# Antibiotics for acute maxillary sinusitis (Review)

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[Intervention Review]

# 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 (Guillemot 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 this review. A search of the database 'System for Information on Grey Literature in Europe (SIGLE)' was intended, but the database was not available via the Internet in November 2005.
For the previous version of this review pharmaceutical companies that manufacture antibiotics used in the treatment of acute sinusitis had been contacted and data and references from all published and unpublished trials on acute sinusitis were requested. Further, three experts in the field had been contacted and asked to review the bibliography of the initial review (1999) for completeness.
There were no language or publication restrictions.

## 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 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 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 included: number of participants in treatment and control groups at start, mean age of participants (plus age range), the number of men and women, the year the study was published, the location where the study was conducted (country and setting where participants were recruited). Characteristics of the intervention that were extracted included: intervention comparisons, courses of antibiotics, and information about co-interventions.

Information on clinical, bacteriological and radiographic outcomes and adverse event rates were extracted. Outcome information was mainly extracted as numbers of participants with clinical failure / non-failure by study group. Relapse within 60 days from the onset of the treatment was classified as a clinical failure.

In some studies the results were stated at more than one period follow up. All data were extracted for pre-selected times, which were 7 to 15 days, 16 to 60 days and over 60 days follow up. Meta-analyses were carried out at these pre-selected times based on the available data.

Final results/decisions were reached by consensus among review authors.

### Data analysis

The data consisted of comparisons for antibiotic versus placebo and antibiotic versus antibiotic. In the meta-analyses of placebo-controlled studies the data of all studies regardless of the antibiotic used were combined. The antibiotic versus antibiotic comparisons were macrolide/cephalosporins versus amoxicillin-clavulanate, non-penicillin antibiotics versus beta-lactamase sensitive penicillins and tetracyclines versus mixed classes of antibiotics. In all studies the outcome results were presented in dichotomous form.

Quantitative analyses of outcomes were performed using an available case data analysis as represented in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 (Deeks 2005). This approach for calculating the response rate uses as a denominator the total number of participants who completed the trial. Risk ratios (RR) were calculated for differences in the intervention and control groups whether treatment had failed or not, along with appropriate standard errors and 95% confidence intervals (CI), using Review Manager (RevMan) version 4.2.7. In assessing the influence of the missing data on the overall results of the placebo-controlled studies (primary outcome measures only), three ways of imputing data were used: assuming the outcomes of participants for whom no outcome was recorded a) as failures, b) as non-failures or c) according to the event rate observed in the control group.

The analyses comparing antibiotic versus antibiotic were performed using available case data without imputation. If the drop-out rate was over 35%, or if it was lower than 35% but there was considerable difference in the drop-out rate between the intervention groups, the study was excluded from the analyses. If the study used intention-to-treat analysis to impute the missing data, it was individually considered whether the data could be used in the analyses.

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 antibiotic, 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

| Study | Comparisons | Diagnostic method | Day assessed | Dropouts | Cured control | Cured antib. | C+I control | C+I antib. | Side effects |
|---|---|---|---|---|---|---|---|---|---|
| Axelsson 1970 (Sweden) | Penicillin V (400 mg three times daily for 10 days) + nasal decongestant (oxymetazoline) versus oxymetazoline | Diagnosis by a radiograph; only patients with secretion included | 10 | 9% | 31% | 46% | 72% | 83% | Penicillin: 8%, Control: 6% |
| Lindbaek 1996a (Norway) | Penicillin V (1320 mg three times daily for 10 days) versus placebo; nasal decongestants and analgesics were allowed but not prescribed in both groups | Clinical symptoms lasting at least 8 days; computer tomography showing opacity or fluid-level | 10 | 2% (combined Lindbaek 1996a + Lindbaek 1996b) | 11% (combined Lindbaek 1996a+ Lindbaek 1996b) | 31% | 89% (combined Lindbaek 1996a + Lindbaek1996b) | 97% | Penicillin: 59%, Placebo: 36% |
| Lindbaek 1996b (Norway) | Amoxicillin ( 500 mg three times daily for 10 days) versus placebo; nasal deconges- | Clinical symptoms lasting at least 8 days; computer tomography showing opac- | 10 | | | 45% | | 98% | Amoxicillin: 56%, Placebo: 36% |

Table 1. Collected information from placebo-controlled studies (*Continued*)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | tants and analgesics were allowed but not prescribed in both groups | ity or fluid-level | | | | | | | |
| Lindbaek 1998a (Norway) | Penicillin V (1320 mg three times daily for 10 days) versus placebo; nasal decongestants and analgesics were allowed but not prescribed in both groups | 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 | 10 | 10% (combined Lindback 1998a + Lindback 1998b) | 43% (combined Lindback 1998a+ Lindback 1998b) | 30% | 86% (combined Lindback 1998a + Lindback1996b) | 91% | Information not available |
| Lindbaek 1998b (Norway) | Amoxicillin (500 mg three times daily for 10 days) versus placebo; nasal decongestants and analgesics were allowed but not pre- | Clinical symptoms lasting at least 8 days; computer tomography showing mucosal thickening of 5 mm or more in any sinus without opac- | 10 | | | 41% | | 86% | Information not available |

**Table 1. Collected information from placebo-controlled studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | scribed in both groups | ity or fluid-level | | | | | | | |
| van Buchem 1997 (The Netherlands) | Amoxicillin (750 mg three times daily for 7 days) versus placebo. Oxymetazoline steam inhalation and paracetamol as needed in both groups | The mean duration of the symptomatic period before treatment 2.2 weeks; radiograph showing > 5 mm mucosal thickening, opacity or air-fluid level | 14 | 4% | 52% | 65% | 77% | 83% | Amoxicillin: 28%, Placebo: 9% |
| Haye 1998 (Norway) | Azithromycin (500 mg once daily for 3 days) versus placebo | 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 | 10-12; 23-27 | 0.6% | 33%; 67% | 58%; 79% | 89%; 88% | 93%; 90% | Azithromycin: 28%, Placebo: 18% |

**Table 1. Collected information from placebo-controlled studies** *(Continued)*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Merenstein 2005 (USA) | Amoxicillin (500 mg twice daily for 10 days) versus placebo | Clinical symptoms > 7 days, purulent nasal discharge, facial pain | 14 | 14% | 42% | 57% | Information not available | Information not available | Amoxicillin: 23%, Placebo: 12% |

### 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 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 66% 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 otolaryngology 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 fulfil 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

Eight
studies compared a non-penicillin antibiotic (cephalosporins, n = 3; macrolides, n = 3; minocycline, n = 1; folate inhibitor, n = 1) to a penicillin-class antibiotic (amoxicillin, n = 7; penicillin V, n = 1), where n is the number of studies.

Seven of these eight studies (involving 1083 participants) provided data for clinical outcome at 7 to 15 days follow up and the data of these studies were combined regardless of the antibiotic used. The studies failed to find a significant difference between antibiotics, with a RR of 0.70 (95% CI 0.47 to 1.06) (Comparison 03, Outcome 01). The drop-out rates of these seven studies ranged from 0% to 32%, and the drop-out rates were approximately equal across the treatment groups in the studies. One study (Haye 1996) provided data at 16 to 60 days follow up, though the study did not find significant difference between the treatment groups with a risk ratio value of 0.67 (95% CI 0.37 to 1.20) (Comparison 03, Outcome 02).

None of the studies reported long-term relapse rates after 60 days. Drop-outs due to adverse effects were infrequent, occurring in 1.3 % and 2.3 % of the non-penicillin and penicillin treated groups, respectively (Comparison 03, Outcome 03).

### Cephalosporins and macrolides versus amoxicillin with clavulanate

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 when the clinical failure was defined as a lack of cure or improvement. These studies found a statistically significant difference for amoxicillin-clavulanate 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).

### Tetracycline antibiotics

Five studies, involving 807 participants, compared a tetracycline (doxycycline, n = 3; tetracycline, n = 1; minocycline, n = 1) to a heterogenous 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 studies 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 (Lindbaek 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 (Lindbaek 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 Lindbaek 1996 (Lindbaek 1996a+Lindbaek 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 Lindbaek 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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