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Antibiotics for acute maxillary sinusitis

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ABSTRACT

Background

Expert opinions vary on the appropriate role of antibiotics for sinusitis, one of the most commonly diagnosed conditions among adults in ambulatory care.

Objectives

We examined whether antibiotics are effective in treating acute sinusitis, and if so, which antibiotic classes are the most effective.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2007, Issue 3); MEDLINE (1950 to May 2007) and EMBASE (1974 to June 2007).

Selection criteria

Randomized controlled trials (RCTs) comparing antibiotics with placebo or antibiotics from different classes for acute maxillary sinusitis in adults. We included trials with clinically diagnosed acute sinusitis, whether or not confirmed by radiography or bacterial culture.

Data collection and analysis

At least two review authors independently screened search results, extracted data and quality assessed trials. Risk ratios (RR) were calculated for differences in the intervention and control groups to see whether or not the treatment was a failure. In meta-analysing the placebo-controlled studies, the data across antibiotic classes were combined. Primary outcomes were the clinical failure rates at 7 to 15 days and 16 to 60 days follow up.
Main results

Fifty-seven studies were included in the review; six placebo-controlled studies and 51 studies comparing different classes of antibiotics. Five studies involving 631 participants provided data for comparison of antibiotics to placebo, when clinical failure was defined as a lack of cure or improvement at 7 to 15 days follow up. These studies found a slight statistical difference in favor of antibiotics, compared to placebo, with a pooled RR of 0.66 (95% confidence interval (CI) 0.44 to 0.98). However, the clinical significance of the result is equivocal, also considering that cure or improvement rate was high in both the placebo group (80%) and the antibiotic group (90%). Based on six studies, when clinical failure was defined as a lack of total cure, there was significant difference in favor of antibiotics compared to placebo with a pooled RR of 0.74 (95% CI 0.65 to 0.84) at 7 to 15 days follow up. None of the antibiotic preparations was superior to each other.

Authors’ conclusions

Antibiotics have a small treatment effect in patients with uncomplicated acute sinusitis in a primary care setting with symptoms for more than seven days. However, 80% of participants treated without antibiotics improve within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level.

PLAIN LANGUAGE SUMMARY

Antibiotics for acute maxillary sinusitis

Antibiotics provide a minor improvement in simple (uncomplicated) sinus infections. However, 8 out of 10 patients improve without antibiotics within two weeks. The small benefit gained may be overridden by the negative effects of antibiotics, both on the patient and on the population in general.

In sinusitis, the membrane-lined air spaces near the nose become infected, which causes pain and discharge from the nose. There are four pairs of sinuses linked to the bony structures around the nose: the maxillary, frontal, ethmoidal and sphenoidal sinuses. Treatment options include antibiotics, decongestants, steroid drops or sprays, mucus-clearing drugs (mucolytics), antihistamines, or sinus puncture and lavage. This review found that antibiotics help some people a bit, but do not make a major difference to most people.
BACKGROUND

Sinusitis is a prevalent and important cause of ill health in adults. In the U.S. alone, an estimated 20 million cases of acute sinusitis occur each year. Sinusitis is the third to fifth most common diagnosis for which an antibiotic is prescribed within primary care settings in Nordic countries (Andre 2002; Rautakorpi 1999) and the U.S. (SAHP 2004). Sinusitis accounts for 15% to 21% of all antibiotic prescriptions for adults in outpatient care.

Acute bacterial maxillary sinusitis is often preceded by an acute viral upper respiratory tract infection (URTI). Up to 90% of patients with acute URTIs have symptoms of rhinosinusitis (Gwaltney 1994) and up to 39% of adults (Puhakka 1998) have reversible abnormalities in the sinus cavity which show up in magnetic resonance imaging or X-ray, following a common cold lasting for one week. It has been estimated that 0.5% to 2% of patients with a common cold have complications in the form of acute bacterial infection of the sinuses (Berg 1986; Gwaltney 1996). However, distinguishing those patients with bacterial infection from those with symptoms of rhinosinusitis with a viral origin is challenging.

A bacterial sinus infection can be caused by one or more bacterial species. Commonly isolated bacteria include Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae), and Moraxella catarrhalis (M. catarrhalis) (Gwaltney 1992; Low 1997). In approximately a third of suspected bacterial sinusitis cases, bacterial cultures from the sinus cavity come back negative (Axelsson 1972; Gwaltney 1992; Jousimies-Somer 1988). Sinusitis is classed as acute or chronic, depending on the pathological findings and duration of symptoms (Low 1997). Acute bacterial sinusitis lasts for less than four weeks duration (Kern 1984). At least some or many cases of chronic sinusitis represent a separate entity with underlying problems, for example, mechanical obstruction of sinus drainage, abnormalities in mucociliary clearance or immunology (Gwaltney 2005).

Typical signs and symptoms include purulent nasal discharge, postnasal drip, sinus pain at palpation, nasal obstruction with poor response to decongestants, unilateral facial pain and maxillary toothache (Axelsson 1972; Williams 1993), but none of the signs or symptoms is diagnostic when presenting alone. Acute bacterial sinusitis is more likely if the symptoms have lasted for more than one week (Gwaltney 2005).

Treatment recommendations for acute sinusitis are divided and range from only treating patients with severe or persistent moderate symptoms and specific bacterial sinusitis findings with narrow spectrum antibiotics (Snow 2001); to treating all patients with acute bacterial sinusitis with broad spectrum antibiotics (Winther 1990). The purpose of antibiotics is to decrease symptoms and restore the normal function of the sinuses, in order to prevent complications and the development of chronic sinusitis.

Unnecessary antibiotic prescriptions should be avoided. In addition to patient-related adverse effects, side effects are associated with resistance to antibiotics among community acquired pathogens. The correlation between resistance and community antibiotic use has been seen in many countries (Albrich 2004; Arason 1996; Bronzwaer 2002; Goossens 2005; Seppälä 1995; Steinke 2001). Not only the volume of antibiotic use but also the selection of broad-spectrum drugs, low dose, and long duration of antibiotic treatment increases antibiotic resistance (Guilleminot 1998; Hay 2005; Odenholt 2003). The European Antimicrobial Resistance Surveillance System EARSS has revealed significant geographical differences in resistance rates within Europe (Goossens 2005); high rates of antibiotic resistance were seen more often in high-consuming countries in southern and eastern Europe. For example, there are remarkable differences between European countries in the prevalence of resistance to penicillin and macrolide antibiotics in treating S. pneumoniae (EARSS 2007). In recent years, an increasing number of published studies have also suggested that antibiotics might have other harmful effects on health through the disturbance of human microbiota (Kilkkinen 2002; Maxwell 2002; Velicer 2004), and perhaps predisposing to new infections (Arason 2005; Howard 1976; Joki-Erkkilä 2000; Margolis 2005; Smith 1997).

The purpose of this systematic review was to quantify the effectiveness of antibiotic therapy for acute sinusitis in ambulatory care settings. The word 'antibiotic' is used as a general term referring to all antibacterials.

OBJECTIVES

To compare the effect of antibiotics versus placebo on clinical failure rates for acute maxillary sinusitis.

To compare different classes of antibiotics for treatment of acute maxillary sinusitis.

To compare the effect of short versus long courses of antibiotics for acute maxillary sinusitis.

To compare the side effects of different treatments.

METHODS

Criteria for considering studies for this review

Types of studies
Randomized controlled trials (RCTs) evaluating and comparing antibiotics to a placebo, or two different classes of antibiotics for acute sinusitis.

Trials having a sample size of at least 30 participants with acute maxillary sinusitis (because in very small samples many estimators are known to be sensitive).

Types of participants
Trials with adults or trials that separately reported data on subgroups of adults were included (adolescents at least 12 years old were accepted, provided there were less than 20% of participants aged under 18).

Acute maxillary sinusitis as defined by: 1) a history of URTI lasting 7 to 30 days, with at least two clinical signs or symptoms: sinus pain at palpation, postnasal drip, purulent nasal discharge, nasal obstruction, unilateral facial pain, maxillary toothache, impaired sense of smell; or 2) radiography, ultrasound, or other imaging; or culture from a sinus secretion obtained by puncture or endoscopy and irrigation or aspiration. In studies where clinical diagnosis was not clearly described, the diagnosis of acute maxillary sinusitis should be confirmed in at least of 80% of participants by imaging or culture.

Trials including a mixed population of acute (symptoms less than 30 days) and non-acute sinusitis or acute exacerbations of chronic sinusitis were included if they separately reported data on the subgroup with acute sinusitis, or if at least 80% of participants had acute sinusitis.

**Types of interventions**

Drug therapies reviewed were: 1) antibiotics versus control, and 2) comparisons between different antibiotic classes.

Trials that focused on antibiotic treatments for complicated sinusitis such as pansinusitis or frontal sinusitis (or solely ethmoidal or sphenoidal sinusitis) or infections of dental origin were excluded. Co-interventions such as decongestants, antihistamines, mucolytics, non-steroidal anti-inflammatory drugs, and corticosteroids were systematically recorded.

**Types of outcome measures**

**Primary outcomes**

Clinical failure rate at 7 to 15 days after the start of treatment. Failure is defined as a lack of cure or improvement of participants with acute maxillary sinusitis at follow up.

Clinical failure rate at 16 to 60 days after the start of treatment. Failure is defined as a lack of cure or improvement of participants with acute maxillary sinusitis at follow up.

**Secondary outcomes**

Clinical failure rate at 7 to 15 days after the start of treatment. Failure is defined as a lack of cure of participants with acute maxillary sinusitis at follow up.

Clinical failure rate at 16 to 60 days after the start of treatment. Failure is defined as a lack of cure of participants with acute maxillary sinusitis at follow up.

Bacteriological failure.

Radiographic failure.

Relapse rates; new acute episodes of sinusitis after 60 days from the start of the initial treatment.

Drop-outs due to adverse effects.

Quality of life.

Ability to work.

**Search methods for identification of studies**

In the previous version of this review, CENTRAL was searched to 2001; MEDLINE was searched from 1966 to 2001; and EMBASE from 1974 to 2001.

In this updated review, we used a new, more specific revised strategy to search for trials in the Cochrane Central Register of Controlled Trials (CENTRAL (The Cochrane Library, 2007, issue 3); MEDLINE (1950 to May 2007); EMBASE (1974 to June 2007). In the revised strategy “antibiotics” was used as an additional keyword and “anti-bacterial agents” as an exploded MeSH term in addition to “sinusitis”. The MEDLINE search terms were run over CENTRAL and adapted for EMBASE.

**MEDLINE (OVID)**

1 exp SINUSITIS/
2 sinusitis.mp.
3 or/1-2
4 exp Anti-Bacterial Agents/
5 antibiotic$.mp.
6 or/4-5
7 3 and 6
8 RANDOMIZED CONTROLLED TRIAL.pt.
9 CONTROLLED CLINICAL TRIAL.pt.
10 RANDOMIZED CONTROLLED TRIALS.sh.
11 RANDOM ALLOCATION.sh.
12 DOUBLE BLIND METHOD.sh.
13 SINGLE-BLIND METHOD.sh.
14 or/8-13
15 Animals/
16 human.sh.
17 15 not 16
18 14 not 17
19 CLINICAL TRIAL.pt.
20 exp Clinical Trials/
21 (clin$ adj25 trial$).ti,ab.
22 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
23 PLACEBOS.sh.
24 placebo$.ti,ab.
25 random$.ti,ab.
26 or/19-25
27 26 not 17
28 18 or 27
29 7 and 28

The function for finding related articles in PubMed was used for those already identified placebo-controlled trials so as to track down additional, relevant articles. Reference lists from the already identified trials and nine systematic reviews considering placebo-controlled study designs (Benninger 2000; de Bock 1997; de Ferranti 1998; Ioannidis 2001; Ioannidis 2002; Ip 2005; Linder 2003; Low 1997; Stalman 1997b) were reviewed for additional, appropriate studies. Included and excluded trials in the previous version were rechecked by using the revised inclusion criteria of
Data collection and analysis

Study selection

Four review authors (AAS, OB, NK, UMR) carried out the baseline searches. At least two review authors independently carried out the selection of papers on the basis of the title, keywords and abstract, and the decisions about eligibility. The full text of every article considered for inclusion was obtained. If the information relevant to the inclusion criteria was not available in the abstract or if the title was relevant but the abstract was not available, the full text of the report was obtained. At least two review authors independently carried out information and data recording, and any disagreements were resolved by consensus among these four review authors.

The inclusion criteria for study selection were: random allocation; antibiotics versus control or antibiotics versus antibiotics; acute maxillary sinusitis defined by clinical signs and symptoms or by radiography, ultrasound, or other imaging or culture; sample size of at least 30 adults with acute sinusitis.

Quality assessment

At least two review authors independently carried out the quality assessment of the included studies (AAS, OB or NK). Any disagreements between them were resolved by consensus. The methodological quality of included studies was assessed using allocation concealment, blinding, completeness of follow up and baseline comparability of the intervention and control groups. Instead of assigning a quality score, the following quality characteristics were described in the tables.

The randomization procedure and allocation concealment were recorded as (A) adequate concealment, (B) ‘random’ allocation reported but the actual method used to conceal it is not known, (C) inadequate concealment, and (D) allocation concealment not used, as described in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 (Higgins 2005). Assessment codes for allocation concealment are described in the ‘Characteristics of included studies’ table. If there was quasi-random or no random allocation, the study was excluded.

Other quality characteristics included information on whether participants and outcome assessors were blinded to the assigned therapy and information on reasons for withdrawals, drop-outs and protocol deviations in the intervention and control groups.

In this review the word ‘drop-out’ is used as a general term referring to the proportion of the participants without known or reported clinical outcome regardless of the reason for missing data. If the drop-out rate was reported to be over 35% or there was significant imbalance in drop-out rates between the intervention and control groups, the study was excluded from the analyses. Excluding the studies with high drop-out rate in the analyses was seen as a quality issue, especially when there is a lack of universal strategies in handling the missing data (Unnebrink 2001). In this review, limiting meta-analyses to studies with a drop-out rate less than 35% was a pragmatic approach to make comparisons without compromising the reliability of the overall results.

Further, information on the baseline comparability of the intervention and control groups and the similarity in using co-interventions between groups were also used as part of the quality assessment. The trials was considered as comparable if the study reported information on the baseline comparability of the intervention and control groups and there was no difference between the groups; and not comparable if there were important baseline differences in demographic characteristics or sinusitis severity rating between the study groups or unclear or no information on comparability.

The risk of bias was assessed for each study. The overall rating of bias was based on the scale reported in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 (section 6.7) (Higgins 2005) for the four characteristics outlined in the previous paragraphs (allocation concealment, blinding, completeness of the follow up and the comparability of the intervention and control groups).

- (A) Low risk of bias (plausible bias unlikely to seriously affect the results) if all criteria were met.
- (B) Moderate risk of bias (plausible bias which raises some doubt about the validity of the results) if one or more of the criteria were partly met.
- (C) High risk of bias (plausible bias which seriously weakens confidence in the results) if one or more criteria were not met.

To be classified as having a low risk of bias, the study had to have adequate random allocation concealment, a double-blind design, comparable intervention and control groups, and there also had to be complete information on drop-outs by study groups.

Data extraction

Data from all included studies were extracted by two review authors (AAS, OB or NK). Data presented only in graphs and figures were extracted whenever possible.

Extracted information relating to the study methodology or quality included: randomization concealment as described in the study, blinding, time follow up, percentage of drop-outs during follow up and baseline comparability of the groups. Characteristics relating to methods that were extracted included: criteria for accepting participants into the study (diagnosis on clinical/radiography/culture basis), definition of cure/failure, and treatment compliance. Characteristics relating to participants that were extracted in-
In cases where more than one antibiotic treatment arms of the same study were used in the same analysis, the event rate in the control group was divided according to the number of arms of the study.

In calculating rates of adverse effects, Peto OR were used as the outcome measure.

The meta-analyses were conducted in RevMan using fixed-effect and random-effects models.

The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran’s test for heterogeneity and by a measure of I-square ($I^2$).

The measure $I^2$ describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A value greater than 50% may be considered to represent substantial heterogeneity.

To test for robustness of results, sensitivity analyses were planned to examine the effect of diagnostic criteria of acute sinusitis (clinical or radiograph) and the classification of the risk of bias on the overall estimates of effect for important outcomes. However, there was insufficient number of trials in any specific intervention group to undertake this.

It was also planned to investigate publication bias using both the Begg and Mazumdar rank correlation test and the Egger regression asymmetry test, but there was an insufficient number of trials to undertake this.

**RESULTS**

**Description of studies**

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

**Search results and selection of studies**

The electronic search based on the new, revised search strategy produced 2030 records, many of which were duplicates. Of these, 1761 records were rejected as definitely not meeting the inclusion criteria simply on the basis of title or abstract. Duplicates were omitted. Checking the lists of the included and excluded studies in the previous version of this review, reviewing reference lists from the already identified trials and systematic reviews and using the function for finding related articles in PubMed yielded six more appropriate trials. Altogether 269 full-text reports were obtained. All non-English language reports were translated to assess the studies. The review authors could read reports in German, Russian and Scandinavian languages. Outside translators were consulted to identify and assess the reports in Portuguese, Spanish, French, Chinese and Japanese. From these 269 reports, 117 were clearly irrelevant for this review. The main reasons for exclusion were: trials without control group, studies with other treatment than an-
tibiotic, studies comparing same classes of antibiotics, and studies regarding children.

In total there were 152 reports to be considered in detail. From these, 60 reports representing 57 individual studies were considered eligible for inclusion in the review (the reasons for exclusion of the 83 studies with 90 reports are reported in the ‘Characteristics of excluded studies’ table). Additional information is needed from one placebo-controlled study to assess whether it meets the inclusion criteria of this review. This study is still awaiting a reply from the trial authors (Stalman 1997a). Another report in Japanese is awaiting a translation in order to be assessed (Miyamoto 2005).

Six of the 57 included studies compared antibiotic treatment to placebo. The remaining 51 studies compared different classes of antibiotics. The studies of Lindbaek 1996 and Lindbaek 1998 were conducted in the same trial but used different randomized study populations with different inclusion criteria, and are handled as separate studies in the study descriptions and analyses. Further, these studies each had two separate comparisons, penicillin versus placebo and amoxicillin versus placebo, which are cited separately. The comparisons penicillin versus placebo are cited as Lindbaek 1996a and Lindbaek 1998a, and the comparisons amoxicillin versus placebo as Lindbaek 1996b and Lindbaek 1998b, respectively. See ‘Characteristics of included studies’ table and Table 1 for included study information.

Table 1. Collected information from placebo-controlled studies

<p>| Study               | Comparisons                                                                 | Diagnost- | Day | Drop- | Cured | Cured | C+I | C+I | Side effects          |
|---------------------|------------------------------------------------------------------------------| method    |     | outs  | control| antib. |     |     |                 |
| Axelson 1970        | Penicillin V (400 mg three times daily for 10 days) + nasal decongestant     | Diagnosis by a radiograph; only patients with secretion included |     | 9%    | 31%   | 46%   | 72% | 83% | Penicillin: 8%, Control: 6% |
| (Sweden)            | (oxymetazoline) versus oxymetazoline                                         |           |     |       |       |       |     |     |                 |
| Lindbaek 1996a      | Penicillin V (1320 mg three times daily for 10 days; clinical symptoms lasting at least 8 days) |     | 10  | 2% (combined Lindbaek 1996a) | 11% (combined Lindbaek 1996a+) | 31% | 89% (combined Lindbaek 1996a +) | 97% | Penicillin: 59%, Placebo: 36% |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Details</th>
<th>Clinical Symptoms</th>
<th>Duration</th>
<th>Resolution</th>
<th>Improvement</th>
<th>Treatment Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindbaek 1996b (Norway)</td>
<td>Amoxicillin (500 mg three times daily for 10 days) versus placebo; nasal decongestants and analgesics were allowed but not prescribed in both groups</td>
<td>Computer tomography showing opacity or fluid-level</td>
<td>10 days</td>
<td>+ Lindbaek 1996b</td>
<td>45%</td>
<td>98%</td>
<td>Amoxicillin: 56%, Placebo: 36%</td>
</tr>
<tr>
<td>Lindbaek 1998a (Norway)</td>
<td>Penicillin V (1320 mg three times daily for 10 days) versus placebo; nasal decongestants and analgesics were allowed but not prescribed in both groups</td>
<td>Clinical symptoms lasting at least 8 days; computer tomography showing mucosal thickening of 5 mm</td>
<td>10 days</td>
<td>10% (combined Lindbaek 1998a + Lindbaek 1998b)</td>
<td>43% (combined Lindbaek 1998a+ Lindbaek 1998b)</td>
<td>30%</td>
<td>86% (combined Lindbaek 1998a + Lindbaek1996b)</td>
</tr>
</tbody>
</table>
Table 1. Collected information from placebo-controlled studies  

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Criteria</th>
<th>Duration</th>
<th>Resolution</th>
<th>% Improvement</th>
<th>% Placebo</th>
<th>% Efficacy</th>
<th>% Placebo</th>
<th>% Efficacy</th>
<th>% Improvement</th>
<th>Placebo: %</th>
<th>Efficacy: %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindbaek 1998b</td>
<td>Amoxicillin (500 mg three times daily for 10 days) versus placebo; nasal decongestants and analgesics were allowed but not prescribed in both groups</td>
<td>Clinical symptoms lasting at least 8 days; computer tomography showing mucosal thickening of 5 mm or more in any sinus without opacity or fluid level</td>
<td>10</td>
<td>41%</td>
<td>86%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Information not available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Buchem 1997</td>
<td>Amoxicillin (750 mg three times daily for 7 days) versus placebo. Oxymetazoline steam inhalation and paracetamol as needed in both groups</td>
<td>The mean duration of the symptomatic period before treatment 2.2 weeks; radiograph showing &gt; 5 mm mucosal thickening, opacity or air-fluid level</td>
<td>14</td>
<td>4%</td>
<td>52%</td>
<td>65%</td>
<td>77%</td>
<td>83%</td>
<td>57%</td>
<td>77%</td>
<td>Amoxicillin: 28%, Placebo: 9%</td>
<td></td>
</tr>
</tbody>
</table>
### Antibiotics versus placebo

Six trials involving 747 participants evaluated antibiotic treatments compared with non-antibiotic control for acute maxillary sinusitis (Axelsson 1970; Haye 1998; Lindbaek 1996a+Lindbaek 1996b; Lindbaek 1998a+Lindbaek 1998b; Merenstein 2005; van Buchem 1997). Two studies compared amoxicillin versus placebo (Merenstein 2005; van Buchem 1997), two studies compared penicillin V and amoxicillin to placebo (Lindbaek 1996a+Lindbaek 1996b; Lindbaek 1998a+Lindbaek 1998b), and one study compared azithromycin to placebo (Haye 1998). The study by Axelsson 1970 did not have a placebo group but the comparison of penicillin V plus oxymetazoline versus oxymetazoline alone was included in this review. The study by Lindbaek 1998 is the same study as Lindbaek 1996 but it used a separate randomized population. Thus three studies had more than two treatment arms (Axelsson 1970; Lindbaek 1996a+Lindbaek 1996b; Lindbaek 1998a+Lindbaek 1998b). Nasal decongestants and analgesics were allowed but not prescribed in the three studies, and one study used a decongestant as a supplementary therapy and control group treatment (Axelsson 1970).

Of the six studies, three were conducted in Norway (Haye 1998; Lindbaek 1996a+Lindbaek 1996b; Lindbaek 1998a+Lindbaek 1998b), one in Sweden (Axelsson 1970), one in the USA (Merenstein 2005) and one in The Netherlands (van Buchem 1997). In two studies diagnosis was based on clinical signs and symptoms lasting at least seven days (Haye 1998; Merenstein 2005). In four other studies, diagnosis was confirmed by a radiograph (criteria: secretion in the study of Axelsson 1970; and mucosal thickening more than 5 mm, presence of air-fluid level or total opacification in the van Buchem 1997 study); or by a computer tomography (criteria: presence of air-fluid level or total opacification in the

### Table 1. Collected information from placebo-controlled studies

<table>
<thead>
<tr>
<th>Study (Country)</th>
<th>Antibiotic</th>
<th>Clinical symptoms</th>
<th>Duration</th>
<th>Improvement</th>
<th>Adverse events</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haye 1998 (Norway)</td>
<td>Azithromycin (500 mg once daily for 3 days) versus placebo</td>
<td>Clinical symptoms lasting 11-29 days (symptoms: purulent secretion, maxillary sinus tenderness and/or pain); radiograph taken to exclude maxillary sinusitis based on more than 6 mm mucosal thickening</td>
<td>10-12; 23-27</td>
<td>0.6%</td>
<td>33%; 67%; 58%; 79%; 89%; 88%; 93%; 90%</td>
<td>Azithromycin: 28%, Placebo: 18%</td>
</tr>
<tr>
<td>Merenstein 2005 (USA)</td>
<td>Amoxicillin (500 mg twice daily for 10 days) versus placebo</td>
<td>Clinical symptoms &gt; 7 days, purulent nasal discharge, facial pain</td>
<td>14</td>
<td>14%</td>
<td>Information not available</td>
<td>Information not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amoxicillin: 23%, Placebo: 12%</td>
<td></td>
</tr>
</tbody>
</table>
study by Lindbaek 1996 (Lindbaek 1996a; Lindbaek 1996b); and mucosal thickening of 5 mm or more without fluid level or total opacification in the study by Lindbaek 1998 (Lindbaek 1998a; Lindbaek 1998b)). In one study (Haye 1998) radiography was used to exclude the presence of empyema.

Participants were recruited from community-based general practices in five of the six studies; the study by Axelsson 1970 did not describe the treatment setting. Participants’ average age was approximately 37 years, and approximately 60% were women. Ear, nose and throat (ENT) co-morbidity was assessed only in one study (van Buchem 1997) which reported 12% of participants with an allergic disease.

Clinical cure or failure were not defined in two studies (Axelsson 1970; van Buchem 1997). In addition to clinical outcomes, radiological outcomes were reported in two studies (Lindbaek 1996a; Lindbaek 1996b; van Buchem 1997). No studies reported bacteriological outcomes.

Three studies were financially supported by government/academic funding (Lindbaek 1996a; Lindbaek 1996b; Lindbaek 1998a; Lindbaek 1998b; Merenstein 2005). Three studies did not identify a source of support (Axelsson 1970; Haye 1998; van Buchem 1997).

Comparison of antibiotic versus antibiotic

Fifty-one studies comparing different classes of antibiotics were included in the review. Treatment comparisons were: non-penicillin antibiotic versus beta-lactamase sensitive penicillins (n = 8), non-tetracycline versus tetracycline (n = 5, of which one study was also included in the comparison of non-penicillin antibiotic versus beta-lactamase sensitive penicillins), macrolides versus amoxicillin-clavulanate (n = 8), cephalosporins versus amoxicillin-clavulanate (n = 10), and miscellaneous comparisons (n = 21). Forty-two studies had two treatment arms, nine studies had three treatment arms. Studies were financially supported mostly by a pharmaceutical company (n = 36) and in four further studies at least one of the authors had an affiliation with a pharmaceutical company. Eleven studies did not identify a source of support.

Topical decongestants and/or antihistamines were prescribed in five studies. They were allowed but not prescribed in 19 studies, they were prohibited in 1 study, and not described in 25 studies. One trial prescribed nasal corticosteroids as part of the intervention (Pessey 1996).

Participants were recruited from otorhinolaryngology speciality settings in 16 studies, primary care settings in 11 studies, and mixed settings in three studies. Twenty-one studies did not describe the recruitment or treatment setting or it was unclear. Participants’ average age was approximately 38 years; two studies did not report the mean age of the participants. In 36 studies, the male to female ratio was about 1:1 or 1:1.5. Twelve studies assessed ENT co-morbidity.

Diagnosis was based only on clinical signs and symptoms in one study. In 39 studies diagnosis was confirmed by a radiograph and in 11 studies by radiograph and/or culture. In addition to clinical outcomes, bacteriological outcomes were reported in 24 studies and radiological outcomes in 11 studies. Only one study reported the effects on function or quality of life.

The ‘Characteristics of excluded studies’ table presents the reasons for exclusion of controlled clinical studies. Only those controlled clinical studies which compared antibiotic treatment with placebo or antibiotic versus antibiotic of different classes for acute maxillary sinusitis were included in the table. Studies without a control group were excluded in the table.

In the ‘Characteristics of excluded studies’ table, eight studies were placebo-controlled and 75 studies compared different classes of antibiotics. The reasons for exclusion were varied and in many studies, there were several reasons for exclusion. In 19 studies one of the reasons for exclusion was no mention of random allocation or the study design was clearly not randomized. Of these, two studies were placebo-controlled. In the six other randomized placebo-controlled studies, the diagnostic criteria of acute sinusitis did not fulfill the inclusion criteria for this review.

Risk of bias in included studies

Quality assessment for placebo-controlled studies

Random allocation concealment was classified as adequate (A) in two studies (Merenstein 2005; van Buchem 1997) and in four studies ‘random’ allocation was reported but the actual method used to conceal it is not known (B) (Axelsson 1970; Haye 1998; Lindbaek 1996a; Lindbaek 1996b; Lindbaek 1998a; Lindbaek 1998b).

Five of the six studies documented a double-blind design. The study by Axelsson 1970 did not report blinding of the patient or investigator or analyst.

All placebo-controlled studies reported drop-out rates adequately by study group. The reported drop-out rates were between 0.6% to 14% at 7 to 15 days follow up. In five of the six studies, the intervention and control groups were assessed as comparable at baseline and during the study. In one study, the information on comparability was insufficient to assess whether the groups were comparable at baseline or not (Axelsson 1970). Two studies were assessed as having a low risk of bias (Merenstein 2005; van Buchem 1997). One study (Axelsson 1970) was assessed as having a high risk of bias, and the other three studies as having a moderate risk of bias.

Quality assessment for studies comparing antibiotic to antibiotic

Random allocation concealment was classified as adequate concealment (A) in nine studies (Adelglass 1998a; Clifford 1999; Gehanno 1996a; Gehanno 1998; Gehanno 2004; Henry 2004; Pessey 2001; Sher 2002; UpChurch 2006). In 42 studies random
allocation was classified as (B) (‘random’ allocation reported but the actual method used to conceal it is not known).
Twenty-two studies documented a double-blind design. Ten studies reported single, investigator-blinded design and eighteen studies were unblinded. One study did not report on blinding at all. Most of the studies reported drop-out rates adequately by study group. The reported drop-out rates ranged from 0% to 62% at different follow ups; 38 studies had a drop-out rate of less than 20%. In 39 of the 51 studies the intervention and control groups were assessed to be comparable at baseline and during the study. Five studies were assessed as having a low risk of bias (Clifford 1999; Gehanno 2004; Henry 2004; Pessey 2001; UpChurch 2006); 25 studies were assessed as having a moderate risk of bias and the other 21 studies as having a high risk of bias.

Effects of interventions
Clinical outcomes were reported in all trials and evaluated quantitatively. Radiological and bacteriological outcomes were evaluated only for placebo-controlled studies. However, none of the placebo-controlled studies reported bacteriological outcomes. Radiographic outcomes were described qualitatively due to the small number of trials reporting these data.

Antibiotics versus placebo

Clinical failure defined as a lack of cure or improvement at 7 to 15 days follow up
Five studies involving 631 participants provided data for comparison of antibiotics to placebo when clinical failure was defined as lack of cure or improvement at 7 to 15 days follow up. These studies found a statistically significant difference in favor of antibiotics compared to placebo with a RR of 0.66 (95% CI 0.44 to 0.98) based on a random-effects model using available case data (Comparison 01, Outcome 01). (The result was almost the same as using a fixed-effect model). The result was also the same when study data of Lindbaek 1996 and Lindbaek 1998 were combined and analyzed together to double check the result. The drop-out rates of the five placebo-controlled studies ranged from 0.6% to 10% and there was no significant difference in drop-out rates between the antibiotic and placebo-controlled groups. Assuming the missing data as failures, there was no significant benefit for the antibiotics with a RR of 0.71 (95% CI 0.50 to 1.02). Assuming the missing data as cures or improvements, there was some benefit for the antibiotics with a RR of 0.65 (95% CI 0.43 to 0.98). Assuming the missing data according to the event rate observed in the control group, there was some benefit for antibiotics with a RR of 0.67 (95% CI 0.45 to 0.99). By excluding the studies of Lindbaek 1996 and Lindbaek 1998 in the analyses, because of the uncertainty in dichotomising the five-class definition of response, there was no significant benefit for antibiotics with a RR of 0.70 (95% CI 0.45 to 1.07). There was no statistically significant heterogeneity between studies in those analyses.

In all five studies the cure or improvement rates in the placebo-controlled group was on average 83%; range 72% to 89% (Table 1). One of the studies was assessed as having a low risk of bias, one a high risk of bias and the other three as having a moderate risk of bias.

Clinical failure defined as a lack of cure or improvement at 16 to 60 days follow up
Only one of these five studies provided data for antibiotic versus placebo comparison at 16 to 60 days follow up (Haye 1998) (Comparison 01, Outcome 02). The difference failed to reach significance with a RR of 0.85 (95% CI 0.36 to 1.98). All randomized participants were evaluable at follow up in this study.

Clinical failure defined as a lack of cure at 7 to 15 days follow up
Six studies were included in this meta-analysis comparing antibiotic to placebo at 7 to 15 days follow up. These studies found a significant benefit for antibiotics with a RR of 0.74 (95% CI 0.65 to 0.84). There was no statistically significant heterogeneity between studies. The results are presented graphically in Comparison 01, Outcome 03. Two of the studies were assessed as having a low risk of bias, one a high risk of bias and the other three as having a moderate risk of bias.

Clinical failure defined as a lack of cure at 16 to 60 days follow up
One of these six studies provided data for antibiotic versus placebo comparison at 16 to 60 days follow up (Haye 1998) (Comparison 01, Outcome 04). The difference failed to reach statistical significance with a RR of 0.63 (95% CI 0.38 to 1.05).

Relapse rate after 60 days
Only one study reported long-term relapse rates (van Buchem 1997). During a one-year follow up after the primary end-point at day 14, relapse and recurrence rates were not significantly different between antibiotic (21%) and placebo (17%) groups RR of 1.25 (95% CI 0.72 to 2.19) (Comparison 01, Outcome 05).

Radiographic failure
Radiographic outcomes were reported in two studies (Lindbaek 1996a + Lindbaek 1996b; van Buchem 1997) and the results were consistent with the clinical outcomes in the individual studies. In the study by Lindbaek 1996, computer tomography scores improved significantly more for individuals treated with antibiotics. In the study by van Buchem 1997, more participants treated with antibiotics showed radiographic resolution (74% versus 60%).
Bacteriological failure

None of the studies reported this outcome.

Drop-outs due to side effects

Three studies did not report any drop-outs due to side effects in the antibiotic or control groups. In all, drop-outs due to adverse effects were rare in both groups: 6 out of 426 (1.4%) in antibiotic groups, and 1 out of 349 (0.3%) in control groups (Comparison 01, Outcome 06).

Quality of life and ability to work

None of the studies reported outcomes on quality of life and ability to work.

Antibiotics versus antibiotics

In comparisons of antibiotic versus antibiotic, the data were analyzed only for the primary outcomes measures: clinical failure rate at 7 to 15 days follow up and at 16 to 60 days follow up (clinical failure defined as lack of cure or improvement) and for the following secondary outcome measures: relapse rates and drop-outs due to adverse effects.

Non-penicillins versus beta-lactamase sensitive penicillins

Eighteen studies compared a cephalosporin or a macrolide (cephalosporin, n = 10; macrolide, n = 8) to amoxicillin-clavulanate. Fourteen studies provided data for meta-analyses; eight studies compared cephalosporin (other than first generation) to amoxicillin-clavulanate and six studies compared macrolides (azithromycin, clarithromycin or roxithromycin) to amoxicillin-clavulanate.

Six studies, involving 1891 participants, provided data for comparison of cephalosporins to amoxicillin-clavulanate at 7 to 15 days follow up. These studies failed to find any significant difference between the antibiotics, with a RR of 1.38 (CI 1.04 to 1.82) (Comparison 02, Outcome 01). The drop-out rates ranged from 0% to 21%, and the drop-out rates were approximately equal across the treatment groups in the studies.

Seven studies provided data for comparison of cephalosporins to amoxicillin-clavulanate at 16 to 60 days follow up. These studies did not find any significant difference between the antibiotics, with a RR of 1.10 (CI 0.88 to 1.36) (Comparison 02, Outcome 02).

Six studies, involving 1547 participants, provided data for comparison of macrolides to amoxicillin-clavulanate at 7 to 15 days follow up. These studies failed to reach significant difference between the antibiotics with risk ratio value of 0.88 (95% CI 0.64 to 1.20) (Comparison 02, Outcome 04). The drop-out rates ranged from 6% to 15%. Three studies provided data for comparison of macrolides to amoxicillin-clavulanate at 16 to 60 days follow up. These studies did not find any significant difference between the antibiotics, with a RR of 0.77 (95% CI 0.47 to 1.27) (Comparison 02, Outcome 05).

None of the studies comparing cephalosporins or macrolides to amoxicillin-clavulanate reported long-term relapse rates after 60 days.

Drop-outs due to adverse effects occurred significantly less often in the macrolide group (1.7%) compared to the amoxicillin-clavulanate group (5.1%) treated participants with Peto odds ratio (OR) of 0.37 (95% CI 0.22 to 0.63) (the macrolide group ranged from 0% to 3.4%; the amoxicillin-clavulanate group ranged from 0% to 10.3%) (Comparison 02, Outcome 06). Participants dropped out significantly more often also in the amoxicillin-clavulanate group (4.2%) compared to the cephalosporin group (1.3%) with a Peto OR of 0.33 (95% CI 0.21 to 0.52) (in the cephalosporin group range 0% to 2.1%; in the amoxicillin-clavulanate group 0% to 7.3%) (Comparison 02, Outcome 03).

Cephalosporins and macrolides versus amoxicillin with clavulanate

Tetracycline antibiotics

Five studies, involving 807 participants, compared a tetracycline (doxycycline, n = 3; tetracycline, n = 1; minocycline, n = 1) to a heterogeneous mix of antibiotics (folate inhibitor, n = 2; cephalosporin, n = 1; macrolide, n = 1; amoxicillin, n = 1). All these studies provided data for clinical failure defined as a lack of cure or improvement at 7 to 15 days follow up, and the data from these stud-
ies were combined, despite the antibiotic used. The studies failed to find a significant difference between antibiotics, with a RR of 1.09 (95% CI 0.70 to 1.71) (Comparison 04, Outcome 01). The drop-out rates of these five studies ranged from 0% to 20%, and the drop-out rates were approximately equal across the treatment groups in the studies.

None of the studies reported long-term relapse rates after 60 days. Drop-outs due to adverse effects were infrequent, occurring in 2.6% and 3.5% of the tetracycline and mixed classes of antibiotics groups, respectively (Comparison 04, Outcome 02).

Miscellaneous comparisons

Twenty-one studies made the following comparisons: macrolide to fluoroquinolone (n = 5), fluoroquinolone to cephalosporin (n = 4), macrolide to cephalosporin (n = 3), fluoroquinolone to amoxicillin-clavulanate (n = 5), streptogramin to cephalosporin (n = 2) and faropenem to cephalosporin (n = 2). None of these studies reported a statistically significant difference in the clinical outcomes.

Comparison of the effect of short versus long courses of antibiotics

This comparison was not performed because there were no placebo-controlled studies available to undertake it.

Discussion

Effectiveness

Antibiotics versus placebo

In this review, antibiotics were on average slightly more effective than placebo for relieving signs and symptoms at 7 to 15 days in participants with acute sinusitis diagnosed either clinically or by radiograph. The average improvement rate was 90% in the antibiotic groups and 80% in the control groups using available case data. On the other hand, the significant difference for antibiotics in increasing the number of the participants with a total cure at 10 to 14 days follow up might indicate a faster cure rate by antibiotics than without (the average cure rate was about 52% in antibiotic group and 38% in control group). Based on one study with a moderate risk of bias which provided data also at 23 to 27 days follow up (Haye 1998), there was no significant difference in the failure rates between the antibiotic and placebo groups, irrespective of the definition of the failure in this review. Four studies (Axelsson 1970; Haye 1998; Lindbaek 1996a+Lindbaek 1996b; Merenstein 2005) also reported improvement rates prior to one week follow up. Two of the four studies reported considerably higher improvement rates for antibiotic than placebo (Lindbaek 1996: improvement rate 60% versus 36% at day three; Merenstein 2005: the average number of days to improvement consistently 2 to 2.5 days shorter in the antibiotic group among those patients who were entirely improved by day 14). The other two studies reported only minor difference between the groups at day 3 to 5 (Axelsson 1970: improvement rate 69% antibiotic versus 65% placebo group; Haye 1998: 80% versus 79%, respectively).

Although statistical significance for antibiotics was found, the clinical significance of the results for antibiotics is questionable because of the considerable improvement rate in the placebo group and because the benefit of the possible faster cure rate needs to be weighed against the potential for adverse effects at both the individual and population level. The results were based on studies of penicillin, amoxicillin and azithromycin performed in middle and northern Europe (five studies - Axelsson 1970; Haye 1998; Lindbaek 1996a+Lindbaek 1996b; Lindbaek 1998a+Lindbaek 1998b; van Buchem 1997) and in the USA (one study - Merenstein 2005).

Different classes of antibiotics

In the study designs comparing different classes of antibiotics the antibiotics had a similar efficacy with each other. However, at 7 to 15 days follow up, the risk of clinical failure was statistically significantly lower for amoxicillin-clavulanate than for cephalosporins, but the significance of the difference disappeared at longer follow up.

Applicability

Setting and diagnostic methods

As the role of the radiographs in diagnosing acute sinusitis is controversial, we decided to include trials that included participants only on clinical criteria. The diagnosis of acute maxillary sinusitis was based solely on clinical diagnosis in two studies (Haye 1998; Merenstein 2005), confirmed by radiograph in two studies (Axelsson 1970; van Buchem 1997) and confirmed by computer tomography (CT) scan in two studies (Lindbaek 1996a+Lindbaek 1996b; Lindbaek 1998a+Lindbaek 1998b). In the study by Lindbaek 1996 (Lindbaek 1996a+Lindbaek 1996b) the acute maxillary sinusitis was confirmed by CT scan showing opacity or air-fluid level, the studies with radiograph also accepted participants with mucosal thickening. Two studies reported that bacteriological samples were taken. The study by Lindbaek 1996 (Lindbaek 1996a+Lindbaek 1996b) reported that in 58% of participants bacteriological specimens obtained from the nasopharynx grew bacteria connected with sinusitis. The study by Haye 1996 reported that only in some samples taken from the posterior part of the nasal cavity, growth of pathogenic bacteria was obtained. On the whole, the proportion of participants with true bacterial sinusitis remained unclear in the placebo-controlled studies. Participants in five of the six placebo-controlled studies were recruited from community-based general practices. Thus the results in this review
are valid in general practice setting where these kind of patients are frequently treated.

Strengths and weaknesses of diagnostic options
The diagnosis of acute sinusitis is challenging in primary care, especially differentiating between a viral or bacterial origin of disease. The high proportion of participants that improved in the non-antibiotic group indicates that only some of the participants defined (by these criteria) as having acute sinusitis benefit from antibiotic treatment. Clinical examination is sensitive in ruling out sinusitis (Williams 1993) but not in identifying bacterial disease. Specific methods would be needed to find the subgroups of patients that might benefit from antibiotics. Some official opinions support the practice of diagnosing acute maxillary sinusitis by clinical examination. For example, the expert panel of five national societies in the USA has stated that sinusitis can be diagnosed, in the majority of patients, by using only the history and physical examination (Meltzer 2004). In the referral guidelines for imaging of the European Commission, radiograph is not indicated as a routine diagnostic method (ECRP 2007). Further, it states that thickened mucosa is a non-specific finding and may occur in asymptomatic patients. CT scan has a role in cases of treatment failure suspicion of complications or malignancy or when surgery is considered (ECRP 2007; Meltzer 2004). In Nordic countries, the diagnosis of sinusitis is often confirmed by means of an ultrasound device that is suitable for primary care but requires training and experience in its use. Sinusitis can be ruled out in patients with no fluid retention in sinuses with this method, which may reduce the use of antibiotics (Puhakka 2000; Varonen 2003b).

Duration of signs and symptoms
Bacterial sinusitis is more probable if the signs and symptoms have lasted at least seven days (Meltzer 2004), and therefore studies with shorter illness duration without confirmed diagnosis by radiograph or culture were excluded. Acute exacerbations of chronic sinusitis were considered as part of the chronic form of the disease, which is a separate and more complicated entity, often related to background factors that have an effect on recovery. Therefore, studies with acute exacerbations of chronic sinusitis were included only if they reported separately data on the subgroup with acute sinusitis, or if not reported separately at least 80% of participants with acute sinusitis.

Adverse effects
The adverse effects rates of penicillin and amoxicillin differed among the placebo-controlled studies. In one study (Axelsson 1970) the rate for penicillin was 8% (in the control group 6%) and in another study (Lindback 1996a) 59% (in the placebo group 36%). The adverse effect rate for amoxicillin was 23% and 28% in two studies (Merenstein 2005; van Buchem 1997) and 56% in one study (Lindback 1996b), while the rate for placebo was 12%, 9% and 36%, respectively. The most commonly reported adverse effects in antibiotic groups were: gastrointestinal problems (for example, diarrhoea, abdominal pain, vomiting) and skin rash. However, drop-outs due to adverse effects were rare (1.4%) for penicillin, amoxicillin and azithromycin in the placebo-controlled studies.

In the antibiotic versus antibiotic comparisons, the drop-outs due to adverse effects occurred significantly less often in the macrolides (Comparison 02, Outcome 06) and cephalosporins (Comparison 02, Outcome 03) compared to the amoxicillin-clavulanate group.

In 2 of the 14 studies, the drop-out rate due to adverse effects in the amoxicillin-clavulanate group was about 10%, in the macrolide and cephalosporin groups the drop-out rate due to adverse events was under 2%, except in one with a drop-out rate of 3%. One problem in the sinusitis trials is that standardized information on side effects is available in less than half the cases (Ioannidis 2002). It may be that the true rate of side effects equals or even exceeds the marginal benefits of the treatments.

Methodological issues affecting the results

Diagnosis
The data of all placebo-controlled studies were combined despite which antibiotic was used because we anticipated that there would be only a few placebo-controlled studies available in the analyses. Further, we saw that it was presumable that researchers in different countries had had local reasons for selecting particular antibiotics for their trials, taking into account for example, local resistance rates to antibiotics among community-acquired pathogens. We expected that the diagnostic method in the individual study (clinical diagnosis alone/radiological confirmation) would have had an influence on the results. However, the analyses did not show statistically significant heterogeneity between the individual study results. Clinical diversity was, however, seen in the study by Lindback 1996 (Lindback 1996a+Lindback 1996b) compared to the other studies. This study differed in accepting solely participants with opacity or fluid-level in the sinuses, not with mucosal thickening alone, by using CT scan. The study also reported pathogenic bacteria connected with acute sinusitis in 58% of participants. It is obvious that the participants selected for this study represented participants with a more severe pattern of disease. If the study by Lindback 1996 is excluded from the analyses because of the clinical diversity, the statistical significance for antibiotics disappears in the meta-analysis in the cases where the outcome is failure, defined as lack of cure or improvement.

Definition of cure
The definitions of cure, improvement and failure in individual studies can influence the data extraction and the results, both at study and meta-analysis levels, especially in cases where there are...
only a few studies available in the analyses. In studies with a dichotomous classification of the outcomes, the criteria can be differently defined than in the studies with multi-level classifications of cure and improvement. In this review, one study classified the success dichotomously. Most categories were used in the studies by Lindbaek 1996 (Lindbaek 1996a+Lindbaek 1996b) and Lindbaek 1998 (Lindbaek 1998a+Lindbaek 1998b). The outcomes were classified into five categories: restored, much better, somewhat better, unimproved and worse. Two other studies reported outcomes in three categories and one in four categories. Dichotomising different outcome classifications in individual studies causes some uncertainty in the analyses.

**Timing of outcome measurement**

In this review the primary outcome was the failure at 7 to 15 days after the start of the treatment because recovery from acute maxillary sinusitis takes generally more than one week (Gwaltney 2005). However, from the patients’ perspective, fast symptom relief is important and data is needed also on short-term improvement. The placebo-controlled studies in this review gave insufficient information to make conclusions on the short-term improvement of patients’ symptoms. On the other hand, longer follow up times would be needed to assess the efficacy in the longer term and to assess potential adverse effects. There is some evidence from other respiratory tract infections that the use of antibiotics increases relapse rates and may end up increasing antibiotic consumption (Arason 2005; Joki-Erkkilä 2000). Therefore, in optimal circumstances, the sinusitis trials should monitor signs, infection rates and drug use over one year.

**Duration of treatment**

One of our aims was to evaluate the effect of short and long courses of antibiotics. Our view is that for this purpose, antibiotic versus antibiotic study designs without non-antibiotic group are not valid enough. Unfortunately, there were no placebo-controlled studies available to undertake this comparison. Because antibiotics also have side effects, more placebo-controlled trials are needed to focus on finding the optimal duration of treatment and those subgroups that might benefit from the treatment. The same applies to other respiratory tract infections in primary health care.

**Antibiotic versus antibiotic comparisons**

Amoxicillin and penicillin have the advantage of low cost but are often recommended at a three-times-a-day dose, a dosing schedule associated with decreased compliance compared to once or twice daily regimens. A more serious concern is the rising prevalence of beta-lactamase-producing organisms and penicillin and macrolide resistant pneumococci. In eight studies comparing non-penicillin antibiotics to a beta-lactamase sensitive penicillins, clinical outcomes were virtually identical. These studies were conducted mostly in the 1990s, four of them in the USA, three in Nordic countries and one in Switzerland. Among the newer, extended-spectrum antibiotics, the long-term efficacy (at 16 to 60 days follow up) was similar but amoxicillin-clavulanate had significantly more adverse effects than cephalosporins and macrolides. At 7 to 15 days follow up, however, the risk of clinical failure was statistically significantly lower for amoxicillin-clavulanate than for cephalosporins, but the significance of the difference disappeared at longer follow up. The studies were conducted in the 1990s and 2000s. None of the antibiotic preparations was superior to each other. Given the similar efficacy, the differences in the adverse effects, costs, and risk of promoting bacterial resistance should be considered when choosing antibiotic treatment for acute sinusitis.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

Antibiotics cause a small treatment effect in patients with uncomplicated acute sinusitis in a primary care setting with symptoms for more than seven days. However, 80% of patients treated with a placebo also improve within two weeks. The clinician needs to weigh the moderate benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level.

**Implications for research**

Given the small number of trials, additional good-quality placebo-controlled trials are needed to identify the potential subgroups of sinusitis patients that may benefit from antibiotics. Different treatment durations should also be studied in placebo-controlled settings. Diagnosis should be made on pre-specified clinical criteria which also allow subgroup analyses according to severity of the disease. Special attention should be paid to identifying the prognostic factors of sinusitis and in finding factors that potentially modify the treatment effect, such as co-morbid conditions (for example, asthma, allergies), lifestyle and other individual factors (for example, smoking). Effects on functional status, work performance and quality of life may provide important additional information. The trials should be double-blinded, with adequate allocation and concealment procedures, and should report clinical outcomes and time to clinical response. Large trials may be needed to identify clinical predictors of the need for antibiotics.

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gatifloxacin versus 10-day amoxicillin/clavulanate in patients with

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dalone and cefuroxime axetil for the treatment of acute bacte-
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Berg 1986

Bonzwaer 2002

de Bock 1997

de Ferrari 1998

Deeks 2005

EARSS 2007

ECCR 2007

Goossens 2005

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Gwaltney 1994
Antibiotics for acute maxillary sinusitis (Review)

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Gwaltney 2005

Hay 2005

Higgins 2005

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Ioannidis 2002

Ip 2005

Joki-Erkkilä 2000

Jousimies-Somer 1988

Kern 1984

Kilkkinen 2002

Linder 2003

Low 1997

Margolis 2005

Maxwell 2002

Meltzer 2004

Odenholt 2003

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* Indicates the major publication for the study

## Characteristics of Studies

**Characteristics of included studies** [ordered by study ID]
Adelglass 1998a

**Methods**
Randomized, single-blind study (investigator). Diagnosis of acute sinusitis confirmed radiographically by at least 5 mm mucosal thickening, opacification or air-fluid level. Information on baseline comparability of intervention and control groups adequately reported (groups comparable). Outcomes assessed by an investigator; cure defined as disappearance of clinical signs and symptoms without need for further antimicrobial therapy. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 12%

**Participants**
The study setting was not described. Subjects were 40 years old on average (range 18 to 83) and included 122 men and 69 women. ENT co-morbidity was assessed; about 50% of patients had hay fever. Country - USA

**Interventions**
Two treatment arms:
- Group 1: Levofloxacin 500 mg daily for 14 days
- Group 2: Clarithromycin 500 mg BID for 14 days
Acetaminophen and diphenhydramine were allowed

**Outcomes**
Clinical outcomes were assessed in 190 out of 216 randomized patients (in 101 out of 108 patients in levofloxacin group and in 89 out of 108 patients in clarithromycin group). Outcomes were assessed on day 16 to 19. Radiographic and bacteriological outcomes were not reported

**Notes**
Study funding by a pharmaceutical company

**Risk of bias**

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Adelglass 1998b

**Methods**
Randomized, unblinded trial. Diagnosis by clinical signs and symptoms (mean duration of symptoms prior to enrollment 9 days ) and radiograph showing at least 4 mm mucosal thickening. Information on baseline comparability of intervention and control groups adequately reported (groups comparable). Cure defined as absence of symptoms or a score of 1 or less on a 10 point symptom scale. At least 80% of assigned doses were taken by 94% of subjects. Proportion of the participants without known or reported clinical outcome 21% on day 11 to 15

**Participants**
The study setting was not described. Mean age approximately 37; 128 men and 150 women. About 40% of patients had EENT diseases. Country - USA

**Interventions**
Two treatment arms
- Group 1: Cefprozil 500 mg twice daily for 10 days
- Group 2: Amoxicillin-clavulanate (500 mg/125 mg) three times daily for 10 days
Mucolytics and decongestants allowed and taken by < 50%
Adelglass 1998b (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Clinical outcomes assessed at day 11 to 15 in 219 out of 278 randomized patients (in 108 out of 140 patients in cefprozil group and in 111 out of 138 patients in amoxicillin-clavulanate group). Second follow-up 2 weeks post treatment. Radiographic and bacteriological outcomes not reported</th>
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Adelglass 1999

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<tr>
<th>Methods</th>
<th>Randomized, unblinded trial. Diagnosis by clinical symptoms and radiograph showing at least 4 mm mucosal thickening, opacification or air-fluid level. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Cure defined as absence of symptoms and stable or improved radiograph. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 13%</th>
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<tr>
<td>Participants</td>
<td>Participants were recruited from community based primary care and otolaryngology clinics. Mean age 39 (range 18 to 85): 225 men and 390 women. Country - USA</td>
</tr>
</tbody>
</table>
| Interventions                                 | Two treatment arms  
Group 1: Levofloxacin 500 mg daily for 10 to 14 days  
Group 2: Amoxicillin-clavulanate (500 mg/125 mg) three times daily for 10 to 14 days  
Antihistamines and decongestants encouraged |
| Outcomes                                      | Clinical outcomes assessed at day 13 in 535 out of 615 randomized patients. Radiographic outcomes not reported                                                                                                                                 |
| Notes                                         | Study funding by a pharmaceutical company                                                                                                                                                                                                                  |
| Risk of bias                                  |                                                                                                           |
| Item              | Authors' judgement | Description          |
| Allocation concealment?                         | Unclear          | B - Unclear          |
**Arndt 1994**

**Methods**
Randomized, unblinded study. Diagnosis = clinical evidence, an abnormal radiograph and nasal swab. Radiographic criteria not described. Information on baseline comparability of intervention and control groups adequately reported (groups comparable). Cure defined as “complete resolution of clinical signs/symptoms of infection”; improvement as “clear regression of clinical signs within 4 to 5 days without having entirely disappeared on completion of therapy.” Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 20%

**Participants**
Participants were recruited from academic, out-patient otolaryngology clinics. Subjects were 33 years old on average (range 18 to 65) and included 25 men and 31 women. Country - Germany

**Interventions**
Two treatment arms
- Group 1: Brodimoprim 200 mg once daily for 8 to 12 days
- Group 2: Doxycycline 100 mg once daily for 8 to 12 days
Analgesics were the only concomitant therapy allowed

**Outcomes**
Clinical and radiographic outcomes were assessed in 56 out of 70 randomized patients. Outcomes were assessed on day 8 to 12 after randomization. Bacteriological outcomes were reported in 50 patients

**Notes**
One of the authors was affiliated with a pharmaceutical company

**Risk of bias**

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**Arrieta 2007**

**Methods**
Randomized, unblinded design. Diagnosis by clinical signs and symptoms lasting 7 to 28 days, confirmed by computed tomography or x-ray (criteria not specified). Culture by sinus puncture or endoscopy of middle meatus, or both (51% of participants had at least 1 causative organism identified before study entry). Information on comparability of intervention and control group at baseline adequately reported (groups comparable). Clinical resolution was defined as total resolution of signs and symptoms related to acute sinusitis and, at least, improvement in the radiographic or computer tomographic scan appearance of the sinuses to the extent that no additional or alternative antimicrobial therapy was necessary. Treatment compliance 80%. There was not a clear statement for drop-outs

**Participants**
Multicentre (31 centers), multinational trial (Argentina, Brazil, Chile and Mexico). Demographic data reported for per protocol population at baseline: 459 outpatients, 172 men and 287 women; mean age was 37 years. ENT co-morbidity was not assessed

**Interventions**
Two treatment arms:
- Group 1: Moxifloxacin 400 mg once daily for 7 days;
- Group 2: Amoxicillin-clavulanate 500/125 mg three times daily for 10 days.
Concomitant therapies were not reported
**Outcomes**  
Clinical outcomes for per protocol population (patients who completed the course of treatment) were assessed on day 7 to 14 after the end of treatment in 459 out of 575 randomized participants (in 226 out of 289 participants in moxifloxacin group and in 233 out of 286 participants in amoxicillin/clavulanate group). Bacteriological outcomes for per protocol population were assessed in 234 participants.

**Notes**  
Study funded by a pharmaceutical company.

### Risk of bias

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**Axelsson 1970**

**Methods**  
Randomized trial. Blinding was not reported. Diagnosis by a radiograph; only patients with secretion were included. Secretion was confirmed by aspiration for those with completely opaque maxillary sinuses. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical outcomes assessed by an investigator but “cure” and “improvement” were not defined. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 9% on day 10.

**Participants**  
The study setting was not described. It is unclear if participants were a convenience sample or a consecutive series of eligible patients. Subjects were 33 years old on average (range 13-80) and included 62 men and 94 women. Patients with a history of nasal allergy were excluded. Country - Sweden.

**Interventions**  
Four treatment arms: (only groups 1 and 3 used in the analysis)  
Group 1: Oxymetazoline only (no placebo control)  
Group 2: Oxymetazoline plus sinus irrigation  
Group 3: Oxymetazoline plus Penicillin V 400 mg three times daily for 10 days  
Group 4: Oxymetazoline plus Lincomycin 500 mg three times daily for 8 days

**Outcomes**  
Clinical outcomes were assessed in 142 out of 156 randomized patients (in 35 out of 38 patients in penicillin group and in 32 out of 34 patients in oxymetazoline group). Outcomes were assessed on day 10 after randomization. Patient related radiographic outcomes were not reported.

**Notes**  
There was no identified funding source.

### Risk of bias

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</table>
### Boezeman 1988

**Methods**
Randomized, but unblinded trial. Diagnosis by clinical symptoms, confirmed by radiograph showing sinus opacity and positive culture taken near the ostium of, or by aspiration from maxillary sinus. Information on comparability of intervention and control groups at baseline adequately reported (groups not comparable). Clinical outcomes assessed by an investigator but a definition of clinical cure was not given. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 18%

**Participants**
The study setting was not described. Outpatients were 30 years old on average (range 13 to 76) and included 23 men and 10 women. Country - The Netherlands

**Interventions**
Two treatment arms
- Group 1: Spiramycin 1000 mg twice daily for 10 days
- Group 2: Doxycycline 200 mg on day 1 then 100 mg each day for 10 days
Nasal decongestants were allowed but were not given as part of the study treatment

**Outcomes**
Clinical outcomes were assessed in 27 out of 33 randomized patients (in 15 out of 18 patients in doxycycline group and in 12 out of 15 patients in spiramycin group). Outcomes were assessed on day 11 after randomization. Radiographic and bacteriological outcomes were reported for 27 of 33 patients

**Notes**
There was no identified funding source

### Risk of bias

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### Buchanan 2003

**Methods**
Randomized, double-blind design. Diagnosis by clinical signs and symptoms lasting at least seven days, confirmed by radiograph showing at least 10 mm mucosal thickening, opacification or air fluid level in a sinus radiograph or CT. Bacteriological specimens were obtained by sinus puncture (in US sites) or endoscopy collection (non-US sites). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure assessed by investigators and defined as dichotomous - either cure or failure. Cure defined according to the following criteria: return to preinfection state, with no ABMS-related signs and symptoms present, as determined on a scale of 0 to 3 points in which 0 = absent, 1 = mild, and 3 = severe, supplemented by a sinus X-ray/CT scan confirming no worsening of infection or the presence of only those residual symptoms indicative of a normal course of clearance in the infection process, with no requirement for additional antibiotic treatment. Compliance among available patients were in average 95% (assessed by unused capsule count). Proportion of the participants without known or reported clinical outcome 28%

**Participants**
Multicenter, multinational trial (USA, Argentina, France, South Africa). 148 men and 208 women, mean age about 40 years (range from 14 to 84). ENT co-morbidity was not assessed
**Buchanan 2003**  (Continued)

| Interventions | Two treatment arms  
|               | Group 1: Telithromycin 800 mg once daily for 5 days  
|               | Group 2: Cefuroxime axetil 250 mg twice daily for 10 days  
|               | Concomitant treatments were not described  

| Outcomes | Clinical outcomes assessed on day 16 to 24 in 278 out of 385 randomized patients. Bacteriologic outcomes assessed on day 16 to 24 in 149 patients. Radiologic outcomes were not reported  

| Notes | Study funding by a pharmaceutical company  

### Risk of bias

| Item | Authors' judgement | Description  
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**Burke 1999**

| Methods | Randomized, double-blind trial. Diagnosis by symptoms lasting 1 to 4 weeks and radiograph showing air-fluid level, opacity or at least 6 mm mucosal thickening. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Compliance assessed. Proportion of the participants without known or reported clinical outcome 16%  

| Participants | Mixed otolaryngology and primary care. Mean age 40; 178 men, 279 women. Country: U.S.A.  

| Interventions | Two treatment arms  
|               | Group 1: Cefuroxime axetil 250 mg twice daily for 10 days  
|               | Group 2: Moxifloxacin 400 mg daily for 10 days  

| Outcomes | Clinical outcomes were assessed on day 17 to 24 in 457 out of 542 randomized patients. Radiographic outcomes not reported  

| Notes | Study funding provided by a pharmaceutical company  

### Risk of bias

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**Calhoun 1993**

**Methods**
Randomized, single-blind trial (investigator). Diagnosis established by clinical symptoms and abnormal radiograph (criteria not reported). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator. Clinical cure defined as signs and symptoms of infection resolved. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 18%.

**Participants**
Consecutive patients were recruited from academic, primary care clinics. Mean age was 37 (range 14 to 77); 84 women and 58 men. ENT co-morbidity was not assessed. Country: U.S.A.

**Interventions**
Two treatment arms

- **Group 1:** Clarithromycin 500 mg twice daily for 7 to 14 days
- **Group 2:** Amoxicillin 500 mg three times daily for 7 to 14 days

Both groups received oxymetazoline 2 sprays twice daily for 3 days.

**Outcomes**
Clinical outcomes were assessed in 116 out of 142 randomized patients (in 55 out of 70 patients in clarithromycin group and in 61 out of 72 patients in amoxicillin group). Outcomes were assessed on day 7 to 16 after randomization. Radiographic outcomes were assessed in 116 out of 142 patients randomized. Bacteriological outcomes were not reported.

**Notes**
Study funding was provided by a pharmaceutical company.

**Risk of bias**

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**Camacho 1992**

**Methods**
Randomized, single-blind design (investigator). Clinical diagnosis of acute sinusitis and an abnormal radiograph (mucosal thickening, opacity or air-fluid level). Sinus puncture performed. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical outcomes assessed by an investigator; cure defined as "resolution of clinical symptoms with radiographic evidence of sinus decongestion with no further therapy required". Improvement defined as "clinical symptoms substantially reduced but radiographic evidence of residual sinus congestion". Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 25%.

**Participants**
Patients were recruited from academic and community settings; probably otolaryngology practices. Mean age = 35 (range 18 to 79); 171 men and 146 women. ENT co-morbidity was not assessed. Countries - Brazil, Chile, Columbia, U.S.A.

**Interventions**
Two treatment arms

- **Group 1:** Cefuroxime axetil 250 mg twice daily for 10 days
- **Group 2:** Amoxicillin-clavulanate 500 mg three times daily for 10 days

Concomitant therapies were not described.
### Camacho 1992 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Clinical outcomes were assessed in 239 out of 317 randomized patients (in 115 out of 157 patients in cefuroxime axetil group and in 124 out of 160 patients in amoxicillin-clavulanate group). Radiographic outcomes were not reported. Bacteriological outcomes were assessed in 76 participants</th>
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### Chatzimanolis 1998

| Methods                      | Randomized, unblinded design. Diagnosis of acute or recurrent sinusitis documented by clinical and endoscopic findings, bacteriology (sinus puncture) and X-ray. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical cure not defined. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 7% |
|------------------------------|--------------------|-------------|
| Participants                 | Study setting not described. Mean age 38; 34 men and 26 women. ENT co-morbidity not assessed. Country - Greece |
| Interventions                | Two treatment arms |
|                              | Group 1: Roxithromycin 150 mg twice daily for 10-14 days |
|                              | Group 2: Amoxicillin-clavulanate (500 mg/ 125 mg) three times daily for 10 to 15 days |
|                              | Concomitant treatments not reported |
| Outcomes                     | Clinical outcomes reported on day 10 to 17 for 56 out of 60 randomized subjects (for 29 out of 31 patients in roxithromycin group and for 27 out of 29 patients in amoxicillin-clavulanate group). Radiographic outcomes not reported by group |
| Notes                        | Study funded by a pharmaceutical company |

#### Risk of bias

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### Clement 1998

**Methods**
Randomized, unblinded design. Clinical diagnosis of ethmoid or maxillary sinusitis confirmed by fiberoptic examination (purulent discharge from ostium of affected sinus) and computed tomography (criteria not specified). Pus samples were collected endoscopically for bacteriological culture. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes assessed by an investigator but were not defined. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 8% on day 10 to 14

**Participants**
Participants were recruited from otolaryngology clinics. Mean age 41; 103 men, 151 women. ENT comorbidity not assessed. Country - Belgium

**Interventions**
Two treatment arms
- **Group 1:** Azithromycin 500 mg daily for 3 days
- **Group 2:** Amoxicillin 500 mg/clavulanic acid 125 mg three times daily for 10 days
Concomitant therapies (decongestants, corticosteroids, mucolytics) were allowed but not prescribed. 133 subjects used a concomitant treatment

**Outcomes**
Clinical outcomes were assessed on day 10 to 14 in 233 of 254 participants (in 151 out of 165 patients in azithromycin group and in 82 out of 89 patients in amoxicillin-clavulanate group) and on day 21 to 28 in 210 of 254 participants. Bacteriological outcomes were assessed in 100 subjects

**Notes**
Study funding provided by a pharmaceutical company

### Risk of bias

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### Clifford 1999

**Methods**
Randomized, double-blind trial. Clinical diagnosis, confirmed by radiograph showing air-fluid level, opacification or at least 6 mm mucosal thickening. Acute sinusitis and acute exacerbation of chronic sinusitis included (acute reported separately). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Cure defined as symptom resolution and radiographic improvement. Proportion of the participants without known or reported clinical outcome 18% for the whole study population

**Participants**
Study setting not described. Mean age approximately 41 (range 18 to 76); 187 men and 270 women. 25% of patients with acute exacerbation of chronic sinusitis in efficacy-valid population. About 26% of patients had allergic rhinitis. Country: USA

**Interventions**
Two treatment arms
- **Group 1:** Ciprofloxacin 500 mg twice daily for 10 days
- **Group 2:** Clarithromycin 500 mg twice daily for 14 days
Decongestants allowed. Nasal corticosteroids prohibited
### Clifford 1999 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Clinical outcomes were assessed at day 14 for efficacy-valid population of 342 patients with acute maxillary sinusitis. (Efficacy-valid population was defined as patients who completed the course of treatment and did not use other antimicrobial agents concomitantly with the study drug). Radiographic outcomes not reported</th>
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### Dubois 1993

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, single blind (investigator) trial. Diagnosis established by symptoms, an abnormal maxillary radiograph (minimum criteria were not given) and a positive culture of sinus fluid (collected by puncture or endoscopically). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes assessed by an investigator; “cure” defined as pretreatment signs and symptoms resolved; “improvement” defined as improved but not resolved.” Treatment compliance not reported but patients had to take at least 70% of prescribed treatment to be included in the efficacy analysis. Proportion of the participants without known clinical outcome 48%; patients excluded mostly due to negative culture. Because the overall drop-out rate was extremely high, data was not used in the meta-analyses in this review</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Patients were recruited from outpatient ENT and primary care settings. It is unclear if the study sample represents a consecutive series of patients or a convenience sample. Country: Canada</td>
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</table>
| Interventions | Two treatment arms  
Group 1: Clarithromycin 500 mg every 12 hours for a maximum of 14 days  
Group 2: Amoxicillin-clavulanate 500 mg every 8 hours for a maximum of 14 days  
Both groups received oxymetazoline 0.05% nasal sprays twice daily for the first 3 days |
| Outcomes | Clinical, radiographic, and bacteriological outcomes were assessed in 260 out of 497 randomized patients (in 132 out of 246 patients in clarithromycin group and in 128 out of 251 patients in amoxicillin-clavulanate group). Outcomes were assessed on day about 15 after randomization |
| Notes | Study funding provided by a pharmaceutical company |

### Risk of bias

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**Ferguson 2004**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, double-blind study. Diagnosis by clinical signs and symptoms, confirmed by radiograph showing at least 10 mm mucosal thickening, total sinus opacity or air-fluid level in a sinus radiograph. Pretreatment cultures of rhinoscopic aspirations or deep nasal Calgiswab samples were compared with cultures taken at 17 to 24 days of follow up. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcome was considered a failure if either all signs and symptoms were unchanged or worsened or sinus X-ray film findings worsened or both. Treatment compliance reported as over 90% assessed by capsule counts. Proportion of the participants without known or reported clinical outcome 8 % on day 17 to 24</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Multicenter study, 41 sites in USA. Median age approximately 45 (range 18 to 85); 123 men and 199 women. ENT co-morbidity not described</td>
</tr>
<tr>
<td>Interventions</td>
<td>Two treatment arms Group 1: Telithromycin 800 mg once daily for 5 days Group 2: Moxifloxacin 400 mg once daily for 10 days</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical outcomes were assessed at days 17 to 24 in 322 of 349 randomized participants ( in 159 out of 173 patients in telithromycin group and in 163 out of 176 patients in moxifloxacin group). Long-term follow up at 31 to 36 days. Bacteriological outcomes were assessed in 84 subjects</td>
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<td>Notes</td>
<td>Study funding by a pharmaceutical company</td>
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**Gehanno 1996a**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, unblinded study. Diagnosis established by clinical symptoms and radiograph showing sinus opacity or air-fluid level. Culture based on the sample from the middle meatus; 79% of patients had positive cultures. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes assessed by investigator; cure defined as resolution of facial pain, purulent discharge, air-fluid level by radiograph and no recurrence of symptoms. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 7%</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Multicenter study, 284 outpatients; 136 men and 148 women. Mean age was 40. Fewer than 25% of subjects had concurrent allergic disease. Country: France</td>
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</tbody>
</table>
*Gehanno 1996a (Continued)*

| Interventions | Two treatment arms
| | Group 1: Clarithromycin 500 mg daily for 8 days
| | Group 2: Amoxicillin/clavulanic acid 500 mg three times daily for 8 days
| | Concomitant therapy with paracetamol allowed
| Outcomes | Clinical outcomes were assessed about on day 10 in 263 out of 284 randomized patients (in 134 out of 145 patients in clarithromycin group and in 129 out of 139 patients in amoxicillin-clavulanate group). Radiographic and bacteriological outcomes were not reported
| Notes | Study funding was by a pharmaceutical company

**Risk of bias**

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*Gehanno 1996b*

| Methods | Randomized, double-blind study. Diagnosis by clinical signs and symptoms, confirmed by radiograph (criteria not reported) and/or bacteriological culture of the middle meatus aspirate (76% of patients had a positive culture). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical success defined as resolution of all signs and symptoms. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 21% |
| Participants | Multicentre study. 376 outpatients; 160 men and 216 women, mean age about 41 years. ENT co-morbidity was not assessed. Country - France |
| Interventions | Two treatment arms
| | Group 1: Sparfloxacin 200 mg for 5 days
| | Group 2: Cefuroxime axetil 250 mg twice daily for 8 days
| Outcomes | Clinical outcomes were assessed at days 11 to 12 in 302 of 382 randomized participants (in 153 out of 193 patients in sparfloxacin group and in 149 out of 189 patients in cefuroxime axetil group) |
| Notes | There was no identified funding source

**Risk of bias**

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</table>
### Gehanno 1998

**Methods**
Randomized, unblinded trial. Diagnosis by symptoms and radiograph showing > 5 mm mucosal thickening, sinus opacity or air-fluid level. A causative pathogen was isolated in the pus sample at study entry, in 51% of the 241 patients enrolled. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 2%

**Participants**
Participants recruited from community based otolaryngology clinics. Mean age 42; 105 men and 136 women. Country: France

**Interventions**
Two treatment arms
- Group 1: Cefatrizine 500 mg twice daily for 10 days
- Group 2: Amoxicillin-clavulanate 500 mg three times daily for 10 days
- Vasocostrictors and paracetamol allowed

**Outcomes**
Clinical outcomes assessed on days 10 to 12 in 236 out of 241 randomized patients (in 121 out of 123 patients in cefatrizine group and in 115 out of 118 patients in amoxicillin-clavulanate group). Relapse assessed at day 30. Radiographic outcomes assessed in 214. Bacteriologic outcomes not reported

**Notes**
Study funding by a pharmaceutical company

### Risk of bias

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### Gehanno 2004

**Methods**
Randomized, double-blind design. Diagnosis by clinical signs and symptoms, confirmed by radiograph showing at least 5 mm mucosal thickening, opacity or air-fluid level. A rhinoscopic bacteriologic sampling was made on the middle nasal meatus (cultures were positive in 46% of participants). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure based on resolution of symptoms. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 6%

**Participants**
Participants were recruited by otorhinolaryngologists. The mean age of the subjects was 43 years; women 60% and men 40%. Multinational trial (France, Tunisia, Poland, Argentina)

**Interventions**
Two treatment arms
- Group 1: Pristinamycin 1 g BID for 4 days
- Group 2: Cefuroxime axetil 250 mg BID for 5 days

**Outcomes**
Clinical outcomes were assessed on day 12 to 19 in 458 out of 485 randomized patients. Radiographic and bacteriological outcomes not reported
**Gehanno 2004** *(Continued)*

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**Gwaltney 1997**

**Methods**

Randomized, investigator-blind design. Clinical diagnosis confirmed by radiograph (criteria not specified). Bacterial cultures obtained by sinus aspirations. The intervention and control groups were assessed to be comparable at baseline. Cure and improvement reported as combined outcome. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 20%

**Participants**

Study setting not described. Median age 35; 789 men and 1009 women. ENT co-morbidity not described. Countries - U.S.A. and Europe

**Interventions**

Three treatment arms

- Group 1: Cefdinir 600 mg once daily for 10 days
- Group 2: Cefdinir 300 mg twice daily for 10 days
- Group 3: Amoxicillin-clavulanate (500 mg) three times daily for 10 days
Concomitant treatments not reported
Group 1 and Group 3 used in the analysis

**Outcomes**

Clinical outcomes reported at day 7 to 14 in 1446 out of 1798 people randomized (in 474 out of 585 patients in cefdinir 600 mg once daily group and in 491 out of 603 patients in amoxicillin-clavulanate group). Second follow up at 3 to 5 weeks. Radiographic outcomes not reported. Bacteriological outcomes not reported by group

**Notes**

Study funding by a pharmaceutical company

**Risk of bias**

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</table>
### Haye 1996

| **Methods** | Randomized, double-blind design. Diagnosis established clinically (symptoms lasting for 10 to 30 days) and radiograph showing at least 6 mm mucosal thickening. Culture was not done. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes assessed by investigator; cure defined as "disappearance of all pretreatment symptoms relevant to infection." Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 0.9% on day 10 to 12 |
| **Participants** | Patients recruited from general practices in Norway; 150 men and 288 women. Mean age 40 (range 19-71). ENT co-morbidity was not assessed. Country - Norway |
| **Interventions** | Two treatment arms  
Group 1: Azithromycin 500 mg daily for 3 days  
Group 2: Phenoxymethylpenicillin 1.3 grams three times daily for 10 days  
Concomitant therapies were not described |
| **Outcomes** | Clinical outcomes were assessed in 434 out of 438 randomized patients on day 10 to 12 and in 436 out of 438 patients on day 23 to 27. Radiographic and bacteriological outcomes were not reported |
| **Notes** | Study funding by a pharmaceutical company |

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### Haye 1998

| **Methods** | Randomized, double-blind design. Clinical diagnosis of acute sinusitis was based on clinical findings, which had to include one or both of the following signs: presence of nasal secretion (purulent at the time of examination) for > 10 and < 30 days, and maxillary sinus tenderness and/or pain of < 30 days duration (87% had both signs). Radiograph was taken to exclude patients with more than 6 mm mucosal thickening, complete opacity or an air-fluid level. Samples of nasal secretions (cotton-tipped swabs) were taken from the posterior part of the nasal cavity in 75 patients (only some samples had the growth of pathogenic bacteria). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical failure defined as no change or a worsening of the pretreatment symptoms and relapse if there was initial improvement or disappearance of pretreatment symptoms followed by worsening (failure and relapse figures are combined in the analyses in this review). Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 0.6% on day 10 to 12 |
| **Participants** | Patients recruited from Norwegian General Practices. 44 men and 125 women; mean age 40 (range 21 to 70) years in the azithromycin group and 43 (range 18 to 68) years in placebo group. ENT co-morbidity was not assessed. Country - Norway |
### Haye 1998

(Continued)

| Interventions | Two treatment arms  
|               | Group 1: Azithromycin 500 mg once daily for 3 days  
|               | Group 2: Placebo once daily for 3 days |

| Outcomes | Clinical outcomes were assessed on day 10 to 12 in 168 out of 169 subjects randomized (in 86 out of 87 patients in antibiotic group and in 82 out of 82 patients in placebo group) and on day 23 to 27 in 169 participants |

| Notes | There was no identified funding source |

### Risk of bias

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### Henry 2003

| Methods | Randomized, double-blind study. Diagnosis by clinical signs and symptoms (presence of either purulent nasal discharge or facial pain and/or pressure and/or tightness for 7 to 28 days), confirmed radiologically by presence of opacity or air-fluid level or mucosal thickening of more than 6 mm. Mean duration of symptoms prior to enrollment about 13 days. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical response was assessed by investigator; cure was defined as resolution of signs and symptoms to the level that existed prior to the occurrence of the acute illness; improvement defined as partial but incomplete resolution of the signs and symptoms. Compliance was measured by investigators reporting exact doses taken, reasons for missed doses, and the amounts of study medication returned by subjects at the end of therapy visit. Compliance was reported as 99% in 3-day azithromycin group and 82% in amoxicillin-clavulanate group. There was not a clear statement for drop-outs |

| Participants | Multicenter study. 936 outpatients, 381 men and 555 women; mean age was 41 years (range 18 to 84). Allergic rhinitis was reported in 39% of patients. Country - USA |

| Interventions | Three treatment arms: (only groups 1 and 3 used in this analysis)  
|               | Group 1: Azithromycin 500 mg once daily for 3 days  
|               | Group 2 : Azithromycin 500 mg once daily for 6 days  
|               | Group 3 : Amoxicillin-clavulanate 500/125 mg three times daily for 10 days  
|               | Concomitant treatments not reported |

| Outcomes | Clinical outcomes for per protocol population were assessed at days 8 to 15 in 799 out of 941 randomized patients (in 269 out of 312 patient in azithromycin for 3 days - group and in 259 out of 313 patients in co-amoxiclav group). Second follow up at days 22-36. Radiographic outcomes were not reported |

| Notes | Study funding by a pharmaceutical company |
### Henry 2003  
(Continued)

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### Henry 2004

**Methods**
Randomized, double-blind study. Clinical diagnosis (presence of facial pain/pressure/tightness over 1 or both maxillary sinus areas, facial swelling, or toothache, as well as purulent discharge for > 7 and < 21 days) was confirmed by radiograph or CT (opacification or air/fluid level). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical response was assessed by investigator and cure was defined as resolution of at least 1 of the acute signs and symptoms of the original infection, with no worsening in the remaining symptoms or the radiographic appearance of the sinus. Compliance was assessed by inspection of returned blister cards and by counting unused study medication; but not reported. Proportion of the participants without known or reported clinical outcome 11%

**Participants**
Multicenter, multinational study (USA, Poland). 271 ambulatory patients, 146 women and 95 men, mean age was about 41 years. ENT comorbidity was not assessed

**Interventions**
Two treatment arms  
Group 1: Cefdinir 600 mg once daily for 10 days  
Group 2: Levofloxacin 500 mg once daily for 10 days  
There was no restriction on the use medications for symptom relief (decongestants, antihistamines)

**Outcomes**
Clinical outcomes were assessed in 241 out of 271 randomized patients on 19 to 24 days. Radiographic outcomes were assessed in 239 patients on 19 to 24 days

**Notes**
Study funding by a pharmaceutical company

### Risk of bias

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</table>
Methods
Randomized, double-blind trial. Diagnosis established by symptoms of acute, recurrent, or chronic sinusitis with a positive radiograph showing, at a minimum, mucosal thickening. Sinus puncture was performed. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical outcomes assessed by investigator; improvement defined as “the patient’s signs and symptoms had improved or resolved during therapy.” No separate categories for “cured” and “improved.” Treatment compliance reported as about 97% assessed by pills taking by patients. Proportion of the participants without known or reported clinical outcome 11% for the whole study population.

Participants
Patients were recruited from community based otolaryngology clinics. Subjects were 38.4 years old on average (range 16 to 73) and included 50 men and 58 women. ENT co-morbidity was assessed: fewer than 25% of subjects had chronic sinusitis. Country - U.S.A.

Interventions
Two treatment arms
Group 1: Cefaclor 500 mg twice daily for 10 days
Group 2: Amoxicillin 500 mg three times daily for 10 days
The use of concomitant therapies was not specified

Outcomes
Clinical outcomes were assessed in 96 out of 108 randomized patients overall. Fifty-six participants with acute sinusitis and 25 participants with recurrent acute sinusitis with more than one episode per year with clinical improvement between episodes were considered in this review (15 participants with chronic sinusitis were not included). Outcomes were assessed on day 10 to 12 after randomization. Radiographic and bacteriological outcomes were not measured.

Notes
Study was funded by a pharmaceutical company

Risk of bias

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Jareoncharsri 2004

Methods
Randomized, unblinded design. Diagnosis by clinical symptoms and signs confirmed by the finding of mucopurulent discharge in the middle meatus or maxillary ostium as seen by nasal endoscopy and abnormal radiograph (criteria not specified); about 88% of patients had air-fluid level or opacity on X-ray. Bacteriological specimens were collected by sinus aspiration. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure was assessed by investigators using a 4-point scale; cure was defined as complete clinical resolution of signs and symptoms and no evidence of remaining disease on radiograph; improvement defined as incomplete clinical resolution of signs and symptoms, improvement of X-ray findings. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 2%
### Participants
Patients (n = 60) were recruited from two otolaryngologic centers. Mean age 36 (range 17 to 68); 23 men and 37 women. 20% of patients with acute exacerbation of chronic sinusitis (n = 12). About 28% of patients had allergic rhinitis. Country - Thailand

### Interventions
Two treatment arms
Group 1: Levofloxacin 300 mg once daily for 14 days
Group 2: Co-amoxiclav 625 mg three times a day for 14 days
Concomitant treatments were not described

### Outcomes
Clinical outcomes were assessed in 47 out of 48 randomized patients with acute maxillary sinusitis. Outcomes were assessed on day 21 after the start of treatment. Bacteriological outcomes were assessed in 37 patients with acute maxillary sinusitis on day 14

### Notes
Study funding was provided by a pharmaceutical company

### Risk of bias

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### Karma 1991

**Methods**
Randomized trial; single blind (investigator). Diagnosis was established by at least one symptom of sinusitis plus an antral puncture showing fluid. Radiographs showed findings "suggestive" of sinusitis. Information on comparability of intervention and control groups at baseline sufficiently reported (groups comparable). Clinical outcomes were assessed by an investigator. Clinical cure was defined as "pretreatment signs and symptoms of infection resolved." Improvement was defined as "improvement but not complete resolution of the infection." Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 33% on day 11 to 13

**Participants**
Patients were recruited from academic, outpatient, otolaryngology clinics. Mean age was approximately 30 (range 17 to 69); 89 men and 11 women. Country - Finland and Sweden

**Interventions**
Two treatment arms
Group 1: Clarithromycin 500 mg twice daily for 9 to 11 days
Group 2: Amoxicillin 500 mg every 8 hours for 9 to 11 days
Both groups received oxymetazoline 0.05% twice daily for the first 3 days

**Outcomes**
Clinical outcomes were assessed in 67 out of 100 randomized patients (in 32 out of 50 patients in clarithromycin group and in 35 out of 50 patients in amoxicillin group) on day 11 to 13. Radiographic outcomes were assessed in 68 subjects; bacteriological outcomes were assessed in 30 patients

**Notes**
There was no identified funding source
### Karma 1991 (Continued)

#### Risk of bias

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#### Klapan 1999

**Methods**

Randomized, unblinded design. Diagnosis based on symptoms (lasting on average 7 days) and radiograph showing at least 4 mm mucosal thickening, opacity or air-fluid level. Sinus puncture performed in a subset of patients. Information on comparability of intervention and control groups at baseline sufficiently reported (groups comparable). Cure defined as complete disappearance of signs and symptoms; improvement as partial disappearance of symptoms without need for further antibiotics. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 6%

**Participants**

The study setting not described. Mean age approximately 33 years old (range 15 to 50); 77 men and 23 women. Coexisting allergic rhinitis in 30%. Country - Croatia

**Interventions**

Two treatment arms

- **Group 1**: Azithromycin 500 mg daily for 3 days
- **Amoxicillin-clavulanate** (500 mg/125 mg) three times daily for 10 days
- Concomitant treatments not reported

**Outcomes**

Clinical outcomes assessed on day 10 to 12 in 94 out of 100 randomized patients (in 47 out of 50 patients in azithromycin group and in 47 out of 50 patients in amoxicillin-clavulanate group); and 4 weeks after the initiation of treatment in 89 patients. Bacteriological cure assessed in 47 subjects. Radiographic outcomes not reported

**Notes**

Study was funded by a pharmaceutical company

### Klapan 1999

#### Risk of bias

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#### Lasko 1998

**Methods**

Randomized, double-blind design. Clinical diagnosis confirmed by radiograph showing > 5 mm mucosal thickening, opacity or air-fluid level. Information on baseline comparability of intervention and control groups adequately reported (groups comparable). Cure defined by symptom resolution. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 19%

**Participants**

Setting not described. Mean age 40; 102 men and 134 women. Country - Canada
### Lasko 1998 (Continued)

| Interventions | Two treatment arms  
|               | Group 1: Levofloxacin 500 mg daily for 10 to 14 days  
|               | Group 2: Clarithromycin 500 mg twice daily for 10 to 14 days  
|               | Antihistamines and decongestants, antihistamines, prohibited unless being used at study entry  
| Outcomes | Clinical outcomes reported at day 12 to 19 in 191 out of 236 participants randomized. Radiographic and bacteriological outcomes not reported  
| Notes | Study funding by a pharmaceutical company  

#### Risk of bias

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### Lindbaek 1996a

| Methods | Randomized, double-blind design. Clinical diagnosis of acute sinusitis (> 7 and < 30 days), confirmed by computed tomography (the criteria for confirming the diagnosis were presence of fluid level or total opacification in any sinus). Bacteriological specimens were obtained from the nasopharynx of 125 patients (42% had “normal nasal flora”). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Patients assessed response as “restored”, “much better”, “somewhat better”, “unimproved” or “worse.” Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 2% on day 10  
| Participants | Patients recruited from Norwegian General Practices. 45 men and 85 women; mean age 39 (range 16 to 74) years. ENT co-morbidity was not assessed. Country - Norway  
| Interventions | Three treatment arms  
|               | Group 1: Penicillin V 1320 mg three times daily for 10 days  
|               | Group 2: Amoxicillin 500 mg three times daily for 10 days  
|               | Group 3: Placebo three times daily for 10 days  
|               | Nasal decongestants and analgesics were allowed but not prescribed  
|               | Penicillin versus placebo is compared for this reference  
| Outcomes | Clinical and radiographic outcomes were assessed on day 10 in 127 out of 130 subjects randomized (in 83 out of 86 patients in antibiotic groups and in 44 out of 44 patients in placebo group)  
| Notes | Study was funded by government sources  

#### Risk of bias

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**Lindbaek 1996b**

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**Lindbaek 1998a**

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<td>Randomized, double-blind design. Clinical diagnosis of acute sinusitis (&gt; 7 and &lt; 30 days), confirmed by computed tomography showing mucosal thickening of 5 mm or more in any sinus without fluid level or total opacification. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Patients assessed response as &quot;restored&quot;, &quot;much better&quot;, &quot;somewhat better&quot;, &quot;unimproved&quot; or &quot;worse.&quot; Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 10% on day 10</td>
</tr>
<tr>
<td>Participants</td>
<td>Patients recruited from Norwegian General Practices. 27 men and 43 women; mean age 40 (range 16 to 83) years. ENT co-morbidity was not assessed. Country - Norway</td>
</tr>
<tr>
<td>Interventions</td>
<td>Three treatment arms</td>
</tr>
<tr>
<td></td>
<td>Group 1: Penicillin V 1320 mg three times daily for 10 days</td>
</tr>
<tr>
<td></td>
<td>Group 2: Amoxicillin 500 mg three times daily for 10 days</td>
</tr>
<tr>
<td></td>
<td>Group 3: Placebo three times daily for 10 days</td>
</tr>
<tr>
<td></td>
<td>Nasal decongestants and analgesics were allowed but not prescribed</td>
</tr>
<tr>
<td></td>
<td>Penicillin versus placebo is compared for this reference</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical outcomes were assessed on day 10 in 63 out of 70 subjects randomized (no information for drop-outs per group)</td>
</tr>
</tbody>
</table>
### Lindbaek 1998a

| Notes | Study was funded by government sources |

| **Risk of bias** |
|------------------|----------------------------------------|
| **Item** | **Authors’ judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

### Lindbaek 1998b

Methods

Study entered twice to allow comparisons from the three treatment arms to be analysed. Placebo group for two different comparisons has been halved.

Participants

Interventions

Amoxicillin versus placebo is compared for this reference.

Outcomes

Notes

| **Risk of bias** |
|------------------|----------------------------------------|
| **Item** | **Authors’ judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

### Luterman 2003

Methods

Randomized, double-blind trial. Diagnosis by clinical symptoms and by radiograph showing air-fluid level, opacity or at least 6 mm mucosal thickening. Sinus puncture performed in a small subset of patients. About 60% of patients had had symptoms for longer than 7 days before enrollment to the study. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure defined as disappearance of infection, clinical improvement, or a return to the preinfection state with regard to all signs and symptoms and sinus X-ray findings that were normal, improved, or at least not worse. Treatment compliance was reported over 90% of patients in each group taking at least 70% of their doses. Proportion of the participants without known or reported clinical outcome 44% on day 17 to 24; data not used in the meta-analyses in this review.

Participants

Multicenter, multinational trial (USA, Canada, South Africa, Argentina and Chile). Demographic data reported for modified intent-to-treat population at baseline: patients mean age was 39 years (range 16 to 84); 248 men and 359 women. ENT co-morbidity was not assessed.
**Luterman 2003**

(Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Three treatment arms</th>
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<tbody>
<tr>
<td></td>
<td>Group 1: Telithromycin 800 mg once daily for 5 days</td>
</tr>
<tr>
<td></td>
<td>Group 2: Telithromycin 800 mg once daily for 10 days</td>
</tr>
<tr>
<td></td>
<td>Group 3: Amoxicillin-clavulanate 500/125 mg three times daily for 10 days</td>
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<tr>
<td></td>
<td>Concomitant therapies were not reported</td>
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</table>

| Outcomes | Clinical outcomes were assessed on day 17 to 24 in 423 out of 754 randomized participants; and on day 31 to 45 in 399 participants. Bacteriological outcomes were assessed in 24 participants |

| Notes | Study funded by a pharmaceutical company |

**Risk of bias**

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<th>Item</th>
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</table>

**Matthews 1997**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, unblinded design. Diagnosis by clinical symptoms and signs, confirmed by radiograph showing opacity, clouding or air-fluid level. Acute and chronic sinusitis included (acute reported separately). Information on comparability was insufficient to assess whether the intervention groups with acute sinusitis were comparable at baseline or not. Success defined as cure or improvement. Proportion of the participants without known or reported clinical outcome 24% among participants with acute sinusitis. Data not used in the meta-analyses of this review because time points for outcome measure are not clearly reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Subjects recruited from otolaryngology clinics. Mean age of 42 (range 18 to 78). 93 of 182 subjects had acute sinusitis. Country - U.S.A.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Two treatment groups</td>
</tr>
<tr>
<td></td>
<td>Group 1: Cefixime 400 mg once daily for 10 to 14 days</td>
</tr>
<tr>
<td></td>
<td>Group 2: Amoxicillin 500 mg three times daily for 10 to 14 days</td>
</tr>
<tr>
<td></td>
<td>Aspirin prohibited. Tylenol, topical decongestants allowed</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical outcomes reported in 71 out of 93 randomized patients with acute sinusitis (in 37 out of 49 patients in cefixime group and in 34 out of 44 patients in amoxicillin group). Bacteriological outcomes assessed in 31 participants with acute sinusitis. Drop-outs due to adverse events reported for acute and chronic sinusitis combined</td>
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<tr>
<td>Notes</td>
<td>Study funding not stated</td>
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**Risk of bias**
### Matthews 1997

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### Mattucci 1986

#### Methods
Randomized trial; unblinded. Diagnosis was established by a clinical diagnosis of acute sinusitis plus a radiograph showing "clouding" of the nasal sinus and a positive culture from or near the sinus ostium. Information on comparability of intervention and control groups at baseline adequately reported (groups not comparable). Clinical outcomes were assessed by an investigator; clinical cure was not defined. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 21%

#### Participants
Patients were recruited from outpatient otolaryngology clinics. Subjects were 40 years old on average (range 12 to 76) and included 23 men and 35 women. ENT co-morbidity was not assessed. Country - U.S.A.

#### Interventions
Two treatment arms
- **Group 1:** Minocycline 100 mg twice daily for 10 to 20 days (mean 11.6)
- **Group 2:** Amoxicillin 250 mg every 8 hours for 10 to 20 days (mean 11.4)
Both groups were allowed to take decongestants or analgesics but these were not prescribed by the investigators

#### Outcomes
Clinical outcomes were assessed in 47 out of 58 randomized patients (in 25 out of 29 patients in minocycline group and in 22 out of 29 patients in amoxicillin group). Outcomes were assessed on day 10 to 20 after randomization. Radiographic outcomes were assessed in 42 patients and bacteriological in 46

#### Notes
There was no identified funding source

### Risk of bias

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</table>
### Merenstein 2005

**Methods**
Randomized, double-blind design. Clinical diagnosis of acute sinusitis was based on clinical findings, which had to include at least one of the followings: purulent nasal discharge predominating on one side, facial pain on one side, purulent nasal discharge on both sides, pus in the nasal cavity, lasting for at least 7 days. About 50% of patients had at least two of these signs at baseline (the study did not report any subjective symptoms); mean duration of symptoms prior to enrollment was 11 days. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure defined as dichotomous—either “completely improved” or “not improved”. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 14% on day 14.

**Participants**
Patients recruited from a suburban primary care office. 42 men and 93 women; mean age 34 years. ENT co-morbidity was not assessed. Country - USA

**Interventions**
Two treatment arms
- Group 1: Amoxicillin 500 mg twice daily for 10 days
- Group 2: Placebo twice daily for 10 days

**Outcomes**
Clinical outcomes were assessed on day 14 in 116 out of 135 subjects randomized (in 56 out of 67 patients in antibiotic group and in 60 out of 68 patients in placebo group).

**Notes**
Study was funded mostly by academic sources

**Risk of bias**

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### Murray 2005

**Methods**
Randomized, double-blind trial. Clinical diagnosis of acute sinusitis (> 6 and < 29 days), confirmed by radiograph (the criteria for confirming the diagnosis were presence of air-fluid level or total or partial opacification). Sinus puncture for all patients. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator. Clinical failure was defined as the persistence or worsening of signs and symptoms requiring additional antibiotics or development of new signs and symptoms requiring antibiotics. Treatment compliance reported over 96%. Proportion of the participants without known or reported clinical outcome 6%.

**Participants**
Multicenter study; 81 outpatient centers in the United States, India, Europe, and Latin America. 225 men and 313 women; mean age 38 (range 18 to 88) years. ENT co-morbidity was assessed; about one third of patients suffered from allergic rhinitis.
### Murray 2005  (Continued)

| Interventions | Two treatment arms  
|               | Group 1: Azithromycin-micropheres 2 g single dose  
|               | Group 2: Levofloxacin 500 mg once daily for 10 days |

| Outcomes      | Clinical outcomes were assessed at days 17 to 24 in 507 out of 541 subjects randomized |

| Notes         | Study funded by a pharmaceutical company |

| Risk of bias  |

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### Nyffenegger 1991

| Methods       | Randomized, unblinded study. Diagnosis was established by a clinical diagnosis of acute sinusitis, confirmed by a radiograph (criteria were not specified), transillumination, and a positive bacterial culture obtained from samples of discharge from the sinuses. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator. Clinical cure was defined as complete disappearance of clinical symptoms at completion of treatment; improvement was defined as a clear regression of the clinical symptomatology. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 0% |

| Participants  | Patients were recruited from an outpatient otolaryngology clinic. Patient represented a convenience sample, not a consecutive series. Patients were 37.8 years old on average (range 18 to 75) and included 30 men and 50 women. ENT co-morbidity was not assessed. Country - Switzerland |

| Interventions | Two treatment arms  
|               | Group 1: Brodimoprim 200 mg once daily for 7 to 10 days  
|               | Group 2: Amoxicillin 750 mg three times daily for 7 to 10 days.  
|               | Mucolytic nose drops and steam inhalations were allowed but not prescribed as part of the intervention |

| Outcomes      | Clinical outcomes were assessed in 80 out of 80 randomized patients. Outcomes were assessed on day 7 to 10 after randomization. Radiographic outcomes were not reported. Bacteriological outcomes were reported for 40 patients |

| Notes         | One of the authors was affiliated with a pharmaceutical company |

| Risk of bias  |

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O’Doherty 1996

Methods
Randomized, unblinded design. Patients with otitis media, pharyngitis/tonsillitis, or sinusitis included. Sinusitis diagnosis was established clinically and confirmed by a radiograph (criteria not given). Throat swabs, nasopharyngeal swabs, or exudates, as appropriate, were collected for bacterial culture. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical outcomes were assessed by an investigator; clinical cure defined as “disappearance of all signs and symptoms of infection”. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 14%

Participants
Recruitment settings were not described. Mean age was 35 for all diagnoses. ENT co-morbidity was not assessed. Countries - U.K., Ireland

Interventions
Two treatment arms
Group 1: Azithromycin 500 mg daily for 3 days
Group 2: Cefaclor 250 mg three times daily for 10 days
Adjuvant treatments were not described

Outcomes
Clinical outcomes were assessed on day 11 to 15 and reported separately for 78 out of 91 randomized patients with sinusitis. Radiographic outcomes were not reported. Bacteriological outcomes were assessed in 18 patients

Notes
There was no identified funding source

Risk of bias

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Olmo 1994

Methods
Randomized, unblinded design. Diagnosis was established by clinical symptoms and a radiograph showing sinus opacity or air-fluid level. 66% of patients had positive culture. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical outcomes were assessed by an investigator; clinical cure was "remission of symptoms within the treatment time. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 0% on day 10

Participants
Participants were recruited from emergency rooms. Mean age was not reported (>= 20 for inclusion); 28 men and 19 women. ENT co-morbidity was not assessed. Country - Spain
### Olmo 1994 (Continued)

| Interventions | Two treatment arms  
|               | Group 1: Cefuroxime axetil 500 twice daily for 8 days  
|               | Group 2: Amoxicillin/clavulanate 500 three times daily for 8 days  
|               | Adjuvant therapies were not described  

| Outcomes | Clinical outcomes were assessed on day 10 in 47 out of 47 randomized patients. Radiographic and bacteriological outcomes were not reported  
| Notes | There was no identified funding source  

| **Risk of bias** |  
| **Item** | **Authors' judgement** | **Description** |  
| Allocation concealment? | Unclear | B - Unclear  

### Otte 1983

| Methods | Randomized, double-blind design. Diagnosis based on symptoms and abnormal radiograph (criteria not given). Bacteriological culture was performed. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical cure based on resolution of symptoms and normal radiograph. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 0% on day 10  
| Participants | Patients recruited from outpatient otolaryngology clinics. Mean age was 32 (range 17 to 56); 12 men and 19 women. ENT co-morbidity was not assessed. Country - Chile  
| Interventions | Two treatment arms  
|               | Group 1: Sulfamethopyrazin 200 mg/ trimethoprim 250 mg, two doses on day one, then one dose per day for 10 days  
|               | Group 2: Tetracycline 500 mg four times daily for 10 days  
|               | Adjuvant therapies were not described  

| Outcomes | Clinical outcomes were assessed on day 10 in all 31 patients randomized. Bacteriological outcomes were reported for 27 patients  
| Notes | There was no identified funding source  

| **Risk of bias** |  
| **Item** | **Authors' judgement** | **Description** |  
| Allocation concealment? | Unclear | B - Unclear  

**Antibiotics for acute maxillary sinusitis (Review)**

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Methods**

Randomized, double-blind design. Diagnosis established clinically and by a radiograph showing at least 5 mm mucosal thickening, sinus opacity or fluid-level. Culture was not done. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator and clinical cure was defined as resolution of clinical symptoms and radiographic cure or improvement. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 4% on day 10.

**Participants**

Participants were recruited from community, otolaryngology clinics. Mean age = 43; 99 men and 143 women. ENT co-morbidity was not assessed. Country - France.

**Interventions**

Three treatment arms: (only groups 2 and 3 used in this analysis)
- **Group 1**: Cefixime 200 mg twice daily for 4 days
- **Group 2**: Cefixime 200 mg twice daily for 10 days
- **Group 3**: Amoxicillin clavulanic acid 500 mg three times daily for 10 days

All groups received prednisolone 40 mg daily and Oxymetazoline 3 sprays daily for 4 days.

**Outcomes**

Clinical outcomes were assessed on day 10 to 15 in 242 out of 253 randomized patients (in 85 out of 87 patients in cefixime for 10 days group and in 77 out of 82 patients in amoxicillin clavulanic acid group). Second follow up at 33 days. Radiographic and bacteriological outcomes were not reported.

**Notes**

There was no identified funding source.

### Risk of bias

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**Pessey 2001**

Randomized, double-blind design. Diagnosis based on clinical signs and symptoms confirmed by radiograph (total opacity of sinus or air-fluid level). Culture based on an aspirate from the middle meatus; 52% of patients had positive cultures. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure based on resolution of symptoms. Treatment compliance over 90%. Proportion of the participants without known or reported clinical outcome 0.6% on day 8.

**Participants**

Multicentre study, 47 community-based ENT specialists in ten regions. Mean age = 43 years; men 141 and 167 women. ENT co-morbidity was not assessed. Country - France.

**Interventions**

Two treatment arms
- **Group 1**: Pristinamycin 1000 mg two times daily for 8 days
- **Group 2**: Cefuroxime axetil 500 mg twice daily for 8 days

Nasal decongestants prescribed for three days.
Outcomes
Clinical outcomes were assessed on day 8 in 308 out of 310 randomized patients. Follow up (29 - 36 days) for those patients who were cured at the end of treatment. Patient related radiographic and bacteriological outcomes were not reported.

Notes
There was no identified funding source.

Risk of bias

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Rakkar 2001

Methods
Randomized, unblinded design. Diagnosis of acute sinusitis was based on clinical findings (purulent nasal discharge, nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar tenderness/pain); lasting for at least 7 days. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical response was assessed by investigator and cure was defined as disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy was not required. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 3 %

Participants
Multicentre study; primary care patients. 156 men and 315 women; mean age approximately 42 (range 18-87) years. ENT co-morbidity was not assessed. Country - USA

Interventions
Two treatment arms
Group 1: Moxifloxacin 400 mg once daily for 10 days
Group 2: Amoxicillin clavulanate 875 mg twice daily for 10 days
Oral or nasal decongestants or antihistamines were permitted

Outcomes
Clinical outcomes were assessed on day 24 to 31 in 463 out of 475 randomized participants (in 230 out of 238 patients in moxifloxacin group and in 233 out of 237 patients in amoxicillin clavulanate group)

Notes
Study funding by a pharmaceutical company

Risk of bias

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</table>
### Riffer 2005

**Methods**
Randomized, investigator-blinded design. Diagnosis by clinical symptoms and opacification or an air/fluid level in a sinus radiograph or CT. Sinus fluid samples were obtained by aspiration or fiberoptic endoscopy. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure defined as resolution or improvement in purulent nasal discharge and at least one additional sinusitis sign or symptom observed at baseline. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 15% on day 16 to 18

<table>
<thead>
<tr>
<th>Participants</th>
<th>Multi-center, multi-country trial. Mean age was 37 (range 13 to 79); 194 men and 243 women. ENT co-morbidity was not assessed</th>
</tr>
</thead>
</table>
| Interventions | Two treatment arms  
Group 1: Clarithromycin ER 1000 mg once daily for 14 days  
Group 2: Amoxicillin/clavulanate 875/125 mg twice daily for 14 days  
Oral sympathomimetic agents, nasal decongestants and antihistamines were used by 23.8%, 8.9% and 6.9% of patients, respectively |
| Outcomes | Clinical outcomes were assessed on day 16 to 18 in 373 of 437 randomized participants (in 188 out of 221 patients in clarithromycin group and in 185 out of 216 patients in amoxicillin-clavulanate group) and on day 24 to 31 in 361 participants. Bacteriological outcomes assessed on day 16 to 18 in 109 of 218 participants. Radiographical outcomes assessed on day 24 to 31 in 366 of 423 participants. Quality of life measured by symptom assessment and the SNOT-16-test |

**Risk of bias**

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### Russell 1997

**Methods**
Randomized trial. Blinding not stated. Diagnosis by clinical signs and symptoms, confirmed by X-ray or CT (opacification, air/fluid level or mucosal thickening). Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical outcomes were assessed by an investigator; clinical cure defined as all clinical signs and symptoms were resolved and no new clinical signs and symptoms were present and/or the follow-up radiograph showed resolution/improvement. Approximately 80% of patients received the prescribed antibiotic course. Proportion of the participants without known or reported clinical outcome 11%

| Participants | Study setting not described. Mean age was approximately 38 (range 13 to 79); 172 men and 256 women. 84% of patients had a history of EENT-related medical conditions. Country - USA |

**Notes**
Study funding by a pharmaceutical company
### Russell 1997 (Continued)

| Interventions | Three treatment arms: (groups 1 and 3 used in this analysis)  
|               | Group 1: Cefprozil 250 mg twice daily for 10 to 15 days  
|               | Group 2: Cefprozil 500 mg twice daily for 10 to 15 days;  
|               | Group 3: Amoxicillin-clavulanate (500 mg/125 mg) three times daily for 10 to 15 days; Adjuvant therapies permitted but not described |
| Outcomes      | Clinical outcomes were assessed on day 10 to 20 after the end of therapy in 428 out of 479 patients (in 146 out of 158 patients in cefprozil 250 mg group, in 147 out of 160 patients in cefprozil 500 mg group and in 135 out of 161 patients in amoxicillin-clavulanate group). Radiographic and bacteriological outcomes not reported |
| Notes         | Study funding was by a pharmaceutical company |

### Risk of bias

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### Sher 2002

| Methods                      | Randomized, investigator-blinded design. Diagnosis by clinical signs and symptoms lasting at least seven days, confirmed by radiograph showing at least 5 mm mucosal thickening, opacification or air fluid level in a sinus radiograph. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator and clinical cure was defined as improvement in or resolution of all acute signs and symptoms of the original infection, with no need for further antimicrobial therapy. Treatment compliance was over 80% by counting unused study medication. Proportion of the participants without known or reported clinical outcome 9% |
| Participants                 | Multicenter study; 30 centres. Subjects were 42 years old on average (range 18 to 89); 159 men and 286 women. ENT co-morbidity was assessed; for example, 60% of patients had a history of allergic rhinitis. Country - USA |
| Interventions                | Three treatments arms  
|                             | Group 1: Gatifloxacin 400 mg once daily for 5 days  
|                             | Group 2: Gatifloxacin 400 mg once daily for 10 days  
|                             | Group 3: Amoxicillin/clavulanate 875 mg twice daily for 10 days  
|                             | Decongestants and antihistamines were allowed |
| Outcomes                    | Clinical outcomes were assessed at days 1 to 3 and at days 7 to 14 after the completion of treatment in 405 out of 445 randomized patients. Radiographic and bacteriological outcomes not reported |
| Notes                       | One of the authors was affiliated with a pharmaceutical company |
### Siegert 2000

**Methods**
Randomized, double-blind trial. Diagnosis by symptoms and radiograph (mucosal thickening, opacification or air-fluid level) or aspiration. Clinical cure was not defined. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 5%.

**Participants**
Multicentre (60 centres), multinational trial (Finland, France, Germany, Greece, Israel, Spain, Sweden). Mean age 40; 220 men, 273 women. ENT comorbidity not reported.

**Interventions**
- Two treatment arms
  - Group 1: Cefuroxime axetil 250 mg twice daily, 10 days
  - Group 2: Moxifloxacin 400 mg daily, 7 days

**Outcomes**
Clinical outcomes assessed on day 14 in 468 out of 493 randomized. Bacteriological outcomes in 224; radiographic outcomes not assessed.

**Notes**
Study funding was by a pharmaceutical company.

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### Siegert 2003

**Methods**
Randomized, double-blind trial. Diagnosis by clinical symptoms and radiograph showing at least 6 mm mucosal thickening, opacification or air-fluid level. Sinus material for bacteriological culture by puncture or by middle meatus swab under endoscopic guidance. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure defined as disappearance of signs and symptoms or significant improvement and no further therapy required. Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 19% on day 14 to 23.

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### Risk of bias

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**Antibiotics for acute maxillary sinusitis (Review)**

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Participants  Multicentre, multinational trial. Patients were enrolled by otolaryngologists at 43 centres in seven countries: France, Germany, Greece, Israel, Lithuania, Spain and Sweden. Subjects were 42 years old on average and included 193 men and 259 women. ENT co-morbidity was not assessed

Interventions  Two treatment arms
Group 1: Faropenem daloxate 300 mg twice daily for 7 days
Group 2: Cefuroxime axetil 250 mg twice daily for 7 days
Decongestants, antihistamines and mucolytics were allowed. Intranasal or oral corticosteroids were not permitted

Outcomes  Clinical outcomes assessed on day 14 to 23 in 452 out of 558 randomized participants. Bacteriological outcomes were assessed in 136 participants

Notes  Study funding was by a pharmaceutical company

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SSG 1993

Methods  Randomized, double-blind trial. Diagnosis was established by purulent rhinorrhea, a radiograph consistent with sinusitis or a sinus puncture and that isolated a bacterial pathogen (about 50% of patients had a pathogen). Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator. Clinical cure was defined as resolution of pretreatment signs and symptoms and no recurrence within 72 hours post-treatment; improvement was defined as a reduction in the number or severity of signs and symptoms but without complete resolution. Compliance with treatment was not reported. Proportion of the participants without known or reported clinical outcome 2%

Participants  Patients were recruited from out-patient otolaryngology clinics. Demographic data reported only for evaluable patients (defined as patients with isolated bacterial pathogen plus no protocol violations): mean age approximately 35 (range 16 to 73); 186 men and 152 women. ENT co-morbidity was not assessed. Countries - Sweden, Finland, Iceland

Interventions  Two treatment arms
Group 1: Loracarbef 400 mg twice daily for 10 days
Group 2: Doxycycline 200 mg first dose followed by 100 mg daily for 10 days
Adjuvant therapies were not described
### SSG 1993 (Continued)

| Outcomes | Clinical outcomes were assessed in 648 out of 662 randomized patients (in 323 out of 330 patients in doxycycline group and in 325 out of 332 patients in loracarbef group). Outcomes were assessed on day 7 to 13 after randomization. Radiographic outcomes were not reported. Bacteriological outcomes were assessed in 324 participants |
| Notes | Study funding was by a pharmaceutical company |

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### Stefansson 1998

**Methods**

Randomized, double-blind trial. Diagnosis by symptoms and sinus opacity or air-fluid level on radiograph. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Treatment compliance was not reported. Proportion of the participants without known or reported clinical outcome 4% on day 10 to 14

**Participants**

Study setting not described. Mean age 37; 157 men and 213 women. ENT-comorbidity was not assessed.

Countries - 8 European, Middle Eastern, and African

**Interventions**

Two treatment arms

Group 1: Cefuroxime axetil 250 mg twice daily for 10 days

Group 2: Clarithromycin 250 mg twice daily for 10 days

Nasal corticosteroids prohibited; other adjuvant treatments not described

**Outcomes**

Clinical outcomes were assessed on day 10 to 14 in 354 out of 370 randomized participants. Second follow up on day 38 to 48 in 310 participants. Radiographic and bacteriological outcomes were not reported

**Notes**

Study funding was by a pharmaceutical company

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</table>
### Sterkers 1997

**Methods**
Randomized, unblinded design. Diagnosis by symptoms (duration not described) and fluid or opacity on radiograph. Information on comparability was insufficient to assess whether the groups were comparable at baseline or not. Clinical cure defined as - disappearance of purulent nasal discharge. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 13%

<table>
<thead>
<tr>
<th>Participants</th>
<th>Multicenter, but settings not described. Mean age approximately 41; 178 men and 280 women. Country - France</th>
</tr>
</thead>
</table>
| Interventions | Three treatment arms: (only group 1 - the standard dosing and group 3 used in this analysis)  
Group 1: cefibuten 400 mg once daily for 8 days  
Group 2: cefibuten 200 mg twice daily for 8 days  
Group 3: amoxicillin-clavulanate (500 mg/125 mg) three times daily  
Adjuvant treatments not described |
| Outcomes     | Overall, clinical and radiographic outcomes reported on day 10 in 400 out of 458 randomized patients  
(in 134 patients out of 152 in cefibuten 400 mg once daily group; 138 out of 157 in cefibuten 200 mg twice daily group and 128 out of 149 patients in amoxicillin-clavulanate group); 50 excluded post-randomization due to negative radiograph. Second follow up on day 40 after randomization |

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### Steurer 2000

**Methods**
Randomized, investigator blinded trial. Diagnosis by clinical signs and symptoms, confirmed by a radiograph (criteria not specified). Sinus aspirate and culture (one or more pathogens were isolated from the maxillary sinus aspirates of 66% patients). Clinical cure defined dichotomously - “cure” or "failure". Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Compliance not reported. Proportion of the participants without known clinical outcome was not reported. Patients who had no follow up clinical assessments were categorized as failures in the ITT analyses. Because there was no information of the data without imputation; the data was not used in the meta-analyses in this review

<table>
<thead>
<tr>
<th>Participants</th>
<th>Patients recruited from sixteen medical centers throughout Europe. Setting not described. Mean age 31; 336 men, 233 women. ENT comorbidity not reported</th>
</tr>
</thead>
</table>
| Interventions | Three treatment arms  
Group 1: Cefdinir 600 mg daily, 10 days  
Group 2: Cefdinir 300 mg twice daily, 10 days  
Group 3: Amoxicillin/clavulanate (500 mg/125 mg) three times daily, 10 days |
Steurer 2000  (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Topical nasal decongestants with xylometazoline, oxymetazoline, or naphazoline were permitted but not prescribed</th>
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| Notes | Study funding was by a pharmaceutical company |

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Sydnor 1992

| Methods | Randomized, single blind (investigator). Diagnosis was confirmed by a clinical diagnosis of acute sinusitis and a radiograph consistent with sinusitis (showing mucosal thickening at a minimum). A bacteriologic culture of aspirated maxillary sinus fluid; evaluable patients were required to have positive cultures of pathogens susceptible to both study antibiotics. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure was not defined. Compliance with therapy was not reported. Proportion of the participants without known clinical outcome 62% (patients excluded mostly due to negative culture). Because the overall drop-out rate was extremely high, data was not used in the meta-analyses in this review |
| Participants | The study setting was not well described. Participants mean age was approximately 38 (range 18 to 78); 39 men and 74 women. Country - U.S.A. |
| Interventions | Two treatment arms  
Group 1: Loracarbef 400 mg twice daily for 7 to 10 days  
Group 2: Amoxicillin clavulanate 500 mg/125 mg three times daily for 7 to 10 days  
Adjuvant therapies were not described |
| Outcomes | Clinical outcomes were assessed on day 7 to 13 in 43 of 113 randomized participants. Second follow up at 1 to 2 weeks after the conclusion of therapy. Radiographic outcomes were not reported; bacteriological outcomes were reported for 37 sinuses (not patients) |
| Notes | Study funding was by a pharmaceutical company |

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### UpChurch 2006

**Methods**  
Randomized, double-blind design. Diagnosis by clinical signs and symptoms > 7 days but < 28 days, confirmed by radiograph showing air fluid level, opacification and/or at least 6 mm mucosal thickening. Information on comparability of intervention and control group at baseline adequately reported (groups comparable). Clinical outcomes were assessed by an investigator and clinical cure was defined as resolution or improvement of clinical symptoms and signs such that no additional antimicrobial treatment was necessary. Treatment compliance 91%. Proportion of the participants without known or reported clinical outcome 2%

**Participants**  
Multicenter trial (57 centers) in USA and Canada. 1099 outpatients, 481 male and 618 women. Subjects were 43 years old on average (range 15-90). 37% of patients had a history of allergic rhinitis

**Interventions**  
Three treatment arms:  
Group 1: Faropenem medoxomil 300 mg twice daily for 7 days  
Group 2: Faropenem medoxomil 300 mg twice daily for 10 days  
Group 3: Cefuroxime axetil 250 mg twice daily for 10 days  
Oral or nasal decongestants or antihistamines were allowed.

**Outcomes**  
Clinical outcomes were assessed on day 14 to 31 in 1080 out of 1106 randomized participants (in 357 out of 370 participants in Faropenem medoxomil for 7 days group, in 356 out of 365 participants in Faropenem medoxomil for 10 days group, and in 367 out of 371 participants in Cefuroxime axetil group). Second follow up 28-38 days posttreatment. Radiographic outcomes not reported

**Notes**  
Study funded by a pharmaceutical company

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<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
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### van Buchem 1997

**Methods**  
Randomized, double-blind design. Diagnosis made clinically (the mean duration of the symptomatic period before treatment was 2.2 weeks), confirmed by radiograph showing > 5 mm mucosal thickening, opacity or air-fluid level. Information on comparability of intervention and control groups at baseline adequately reported (groups comparable). Clinical cure was not defined. Treatment compliance reported as 98% assessed by pills taking by patients. Proportion of the participants without known or reported clinical outcome 4% on day 14
### van Buchem 1997 (Continued)

| Participants | Participants were recruited from community-based, general medical practices. Mean age was 34; 79 men and 135 women. ENT co-morbidity was assessed; approximately 12% had allergic disease. Country - The Netherlands |
| Interventions | Two treatment arms  
Group 1: Placebo three times daily for 7 days  
Group 2: Amoxicillin 750 mg three times daily for 7 days  
Adjuvant therapy with oxymetazoline steam inhalation (duration not specified) and paracetamol as needed |
| Outcomes | Clinical and radiographic outcomes were assessed on day 14 for 206 out of 214 participants randomized (in 105 out of 108 patients in antibiotic group and in 101 out of 106 patients in placebo group). Long-term relapse rates during one year. Bacteriological outcomes were not assessed |
| Notes | There was no identified funding source |

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<td>Allocation concealment?</td>
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<td>A - Adequate</td>
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</table>

### von Sydow 1995

| Methods | Randomized, double-blind design. Diagnosis based on clinical symptoms and radiograph showing air-fluid level or opacity (verified by sinus aspiration). Information on baseline comparability of intervention and control groups adequately reported (groups comparable). Failure defined as clinical signs and sinus X-ray points unchanged or worsened. Treatment compliance not reported. Proportion of the participants without known or reported clinical outcome 10% |
| Participants | Participants recruited from academic affiliated, otolaryngology practices. Mean age 33 (range 18 to 78); 149 men and 137 women. ENT co-morbidity was not assessed. Countries - Sweden, Finland, Norway |
| Interventions | Two treatment arms  
Group 1: Cefpodoxime proxetil 200 mg twice daily for 10 days  
Group 2: Amoxicillin 750 mg twice daily for 10 days  
All patients received xylometazoline (nasal decongestant) for up to 7 days |
| Outcomes | Clinical outcomes were assessed on day 11 to 20 in 258 out of 286 participants randomized (in 130 out of 143 patients in cefpodoxime proxetil group and in 128 out of 143 patients in amoxicillin group). Bacteriological outcomes reported in 150 participants |
| Notes | Study funding was by a pharmaceutical company |

### Risk of bias
### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Agbim 1974</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis by clinical signs and symptoms but the minimum duration of those before study entry not reported). Results not reported separately for patients with acute sinusitis</td>
</tr>
<tr>
<td>Alvart 1992</td>
<td>Antibiotic versus antibiotic - study design. Sample size for acute sinusitis &lt; 30</td>
</tr>
<tr>
<td>Axelsson 1971</td>
<td>Antibiotic versus antibiotic - study design. Not randomized study. No clinical outcomes</td>
</tr>
<tr>
<td>Axelsson 1973</td>
<td>Antibiotic versus antibiotic - study design. Not randomized study</td>
</tr>
<tr>
<td>Axelsson 1975</td>
<td>Antibiotic versus antibiotic - study design. Not randomized study. No clinical outcomes, only radiological outcomes</td>
</tr>
<tr>
<td>Axelsson 1981</td>
<td>Antibiotic versus antibiotics - study design. Not randomized study</td>
</tr>
<tr>
<td>Bandak 1999</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis by clinical signs and symptoms but the minimum duration of those before study entry not reported).</td>
</tr>
<tr>
<td>Beatson 1985</td>
<td>Antibiotic versus antibiotic - study design. Inclusion criteria for this review not fulfilled (no definition reported for acute sinusitis)</td>
</tr>
<tr>
<td>Bockmeyer 1994</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis by clinical signs and symptoms but the minimum duration of those before study entry not reported; bacteriological specimens taken from nasal discharge)</td>
</tr>
<tr>
<td>Brodie 1989</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis mainly by clinical signs and symptoms but the minimum duration of those before study entry not reported)</td>
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<tr>
<td>Study</td>
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<tr>
<td>Brook 2006</td>
<td>Antibiotic versus antibiotic</td>
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<tr>
<td>Bucher 2003</td>
<td>Antibiotic versus placebo</td>
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<tr>
<td>Carenfelt 1975</td>
<td>Antibiotic versus antibiotic</td>
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<tr>
<td>Casiano 1991</td>
<td>Antibiotic versus antibiotic</td>
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<td>Correa 1986</td>
<td>Antibiotic versus antibiotic</td>
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<tr>
<td>De Abate 1992</td>
<td>Antibiotic versus antibiotic</td>
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<tr>
<td>De Sutter 2002</td>
<td>Antibiotic versus placebo</td>
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<tr>
<td>Edelstein 1993</td>
<td>Antibiotic versus antibiotic</td>
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<td>Ekedahl 1987</td>
<td>Antibiotic versus antibiotic</td>
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<td>Elies 2001</td>
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<tr>
<td>Falser 1988</td>
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<td>Federspil 1983</td>
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<td>Felstead 1991</td>
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<td>Fiscella 1991</td>
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<td>Freche 1988</td>
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<td>Study</td>
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<tr>
<td>Gananca 1973</td>
<td>Antibiotic versus placebo - study</td>
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<tr>
<td>Garcia 1998</td>
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<tr>
<td>Gladkov 1979</td>
<td>Antibiotic versus dexamethazone and formaldehde - study</td>
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<td>Goumas 1997</td>
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<td>Gurdogan 2001</td>
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<td>Gwaltney 1981</td>
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<td>Hansen 2000</td>
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<tr>
<td>Hebblethwaite 1987</td>
<td>Antibiotic versus antibiotic - study</td>
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<tr>
<td>Henry 1999a</td>
<td>Antibiotic versus antibiotic - study</td>
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<td>Henry 1999b</td>
<td>Antibiotic versus antibiotic - study</td>
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<td>Husfeldt 1993</td>
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<td>Jeppesen 1970</td>
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<td>Johnson 1999</td>
<td>Antibiotic versus antibiotic - study</td>
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<tr>
<td>Karpov 1998</td>
<td>Antibiotic versus antibiotic - study</td>
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<td></td>
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<tr>
<td>Klein 1998</td>
<td>Antibiotic versus antibiotic - study</td>
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Lacroix 2002 | Study mainly designed to identify signs to predict the presence of bacteria in sinusitis. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (median duration of clinical symptoms 4 days; the proportion of patients with confirmed diagnosis by X-ray/culture unclear, at least 40% of patients without confirmation)
---|---
Li 2000 | Antibiotic versus antibiotic - study design. Approximately 67% of participants had chronic sinusitis. Randomisation unclear
---|---
Lopez 1975 | Sample size for acute sinusitis < 30 (7 participants)
---|---
Luchikhin 2005 | Antibiotic versus antibiotic - study design. Sample size for acute maxillary sinusitis < 30
---|---
Mannhardt 1980 | Antibiotic versus antibiotic - study design. Mixed sample of acute (n = 30) and chronic (n = 22) sinusitis. Only combined results are reported
---|---
Manzini 1993 | Antibiotic versus antibiotic - study design. Insufficient information on diagnostic criteria for acute maxillary sinusitis
---|---
Marchi 1990 | Antibiotic versus antibiotic - study design. Random allocation not stated
---|---
Marcolino 1999 | Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms lasting at least four weeks)
---|---
Meltzer 2005 | RCT comparing two intranasal corticosteroids with antibiotic and placebo. Definition and data of the outcome used in this review not reported clearly enough
---|---
Mesure 1973 | Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (no definition of acute maxillary sinusitis). Sample size for acute sinusitis < 30
---|---
Mira 2001 | Antibiotic versus antibiotic - study design. Sample size for acute sinusitis < 30. Insufficient information on diagnostic criteria for acute maxillary sinusitis
---|---
Moorhouse 1985 | Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis on clinical basis; the duration of symptoms before study entry not stated)
---|---
Norrelund 1978 | Antibiotic versus placebo - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis on clinical basis; the duration of symptoms before study entry not stated)
---|---
Olsson 1976 | Antibiotic versus antibiotic - study design. Questionable random allocation. Sample size for acute sinusitis < 30
---|---
Osman 1983 | Antibiotic versus antibiotic - study design. Diagnostic criteria for acute maxillary sinusitis not stated
---|---
Pallestrini 1995 | Antibiotic versus antibiotic - study design. Approximately 27% of patients had acute exacerbation of chronic sinusitis. Results not reported separately for acute maxillary sinusitis
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design Description</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Panosetti 1992</td>
<td>Antibiotic versus antibiotic - study design. Hospitalized patients, ENT ward</td>
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<tr>
<td>Peyramond 1991</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis on clinical basis; duration of symptoms before study entry not stated)</td>
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<tr>
<td>Piragine 1988</td>
<td>Antibiotic versus antibiotic - study design. Sample size for acute sinusitis &lt; 30, (7 participants)</td>
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<tr>
<td>Podvinec 1982</td>
<td>Antibiotic versus antibiotic - study design. Mixed sample of acute (&lt; 80%) and chronic sinusitis. Results not reported separately</td>
<td></td>
</tr>
<tr>
<td>Polonovski 2006</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis on clinical basis, median duration of symptoms 4 days before study entry)</td>
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<tr>
<td>Quick 1973</td>
<td>Antibiotic versus antibiotic - study design. Random allocation not stated. Sample size for acute sinusitis &lt; 30</td>
<td></td>
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<tr>
<td>Quick 1975</td>
<td>Antibiotic versus antibiotic - study design. Random allocation not stated. Sample size for acute sinusitis &lt; 30</td>
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<tr>
<td>Rantanen 1973</td>
<td>Antibiotic versus placebo - study design. Randomisation unclear. Weekly irrigation used as co-intervention</td>
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<tr>
<td>Rechtweg 2004</td>
<td>Antibiotic versus antibiotic - study design. Sample size for acute sinusitis &lt; 30</td>
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<tr>
<td>Rimmer 1997</td>
<td>Antibiotic versus antibiotic - study design. Insufficient information on diagnostic criteria of sinusitis</td>
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<tr>
<td>Roenning 1987</td>
<td>Antibiotic versus antibiotic -study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review Overall clinical outcomes not reported</td>
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<tr>
<td>Salmi 1986</td>
<td>Antibiotic versus antibiotic - study design. Sample size for acute sinusitis &lt; 30</td>
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<tr>
<td>Salmi 1993</td>
<td>Antibiotic versus antibiotic - study design. Mixed respiratory tract infections. Sample size for acute sinusitis &lt; 30. Insufficient information on diagnostic criteria for acute maxillary sinusitis</td>
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</tr>
<tr>
<td>Spindler 1985</td>
<td>Antibiotic versus antibiotic - study design. Inclusion criteria for this review not fulfilled (criteria for acute sinusitis not reported)</td>
<td></td>
</tr>
<tr>
<td>Stahl 1989</td>
<td>Antibiotic versus antibiotic - study design. Included also other URTI than sinusitis. Inclusion criteria for this review not fulfilled; criteria for acute sinusitis not reported, the proportion of participants with chronic sinusitis &gt;20%, and clinical outcomes for acute sinusitis not reported separately</td>
<td></td>
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<tr>
<td>Strachunskii 1993</td>
<td>Antibiotic versus antibiotic - study design. Not randomized study</td>
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<tr>
<td>Sydnor 1989</td>
<td>Antibiotic versus antibiotic - study design. No clinical outcomes</td>
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<tr>
<td>Study Year</td>
<td>Description</td>
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<tr>
<td>Söderström 1991</td>
<td>Antibiotic versus antibiotic - study design. Clinical outcomes not measured for sinusitis (included also other URTI)</td>
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<tr>
<td>Taub 1967</td>
<td>RCT comparing bromelains + antibiotics to antibiotics. Diagnostic criteria for sinusitis not stated. Sample size for acute maxillary sinusitis &lt; 30</td>
<td></td>
</tr>
<tr>
<td>Varonen 2003a</td>
<td>Antibiotics versus placebo - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (about 27% of patients with symptoms less than 6 days at study entry. Ultrasound positive about 50% of patients)</td>
<td></td>
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<tr>
<td>von Sydow 1984</td>
<td>Antibiotic versus antibiotic - study design. Insufficient information (for example, the follow up time and the duration of the therapy were not stated)</td>
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<tr>
<td>Wallace 1985</td>
<td>Antibiotic versus antibiotic - study design. Mixed respiratory tract infections. Insufficient information on diagnostic criteria for acute maxillary sinusitis</td>
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<tr>
<td>Weis 1998</td>
<td>Antibiotic versus antibiotic - study design. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis by clinical signs and symptoms but the minimum duration of those before study entry not reported)</td>
<td></td>
</tr>
<tr>
<td>Westerman 1975</td>
<td>Antibiotic versus antibiotic - study design. Insufficient information on diagnostic criteria for acute maxillary sinusitis</td>
<td></td>
</tr>
<tr>
<td>Young 2003</td>
<td>The study design mainly intended to examine the diagnostic indicators for acute bacterial rhinosinusitis than comparing antibiotic versus placebo. Diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (diagnosis by clinical signs and symptoms; median duration of symptoms 4 days)</td>
<td></td>
</tr>
<tr>
<td>Zbären 1983</td>
<td>Antibiotic versus antibiotic - study design. Sample size for acute maxillary sinusitis &lt; 30</td>
<td></td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. Antibiotics versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up</td>
<td>7</td>
<td>631</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.66 [0.44, 0.98]</td>
</tr>
<tr>
<td>2 Clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up</td>
<td>1</td>
<td>169</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.85 [0.36, 1.98]</td>
</tr>
<tr>
<td>3 Clinical failure defined as a lack of cure at 7 to 15 days of follow up</td>
<td>8</td>
<td>747</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.74 [0.65, 0.84]</td>
</tr>
<tr>
<td>4 Clinical failure defined as a lack of cure at 16 to 60 days of follow up</td>
<td>1</td>
<td>169</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.63 [0.38, 1.05]</td>
</tr>
<tr>
<td>5 Relapse rates after 60 days</td>
<td>1</td>
<td>214</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.25 [0.72, 2.19]</td>
</tr>
<tr>
<td>6 Drop-outs due to adverse effects</td>
<td>8</td>
<td>775</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>2.59 [0.54, 12.45]</td>
</tr>
</tbody>
</table>

### Comparison 2. Macrolide/cephalosporin versus amoxicillin-clavulanate

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ceph versus amox-clav; clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up</td>
<td>6</td>
<td>1891</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.38 [1.04, 1.82]</td>
</tr>
<tr>
<td>2 Ceph versus amox-clav; clinical failure defined as lack of cure or improvement at 16 to 60 days of follow up</td>
<td>7</td>
<td>2115</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.10 [0.88, 1.36]</td>
</tr>
<tr>
<td>3 Drop-outs due to adverse effects (cephalosporins)</td>
<td>8</td>
<td>2860</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.33 [0.21, 0.52]</td>
</tr>
<tr>
<td>4 Macrolides versus amox-clav; clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up</td>
<td>6</td>
<td>1547</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.88 [0.64, 1.20]</td>
</tr>
<tr>
<td>5 Macrolides versus amox-clav; clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up</td>
<td>3</td>
<td>660</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.47, 1.27]</td>
</tr>
<tr>
<td>6 Drop-outs due to adverse effects (macrolides)</td>
<td>6</td>
<td>1760</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.37 [0.22, 0.63]</td>
</tr>
</tbody>
</table>
### Comparison 3. Non-penicillin antibiotics versus beta-lactamase sensitive penicillins

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up</td>
<td>7</td>
<td>1083</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.70 [0.47, 1.06]</td>
</tr>
<tr>
<td>2 Clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up</td>
<td>1</td>
<td>436</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.67 [0.37, 1.20]</td>
</tr>
<tr>
<td>3 Drop-outs due to adverse effects</td>
<td>7</td>
<td>1208</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.58 [0.25, 1.35]</td>
</tr>
</tbody>
</table>

### Comparison 4. Tetracyclines versus mixed classes of antibiotics

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up</td>
<td>5</td>
<td>807</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.09 [0.70, 1.71]</td>
</tr>
<tr>
<td>2 Drop-outs due to adverse effects</td>
<td>5</td>
<td>854</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.73 [0.33, 1.60]</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 1 Antibiotics versus placebo

Outcome: 1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Axelsson 1970</td>
<td>6/35</td>
<td>9/32</td>
<td>18.5 %</td>
<td>0.61</td>
<td>[0.24, 1.52]</td>
</tr>
<tr>
<td>Haye 1998</td>
<td>6/86</td>
<td>9/82</td>
<td>15.9 %</td>
<td>0.64</td>
<td>[0.24, 1.71]</td>
</tr>
<tr>
<td>Lindbaek 1996a</td>
<td>1/39</td>
<td>2/22</td>
<td>2.8 %</td>
<td>0.28</td>
<td>[0.03, 2.94]</td>
</tr>
<tr>
<td>Lindbaek 1996b</td>
<td>1/44</td>
<td>3/22</td>
<td>3.2 %</td>
<td>0.17</td>
<td>[0.02, 1.51]</td>
</tr>
<tr>
<td>Lindbaek 1998a</td>
<td>2/20</td>
<td>1/10</td>
<td>3.0 %</td>
<td>1.00</td>
<td>[0.10, 9.75]</td>
</tr>
<tr>
<td>Lindbaek 1998b</td>
<td>3/22</td>
<td>2/11</td>
<td>5.8 %</td>
<td>0.75</td>
<td>[0.15, 3.85]</td>
</tr>
<tr>
<td>van Buchem 1997</td>
<td>18/105</td>
<td>23/101</td>
<td>50.7 %</td>
<td>0.75</td>
<td>[0.43, 1.31]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>351</strong></td>
<td><strong>280</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.66</strong></td>
<td><strong>[0.44, 0.98]</strong></td>
</tr>
</tbody>
</table>

Total events: 37 (Treatment), 49 (Control)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.42, df = 6 (P = 0.88); I^2 =0.0%
Test for overall effect: Z = 2.08 (P = 0.038)

Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Haye 1998</td>
<td>9/87</td>
<td>10/82</td>
<td>100.0 %</td>
<td>0.85</td>
<td>[0.36, 1.98]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>87</strong></td>
<td><strong>82</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.85</strong></td>
<td><strong>[0.36, 1.98]</strong></td>
</tr>
</tbody>
</table>

Total events: 9 (Treatment), 10 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.38 (P = 0.70)
Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Clinical failure defined as a lack of cure at 7 to 15 days of follow up.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 1 Antibiotics versus placebo

Outcome: 3 Clinical failure defined as a lack of cure at 7 to 15 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axelsson 1970</td>
<td>19/35</td>
<td>22/32</td>
<td>10.6 % 0.79 [ 0.54, 1.16 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haye 1998</td>
<td>36/86</td>
<td>55/82</td>
<td>17.8 % 0.62 [ 0.47, 0.84 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindbaek 1996a</td>
<td>27/39</td>
<td>19/22</td>
<td>20.9 % 0.80 [ 0.61, 1.05 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindbaek 1996b</td>
<td>24/44</td>
<td>20/22</td>
<td>16.8 % 0.60 [ 0.44, 0.81 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindbaek 1998a</td>
<td>14/20</td>
<td>6/10</td>
<td>4.7 % 1.17 [ 0.65, 2.09 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindbaek 1998b</td>
<td>13/22</td>
<td>6/11</td>
<td>3.9 % 1.08 [ 0.57, 2.06 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merenstein 2005</td>
<td>24/56</td>
<td>35/60</td>
<td>11.3 % 0.73 [ 0.51, 1.06 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Buchem 1997</td>
<td>37/105</td>
<td>48/101</td>
<td>14.0 % 0.74 [ 0.53, 1.03 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>407</strong></td>
<td><strong>340</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.74 [ 0.65, 0.84 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 194 (Treatment), 211 (Control)

Heterogeneity: Tau² = 0.00; Chi² = 7.33, df = 7 (P = 0.40); I² = 5%

Test for overall effect: Z = 4.74 (P < 0.00001)
Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 Clinical failure defined as a lack of cure at 16 to 60 days of follow up.

Review: Antibiotics for acute maxillary sinusitis
Comparison: 1 Antibiotics versus placebo
Outcome: 4 Clinical failure defined as a lack of cure at 16 to 60 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haye 1998</td>
<td>18/87</td>
<td>27/82</td>
<td>100.0 % 0.63 [ 0.38, 1.05 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>87</td>
<td>82</td>
<td>100.0 % 0.63 [ 0.38, 1.05 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 18 (Treatment), 27 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.77 (P = 0.077)

Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 Relapse rates after 60 days.

Review: Antibiotics for acute maxillary sinusitis
Comparison: 1 Antibiotics versus placebo
Outcome: 5 Relapse rates after 60 days

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Buchem 1997</td>
<td>23/108</td>
<td>18/106</td>
<td>100.0 % 1.25 [ 0.72, 2.19 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>108</td>
<td>106</td>
<td>100.0 % 1.25 [ 0.72, 2.19 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 23 (Treatment), 18 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
### Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 Drop-outs due to adverse effects.

**Review:** Antibiotics for acute maxillary sinusitis

**Comparison:** 1 Antibiotics versus placebo

**Outcome:** 6 Drop-outs due to adverse effects

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
<th>Weight Peto,Fixed</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axelsson 1970</td>
<td>0/35</td>
<td>0/32</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Haye 1998</td>
<td>0/87</td>
<td>0/82</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Lindbaek 1996a</td>
<td>2/41</td>
<td>0/22</td>
<td></td>
<td>28.6 %</td>
<td>4.77 [ 0.25, 89.36 ]</td>
</tr>
<tr>
<td>Lindbaek 1996b</td>
<td>1/45</td>
<td>0/22</td>
<td></td>
<td>14.1 %</td>
<td>4.43 [ 0.07, 287.85 ]</td>
</tr>
<tr>
<td>Lindbaek 1998a</td>
<td>1/23</td>
<td>0/11</td>
<td></td>
<td>14.0 %</td>
<td>4.39 [ 0.07, 289.40 ]</td>
</tr>
<tr>
<td>Lindbaek 1998b</td>
<td>2/23</td>
<td>0/11</td>
<td></td>
<td>27.2 %</td>
<td>4.59 [ 0.23, 93.02 ]</td>
</tr>
<tr>
<td>Merenstein 2005</td>
<td>0/67</td>
<td>0/68</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>van Buchem 1997</td>
<td>0/105</td>
<td>1/101</td>
<td></td>
<td>16.0 %</td>
<td>0.13 [ 0.00, 6.56 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>426</th>
<th>Control</th>
<th>349</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Peto,Fixed</td>
<td>100.0 %</td>
<td>2.59 [ 0.54, 12.45 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Treatment), 1 (Control)

Heterogeneity: $\chi^2 = 2.67$, df = 4 ($P = 0.62$); $I^2 = 0.0$

Test for overall effect: $Z = 1.19$ ($P = 0.23$)
Analysis 2.1. Comparison 2. Macrolide/cephalosporin versus amoxicillin-clavulanate, Outcome 1. Ceph versus amox-clav; clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 2. Macrolide/cephalosporin versus amoxicillin-clavulanate

Outcome: 1. Ceph versus amox-clav; clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cephalosporins</th>
<th>Amox-clav</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelglass 1998b</td>
<td>15/108</td>
<td>9/111</td>
<td>12.6 %</td>
<td>1.71 [ 0.78, 3.75 ]</td>
<td></td>
</tr>
<tr>
<td>Gehanno 1998</td>
<td>13/121</td>
<td>6/115</td>
<td>8.9 %</td>
<td>2.06 [ 0.81, 5.24 ]</td>
<td></td>
</tr>
<tr>
<td>Gwaltney 1997</td>
<td>49/474</td>
<td>44/491</td>
<td>51.6 %</td>
<td>1.15 [ 0.78, 1.70 ]</td>
<td></td>
</tr>
<tr>
<td>Olmo 1994</td>
<td>0/25</td>
<td>0/22</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Pessey 1996</td>
<td>8/85</td>
<td>5/77</td>
<td>6.7 %</td>
<td>1.45 [ 0.50, 4.24 ]</td>
<td></td>
</tr>
<tr>
<td>Sterkers 1997</td>
<td>23/134</td>
<td>14/128</td>
<td>20.2 %</td>
<td>1.57 [ 0.85, 2.91 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>947</strong></td>
<td><strong>944</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.38 [ 1.04, 1.82 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 108 (Cephalosporins), 78 (Amox-clav)

Heterogeneity: Tau² = 0.0; Chi² = 2.00, df = 4 (P = 0.74); I² = 0.0%

Test for overall effect: Z = 2.27 (P = 0.023)
## Analysis 2.2. Comparison of Macrolide/cephalosporin versus amoxicillin-clavulanate, Outcome 2 Ceph versus amox-clav; clinical failure defined as lack of cure or improvement at 16 to 60 days of follow up.

**Review:** Antibiotics for acute maxillary sinusitis

**Comparison:** Macrolide/cephalosporin versus amoxicillin-clavulanate

**Outcome:** Ceph versus amox-clav; clinical failure defined as lack of cure or improvement at 16 to 60 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cephalosporins</th>
<th>Amox-clav</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelglass 1998b</td>
<td>18/100</td>
<td>16/99</td>
<td>12.4 % 1.11 [ 0.60, 2.06 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camacho 1992</td>
<td>17/115</td>
<td>22/124</td>
<td>13.9 % 0.83 [ 0.47, 1.49 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gehanno 1998</td>
<td>21/119</td>
<td>13/111</td>
<td>11.3 % 1.51 [ 0.79, 2.86 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gwaltney 1997</td>
<td>37/379</td>
<td>30/389</td>
<td>22.0 % 1.27 [ 0.80, 2.01 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pessey 1996</td>
<td>7/75</td>
<td>7/67</td>
<td>4.7 % 0.89 [ 0.33, 2.41 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russell 1997</td>
<td>27/146</td>
<td>30/135</td>
<td>2.16 % 0.83 [ 0.52, 1.32 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterkers 1997</td>
<td>25/133</td>
<td>16/123</td>
<td>14.0 % 1.45 [ 0.81, 2.57 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1067</td>
<td>1048</td>
<td><strong>100.0 % 1.10 [ 0.88, 1.36 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 152 (Cephalosporins), 134 (Amox-clav)

Heterogeneity: Tau² = 0.0; Chi² = 4.58, df = 6 (P = 0.60); I² = 0.0%

Test for overall effect: Z = 0.84 (P = 0.40)
Analysis 2.3. Comparison 2 Macrolide/cephalosporin versus amoxicillin-clavulanate, Outcome 3 Drop-outs due to adverse effects (cephalosporins).

Review: Antibiotics for acute maxillary sinusitis

Comparison: 2 Macrolide/cephalosporin versus amoxicillin-clavulanate

Outcome: 3 Drop-outs due to adverse effects (cephalosporins)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cephalosporins</th>
<th>Amox-clav</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelglass 1998b</td>
<td>3/140</td>
<td>9/138</td>
<td>15.2%</td>
<td>0.35</td>
<td>[0.11, 1.10]</td>
</tr>
<tr>
<td>Camacho 1992</td>
<td>1/157</td>
<td>2/160</td>
<td>3.9%</td>
<td>0.52</td>
<td>[0.05, 5.05]</td>
</tr>
<tr>
<td>Gehanno 1998</td>
<td>2/123</td>
<td>1/118</td>
<td>3.9%</td>
<td>1.88</td>
<td>[0.19, 18.24]</td>
</tr>
<tr>
<td>Gwaltney 1997</td>
<td>8/585</td>
<td>30/603</td>
<td>48.6%</td>
<td>0.31</td>
<td>[0.16, 0.60]</td>
</tr>
<tr>
<td>Olmo 1994</td>
<td>0/25</td>
<td>0/22</td>
<td>0.0%</td>
<td>0.00</td>
<td>[0.00, 0.00]</td>
</tr>
<tr>
<td>Pessey 1996</td>
<td>0/87</td>
<td>6/82</td>
<td>7.7%</td>
<td>0.12</td>
<td>[0.02, 0.61]</td>
</tr>
<tr>
<td>Russell 1997</td>
<td>1/158</td>
<td>7/161</td>
<td>10.3%</td>
<td>0.22</td>
<td>[0.05, 0.89]</td>
</tr>
<tr>
<td>Sterkers 1997</td>
<td>3/152</td>
<td>5/149</td>
<td>10.3%</td>
<td>0.59</td>
<td>[0.14, 2.39]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1427</strong></td>
<td><strong>1433</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.33</strong></td>
<td><strong>[0.21, 0.52]</strong></td>
</tr>
</tbody>
</table>

Total events: 18 (Cephalosporins), 60 (Amox-clav)
Heterogeneity: Chisq = 4.91, df = 6 (P = 0.56); I^2 = 0.0%
Test for overall effect: Z = 4.79 (P < 0.00001)
Analysis 2.4. Comparison 2 Macrolide/cephalosporin versus amoxicillin-clavulanate, Outcome 4 Macrolides versus amox-clav; clinical failure defined as a lack of cure or improvement at 7 to 15 days of foll.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 2 Macrolide/cephalosporin versus amoxicillin-clavulanate

Outcome: 4 Macrolides versus amox-clav; clinical failure defined as a lack of cure or improvement at 7 to 15 days of foll

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Macrolides</th>
<th>Amoxicillin-clavulanate</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatzimanolis 1998</td>
<td>2/29</td>
<td>3/27</td>
<td>3.3%</td>
<td>0.62 [0.11, 3.43]</td>
</tr>
<tr>
<td>Clement 1998</td>
<td>19/151</td>
<td>6/82</td>
<td>12.7%</td>
<td>1.72 [0.72, 4.14]</td>
</tr>
<tr>
<td>Gehanno 1996a</td>
<td>19/134</td>
<td>19/129</td>
<td>28.2%</td>
<td>0.96 [0.53, 1.73]</td>
</tr>
<tr>
<td>Henry 2003</td>
<td>30/269</td>
<td>39/259</td>
<td>49.5%</td>
<td>0.74 [0.47, 1.15]</td>
</tr>
<tr>
<td>Klapan 1999</td>
<td>0/47</td>
<td>0/47</td>
<td>0.0%</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Riffer 2005</td>
<td>4/188</td>
<td>6/185</td>
<td>6.3%</td>
<td>0.66 [0.19, 2.29]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>818</strong></td>
<td><strong>729</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.88 [0.64, 1.20]</strong></td>
</tr>
</tbody>
</table>

Total events: 74 (Macrolides), 73 (Amox-clav)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.28, df = 4 (P = 0.51); I^2 =0.0%
Test for overall effect: Z = 0.83 (P = 0.40)

Analysis 2.5. Comparison 2 Macrolide/cephalosporin versus amoxicillin-clavulanate, Outcome 5 Macrolides versus amox-clav; clinical failure defined as a lack of cure or improvement at 16 to 60 days of foll.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 2 Macrolide/cephalosporin versus amoxicillin-clavulanate

Outcome: 5 Macrolides versus amox-clav; clinical failure defined as a lack of cure or improvement at 16 to 60 days of foll

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Macrolide</th>
<th>Amoxicillin-clavulanate</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clement 1998</td>
<td>17/136</td>
<td>12/74</td>
<td>52.3%</td>
<td>0.77 [0.39, 1.53]</td>
</tr>
<tr>
<td>Klapan 1999</td>
<td>1/43</td>
<td>4/46</td>
<td>5.3%</td>
<td>0.27 [0.03, 2.30]</td>
</tr>
<tr>
<td>Riffer 2005</td>
<td>12/184</td>
<td>13/177</td>
<td>42.5%</td>
<td>0.89 [0.42, 1.89]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>363</strong></td>
<td><strong>297</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.77 [0.47, 1.27]</strong></td>
</tr>
</tbody>
</table>

Total events: 30 (Macrolide), 29 (Amoxicillin-clavulanate)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.07, df = 2 (P = 0.59); I^2 =0.0%
Test for overall effect: Z = 1.02 (P = 0.31)
Analysis 2.6. Comparison 2 Macrolide/cephalosporin versus amoxicillin-clavulanate, Outcome 6 Drop-outs due to adverse effects (macrolides).

Review: Antibiotics for acute maxillary sinusitis

Comparison: 2 Macrolide/cephalosporin versus amoxicillin-clavulanate

Outcome: 6 Drop-outs due to adverse effects (macrolides)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Macrolides n/N</th>
<th>Amox-clav n/N</th>
<th>Peto Odds Ratio Peto,Fixed</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatzimanolis 1998</td>
<td>0/31</td>
<td>3/29</td>
<td>5.1 %</td>
<td>0.12</td>
<td>[ 0.01, 1.18 ]</td>
</tr>
<tr>
<td>Clement 1998</td>
<td>0/165</td>
<td>2/89</td>
<td>3.2 %</td>
<td>0.06</td>
<td>[ 0.00, 1.05 ]</td>
</tr>
<tr>
<td>Gehanno 1996a</td>
<td>5/145</td>
<td>4/139</td>
<td>15.5 %</td>
<td>1.20</td>
<td>[ 0.32, 4.53 ]</td>
</tr>
<tr>
<td>Henry 2003</td>
<td>7/312</td>
<td>28/313</td>
<td>58.7 %</td>
<td>0.28</td>
<td>[ 0.14, 0.56 ]</td>
</tr>
<tr>
<td>Klapan 1999</td>
<td>0/50</td>
<td>0/50</td>
<td>0.0 %</td>
<td>0.0</td>
<td>[ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Riffer 2005</td>
<td>4/221</td>
<td>6/216</td>
<td>17.4 %</td>
<td>0.65</td>
<td>[ 0.19, 2.27 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>924</strong></td>
<td><strong>836</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.37</strong></td>
<td>[ <strong>0.22, 0.63</strong> ]</td>
</tr>
</tbody>
</table>

Total events: 16 (Macrolides), 43 (Amox-clav)

Heterogeneity: Chi² = 6.96, df = 4 (P = 0.14); I² = 43%

Test for overall effect: Z = 3.72 (P = 0.00020)
Analysis 3.1. Comparison 3 Non-penicillin antibiotics versus beta-lactamase sensitive penicillins, Outcome 1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 3 Non-penicillin antibiotics versus beta-lactamase sensitive penicillins

Outcome: 1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Non-penicillin n/N</th>
<th>Penicillin class n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calhoun 1993</td>
<td>5/55</td>
<td>7/61</td>
<td>14.0 % 0.79 [ 0.27, 2.35 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haye 1996</td>
<td>6/220</td>
<td>11/214</td>
<td>17.4 % 0.53 [ 0.20, 1.41 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huck 1993</td>
<td>11/44</td>
<td>8/37</td>
<td>26.0 % 1.16 [ 0.52, 2.57 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karma 1991</td>
<td>3/32</td>
<td>3/35</td>
<td>7.1 % 0.59 [ 0.27, 1.30 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattucci 1986</td>
<td>0/25</td>
<td>1/22</td>
<td>1.7 % 0.29 [ 0.01, 6.89 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyffenegger 1991</td>
<td>2/40</td>
<td>7/40</td>
<td>7.3 % 0.59 [ 0.27, 1.30 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>von Sydow 1995</td>
<td>9/130</td>
<td>15/128</td>
<td>26.6 % 0.59 [ 0.27, 1.30 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>546</strong></td>
<td><strong>537</strong></td>
<td><strong>100.0 % 0.70 [ 0.47, 1.06 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 36 (Non-penicillin), 52 (Penicillin class)
Heterogeneity: Tau² = 0.0; Chi² = 4.07, df = 6 (P = 0.67); I² =0.0%
Test for overall effect: Z = 1.69 (P = 0.092)

Analysis 3.2. Comparison 3 Non-penicillin antibiotics versus beta-lactamase sensitive penicillins, Outcome 2 Clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 3 Non-penicillin antibiotics versus beta-lactamase sensitive penicillins

Outcome: 2 Clinical failure defined as a lack of cure or improvement at 16 to 60 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Non-penicillin n/N</th>
<th>Penicillin class n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haye 1996</td>
<td>17/220</td>
<td>25/216</td>
<td>100.0 % 0.67 [ 0.37, 1.20 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>220</strong></td>
<td><strong>216</strong></td>
<td><strong>100.0 % 0.67 [ 0.37, 1.20 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 17 (Non-penicillin), 25 (Penicillin class)
Heterogeneity: not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
Analysis 3.3. Comparison 3 Non-penicillin antibiotics versus beta-lactamase sensitive penicillins, Outcome 3 Drop-outs due to adverse effects.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Non-penicillin (n/N)</th>
<th>Penicillin class (n/N)</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calhoun 1993</td>
<td>2/70</td>
<td>3/72</td>
<td>22.9 %</td>
<td>0.68 [ 0.12, 4.04 ]</td>
<td></td>
</tr>
<tr>
<td>Haye 1996</td>
<td>0/221</td>
<td>0/217</td>
<td>0.0 %</td>
<td>0.00 [ 0.00, 0.00 ]</td>
<td></td>
</tr>
<tr>
<td>Huck 1993</td>
<td>0/54</td>
<td>1/54</td>
<td>4.7 %</td>
<td>0.14 [ 0.00, 6.82 ]</td>
<td></td>
</tr>
<tr>
<td>Karma 1991</td>
<td>0/50</td>
<td>1/50</td>
<td>4.7 %</td>
<td>0.14 [ 0.00, 6.82 ]</td>
<td></td>
</tr>
<tr>
<td>Mattucci 1986</td>
<td>2/29</td>
<td>2/29</td>
<td>17.8 %</td>
<td>1.00 [ 0.13, 7.49 ]</td>
<td></td>
</tr>
<tr>
<td>Nyffenegger 1991</td>
<td>0/40</td>
<td>0/40</td>
<td>0.0 %</td>
<td>0.00 [ 0.00, 0.00 ]</td>
<td></td>
</tr>
<tr>
<td>von Sydow 1995</td>
<td>4/140</td>
<td>7/142</td>
<td>49.9 %</td>
<td>0.58 [ 0.17, 1.92 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>604</td>
<td>604</td>
<td>100.0 %</td>
<td>0.58 [ 0.25, 1.35 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.37, df = 4 (P = 0.85); I² = 0.0%
Test for overall effect: Z = 1.27 (P = 0.20)
### Analysis 4.1. Comparison of Tetracyclines versus mixed classes of antibiotics, Outcome 1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up.

**Review:** Antibiotics for acute maxillary sinusitis  
**Comparison:** 4 Tetracyclines versus mixed classes of antibiotics  
**Outcome:** 1 Clinical failure defined as a lack of cure or improvement at 7 to 15 days of follow up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Tetracyclines</th>
<th>Mixed group</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arndt 1994</td>
<td>1/26</td>
<td>1/28</td>
<td>2.7 % 1.08 [0.07, 16.35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boezeman 1988</td>
<td>5/15</td>
<td>3/12</td>
<td>13.7 % 1.33 [0.40, 4.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattucci 1986</td>
<td>0/25</td>
<td>1/22</td>
<td>2.0 % 0.29 [0.01, 6.89]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otte 1983</td>
<td>6/17</td>
<td>4/14</td>
<td>18.3 % 1.24 [0.43, 3.53]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSG 1993</td>
<td>23/323</td>
<td>22/325</td>
<td>63.3 % 1.05 [0.60, 1.85]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>406</strong></td>
<td><strong>401</strong></td>
<td><strong>100.0 % 1.09 [0.70, 1.71]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 35 (Tetracyclines), 31 (Mixed group)  
Heterogeneity: Tau² = 0.0; Chi² = 4 (P = 0.93); I² = 0.0%  
Test for overall effect: Z = 0.38 (P = 0.70)

---

**Antibiotics for acute maxillary sinusitis (Review)**  
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Analysis 4.2. Comparison of Tetracyclines versus mixed classes of antibiotics, Outcome 2: Drop-outs due to adverse effects.

Review: Antibiotics for acute maxillary sinusitis

Comparison: 4 Tetracyclines versus mixed classes of antibiotics

Outcome: 2 Drop-outs due to adverse effects

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Tetracycline n/N</th>
<th>Mixed group n/N</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arndt 1994</td>
<td>0/35</td>
<td>3/35</td>
<td>0.13 [0.01, 1.27]</td>
<td>11.6 %</td>
<td>0.00 [0.01, 1.27]</td>
</tr>
<tr>
<td>Boezeman 1988</td>
<td>0/18</td>
<td>0/15</td>
<td>0.0 %</td>
<td>0.0 %</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>Mattucci 1986</td>
<td>2/29</td>
<td>2/29</td>
<td>1.00 [0.13, 7.49]</td>
<td>15.0 %</td>
<td>1.00 [0.13, 7.49]</td>
</tr>
<tr>
<td>Otte 1983</td>
<td>0/17</td>
<td>0/14</td>
<td>0.0 %</td>
<td>0.0 %</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>SSG 1993</td>
<td>9/330</td>
<td>10/332</td>
<td>0.90 [0.36, 2.25]</td>
<td>73.4 %</td>
<td>0.90 [0.36, 2.25]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>429 425</td>
<td></td>
<td>100.0 %</td>
<td>0.73 [0.33, 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 11 (Tetracycline), 15 (Mixed group)
Heterogeneity: Chi² = 2.52, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.79 (P = 0.43)

Feedback

Antibiotics for acute maxillary sinusitis

Summary

There are 4 primary questions to be answered by this systematic review:
1) Is antibiotic therapy effective for acute sinusitis?
2) Which antibiotic is most effective?
3) What is the best duration for antibiotic therapy?
4) Is there a change in the efficacy of antibiotics over time?

Question 1
Firstly, all 4 questions are clinically important. But it is paramount to recognize the interrelationships of all 4 questions, such that, if the answer to the first question is negative, the value of the other answers is significantly diminished. It is therefore essential to include all the evidence unless the exclusion is completely justified.


I agree that the Wald study involving children and the Gananca study from Brazil should be excluded. Gananca trial had only 50 subjects, with 50% more patients in the antibiotic group after randomization. It also had extreme differences in cure rates between antibiotic and placebo groups (15/30 vs. 0/20).

The last 3 trials on this list, according to the recent meta-analysis by de Ferranti et al (BMJ 1998;317:632-7), received a quality score of 5 by the Jadad scale (a maximum score indicating highest quality). The Axelsson study had a score of 1. The Williams et al answered this first question, "Is antibiotic therapy effective?", by excluding Stalman 1997 (with quality score of 5) and by doubling the control group populations in Axelsson 1970 (n=34) and in Lindbaek 1996 (n=44). This artificially created population of 156 controls from 78...
real controls would inflate the contributions of those 2 trials on the outcome. The exclusion of those true placebo-controls in Stalman 1997 (n=94), while adding 78 phantom controls, is not a reasonable approach to answer the antibiotic efficacy question for sinusitis. The Stalman study was excluded, according to the author's, because it did not use radiographic images for diagnosis. The same is true however for the included Axelsson study. Though Axelsson et al. took several different radiographic views of sinuses, they did not describe a radiographic criteria for diagnosis.

Moreover, the relationship between radiograms, even the more advanced images of paranasal sinuses obtained by computed tomography (CT scan), and the clinical description of sinusitis is extremely poor. The 1997 study of Bhattaharyya et al. involving 586 patients (the largest published data set) failed to find any correlation between CT scan results and patient described symptoms of sinusitis (See Arch. Otolaryngol. 1997;123:1189-92). Also note that Williams et al argue that the cure rate differences between Lindbaek and van Buchem were probably related to the diagnostic criteria. That is, a diagnosis confirmed by CT scan is more likely associated with bacterial sinusitis than a diagnosis by radiography. This new theory of differential diagnosis of bacterial sinusitis however is not supported by any published data.

To be consistent, either both Axelsson and Stalman should be included, or both should be excluded. If they are both excluded, then the meta-analysis of Williams et al on the efficacy of antibiotics for sinusitis would depend on only 2 placebo controlled trials - Lindbaek 1996 and van Buchem 1997 - with opposite conclusions.

The Lindbaek study was terminated early with 130 patients instead of the original sample size of 180 subjects. This was done without correction and without predefined stopping rules. Also, the randomization was in a most unusual fashion for a modern clinical trial using dice. Lindbaek et al. do not provide a table, as customary, showing the baseline patient characteristics at entry indicating their randomization was effective. In contrast to those deficits, van Buchem reports this baseline information about randomization and an analysis of prognostic factors on the outcome. It shows that initial severity of sinusitis does not change the results. The van Buchem study has a much higher quality and reliability than the Lindbaek trial. If the entire evidence has to be based on combining or contrasting only those 2 trials, then conclusion has to follow the van Buchem results.

Most important, the Stalman trial which was published 9 months later completely supports the van Buchem results. Among the 3 trials with Jadad score of 5, reasonable people can easily conclude that van Buchem and Stalman clearly show that antibiotics for acute sinusitis are not effective; and, Lindbaek et al. is an outlier. Lindbaek's efficacy claim based on one endpoint (cure) is not sustained by his second endpoint (improvement). This inconsistent outcome and those basic problems associated with early termination and poor randomization perhaps is why Lindbaek results are not replicated by the last 2 trials (van Buchem and Stalman).

I suggest however that we include all 4 clinical trials to combine results and estimate a pooled efficacy. As such, even this would yield still a meager sample size, a total of 648 subjects with only 278 controls. Consequently, this is the entire dataset we have to establish the scientific evidence-base in justifying 15 million antibiotic prescriptions in the U.S. for sinusitis. Instead of finding excuses to exclude the few controls in this limited database, we should savor them.

The answer to the first question, then, is a simple pooling of the results from those 4 clinical trials: Axelsson 1970 (n=112), Lindbaek 1996 (n=130), van Buchem 1997 (n=214), and Stalman 1997(n=192).

In all sinusitis trials the primary outcome measures of at 10-14 days are subjective. Outcomes are not based on some “Gold Standard” but study-variant definitions of cure and success (cure/improvement) by each investigator. Those primary data unfortunately are not based on objective endpoints. A well defined diagnostic criteria, such as combining radiographs with symptoms, validated against a standard is lacking.

I argue that if the entry includes radiograms to make the diagnosis of sinusitis, then to be consistent for at least in defining cure, the primary endpoint should also include both measures (e.g., combination of normal radiograph with symptom free status). If both measures are not negative, then improvement (or scaled improvement) is the only logical alternative. Without a normal radiogram, cured diagnosis would be in contradiction with the entry criteria.

Regardless of these problems associated with an objective and study invariant outcome, the combined results from 4 trials are as follows:

<table>
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<tr>
<th>Endpoint</th>
<th>Antibiotics</th>
<th>Controls</th>
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<tr>
<td>Cure</td>
<td>27/78 + 32/86 + 68/108 + 59/98 = 186/370 or 50.3%</td>
<td>23/34 + 39/44 + 78/106 + 80/94 = 220/278 or 79.1%</td>
</tr>
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</table>
| Success  | 51/78 + 81/86 + 87/108 + 83/98 = 302/370 or 81.6% | Antibiotic-placebo rate difference in cure is 5.7% (OR=1.26) and the rate difference in success is 2.5% (OR=1.17). These marginal differences, neither statistically nor clinically significant, indicate the lack of efficacy of antibiotic therapy for the treatment of acute paranasal sinusitis.

Antibiotics for acute maxillary sinusitis (Review)

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The methods used by Williams et al in their meta-analysis therefore must be re-examined. Relying on magical statistical packages, with interesting inclusions and exclusions, can sometimes lead to positively misleading results. As in this case, claiming antibiotic efficacy for sinusitis is not a reasonable conclusion but perhaps an artifact of meta-analysis.

The answer to this first question, “Are antibiotics for acute sinusitis effective?”, therefore is negative.

Question 2
Now the second question, which antibiotic is most effective, is a less important scientific issue. Notwithstanding, in real life clinical practice, this question continues to be a primary issue because of the ongoing campaign of promoting newer, wider spectrum antibiotics for sinusitis with higher costs.

Though there is no clinical trial which exclusively has focused on bacterial sinusitis caused by resistant bacteria, and which has shown the benefit of such drugs, the emergence of multi-drug resistant bacteria is always cited to advocate those wide spectrum drugs. Therefore, the second part of the Williams meta-analysis is clinically most significant.

Using a large sample size, Williams et al (n=7330 patients in 32 trials) show that there is no superior antibiotic. This result supports the earlier findings of de Bock 1997 (n=3358 patients in 16 trials) and de Ferranti 1998 (n=2717 patients in 27 trials) meta-analyses. The ineffectiveness of wide spectrum drugs are based on a wide collection of clinical trials. In fact, among those 3 meta-analyses, the inclusion of the same trials are not common. The number of trials commonly inclusive between meta-analyses are: Williams - de Ferranti (13/47), Williams - de Bock (3/45), and de Ferranti - de Bock (5/39). This diversity in inclusion/exclusion indicates the arbitrary nature of selection of trials included in meta-analyses while supporting the robustness of conclusions.

Note also that this result, ineffectiveness of wide spectrum antibiotics for sinusitis, is consistent with the meta-analysis findings in acute otitis media. It is a logical result since acute otitis media in general has the same pathogenic bacterial spectrum as acute sinusitis.

There is however an interesting point to consider. If the antibiotics are not better than placebo, then it is logical not to find a superior antibiotic for sinusitis. Unless each new antibiotic is concurrently matched with a placebo control in the primary clinical trial, it would be impossible to show the usefulness of new, wide spectrum antibiotics. Without such data, I think it is irresponsible to advocate wide spectrum antibiotics for sinusitis.

I hope that Williams et al would reduce the complexity of their presentation to make this point by decreasing the number of figures and by selecting a single primary endpoint to display. I suggest success (cure/improvement) as the measure of choice as I discussed above. The remaining measures can be simply stated as not being different with some odds ratios or rate differences. Also, those redundant figures with confidence intervals all over the place, are they necessary? It only illustrates that poor evidence is being included in the meta-analysis.

I suggest that their Summary figure should also include sample sizes, exclude tetracycline’s, include duration of therapy analysis (short vs. long), and finally include some cumulative meta-analysis to indicate change in efficacy over time.

Question 3
Authors conclude in recommending 10-days of amoxicillin therapy for acute sinusitis but do not provide evidence-based arguments for selecting this particular duration of therapy. This is not scientific and somewhat odd, because a few years ago, Dr. Williams published arguably the best study showing that 3-days of antibiotic therapy is as good as the standard 10-days of therapy (See JAMA 1995;273:1015-21).

A recent review by Pichichero and Cohen (Pediatr Infect Dis J 1997;16:680-95) indicates that there are at least 5 published studies involving adult patients which show that short duration therapy is as effective as long duration therapy. I suggest Williams et al provide a meta-analysis to answer this question or explain why such combination of data is not possible. This part on duration of therapy I think is extremely important.

Question 4
The recent increase in the prevalence of multi-drug resistant bacteria is clearly shown to be changing rapidly and is caused by the misuse or overuse of antibiotics. However, the research about the change of efficacy of antibiotics in vivo for common respiratory diseases is lacking. This is an important question. I am not sure how it can be answered. The approach taken by Williams et al seems a reasonable one, but I doubt that it can really answer the question of changing antibiotic efficacy for sinusitis.

The change in efficacy over time perhaps can be best approached by using a cumulative meta-analysis (See N Engl J Med 1992;327:248-54, JAMA 1992;268:240-8). Williams et al state that they have performed such a cumulative meta-analysis as well as a meta-regression. However, they do not show those results. I think the cumulative meta-analysis involving 32 trials in some chronological order (by the date of the trial, and not the publication date) would be an excellent figure to make the point.

We must also keep in mind another possibility. The lack of change in efficacy over time, suggesting that the emergence of drug resistant bacteria had no effect, could be simply untrue but related to the ineffectiveness of antibiotics for sinusitis in general.

With $2 billion over the counter medications, 15 million antibiotic prescriptions, 17 million office visits, 300,000 endoscopic sinus surgeries, and 37 million Americans suffering from chronic sinus disease, this is not a trivial healthcare issue. If the Cochrane is going
to enter a systematic review in its library, it should be based on the best evidence and analysis. William et al require many changes and much improvement before it is suitable for the Cochrane database.

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
Dr. Cantekin identifies the question - "are antibiotics more effective than placebo for acute sinusitis" as critically important but disagrees with a number of our methods for answering this question. We will address each point.

First, it is stated that the control populations are double counted. This is an important and difficult methodological issue that occurs when trials have more than two treatment arms. It was only problematic for the Lindbaek trial, which had amoxicillin, penicillin, and placebo arms. To avoid "double counting," we analyzed the amoxicillin and penicillin trials separately, thereby including the control populations only once in each of these separate analyses.

Second, it is argued that the Stalman trial should be included in the analysis. We agree that the Stalman study is high quality, but it was excluded because it lacked a diagnostic radiographic or sinus puncture. Our review was restricted to studies enrolling adult subjects with sinusitis as determined by clinical symptoms and either an abnormal radiographic or sinus aspiration (the Stalman study used neither).

Because clinical symptoms alone lead to relatively high rates of misclassification, we thought the requirement for an objective measure (x-ray or aspiration) was important. Studies with high rates of misclassification may include large proportions of subjects without bacterial sinusitis, leading to a negative result because antibiotics are unlikely to help allergic or viral rhinosinusitis. These criteria were applied to all studies considered for inclusion. Although we excluded studies without a diagnostic criterion standard, authors of other literature syntheses on this topic, have used more liberal inclusion criteria by dropping the requirement for an objective measure of sinusitis. Their results were consistent with our findings (Risk ratio to prevent clinical failure 0.54; 95% CI 0.37 to 0.79). (1)

Third, simple pooling is suggested as an appropriate method for combining trial results. We disagree. Simple pooling (as opposed to meta-analytic techniques), can lead to biased results for a variety of reasons. These include bias if there is imbalance in the number of subjects in treatment arms, underestimation of the variance, and inappropriate weighting of small and large trials. Further, it is not possible to evaluate heterogeneity through simple pooling.

Next, the reviewer reaches the conclusion that antibiotics are no more effective than placebo. Although the trials are few, and the results limited to patients with maxillary sinusitis confirmed radiographically or by aspiration, we interpret the current evidence as showing that penicillin is more effective than placebo and that there are similar, but more heterogeneous findings for amoxicillin.

Because clinical symptoms alone lead to relatively high rates of misclassification, we thought the requirement for an objective measure (x-ray or aspiration) was important. Studies with high rates of misclassification may include large proportions of subjects without bacterial sinusitis, leading to a negative result because antibiotics are unlikely to help allergic or viral rhinosinusitis. These criteria were applied to all studies considered for inclusion. Although we excluded studies without a diagnostic criterion standard, authors of other literature syntheses on this topic, have used more liberal inclusion criteria by dropping the requirement for an objective measure of sinusitis. Their results were consistent with our findings (Risk ratio to prevent clinical failure 0.54; 95% CI 0.37 to 0.79). (1)

The issue of cumulative meta-analysis is important. We report the findings of these results without showing the forest plots because of limitations of the software. For newer non-penicillins vs. penicillins, there was no effect over time for clinical cure (p=0.17) or for clinical cure or improvement (p=0.60). It is difficult to draw robust conclusions from this analysis because clinically important changes (other than bacterial resistance) may affect the results.

The reviewer asks for an analysis addressing the duration of treatment. We agree that treatment duration is a clinically important issue. In fact we completed a study showing therapeutic equivalency for 3 vs. 10 days of TMP/SMX. (2) This study was excluded from the current literature synthesis because it was a within class antibiotic comparison (not eligible). Four other studies compared two antibiotics with differing duration of treatment. Three of these compared two different antibiotics for differing duration making it difficult to isolate treatment duration as the key variable. Only one study compared two durations for the same antibiotic (cefixime 4 vs. 10 days) and found similar efficacy. Because of differing pharmacokinetics and tissue penetration, we do not think it is wise to generalize results about TMP/SMX and cefixime to antibiotics in general. Readers should incorporate these findings cautiously. Because study duration was not one of our study questions, we have not done a systematic search to identify relevant literature. We will consider adding this question to future reviews.

We strongly endorse the reviewers call for more clinical trials in this area, particularly with placebo control and look forward to other readers' comments.

Reference List
(1) de Ferranti SD, Ioannidis JPA, Lau J, Anninger WV, Barza M. Are amoxycillin and folate inhibitors as effective as other antibiotics for acute sinusitis? A meta-analysis. BMJ 1998;317:632-637
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.

John W. Williams Jr

**Contributors**

Erdem Cantekin

This response was originally added to the Cochrane Review in 2000.

### Amoxicillin results for cure

**Summary**

The heterogeneity in this outcome may be explained by the choice of cure as your outcome measure. You are pooling relative benefit instead of relative risk. If the outcome is entered as failure to cure the heterogeneity disappears and the pooled RR is significant even with a random model. RR = 0.68 (95% CI 0.55 to 0.83).

In my view it is therefore wrong to conclude that Amoxicillin does not have significant benefit in maxillary sinusitis.

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**

The current author group has analysed the data differently to the earlier authors group. Unlike the previous version, in the meta-analyses the data of all placebo-controlled studies were combined across antibiotic classes. In the new analyses pooled risk ratios using the clinical failure rate as an outcome measure were calculated.

The new meta-analyses results do not have any statistically significant heterogeneity between the individual study results.

The data of all placebo-controlled studies were combined despite which antibiotic was used because it was anticipated that there would be only a few placebo-controlled studies available in the analyses. Further, it was presumed that researchers in different countries had had local reasons for selecting particular antibiotics for their trials, taking into account for example, local resistance rates to antibiotics among community acquired pathogens.

This reply was added 09/10/07

**Contributors**

Christopher Cates

This Feedback comment was posted 1999

### WHAT’S NEW

Last assessed as up-to-date: 28 May 2007.

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<th>Changes</th>
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<td>20 December 2007</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>5 October 2007</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
<tr>
<td>28 May 2007</td>
<td>New search has been performed</td>
<td>Searches updated</td>
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HISTORY
Protocol first published: Issue 1, 1997
Review first published: Issue 3, 1999

CONTRIBUTIONS OF AUTHORS
Anneli Ahovuo-Saloranta (AAS) was responsible for study selection, data extraction and analysis, and writing the review.
Oleg Borisenko (OB) and Niina Kovanen (NK) were responsible for study selection, data extraction, and writing the review.
Ulla-Maija Rautakorpi (UMR) was responsible for study selection, and writing the review.
Marjukka Mäkelä (MM), Helena Varonen (HV), and John Williams (JW) were responsible for writing the review.

DECLARATIONS OF INTEREST
None known.

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