatic fever: the effect of time of initiation of treatment of streptococcal infections on the immune response of the host. J Clin Invest 1953, 32:630-632.
- Houser HB, Eckhardt GC, Hahn EO, Denny FW, Wannamaker LW, Rammelkamp CH: Effect of aureomycin treatment of streptococcal sore throat on the streptococcal carrier state, the immunologic response of the host, and the incidence of acute rheumatic fever. Pediatrics 1953, 12(6):593-606.

Thanks,
Marlys LeBras BSP, ACPR, PharmD

References:

1. Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. BMC Cardiovascular Disorders 2005;5:11.

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Reply

We would like to thank you for alerting us to the omission of these early research studies in our review. We will seek to redress this in our coming update by reviewing the studies against our inclusion / exclusion criteria and revising the results accordingly if these studies do meet the inclusion criteria.

Contributors

Anneliese Spinks

Antibiotics for sore throat, 4 November 2019

Summary

I had a hard time understanding the assumed and corresponding risks in the Summary of Findings table - the groups seem mixed up. After doing a manual calculation and also checking earlier versions I'm now convinced that you confused "placebo" and "antibiotics".

Best regards,
Jon Pallon

Reply

Thank you for drawing to our attention the error in the column headings. We have now corrected this mistake so that the information in the table is consistent with the review findings.

Contributors

Anneliese Spinks

WHAT'S NEW

Date	Event	Description
6 April 2021	New citation required but conclusions have not changed	No changes to the review conclusions
6 April 2021	New search has been performed	We included three new trials (including two historic trials) (Brock 1953; de la Poza Abad 2016; Houser 1953).

HISTORY

Protocol first published: Issue 1, 1997
Review first published: Issue 2, 1997

Date	Event	Description
6 January 2020	Amended	Response to feedback comment added.
6 November 2019	Feedback has been incorporated	Feedback comment added.
6 October 2016	Feedback has been incorporated	Feedback added.

Date	Event	Description
28 January 2014	Feedback has been incorporated	Feedback comment and author reply added to the review.
11 July 2013	New search has been performed	Searches conducted. We did not identify any new trials for inclusion, but we excluded three new trials (Kapur 2011; Kolobukhina 2011; Supajatura 2012).
11 July 2013	New citation required but conclusions have not changed	Our conclusions remain unchanged.
18 May 2011	New search has been performed	Searches conducted. No new studies were identified, and our conclusions remain unchanged.
17 February 2010	Amended	Contact details updated.
21 January 2010	Amended	Contact details updated.
25 November 2008	New search has been performed	Searches conducted. No new studies were identified, and conclusions remain unchanged.
27 August 2008	Feedback has been incorporated	Typographical error in the Abstract corrected.
12 July 2008	Amended	Converted to new review format
18 October 2006	Feedback has been incorporated	Feedback added.
9 March 2006	New search has been performed	In this 2006 update data were added from one new study by Zwart 2003. Additionally, reported statistics were changed from odds ratios to more clinically meaningful relative risks (using a random-effects model). Since the update for this review was submitted to the Cochrane Library (Issue 4, 2006), we have been alerted to an error in the data extraction. This error involved switching the number of participants experiencing headache on day three 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 (risk ratio 0.47, 95% confidence interval 0.38 to 0.58).
22 May 2003	New search has been performed	Searches conducted.
8 May 2000	New search has been performed	Searches conducted.
30 June 1999	New search has been performed	Searches conducted.
31 March 1996	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

Anneliese Spinks has declared that they have no conflict of interest.

Paul Glasziou is on the board of Therapeutic Guidelines Limited and holds a research grant from the National Health and Medical Research Council on antibiotic resistance.

Chris Del Mar has received funding from the National Health and Medical Research Council for antibiotic resistance and from the Cochrane Acute Respiratory Infections Group and some consultancies (GSK for advice about vaccines for otitis media, and a local pharmaceutical company contemplating analgesic ear drops for otitis media).

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no substantial differences in the methods of data extraction or analysis between earlier versions of this review and the current 2021 update.

We revised decision making and reporting for risk of bias items and certainty of evidence levels in this update, as recommended by the Cochrane Acute Respiratory Infections Group in order to comply with current Cochrane methodological standards.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Fever [drug therapy]; *Otitis Media [drug therapy]; Pain [drug therapy]; *Pharyngitis [drug therapy]

MeSH check words

Adult; Child; Humans; Infant