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Antibiotics for clinically diagnosed acute rhinosinusitis in adults (Review)

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[Intervention Review]

Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Marieke B Lemiengre[1], Mieke L van Driel[1,2,3], Dan Merenstein[4], James Young[5], An IM De Sutter[1,6]

[1]Department of General Practice and Primary Health Care, Ghent University, Ghent, Belgium. [2]Discipline of General Practice, School of Medicine, The University of Queensland, Brisbane, Australia. [3]Centre for Research in Evidence-Based Practice, Bond University, Gold Coast, Australia. [4]Department of Family Medicine, Georgetown University Medical Center, Washington, DC, USA. [5]Basel Institute for Clinical Epidemiology, University Hospital Basel, Basel, Switzerland. [6]Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

Contact address: Marieke B Lemiengre, Department of General Practice and Primary Health Care, Ghent University, 6K3, De Pintelaan 185, Ghent, 9000, Belgium. marieke.lemiengre@ugent.be.

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ABSTRACT

Background

In primary care settings, the diagnosis of rhinosinusitis is generally based on clinical signs and symptoms. Technical investigations are not routinely performed, nor recommended. Individual trials show a trend in favour of antibiotics, but the balance of benefit versus harm is unclear.

Objectives

To assess the effect of antibiotics in adults with clinically diagnosed rhinosinusitis in primary care settings.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2012), MEDLINE (January 1950 to February week 4, 2012) and EMBASE (January 1974 to February 2012).

Selection criteria

Randomised controlled trials (RCTs) of antibiotics versus placebo in participants with rhinosinusitis-like signs or symptoms.

Data collection and analysis

Two authors independently extracted data and assessed the risk of bias. We contacted trial authors for additional information. We collected information on adverse effects from the trials.

Main results

We included 10 trials involving 2450 participants. Overall, the risk of bias in these studies was low. Irrespective of the treatment group, 47% of participants were cured after one week and 71% after 14 days. Antibiotics can shorten the time to cure, but only five more participants per 100 will cure faster at any time point between 7 and 14 days if they receive antibiotics instead of placebo (number needed to treat to benefit (NNTB)) 18 (95% confidence interval (CI) 10 to 115, I^2 statistic 0%, eight trials). Purulent secretion

resolves faster with antibiotics (odds ratio (OR) 1.58 (95% CI 1.13 to 2.22)), (NNTB 11, 95% CI 6 to 51, I^2 statistic 0%, three trials). However, 27% of the participants who received antibiotics and 15% of those who received placebo experienced adverse events (OR 2.10, 95% CI 1.60 to 2.77) (number needed to treat to harm (NNTH)) 8 (95% CI 6 to 13, I^2 statistic 13%, seven trials). More participants in the placebo group needed to start antibiotic therapy because of an abnormal course of rhinosinusitis (OR 0.49, 95% CI 0.36 to 0.66), NNTH 20 (95% CI 14 to 35, I^2 statistic 0%, eight trials). Only one disease-related complication (brain abscess) occurred in a patient treated with antibiotics.

Authors' conclusions

The potential benefit of antibiotics in the treatment of clinically diagnosed acute rhinosinusitis needs to be seen in the context of a high prevalence of adverse events. Taking into account antibiotic resistance and the very low incidence of serious complications, we conclude that there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis. This review cannot make recommendations for children, patients with a suppressed immune system and patients with severe disease, as these populations were not included in the available trials.

PLAIN LANGUAGE SUMMARY

Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Acute rhinosinusitis is a common condition that involves blockage of the nose passage and mucus in the sinuses. The diagnosis of acute rhinosinusitis in this review is based on clinical symptoms only, i.e. purulent discharge from the nose or other rhinosinusitis-like symptoms, such as unilateral facial pain or pressure, pain when bending forward, pain in the upper teeth or when chewing, and post-nasal drip. It is often caused by a viral upper respiratory tract infection of which only 0.5% to 2% of cases are estimated to be complicated by a bacterial rhinosinusitis. Nevertheless, antibiotics (used to treat bacterial infections) are often prescribed. Unnecessary prescribing contributes to antimicrobial resistance in the community. Therefore, in order to provide clinicians and patients with evidence-based guidance for management, it is important to assess the effect of antibiotics in acute rhinosinusitis.

We found 10 trials with a low risk of bias involving 2450 participants. Overall, about half of all participants were cured after one week with antibiotic or placebo treatment and three-quarters were cured after 14 days. Antibiotics can shorten the time to cure, but only five more participants per 100 will cure faster after 7 to 14 days if they receive antibiotics instead of placebo, or 18 participants will need to be treated with antibiotics for one extra patient to be cured more quickly. However, for every eight patients treated with antibiotics one patient experiences an adverse event caused by the treatment. The rate of serious complications was very low in both the placebo and antibiotic treatment groups.

Given the lack of clear benefit in terms of rapid recovery and the increase in side effects in participants treated with antibiotics, antibiotics are not recommended as first line treatment in adults with clinically diagnosed acute rhinosinusitis. This review cannot make recommendations for treatment of children, patients with a suppressed immune system and patients with severe disease as these populations were not included in the available trials. More studies are needed to identify which patients might benefit from antibiotics.

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

Antbiotics compared to placebo for clinically diagnosed acute rhinosinusitis in adults

Patient or population: clinically diagnosed acute rhinosinusitis in adults
Settings: general practice (8 studies), otolaryngology outpatient clinics of a university hospital (2 studies), medical centres (1 study)
Intervention: antibiotics
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antbiotics				
Cure	**55 per 100**	**60 per 100** (56 to 65)	**OR 1.25** (1.02 to 1.53)	1687 (8 studies)	⊕⊕⊕⊕ **high**	
Resolution of purulent secretion	**60 per 100**	**70 per 100** (63 to 77)	**OR 1.58** (1.13 to 2.22)	660 (3 studies)	⊕⊕⊕⊕ **high**	
Side effects	**15 per 100**	**27 per 100** (22 to 33)	**OR 2.10** (1.60 to 2.77)	1371 (7 studies)	⊕⊕⊕⊕ **high**	
Diarrhoea	**10 per 100**	**17 per 100** (12 to 24)	**OR 1.81** (1.18 to 2.78)	816 (4 studies)	⊕⊕⊕⊕ **high**	
Treatment failure	**11 per 100**	**6 per 100** (4 to 7)	**OR 0.49** (0.36 to 0.66)	2175 (8 studies)	⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

BACKGROUND

Description of the condition

Acute rhinosinusitis is defined as an acute infection of the nasal passages and the paranasal sinuses. It is one of the most common diagnoses made in general practice and one of the most frequent reasons for prescribing antibiotics (McCaig 1995; USDHHS 1996; Willet 1994). Rhinosinusitis is a more exact term than sinusitis since it takes into account the fact that inflammation of the sinuses is unlikely to occur without inflammation of the mucous membranes of the nose. The term 'sinusitis' will only be used when inflammation of a specific sinus (confirmed by radiology or ultrasound) is mentioned (for example, maxillary sinusitis). In older studies the term sinusitis is often used when referring to rhinosinusitis.

Description of the intervention

In this review, we investigated the effectiveness of antibiotics versus placebo in participants with clinically diagnosed acute rhinosinusitis. Three Cochrane Reviews have previously focused on antibiotic treatment in patients with acute infections of the nose, sinuses or both (Ahovuo-Saloranta 2011; Arroll 2010; Morris 2002). One review studied only patients with clinical signs and symptoms of rhinosinusitis lasting at least seven days, or acute maxillary sinusitis confirmed by a radiograph or a computer tomography (Ahovuo-Saloranta 2011). In these patients, antibiotics were of limited benefit: antibiotics reduced the risk of clinical failure (lack of total cure) at seven to 15 days follow-up. A second Review looked at the effect of antibiotics in patients with an acute upper respiratory tract infection with less than seven days of symptoms, or acute purulent rhinitis of less than 10 days duration (Arroll 2010). The authors concluded that there was insufficient evidence to warrant the use of antibiotics for upper respiratory tract infections in children or adults presenting with these symptoms. Finally, the Morris 2002 review considered antibiotic treatment in children with persistent nasal discharge. The authors concluded that antibiotics have some benefit in the short- and medium-term in children with purulent rhinorrhoea for more than 10 days, or in older children with radiologically confirmed rhinosinusitis.

How the intervention might work

Acute rhinosinusitis can be caused by a viral or a bacterial infection. Acute viral rhinosinusitis is a viral upper respiratory tract infection (or common cold) which, in the majority of cases, also involves the sinuses. Gwaltney 1994 showed that 87% of patients with a common cold also have sinus abnormalities on a computerised tomography (CT) scan. Antibiotics are unnecessary in viral rhinosinusitis. They contribute to bacterial resistance and, in general, have no beneficial effect (Hickner 2001).

Only a minority of patients (0.5% to 2%) develop bacterial rhinosinusitis (Berg 1986; Gwaltney 1996). In this instance, antibiotics may be indicated to speed up recovery or prevent suppurative complications. The problem is that the clinical diagnosis of bacterial rhinosinusitis is difficult (Lindbaeck 2002). Consequently the notions 'viral' and 'bacterial' are not very workable in daily practice and there is a pressing need to identify, on a clinical basis, those patients who will benefit from antibiotics (Lanza 1997).

Why it is important to do this review

Notwithstanding the above cited reviews, one piece of evidence is still missing. In primary care settings, technical investigations are not routinely performed, nor recommended in patients with nasal or paranasal symptoms (Hickner 2001; Low 1997; RCRWP 2003). As a result, in the majority of patients with rhinosinusitis, the diagnosis is based on clinical signs and symptoms. However, previously published Cochrane Reviews (Ahovuo-Saloranta 2011; Arroll 2010; Morris 2002) do not cover the group of patients with clinically diagnosed rhinosinusitis and therefore, cannot answer the question as to whether patients should be treated with antibiotics. Individual trials show a trend in favour of antibiotics for these patients. A systematic review may provide a clearer answer and an estimate of the potential effect size.

OBJECTIVES

1. To determine the efficacy of antibiotics compared to placebo, in reducing duration or severity of general and specific rhinosinusitis symptoms in patients with clinically diagnosed acute rhinosinusitis.

2. To determine if antibiotics have any influence on outcomes for patients with clinically diagnosed acute rhinosinusitis.

3. To determine whether there are significant adverse outcomes associated with placebo therapy for patients with clinically diagnosed acute rhinosinusitis.

4. To determine whether there are significant adverse effects with antibiotic therapy for patients with clinically diagnosed acute rhinosinusitis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) comparing antibiotics with placebo in people with rhinosinusitis-like signs or symptoms. We considered trials including participants with an upper respiratory tract infection or common cold if the majority of participants had rhinosinusitis-like complaints, or if participants with rhinosinusitis-like complaints could be analyzed separately. We excluded the following studies.

1. Trials in which participants were included on the basis of a technical investigation, including imaging studies such as plain radiographs or CT scans, laboratory investigations such as measurement of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), bacteriological or cytological investigations.
2. Studies comparing one antibiotic with another; trials comparing the use of antibiotics versus other medications.
3. Trials in which more than 50% of participants were considered to have a common cold.
4. Trials in which participants had signs and symptoms for more than 30 days.
5. Trials in which participants were not randomised, or trials that did not include a placebo arm.

Types of participants

We considered all trials in which participants with the clinical diagnosis of acute rhinosinusitis were randomly assigned to a treatment with an antibiotic or a placebo. The clinical diagnosis of acute rhinosinusitis was based on the presence of clinical signs or symptoms that are associated with the presence of fluid in the sinuses in diagnostic studies or that are mentioned in clinical practice guidelines as indicating rhinosinusitis. These included: started with a common cold or experiences the two phases of the illness (i.e. catches a cold, feels better after a few days, then feels worse again), purulent nasal discharge, unilateral maxillary pain, pain in the upper teeth, pain when chewing, post-nasal drip, pain on bending forward, and duration of complaints for more than seven days.

The review was limited to studies of adults (18 years of age and older), as studies on children were reviewed by Morris (Morris 2002). The duration of complaints was 30 days or less to exclude participants with subacute or chronic rhinosinusitis, where the infection is probably not the primary cause of the inflammation (Bachert 2003).

Types of interventions

We included only RCTs that compared antibiotic therapy versus placebo. We included trials which allowed concurrent use of other medications if they allowed equal access for participants in both the antibiotic and placebo group.

Types of outcome measures

Primary outcomes

1. The proportion of participants cured at a specific time point.

Secondary outcomes

1. Ratings of measures of overall well-being.
2. Severity or duration of different clinical symptoms.
3. Use of concomitant medications.
4. Adverse effects.
5. Clinical failure and serious adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2; www.thecochranelibrary.com (accessed 10 October 2012), MEDLINE (January 1950 to February week 4, 2012) and EMBASE (January 1974 to February 2012).

We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE; sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search terms to search EMBASE (see Appendix 2). We imposed no language or publication restrictions.

Searching other resources

We scrutinised the reference lists of identified trials, systematic reviews and relevant guidelines for other eligible trials.

Data collection and analysis

Selection of studies

One author (ML) carried out the selection of papers on the basis of titles, keywords and abstracts, and excluded trials that clearly did not meet the inclusion criteria of the review. In the selection procedure, we used the following strategy. First, we screened titles and keywords using specific criteria: the study population consisted of adults (we excluded studies with children, animals, cadavers or in vitro research); the main topic of the study was acute rhinosinusitis or upper respiratory tract infection in general (we excluded studies about specific kinds of rhinosinusitis, specific kinds of bacteria,

rhinosinusitis in a specific group of patients (e.g. HIV positive patients), rhinosinusitis in surgical settings and chronic sinusitis); randomised controlled trials (RCTs), (we excluded cohort studies, reviews, meta-analyses, case reports, retrospective studies, guidelines, letters to the Editor, editorials, observational trials, comments, qualitative research, case-control studies, and secondary analyses of RCTs); the comparison was antibiotic versus placebo (we excluded studies that compared antibiotics versus antibiotics, other treatment versus placebo, other treatment versus antibiotics, and different lengths or doses of antibiotics); and clinical diagnosis of rhinosinusitis (we excluded studies that included patients diagnosed on the basis of radiography, CT scan, laboratory results, ultrasonography or bacteriology). If the title was not informative, we read the abstract and executed the same selection procedure. If the information relevant to the inclusion criteria was not available in the title, keywords or abstract, or if the title and keywords were not informative and the abstract was not available, we retrieved the full-text of the report. We obtained the full-text of every article considered for inclusion. Two authors (ML, ADS) assessed papers that passed this initial review for inclusion.

Data extraction and management

Two authors (ML, ADS) independently performed data extraction and we resolved disagreements by consensus. We extracted data on the trial methodology, including study design, study protocol and statistical analysis. We extracted information about participants, including the total number of participants, setting, inclusion and exclusion criteria, age, country of recruitment and the year of publication of the paper. We extracted characteristics of the intervention including the number of intervention groups, intervention comparisons, type of antibiotics, dosage and length of the antibiotic course, and allowance to use concomitant medication. Furthermore, we extracted data on primary and secondary outcomes. Finally, we extracted information about the proportion of participants cured at a specific time point, ratings of measures of overall well-being, duration or severity of different clinical symptoms, frequency of unfavourable clinical evolution, and adverse effects.

Assessment of risk of bias in included studies

We assessed the methodological quality of the included studies as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) which evaluates allocation, blinding, incomplete outcome data, selective reporting and other potential sources of bias. Two review authors (ML, ADS) independently categorised studies as low risk of bias (all criteria met to satisfaction), risk of bias (one or more criteria partially met) or high risk of bias (one or more criteria not met). There were no disagreements between the reviews authors.

Measures of treatment effect

The data consisted of comparisons of antibiotic versus placebo. We investigated the overall effect of antibiotics in adult participants with clinically diagnosed rhinosinusitis.

Unit of analysis issues

In cases with multiple treatment groups, we compared the event rates in the treatment arms with antibiotics as intervention with the event rates in the treatment arms with placebo. We didn't include cluster-randomised trials in the review.

Dealing with missing data

We performed the analyses comparing antibiotic versus placebo using available data. We asked the trial authors of Merenstein 2005 for information about the allocation process. If the pooling of event rates was not possible because of lack of published data, we compared the published results from the individual trials with the results of the pooled data. If in studies the drop-out rate was over 35% or lower than 35% but with considerable difference in the drop-out rate in the intervention groups, we excluded the study from the analyses. If the study used intention-to-treat (ITT) analysis to impute missing data, we considered on a case by case basis whether the data could be used in the analyses. We discuss this where applicable.

Assessment of heterogeneity

We assessed variability among studies for statistical heterogeneity using The Cochrane Collaboration's test for heterogeneity and the I^2 statistic. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. We considered a value greater than 50% to represent substantial heterogeneity. In that case, we used a random-effects model, as indicated in the Results section.

Assessment of reporting biases

We did not use a funnel plot to assess the likelihood of publication bias as less than 25 studies were available for analysis.

Data synthesis

We presented cure rates, expressing treatment success (dichotomous variable) at a specific time point, as odds ratios (ORs), reflecting differences in the intervention and control groups, along with the appropriate 95% confidence intervals (CIs), using Review Manager 5.1 (RevMan 2011). In assessing the influence of missing data on the overall results, we used three ways of imputing data: assuming the outcomes of participants from whom no outcome was recorded 1) as cured, 2) as not cured, or 3) according to the cure rate observed in the control group. Secondly, we calculated ORs for adverse events. If the event rates were below 1%, we used

the Peto OR as this method is found to be the least biased and most powerful method providing the best CI coverage if there is no substantial imbalance between treatment and control group sizes within studies, and treatment effects are not exceptionally large, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

The included studies were sufficiently homogeneous in terms of participants.

Subgroup analysis and investigation of heterogeneity

We extracted data about purulent secretion, pain, general feeling of illness, illness duration, restriction of daily activities, intake of analgesics and nasal decongestants, side effects, treatment failure and serious adverse events. Data pooling was possible for purulent secretion, side effects and treatment failure.

In case of heterogeneity, we searched for outliers in the forest plot and we investigated whether exclusion of the outlier had an impact on the pooled result.

Sensitivity analysis

In general, we considered the risk of bias of studies included in the meta-analysis as low and therefore we did not perform a sensitivity analysis for the impact of risk of bias on the overall outcome.

RESULTS

Description of studies

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

Results of the search

We identified 1347 records from our electronic searches, after deleting duplicates. Following the selection procedure as described above, we rejected 899 records and included four papers on the basis of the title or keywords (Bladt 1998; Bucher 2003; Stalman 1997; Varonen 2003). We rejected another 386 records and included six papers after reading the abstract (De Sutter 2002; Garbutt 2012; Kaiser 2001; Merenstein 2005; Norrelund 1978; Williamson 2007). We translated all non-English language report abstracts to assess the studies. In total we retrieved 46 full-text reports, because the title was not informative and the abstracts were missing or did not provide sufficient information to decide whether to include or not. We rejected 45 records and included one paper (Meltzer 2005) after reading the full-text report. Besides this, we rejected six conference reports. Bladt 1998 contained a translation of Stalman 1997 in Dutch and we decided to use the data from the original article.

Included studies

In total, 10 trials met all inclusion criteria for our review. These trials involved 2450 participants evaluating antibiotics compared with placebo for acute rhinosinusitis (1239 in the intervention group, 1211 in the placebo group) (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007).

Overall, 4.8% of the included participants dropped out. In accordance with the predefined inclusion criteria of this review, all included studies used only clinical signs and symptoms to admit participants in their study. The three most used inclusion criteria were nasal discharge (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007), facial pain (Bucher 2003; Garbutt 2012; Meltzer 2005; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007) and common cold or upper respiratory tract infection (De Sutter 2002; Kaiser 2001; Stalman 1997; Varonen 2003). Bucher 2003 and Kaiser 2001 included patients with pus in the nasal cavity on rhinoscopy. In three other studies (Merenstein 2005; Varonen 2003; Williamson 2007) it was one of the clinical criteria for inclusion. Common exclusion criteria were recent antibiotic use (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Merenstein 2005; Stalman 1997; Varonen 2003; Williamson 2007), severe illness (Kaiser 2001; Meltzer 2005; Stalman 1997), symptoms of complicated rhinosinusitis (De Sutter 2002; Garbutt 2012; Varonen 2003), long-lasting complaints before inclusion (Bucher 2003; De Sutter 2002; Stalman 1997; Varonen 2003), chronic ear-nose-throat (ENT) disease (Bucher 2003; Kaiser 2001; Meltzer 2005; Varonen 2003; Williamson 2007), comorbidity (De Sutter 2002; Kaiser 2001; Merenstein 2005; Stalman 1997; Williamson 2007), previous sinus surgery (Merenstein 2005; Varonen 2003), immune deficiency (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Merenstein 2005), allergy for study medication (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007), pregnancy or lactation (Bucher 2003; De Sutter 2002; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007) and inability to follow the protocol (language or mental problems) (Bucher 2003; De Sutter 2002; Garbutt 2012; Stalman 1997). Because of the occurrence of a brain abscess in the placebo group, after 2000, Bucher 2003 excluded participants with a CRP-level greater than 100 mg/L, a C-reactive protein (CRP)-level between 50 and 99 mg/L if clinical worsening, or an increase in CRP higher than 100 mg/L occurring three days after inclusion as a safety measure. Finally, no participants had to be excluded because of this new reason for exclusion.

In this review, we excluded participants younger than 18 years. Kaiser 2001 excluded participants with a positive pharyngeal culture for *Streptococcus pyogenes (S. pyogenes)*. Stalman 1997 excluded

participants who used xylometazoline nose drops for more than seven days, received antacid or iron treatment or were referred to an ear,nose and throat (ENT) specialist. Garbutt 2012 excluded participants who rated their symptoms as very mild or mild. Six studies compared amoxicillin to placebo (De Sutter 2002; Garbutt 2012; Meltzer 2005; Merenstein 2005; Varonen 2003; Williamson 2007). Three of these studies had more than one treatment arm. One of these compared amoxicillin, penicillin V and doxycycline to placebo (Varonen 2003). The other two studies had three intervention arms, Meltzer 2005 (monometasone furoate nasal spray once daily, monometasone furoate nasal spray once daily, amoxicillin), and Williamson 2007 (budesonide nasal spray, amoxicillin, budesonide nasal spray and amoxicillin). These three interventions were compared to placebo. One study compared pivampicillin (Norrelund 1978), one azithromycin (Kaiser 2001), one doxycycline (Stalman 1997), and one amoxicillin/clavulanic acid (Bucher 2003) to placebo.

All antibiotics were given orally. Nasal decongestants and analgesics were allowed in seven studies (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Norrelund 1978; Stalman 1997; Varonen 2003) and not permitted in one study (Meltzer 2005). In three studies, nasal decongestants were prescribed for every participant (Bucher 2003; Garbutt 2012; Norrelund 1978). In two studies intake of this medication was not mentioned (Merenstein 2005; Williamson 2007). In Garbutt 2012, cough syrup was prescribed for every participant (dextromethorphan hydrobromide or guaifenesin).

Participants were recruited from primary care settings in eight studies (Bucher 2003; De Sutter 2002; Garbutt 2012; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007). In one of these studies, walk-in participants and non-referred participants from otolaryngology outpatient clinics of the University Hospital were also enrolled (Bucher 2003). Kaiser 2001 recruited participants from an outpatient clinic of a University Hospital. In Meltzer 2005, participants from 14 medical centres worldwide were enrolled. Their setting was not described.

The average age of the participants was approximately 37 years. One study did not report the mean age but we could calculate a median age between 30 and 39 years (Norrelund 1978). The male to female ratio was about 5:8. The mean duration of symptoms before inclusion was approximately seven days (Bucher 2003; De Sutter 2002; Kaiser 2001; Meltzer 2005; Merenstein 2005; Stalman 1997; Williamson 2007). In Garbutt 2012, the mean duration of symptoms at baseline was 11 days.

Clinical cure or improvement as primary outcome was defined in all trials, except for Garbutt 2012 and Meltzer 2005 who used a symptom score as main outcome measure. Garbutt 2012 used the mean change in SinoNasal Outcome Test-16 score, a validated and responsive measure, to measure the effect of treatment on disease-specific quality of life at day three. Meltzer 2005 used the mean AM/PMmajor symptom score (sum of the scores for rhinorrhoea, postnasal drip, nasal decongestion/stuffiness, sinus headache and facial pain/pressure/tenderness on palpation over the paranasal sinuses) over day 2 to 15 of the treatment phase as a primary outcome measure. As these studies did not mention the proportion of participants cured at a specific time point, we could not include them in the pooling. In the trials that used clinical cure or improvement as primary outcome (Bucher 2003; De Sutter 2002; Kaiser 2001; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007), the definitions of cure varied, which is reflected in a variation of cure rate in the placebo group from 30% to 74%. But because the treatment effect did not vary much, pooling was acceptable. In addition, some trials provided information on purulent secretion (Bucher 2003; De Sutter 2002; Meltzer 2005; Norrelund 1978; Stalman 1997), pain (De Sutter 2002; Meltzer 2005; Stalman 1997; Williamson 2007), general feeling of illness (De Sutter 2002; Merenstein 2005; Williamson 2007), illness duration (Merenstein 2005; Norrelund 1978; Varonen 2003; Williamson 2007), restriction of daily activities (Bucher 2003; De Sutter 2002; Garbutt 2012; Stalman 1997; Williamson 2007), intake of analgesics (De Sutter 2002; Norrelund 1978, Stalman 1997; Varonen 2003), intake of nasal decongestants (Stalman 1997; Varonen 2003), side effects (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Merenstein 2005; Norrelund 1978, Stalman 1997; Varonen 2003), clinical failure (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Stalman 1997; Varonen 2003; Williamson 2007), number of participants lost to follow-up (De Sutter 2002; Garbutt 2012; Meltzer 2005; Merenstein 2005; Stalman 1997; Williamson 2007) and serious adverse events (Bucher 2003; Garbutt 2012; Williamson 2007).

In four studies (Bucher 2003; De Sutter 2002; Kaiser 2001; Varonen 2003), radiographs were taken but only Kaiser 2001 used them to assess the outcome. This study found among the subset of participants with radiologically confirmed rhinosinusitis at baseline, a resolution of symptoms in 71% of those in the azithromycin group compared to 60% of those in the placebo group (odds ratio (OR) 1.70, 95% CI 0.67 to 4.28, P = 0.16). In Varonen 2003, all participants underwent an ultrasound of the sinuses and 74 participants tested positive for acute maxillary sinusitis. At the beginning of the study, ultrasound positive and negative participants had similar symptom scores. Varonen et al did not investigate the interaction between the ultrasound result, cure and randomised group. They only reported that in the placebo group, participants who had maxillary sinusitis on the ultrasound seemed to start other antibiotics and seemed to withdraw from the study more often than those with no maxillary sinusitis on ultrasound, but this difference was not statistically significant. At the two-week follow-up, participants with maxillary sinusitis on ultrasound examination had recovered better than those without this finding (respiratory symptom score 2.8 (standard deviation (SD 3.2) versus 4.1 (SD 3.8), P = 0.03).

Three studies (Bucher 2003; Kaiser 2001; Varonen 2003) took laboratory samples: two of them (Kaiser 2001; Varonen 2003)

obtained nasopharyngeal secretions for culture and one (Bucher 2003) measured CRP, leukocytes and neutrophils. Only Kaiser 2001 investigated the interaction between culture result, cure and randomised group. They found that participants with a positive culture in the antibiotic group had lower symptom scores (P = 0.002) and a higher rate of symptom resolution on day seven (respectively, 73% versus 47%; P = 0.007) and a higher cure rate on day eight (respectively, 65% versus 41%; P = 0.032) compared to participants in the placebo group. In the culture negative group, there was no significant difference in symptom resolution on day seven between the antibiotic and placebo group (respectively, 63% versus 69%; P = 0.75).

See Characteristics of included studies table and Table 1.

Excluded studies

In total, 1337 papers did not meet our inclusion criteria. The main reasons for exclusion were: studies with children (167 records), the main topic of the study was not acute rhinosinusitis or upper respiratory tract infection in general (389 records), review articles (137 records), and randomised trials that compared two different antibiotics (175 records).

We excluded 14 RCTs, of which 12 original trials compared antibiotic therapy with placebo in participants with rhinosinusitis-like signs or symptoms. However, each of these studies had an extra inclusion criterion based on a technical investigation: radiology (Axelsson 1970; Hadley 2010; Haye 1998; Pessey 1999; Rantanen 1973; van Buchem 1997b; van Buchem 1997a), computed tomography (Lindbaek 1996; Lindbaek 1998), bacteriology (Gananca 1973; Gananca 1977; Hadley 2010; Lacroix 2002), or laboratory results (Hansen 2000a; Hansen 2000b). van Buchem 1997b was a translation of van Buchem 1997a in Dutch. Hansen 2000b was a translation of Hansen 2000a in Danish.

See table Characteristics of excluded studies.

Risk of bias in included studies

The risk of bias assessment is reported in the Characteristics of included studies table and graphically presented in Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

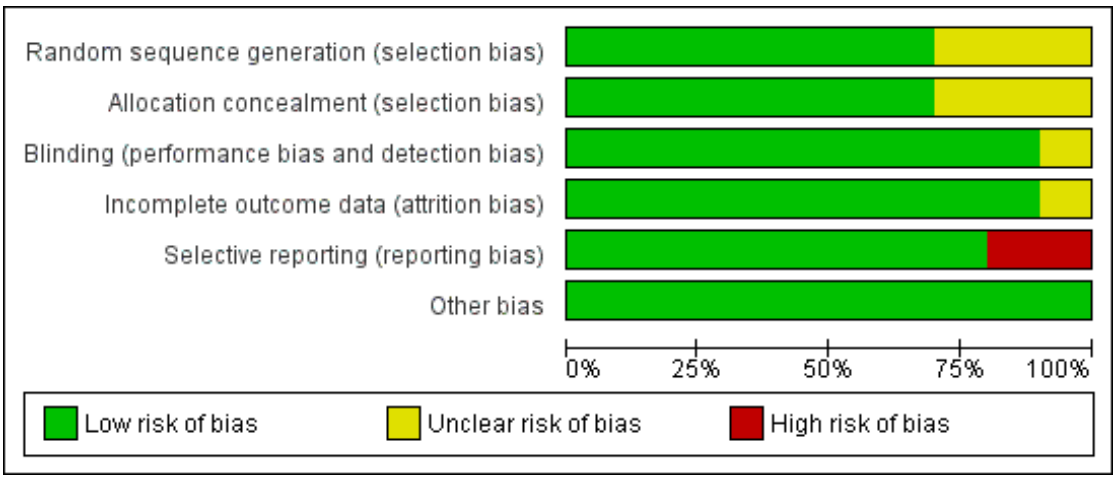
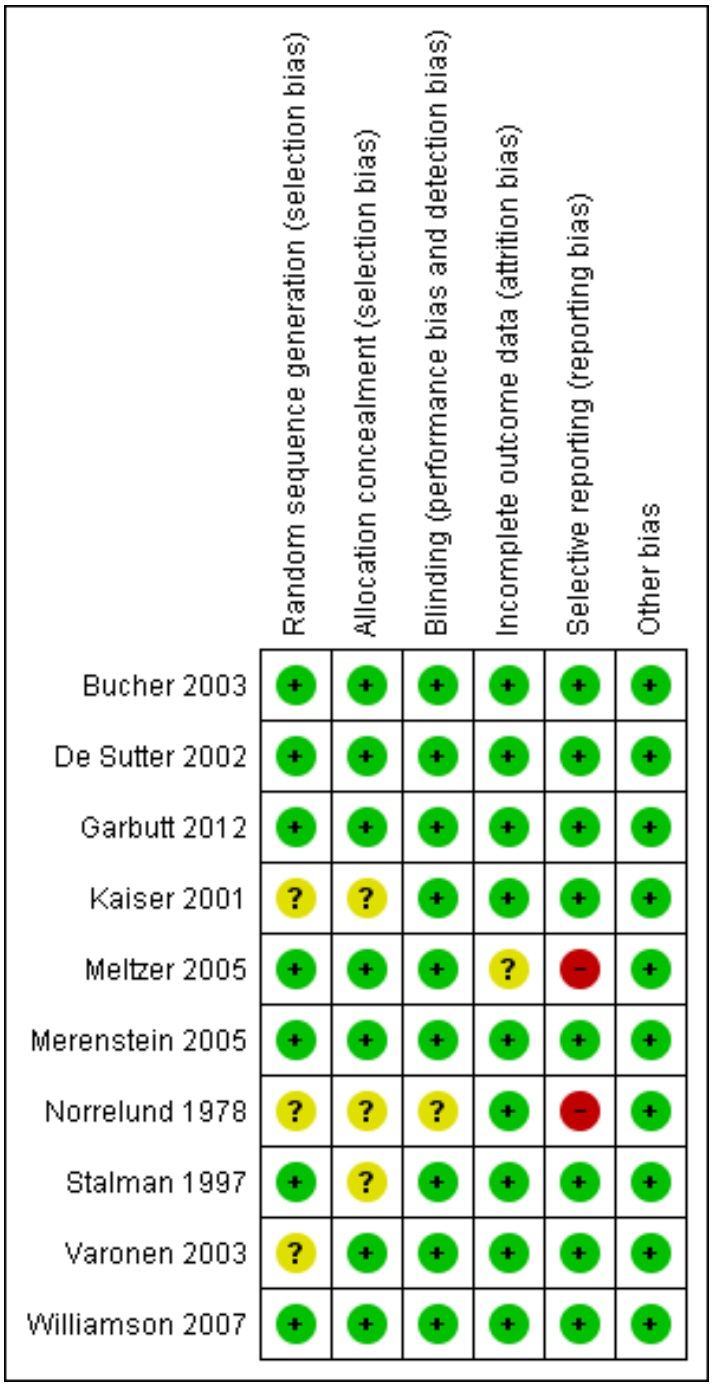


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The allocation sequence was adequately generated in seven studies (Bucher 2003; De Sutter 2002; Garbutt 2012; Meltzer 2005; Merenstein 2005; Stalman 1997; Williamson 2007). Four of these studies used blocked randomisation (Garbutt 2012; Merenstein 2005; Stalman 1997; Williamson 2007), one study used unrestricted randomisation (De Sutter 2002) and two studies combined blocked and stratified randomisation (Bucher 2003; Meltzer 2005). Six studies used a computer random number generator (Bucher 2003; De Sutter 2002; Garbutt 2012; Meltzer 2005; Merenstein 2005; Stalman 1997). Williamson 2007 used random number tables to select the blocks. In three studies there was insufficient information about the sequence generation process (Kaiser 2001; Norrelund 1978; Varonen 2003). Kaiser 2001 only reported a random assignment. Two studies reported a block randomisation procedure but did not specify the process of selecting these blocks (Norrelund 1978; Varonen 2003).

The allocation was adequately concealed in seven studies (Bucher 2003; De Sutter 2002; Garbutt 2012; Meltzer 2005; Merenstein 2005; Varonen 2003; Williamson 2007). Two studies did not provide information on the methods to blind participants and the investigators enrolling participants (Norrelund 1978; Stalman 1997). One study only mentioned that the medication boxes or envelopes were identical for drugs and placebo, but did not state sequential numbering (Kaiser 2001).

Blinding

The allocated intervention was adequately blinded in nine studies (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Merenstein 2005; Stalman 1997; Varonen 2003; Williamson 2007). In these studies, the drug and placebo tablets were identical in colour, shape and taste and blinding of participants and investigators was assured. Norrelund 1978 claimed that the study was double-blinded but provided no information about the blinding procedure.

Incomplete outcome data

The overall post-randomisation drop-out rate was 122/2450 (4.8%).

As described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) the ratio of patients with missing data to participants with events is a good marker of bias due to incomplete data. In the included studies with 'cure' as primary outcome (Bucher 2003; De Sutter 2002; Kaiser 2001; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007), this ratio ranged from 0.01 to 0.33. This value indicates that in these eight studies, the risk of bias due to drop-outs was low.

De Sutter 2002 and Williamson 2007 performed a sensitivity analysis. In these trials, different scenarios did not reveal a significant difference in cure rate between the intervention and control group. Garbutt 2012 did a sensitivity analysis for participants who completed the study drug and those with symptoms for seven days or more and 28 days or less. Findings were consistent with Merenstein 2005. Varonen 2003 chose to impute their drop-outs as treatment failures.

Seven studies followed the intention-to-treat (ITT) principle for the analysis of the main outcome (Bucher 2003; De Sutter 2002; Garbutt 2012; Meltzer 2005; Merenstein 2005; Stalman 1997; Varonen 2003). Three trials included only participants with complete outcome data (Kaiser 2001; Norrelund 1978; Williamson 2007).

Selective reporting

The study protocol was described in all included studies. In nine studies, the primary and secondary endpoints were predefined (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Merenstein 2005; Stalman 1997; Varonen 2003; Williamson 2007). Norrelund 1978 only predefined which symptoms, side effects and medication intakes they would register. Their definition of 'cure' is described for the first time in the section Results. Meltzer 2005 reported most outcomes of interest incompletely and therefore we cannot pool them with data of other trials. The unpublished Schering-Plough trial had exactly the same design as Meltzer 2005 but had a lower odds ratio (OR) (Young 2008), which could suggest selective reporting .

Other potential sources of bias

None of the studies contained design-specific risks of bias or were stopped early. Only in two studies was there a small but not important imbalance of participant characteristics at baseline (Stalman 1997; Williamson 2007). In none of the trials was blinding broken due to side effects. All papers included participants with a diagnosis based on signs and symptoms. The study protocols for participants in the intervention and placebo groups did not differ. Therefore, we can rule out a possible bias due to increased or different diagnostic activity. Five studies were financially supported by government or funding from academic institutions (Garbutt 2012; Merenstein 2005; Stalman 1997; Varonen 2003; Williamson 2007). In six studies, the researchers received grants from the pharmaceutical industry (Bucher 2003; De Sutter 2002; Meltzer 2005; Stalman 1997; Varonen 2003; Williamson 2007). Two studies did not state their source of support (Kaiser 2001; Norrelund 1978).

Patients were recruited from 276 practices. In two trials, all participants were recruited from one site (Kaiser 2001; Merenstein 2005). In eight trials, participants were recruited from multiple sites, with a median of 9.9 participants per practice (range 3.6 to 15.8, 25 th percentile = 6.5, 75 th percentile = 15.5) (Bucher 2003; De Sutter 2002; Garbutt 2012; Meltzer 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Antbiotics compared to placebo for clinically diagnosed acute rhinosinusitis in adults

1. Primary outcome: cure

Eight studies (Bucher 2003; De Sutter 2002; Kaiser 2001; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003; Williamson 2007) defined 'cure' (descriptions are reported in Table 1). The common denominator of all the definitions was the resolution or improvement of major symptoms, evaluated by the participant alone (Bucher 2003; De Sutter 2002; Merenstein 2005; Varonen 2003; Williamson 2007) or by the participant and the investigator (Kaiser 2001; Norrelund 1978; Stalman 1997). As described above in two studies (Garbutt 2012; Meltzer 2005) a difference in symptom score between the antibiotic and placebo group was the primary outcome and could therefore not be included in the pooling.

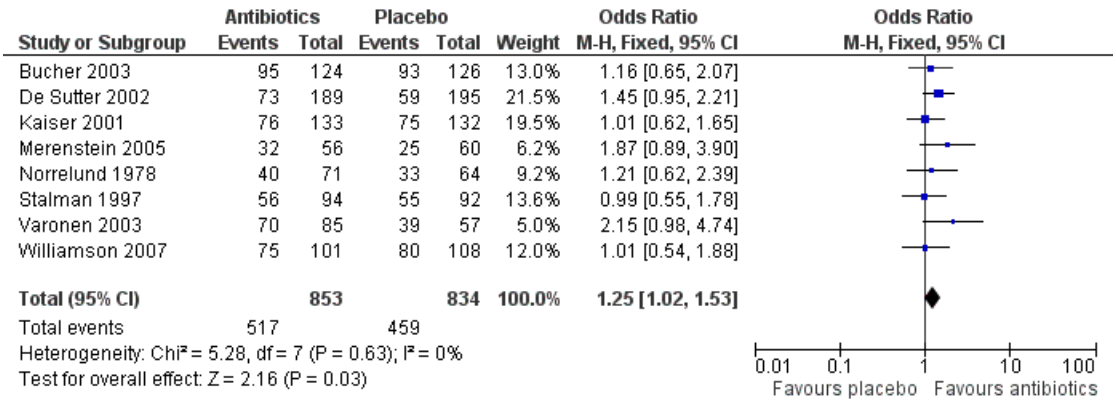
Our intention-to-treat (ITT) population consisted of 2450 participants. We were able to analyze data of 1687 participants (69%). We excluded Meltzer 2005 (499 participants) and Garbutt 2012 (166 participants) because, as described before, their primary outcome measure was not 'cure'.

Despite the choice of the trial authors, we decided to consider participants who started other antibiotics as treatment failures and not as drop-outs. For Kaiser 2001, we decided to use the clinical evaluation as criterion for cure.

Irrespective of treatment group, 47% of participants were cured after one week, 49.5% after 10 days, and 71% after 14 days.

The estimated OR for the overall treatment effect of antibiotics relative to placebo was 1.25 (95% CI 1.02 to 1.53, number needed to treat to benefit (NNTB) 18.0 (95% CI 9.7 to 114.9)), I^2 statistic 0% (Analysis 1.1, Figure 3).

Figure 3. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.1 Overall treatment effect.



We divided the studies into three groups: in the first group cure was assessed at one week (Bucher 2003; Kaiser 2001; Norrelund 1978; Williamson 2007), in the second group around day 10 (De Sutter 2002; Stalman 1997; Williamson 2007) and in the third group at day 14 (Bucher 2003; Merenstein 2005; Varonen 2003; Williamson 2007). The heterogeneity among studies was very low (0% at one week and 10 days, and 6% at 14 days).

There were no significant differences between the treatment groups: after one week, the OR for cure was 1.07 (95% CI 0.81 to 1.41) (Analysis 1.2), after 10 days it was 1.18 (95% CI 0.92 to 1.52) (Analysis 1.3), and after 14 days it was 1.48 (95% CI 0.99 to 2.23) (Analysis 1.4). Meltzer 2005 did not find any difference in symptom score between the antibiotic and placebo group, so we assumed that adding data from this study would not change our overall result. Garbutt 2012 found a significant difference in symptom score at day seven, favouring amoxicillin (mean difference (MD) between groups 0.19 (95% CI 0.024 to 0.35)). This

study also provided data about "significantly improved" participants. Adding this data (Analysis 1.5; Analysis 1.6) did not substantially change the overall result.

For assessment of the influence of missing data on the overall results, three ways of imputing data were used: assuming the outcomes of participants for whom no outcome was recorded 1) as cured, 2) as not cured, or 3) according to the cure rate observed in the control group. Twelve analyses (Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16; Analysis 1.17; Analysis 1.18) revealed no clear differences with the basic analyses. Excluding the studies with an ITT analysis (Bucher 2003; De Sutter 2002; Merenstein 2005; Stalman 1997; Varonen 2003) made the small benefit of antibiotics disappear (OR 1.06, 95% CI 0.76 to 1.47), while pooling only studies with an ITT analysis confirmed the small benefit of antibiotics (OR 1.39, 95% CI 1.02 to 1.79).

Pooling studies in which participants declared themselves as cured (Bucher 2003; De Sutter 2002; Merenstein 2005; Varonen 2003; Williamson 2007) endorsed the benefit of antibiotics (OR 1.40, 95% CI 1.08 to 1.82). Pooling studies in which the investigator decided if the participant was cured (Kaiser 2001; Norrelund 1978; Stalman 1997) showed no benefit of antibiotics (OR 1.05, 95% CI 0.76 to 1.46).

Studies that only included patients with pus on rhinoscopy (Bucher 2003; Kaiser 2001) revealed no benefits with antibiotics (OR 1.07, 95% CI 0.74 to 1.56).

2. Secondary outcomes

2.1. Ratings of measures of overall well-being

Two studies (De Sutter 2002; Merenstein 2005) investigated whether participants' general feeling of illness improved faster with antibiotics. Pooling of data was not possible, because De Sutter 2002 used data from a diary and Merenstein 2005 compared Likert scores at different time points. None found a significant difference in treatment groups.

Williamson 2007 found no significant interaction between baseline severity (feeling unwell and level of restriction on daily activity) and treatment group (antibiotic versus placebo).

2.2. Severity or duration of different clinical symptoms

2.2.1. Purulent secretion

Four studies (De Sutter 2002; Meltzer 2005; Norrelund 1978; Stalman 1997) mentioned outcome data for purulent secretion. Data could be extracted from one study on day eight (Norrelund 1978) and from two studies on day 10 (De Sutter 2002; Stalman 1997). The data for De Sutter 2002 were provided by the research team. Meltzer 2005 published only least-square means data. Outcome was reported by the participants in two studies (De Sutter 2002; Meltzer 2005) and by the investigator in two studies (Norrelund 1978; Stalman 1997).

Irrespective of the timing of the endpoint, the estimated OR for the resolution of purulent secretion was 1.58 (95% CI 1.13 to 2.22), NNTB 10.8 (95% CI 6.1 to 50.8) (Analysis 1.19). There was no substantial heterogeneity among the studies (I^2 statistic = 0%).

Some data on purulent secretion could not be pooled. Norrelund 1978 found in 75% of participants in the antibiotic group and in only 56% in the placebo group at least 50% reduction of secretion on day eight (OR 2.29, 95% CI 1.11 to 4.74, NNTB 5.4, P = 0.002). Furthermore, De Sutter 2002 found a significant mean symptom change between baseline and 10-day follow-up (P = < 0.0001). These results are confirmed by Meltzer 2005 who found a significant difference in least-square means for rhinorrhoea between days two and 15 (P = $\leq$ 0.01).

2.2.2. Pain

Four studies (De Sutter 2002; Meltzer 2005; Stalman 1997; Williamson 2007) provided outcome data for pain. Unfortunately, the outcome measures were too different and raw data were not available and therefore pooling of data was not possible.

Considering pain in general, no study found a difference in pain duration between the antibiotic and placebo groups (De Sutter 2002; Stalman 1997; Williamson 2007). Full resolution of pain occurred between day four and day seven in most participants. Also, when considering specific types of pain, such as unilateral facial pain (De Sutter 2002), pain on bending forward (De Sutter 2002; Stalman 1997), pain in upper teeth or when chewing (De Sutter 2002; Stalman 1997), facial pain, pressure or tenderness (De Sutter 2002; Meltzer 2005) and sinus headache (De Sutter 2002; Meltzer 2005), none of the trials detected a significant difference in pain duration when comparing the antibiotic to the placebo groups.

2.2.3. Illness duration

Three studies (Kaiser 2001; Norrelund 1978; Varonen 2003) calculated the mean illness duration. Two studies compared the illness duration between the antibiotic and placebo groups (Norrelund 1978; Varonen 2003). We could not pool the data because the SDs were not available. Norrelund 1978 found a subjective improvement after an average of 3.5 days in the antibiotic group compared with 3.7 days in the placebo group. They did not mention if this was a significant difference but we can assume that this was not the case. Also, Varonen 2003 did not find a significant difference: the mean illness duration in participants taking antibiotics was 6.0 days, compared with 6.4 days in the placebo group (P = 0.66).

2.2.4. Restriction of daily activities

Four studies (Bucher 2003; De Sutter 2002; Garbutt 2012; Stalman 1997) collected data on the restriction of daily activities due to rhinosinusitis. Pooling of data was not possible because the outcome measures were too different. None of the studies found a significant difference in activity restriction between the antibiotic and placebo groups.

Williamson 2007 found no significant interaction between baseline severity (feeling unwell and level of restriction on daily activity) and treatment group (antibiotic versus placebo).

2.3. Intake of concomitant medication

2.3.1. Intake of analgesics

Seven studies allowed the use of analgesics, i.e. paracetamol (Bucher 2003; De Sutter 2002; Garbutt 2012; Norrelund 1978; Stalman 1997; Varonen 2003) and/or ibuprofen (De Sutter 2002; Kaiser 2001; Norrelund 1978; Varonen 2003). Five of these studies (De Sutter 2002; Garbutt 2012; Norrelund 1978; Stalman 1997; Varonen 2003) also recorded the use of analgesics. It was not possible to pool the data because the raw data were not available or the outcome measures were too different. In four studies (De Sutter 2002; Garbutt 2012; Norrelund 1978; Stalman 1997) there was no effect of antibiotics on the use of analgesics. Varonen 2003 revealed that participants receiving placebo used analgesics more often than those receiving antibiotics (43% in the placebo group, and 26% in the antibiotic group, P = 0.03).

2.3.2. Intake of nasal decongestants

Six studies (Bucher 2003; De Sutter 2002; Kaiser 2001; Norrelund 1978; Stalman 1997; Varonen 2003) allowed the use of xylometazoline nose drops. Garbutt 2012 allowed the use of pseudoephedrine-sustained action. Merenstein 2005 did not mention if nose drops were allowed. In two studies (Meltzer 2005; Williamson 2007) corticosteroid nose drops were part of the intervention. Meltzer 2005 explicitly did not allow the use of concomitant medication that could interfere with the study medication.

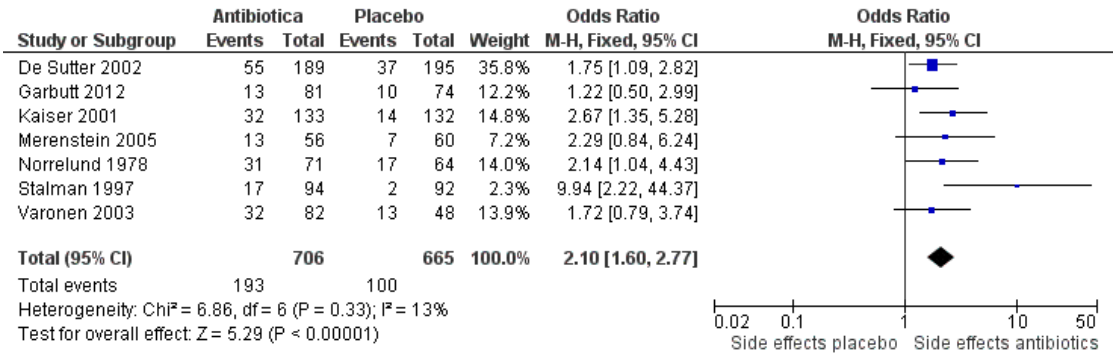
Only two studies registered the intake of nose drops (vasoconstrictors) (Stalman 1997; Varonen 2003) and antihistamines (Varonen 2003). Pooling of data was not possible because the outcome measures were not similar. Neither study found a significant difference in use of these medications. Garbutt 2012 found no difference in the use of pseudoephedrine-sustained action between the antibiotic and placebo group.

2.4. Adverse effects

The adverse effects described in the trials were nausea, vomiting, abdominal pain, stomach pain, diarrhea, skin rash, dizziness, fatigue, hot flashes, jittery feeling, dry mouth, headache, epistaxis and vaginal discharge or pruritus. The most common adverse effects were gastrointestinal.

We pooled data from seven trials on adverse effects in general (De Sutter 2002; Garbutt 2012; Kaiser 2001; Merenstein 2005; Norrelund 1978; Stalman 1997; Varonen 2003). Of the participants who experienced adverse effects, 27.3% received antibiotics and 15% received the placebo. This result was statistically significant (OR 2.10, 95% CI 1.60 to 2.77) (Analysis 1.20, Figure 4), (number needed to treat to harm (NNTH) 8.1 (95% CI 6.0 to 12.5), I^2 statistic = 13%)).

Figure 4. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.13 Side effects.

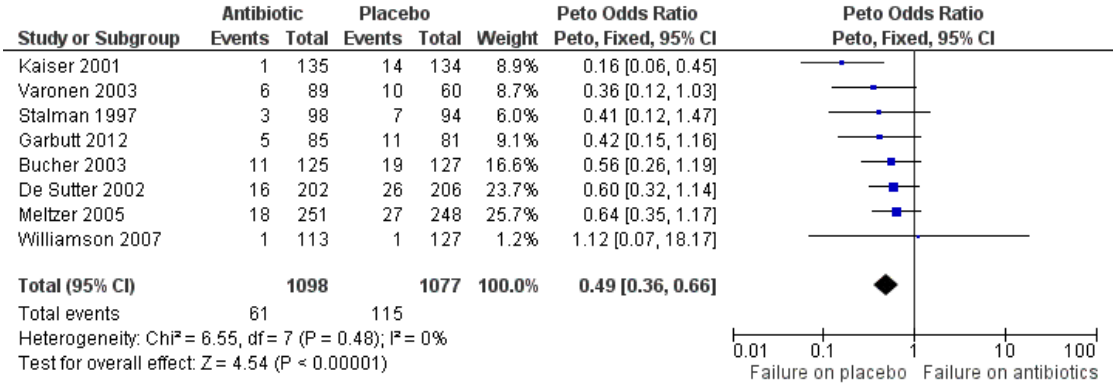


When looking in more detail, we could pool data on diarrhea from four trials (De Sutter 2002; Merenstein 2005; Stalman 1997; Varonen 2003). Of those participants who received antibiotics, 15.9% reported suffering from diarrhea and 10.4% of participants who received placebo suffered from diarrhea. This result was statistically significant (OR 1.81, 95% CI 1.18 to 2.78 (Analysis 1.21), NNTH 18.1 (95% CI 9.9 to 108.7)). We could not pool the results of Bucher 2003, because the raw date were not available, but his results were consistent with ours (OR 3.89, 95% CI 2.09 to 7.25 at seven days; OR 1.71, 95% CI 0.91 to 3.23 at 14 days).
Meltzer 2005 only mentioned that there were no differences in treatment-emergent adverse events among the treatment groups. In his trial, five participants in the amoxicillin group and six in the placebo group discontinued treatment because of adverse events. Williamson 2007 did not provide any information on adverse effects.

2.5. Clinical failure and serious adverse events

We could pool the data on clinical failure from eight trials (Bucher 2003; De Sutter 2002; Garbutt 2012; Kaiser 2001; Meltzer 2005; Stalman 1997; Varonen 2003; Williamson 2007). More participants in the placebo group had to start antibiotic therapy in comparison to the antibiotic group because of an abnormal course of rhinosinusitis (exacerbation, ongoing symptoms, respiratory complications, treatment failure) (10.7% versus 5.5%, OR 0.49 (95% CI 0.36 to 0.66)) (Analysis 1.22, Figure 5), (NNTH 19.5, 95% CI 13.5 to 35.3) .

Figure 5. Forest plot of comparison: 1 Antibiotics versus placebo, outcome: 1.22 Treatment failure.



Only one serious disease-related adverse event occurred (Bucher 2003): after two weeks of symptomatic treatment, a participant who was treated for one week with amoxicillin-clavulanate (1 G twice daily) experienced a brain abscess caused by an amoxicillin-clavulanate-sensitive strain of *Streptococcus milleri (S. milleri)*. The participant was operated on and recovered but was reported to have a residual frontal syndrome.
There were two additional serious adverse events in the placebo group: one myocardial infarction and one severe depressive episode (Bucher 2003). Both were thought to be neither disease nor drug related. Other trials did not report any serious adverse events which means that serious complications in participants with clinically diagnosed acute rhinosinusitis are rare.

DISCUSSION

Summary of main results

Almost one in two participants with clinically diagnosed acute rhinosinusitis are better within one week, and almost three out of four participants within 14 days. Antibiotics shorten the time to cure, but only five more participants per 100 (range one to 10) would cure faster if they took antibiotics instead of placebo. Antibiotics cannot fasten pain relief or the general feeling of illness. Patients who take antibiotics do not resume their daily activities earlier and do not take less analgesics or nasal decongestants than patients treated with placebo. In patients with purulent rhinorrhoea, 10 more patients per 100 (range three to 17) would experience a faster resolution of nasal discharge if antibiotics were given. However, we found that 12 more patients per 100 (range two to 14) would experience side effects of the treatment. This potential

harm needs to be compared to the possible benefit of taking antibiotics in patients with purulent rhinorrhoea. Five fewer patients per 100 (range four to seven) would experience treatment failure if they receive antibiotics instead of placebo (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

In this meta-analysis, we investigated if antibiotic therapy could speed up the recovery process in patients with clinically diagnosed acute rhinosinusitis. In the identified randomised controlled trials (RCTs), the main symptoms used for inclusion were the presence of nasal discharge, facial pain and a common cold or upper respiratory tract infection. This is in line with the clinical presentation of rhinosinusitis in patients in primary care. We did not ask the question "do these patients really suffer from rhinosinusitis and how can we prove this?", as this would require technical investigations that are not routinely performed nor recommended in primary care. We were interested in patients diagnosed with 'acute rhinosinusitis' in primary care and the therapy recommended in that case. Based on the populations included in the studies in this review, we can be reasonably confident that this review covers the general population of patients with rhinosinusitis-like complaints. We cannot draw conclusions about the efficacy of antibiotics in children, patients with a suppressed immune system and patients with serious diseases (e.g. very high fever, prolonged symptoms, septic symptoms such as tachycardia, sweating, and low blood pressure) and patients referred to an ear, nose and throat specialist because of the serious course of the disease or fear of complications, who were not included in the trials and are also unlikely to be included in future placebo controlled trials.

Quality of the evidence

We used the GRADE assessment tool for assessing the level of evidence for each outcome and creating the Summary of findings for the main comparison.

For the outcomes 'cure', 'purulent rhinorrhoea', 'side effects', 'diarrhea' and 'treatment failure', we graded the evidence for the result as 'high'. All studies except one were included in one of the three outcomes, depending on study design. The analyses show a consistent result.

Potential biases in the review process

We carried out a thorough search strategy in several different databases to avoid selection bias. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) part of *The Cochrane Library* Issue 2, 2012 (www.thecochranelibrary.com) (accessed 10 October 2012), MEDLINE (January 1950 to February week 4, 2012) and EMBASE (January 1974 to February 2012). We used a predefined selection procedure for including and excluding studies and followed this strategy consistently. For each relevant reference we have documented the reason for exclusion. The research questions were predefined and answered in the same sequence.

We read the included studies and summarised the information in the table Characteristics of included studies. We assessed the risk of bias rigorously. It is possible we have given undeserved bad points to two studies (Meltzer 2005; Norrelund 1978) but this does not mean that the studies were performed incorrectly. They were evaluated as poor because there was not enough information available in the article.

In some studies raw data were not reported. In that case we estimated the number of events by multiplying the percentage with the total number of participants in that group to make pooling of results possible. Stalman 1997 only mentioned the total cure rate for both groups and stated that there was no difference between both groups. We used the same percentages in both groups for pooling. This assumption could be imprecise, however omitting this data did not substantially change the ORs. Young 2008 had the raw data at their disposal and reported that the exact cure rate was 63% in the placebo group and 66% in the antibiotic group. Using these cure rates in our analysis did not substantially change the ORs (OR 1.27, 95% CI 1.04 to 1.56; NNTB 17, 95% CI 9 to 82) (Analysis 1.23)

The definitions of 'cure' varied in the different trials and this might raise questions about the comparability of the studies, but their underlying interpretation of cure was similar. Besides calculating the overall treatment effect, we divided the studies into three groups: timing of outcome at one week, 10 days and 14 days to assess the effect at various time points.

For the primary outcome 'cure', we checked if inputting missing data in three different ways changed the overall result.

For the secondary outcome 'purulent secretion', data were collected the one time by the patient, the other by clinical inspection. Due to the low number of studies, we did not take this into account.

There was an important variation in choices of antibiotics and dosage schedules. This is possibly due to differences in antibiotic resistance at different time points and in different countries. We assumed that the trial authors' choice of antibiotics was suitable for their countries and local resistance patterns at that point in time. Therefore, we assume this did not influence the effect of the antibiotic treatment on the cure rates, but as bacterial cultures were not performed, we cannot prove this.

As we considered only studies that included patients with clinically diagnosed rhinosinusitis, the proportion of patients with bacterial rhinosinusitis is unknown. However, as described above, we wanted to focus on patients who visited general practitioners with acute rhinosinusitis complaints and who are treated empirically without performing extra technical investigations. This review answers the important clinical question of whether these patients should be treated with antibiotics or not.

Agreements and disagreements with other studies or reviews

We compared our meta-analysis results with those from Rosenfeld 2007, Young 2008 and Falagas 2008.

Rosenfeld 2007 included trials based on a clinical diagnosis, as well as trials that used technical investigations to establish the diagnosis (Gananca 1973; Hansen 2000a; Haye 1998; Lindbaek 1996; Lindbaek 1998; van Buchem 1997a). Norrelund 1978 was excluded because of a language barrier and Williamson 2007 and Garbutt 2012 were not yet published. This study group found a modest antibiotic benefit for patients with uncomplicated acute rhinosinusitis 7 to 12 days after entering a clinical trial (absolute risk difference (RD) 0.15, 95% CI 0.04 to 0.25, RR 1.28, P = 0.007), based on data from Bucher 2003; De Sutter 2002; Gananca 1973; Hansen 2000a; Haye 1998; Kaiser 2001; Lindbaek 1996; Lindbaek 1998; and Stalman 1997. However, there was a high level of heterogeneity (I^2 statistic 80%). The forest plot clearly shows that the benefit of antibiotics is higher in studies with an inclusion based on technical investigations (NNTB 3). The RD of studies that enrolled subjects with a negative imaging, or based strictly on clinical criteria was 0.03 (95% CI -0.02 to 0.08, NNTB 12.5 to 50). This is in accordance with our results. At 14 to 15 days, there was no longer any statistical benefit (results based on data of Bucher 2003; Meltzer 2005; Merenstein 2005; van Buchem 1997a). Benefits were offset by a relative increase of 83% in adverse events (NNTH 9), which is similar to our calculations.

Young 2008 performed a meta-analysis on clinically diagnosed acute rhinosinusitis using individual patient data meta-analysis (IPDMA). An IPDMA is the best way of performing subgroup analyses given that individual patient data of a number of RCTs can be obtained. In this analysis the authors investigated the effect of antibiotics in the subgroup of patients with at least seven days of rhinosinusitis-like symptoms, as guidelines advocate prescribing antibiotics for this patient group (Hickner 2001). This IPDMA was completed by further analysis of the effect of antibiotics in patients with specific signs and symptoms, with the aim of identifying patients who benefit most from antibiotic therapy. Young 2008 included the same trials, except for Norrelund 1978, because they could not get the raw data for the IPDMA and Garbutt 2012 because this trial was not yet published. They included the raw data of Meltzer 2005 and of an identical unpublished trial run by Schering-Plough. The estimated OR for the overall treatment effect of antibiotics relative to placebo was 1.37 (95% CI 1.13 to 1.66, NNTB 15, 95% CI 7 to 190, data IPDMA). The ORs of their analyses of aggregated data were similar (OR 1.35, 95% CI 1.15 to 1.59). This OR for overall treatment effect is slightly higher than in our study, probably due to the favourable results of Meltzer 2005. Young 2008 found that older patients and patients reporting severe symptoms or longer duration of symptoms took longer to cure but they were no more likely to benefit from treatment than other patients. For other patient-reported symptoms (previous common cold or two stages of illness), pain on bending, unilateral facial pain, pain in the teeth and purulent nasal discharge), estimates were not sufficiently precise to draw any conclusion about their prognostic value. Patients with purulent discharge in the pharynx, ascertained by the physician, seemed to cure slower and to have some non-significant benefit of antibiotics (OR 1.60, 95% CI 0.95 to 2.76, NNTB 8, 95% CI 4 to 47). The same was found for patients with a higher temperature (OR 1.28, 95% CI 0.87 to 1.88). As we did not have the raw data, we could not perform this analysis. Young 2008 did not investigate adverse events.

Falagas 2008 included trials in adults or children based on clinical diagnosis and/or technical investigations (extra trials: Gananca 1973; Garbutt 2001 (children); Hansen 2000a; Haye 1998; Kristo 2005 (children); Lindbaek 1996; Lindbaek 1998; Wald 1986 (children)). We excluded Norrelund 1978 because of the language barrier. For Kaiser 2001, we only took into account the subgroup of patients with radiographically confirmed rhinosinusitis. We did not include Garbutt 2012 because this study was not yet published. Falagas 2008 found a higher cure rate in patients taking antibiotics compared to placebo (OR 1.82, 95% CI 1.34 to 2.46, NNTB 9, 95% CI 6 to 15). In this analysis, in only 4 of the 12 trials, the diagnosis was made on clinical criteria only. We did not admit the trials of Kaiser 2001, Meltzer 2005, Stalman 1997 and Varonen 2003 in this analysis because they report only rates for cure or improvement, not for cure only. As in Rosenfeld 2007, the forest plot reveals heterogeneity (I^2 statistic 50%): the trials with inclusion based on technical investigations show more benefit for antibiotics than the ones with inclusion on a clinical basis. Besides this, taking cure or improvement as an outcome measure, Falagas 2008 found that patients with rhinosinusitis benefit from antibiotics (OR 1.64, 95% CI 1.35 to 2.00) NNTB 11 (95% CI 8 to 17). However, for the Meltzer 2005 study, Falagas 2008 used the number of treatment failures as the number of patients that were cured, which makes the cure rate artificially high. The heterogeneity is low but the same trend (more technical investigations, more benefit of antibiotics) can be seen. Falagas 2008 put his positive result into perspective by comparing them to a NNTH (adverse events) of 12 (95% CI 8 to 21), a number that is, irrespective of the different kind of studies included in the analysis, comparable to our results. Falagas 2008 found no significant difference in cure or improvement for adults versus children, imaging versus clinical criteria for inclusion, assessment at 7 to 11 versus 14 to 15 days, nor year of publication.

AUTHORS' CONCLUSIONS

Implications for practice

Our meta-analysis shows that there could be a beneficial therapeutic effect of antibiotics in patients with clinically diagnosed acute rhinosinusitis, but this effect is small and only 5 more patients per

100 will cure faster if they receive antibiotics instead of placebo. The subgroup of patients with purulent discharge could benefit slightly more. However, the benefits need to be seen in the context of the risk of experiencing adverse effects, especially of a gastrointestinal nature. This meta-analysis was directed mainly at patients assessed in a primary care setting and excluded patients that were further investigated with laboratory or radiology tests. Considering the worldwide high antibiotic prescription rate for rhinosinusitis, growing antibiotic resistance and the very low incidence of complications, we can conclude that there is no place for antibiotics in the patient with clinically diagnosed but uncomplicated acute rhinosinusitis. Exceptions should be made for children, patients with a suppressed immune system and patients with severe disease (e.g. very high fever, prolonged symptoms, findings suggestive of severe sepsis such as hypotension) and patients referred to an ear, nose and throat specialist because of confirmed or perceived complications, as there is no evidence available from randomised, placebo controlled trials for these potentially more vulnerable subgroups. Complications are so rare (1/2450 participants) that only case reports can give information about their course, hence evidence that serious complications can be prevented by giving antibiotics early is lacking.

Implications for research

Despite availability of several studies and meta-analyses there is still insufficient data to enable subgroup analysis of patients who could rationally benefit more from antibiotics, e.g. patients with high fever, severe facial pain or rhinorrhoea. Further studies are needed to better predict the success of antibiotic treatment. It may be unlikely that such data will become available as they pose ethical (exposing vulnerable patients to placebo treatment) and feasibility (a relatively small group that would take a long to collect data) issues. Better recording of routinely collected data and morbidity, as well as adverse drug reaction registers might be helpful in answering this question.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Norrelund 1978

Methods	RCT. Clinical diagnosis: participants showed at least 3 symptoms, including at least 1 of the main symptoms (main symptoms: yellow or yellowish-green or possibly blood-stained nasal discharge on blowing the nose; good nasal passage together with a nasal voice; other symptoms: feeling of malaise; headache, particularly behind the eyes, behind the bridge of the nose or corresponding to the maxilla; irritative cough). Registration of symptom score at day 1 and day 8 (purulent secretion, nasal stenosis, general feeling of illness, headache, cough) during visit. Follow-up with diary for 6 days (drug intake, intake of analgesics, intake of nose drops). Questionnaire of side effects (sore throat, nausea, vomiting, stomachache, loose stools, diarrhea, 'other') during second visit. Proportion of the participants without known or reported clinical outcome 3.6% on day 8
Participants	Patients were recruited by 19 general practitioners. Median age not known, but all the participants were older than 14; 55 men and 85 women. Denmark
Interventions	2 treatment arms. Group 1: pivampicillin 700 mg twice daily for 6 days. Group 2: placebo twice daily for 6 days. Concomittant use of nasal decongestants allowed (xylometazoline 0.1% nasal spray, 4 times daily)
Outcomes	Clinical outcomes reported at day 8 in 135 out of 140 people randomised (in 71 out of 73 participants in the pivampicillin group and 64 out of 67 participants in the placebo group). Patients were considered as "cured" if the sum of endpoints for the individual patient was reduced by at least 2/3 on follow-up investigation on day 8. Secondary endpoints were resolution of purulent secretion, resolution of irritative cough, subjective improvement and side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blocked randomisation (each doctor had been sent a box containing 10 glasses, half in random sequence contained an active ingredient). No information about the process of selecting the blocks
Allocation concealment (selection bias)	Unclear risk	No information about the centralisation of randomisation nor the numbering of the glasses
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The glasses contained pivampicillin or identical-looking placebo tablets. No information about the blinding of health care

Norrelund 1978 (*Continued*)

		providers and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate: 5/140 (3.6%). Drop-out balance: 2 out of the pivampicillin group (adherence problems), 3 out of the placebo group (2 because of adverse events, 1 because of adherence problems). The ratio of participants with missing data to participants with events was 0.07. No intention-to-treat analysis
Selective reporting (reporting bias)	High risk	The study protocol is described in the section "methods". The primary and secondary endpoints were not predefined. Nevertheless, they predefined which symptoms, side effects and medication intakes they would register. The definition of "cure" is described for the first time in the section "results"
Other bias	Low risk	There was no information provided about the balance of participant characteristics at baseline, except for gender. With the available information, we cannot detect other reasons for bias (no design-specific risks of bias, the study was not stopped early, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). The authors did not mention a source of support. Patients were recruited from 19 general practitioners, which is an average of 7.1 patients per practice

Stalman 1997

Methods	RCT. Clinical diagnosis: participants showed symptoms of an upper respiratory tract infection for at least 5 days, and 3 main symptoms or 2 main symptoms and 1 other symptom besides (main symptoms: complaints after a common cold or influenza; purulent nasal discharge; pain in the maxillary sinuses on bending forward; other symptoms: predominantly unilateral maxillary pain, toothache, or pain when chewing). Registration of patients' medical history, sex, age, health insurance, season, multiple-choice questions about the duration of complaints, reason for encounter, demand for help, medical history and ear, nose and throat examination during the first visit. Follow-up with diary for 10 days (absenteeism from school or work, frequency of steaming, intake of nose drops and analgesics, intake of study medication, adverse effects). Evaluation by the general practitioner at 10 and 42 days (evaluation of complaints, repeated ear, nose and throat examination). Side effects (nausea, vomiting, abdominal pain, diarrhea, rash, dizziness) were registered. Proportion of the participants without known or reported clinical outcome 3.1% on day 10
Participants	Patients were recruited in 12 collaborating general practices. Mean age 37; 68 men and 124 women. The Netherlands. Exclusion of patients with xylometazoline nose drop treatment lasting more than 7 days, comorbidity (diabetes mellitus, heart failure, immune deficiency), pregnancy or breastfeeding, complaints lasting longer than 3 months, antibiotic treatment in the previous 4 weeks, allergy to doxycycline, severe illness resulting from a sinusitis in one of the other sinuses, antiacid or iron treatment, referral to an ear, nose and throat specialist, inability to speak Dutch
Interventions	2 treatment arms. Group 1: doxycycline 100 mg coated tablets twice daily for 1 day (1st), once daily for 9 days. Group 2: placebo coated tablets twice daily for 1 day, once daily for 9 days. Concomittant treatment: xylometazoline 0.1% nose drops and steam inhalation for 15 minutes 3 times daily as long as they had complaints and paracetamol 500 mg if needed
Outcomes	Clinical outcomes reported at day 10 in 186 out of 192 people randomised (in 94 out of 98 participants in doxycycline group and 92 out of 94 participants in the placebo group). Patients were considered as "cured" if all primary and secondary outcome events were met. Other primary outcomes were resolution of facial pain (McGill-Melzack Pain Questionnaire, recorded daily by the patient, score: none or mild) and resumption of daily activities (recorded daily by the patient, score: normal level). Secondary outcomes were resumption of school or work, intake of analgesics stopped, intake of nose drops stopped, resolution of all initial complaints except a preceding common cold or influenza 10 and 42 days after inclusion and side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were assigned to doxycyline or placebo treatment in blocks of 4 according to a computer-generated randomisation schedule

Allocation concealment (selection bias)	Unclear risk	No information about centralisation of randomisation, numbering of drug containers or opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Doxycycline and placebo appeared and tasted the same. Blinding of patients and treatment team was maintained throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate at day 10: 6/192 (3.1%). Drop-out balance: 4 out of the doxycycline group (2 because of vomiting and abdominal pain) and 2 out of the placebo group. The ratio of participants with missing data to participants with events was 0.05. Discontinuation of trial medication rate: 20/192 (10.4%). Discontinuation of medication balance: 12 out of the doxycycline group (3 for treatment failure, 5 for recurrence, 4 for side effects) and 8 out of the placebo group (7 for treatment failure, 1 for recurrence). All these patients were included in the analysis following the intention to treat principle
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined. Only the definition of "improvement" was not stated clearly
Other bias	Low risk	Concerning the characteristics at baseline, there were slight differences between treatment groups with regard to reason for encounter, demand for help, season, relapse of sinusitis, nasal speech and cervical lymphatic glands. With the available information, we cannot detect other reasons for bias (no design-specific risks of bias, the study was not stopped early, blinding was not broken due to side effects, there was no bias due to increased or different diagnostic activity). This study was supported by grants from the "Nederlandse organisatie voor Wetenschappelijk Onderzoek" and Pharbita Ltd. Patients were recruited from 12 General Practices, which means an average of 15.6 patients per practice

Kaiser 2001

Methods	RCT. Clinical diagnosis: participants presented with common cold or acute sinusitis and had a history of rhinorrhoea of less than 4 weeks and a confirmed upper respiratory tract infection at physical examination, including rhinoscopy. Registration of medical history, examination, including anterior rhinoscopy by ear,nose and throat specialist. Patients were submitted to a rhinoscopy (with aspiration of nasopharyngeal secretions) and sinus radiography (occipitomental view). Follow-up with diary for 7 days (nasal obstruction, rhinorrhoea, fatigue, headache, facial pain, feverishness, cough, sputum, sore throat, postnasal drip and loss of voice). Clinical evaluation at day 8 (cured, improved, same, or worsened; rhinoscopy). Questionnaire after 1 month. Proportion of patients without known or reported clinical outcome: 1.2% at day 8
Participants	Patients were recruited at an outpatient clinic of the University of Geneva Hospital. Median age 35; 127 men and 138 women (gender of 4 drop-outs not described). Switzerland. Exclusion criteria were high fever (> 38.5°C) and an overall clinical impression that antibiotic treatment was absolutely required (~ 4% of the screened population), chronic ear, nose and throat disease, a positive pharyngeal culture for *Streptococcus pyogenes,* known allergy to macrolides, antibiotic treatment in the previous 10 days, immunosuppression and underlying pulmonary disease
Interventions	2 treatment arms. Group 1: azithromycin 500 mg orally once daily for 3 days. Group 2: placebo orally once daily for 3 days. Concomitant treatment with ibuprofen and nasal drops containing oxymetazoline was offered to all patients
Outcomes	Clinical outcomes reported at day 8 in 265 out of 269 people randomised (in 133 participants in the azithromycin group and 132 participants in the placebo group; the assignment of the drop-outs was not mentioned). Patients were considered as "cured" if they achieved resolution of symptoms. Besides this, the cure rate according to the treatment group in the predefined subset of patients with and without *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* was studied. Secondary endpoints were the occurrence of a respiratory complication that required the introduction of open antibiotic treatment and the occurrence of severe sinusitis (defined as worsening of initial symptoms accompanied by facial pain, discharge at middle meatus, or fever)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random assignment. No further information available
Allocation concealment (selection bias)	Unclear risk	Drugs and placebo were in identical containers. No further information available. No information about the centralisation of randomisation nor the numbering of the containers

Blinding (performance bias and detection bias) All outcomes	Low risk	Drugs and placebo had the same shape and taste. Patients and investigators were blinded to the treatment administered. This investigator remained blinded to bacteriological and radiological results, even if an open antibacterial treatment was deemed necessary. The sinus radiograph (occipitomental view) was interpreted independently by 2 radiologists blinded to the clinical results
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate: 4/269 (1.2%). The drop-out balance is not known because the reasons for loss of follow-up are not described. The ratio of participants with missing data to participants with events was 0.03. Open antibiotic treatment (treatment failure): 15/265 (5.7%). Open antibiotic treatment balance: 1 out of the azithromycin group (severe sinusitis), 14 out of the placebo group (severe sinusitis, purulent bronchitis, exudative pharyngitis, otitis media). All these patients seemed to be included in the analysis
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined
Other bias	Low risk	With the available information, we cannot detect reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity) . The authors did not mention a source of support. Patients were recruited from 1 outpatient clinic of the University of Geneva Hospital

De Sutter 2002

Methods	RCT. Clinical diagnosis: participants presented with a respiratory tract infection and had purulent rhinorrhoea. Registration of history, generally ill to very ill, unilateral facial pain, pain on bending forward, pain in upper teeth or when chewing, physical examination, sinus tenderness, pain on bending forward, postnasal discharge on throat inspection, purulent rhinorrhoea on rhinoscopy and body temperature > 37°C at inclusion. Completion of a symptom questionnaire (SNOT-20, 0-5 Likert scale) and 3 questions about pain, indication of the most troublesome symptoms (max 5) at inclusion. Invitation for an optional radiologic examination of the maxillary sinuses (single Waters view) for the estimation of the proportion of sinusitis cases among included patients. Follow-up with diary for 10 days (daily drug intake (trial medication and symptomatic medication), general feeling of illness, presence of nasal discharge, pain and cough, body temperature, occurrence of presumed adverse drug effects and absence from school or work). Clinical evaluation at day 10 (physical examination, symptom questionnaire (SNOT-20, 0-5 Likert scale) and 3 questions about pain, indication of the most troublesome symptoms (max 5)). If patients were insufficiently recovered, general practitioner could prescribe an antibiotic without revealing the previous treatment phase. These patients completed their diary until day 15 and got a new evaluation at day 15. Proportion of patients without known or reported clinical outcome: 5.9% on day 10
Participants	Patients were recruited by 69 general practitioners. Mean age 37 in amoxicillin group and 39 in placebo group; 186 men, 222 women. Belgium. Exclusion criteria was allergy to penicillin or ampicillin, having received antibiotic therapy within the previous week, complaints lasting more than 30 days, abnormality on clinical chest examination, complications of sinusitis (facial oedema or cellulitis; orbital, visual, meningeal, or cerebral signs), pregnancy or lactation, comorbidity that might impair immune competence and inability to follow the protocol because of language or mental health problems
Interventions	2 treatment arms. Group 1: amoxicillin 500 mg 3 times daily for 10 days. Group 2: placebo 3 times daily for 10 days. Concomittant use of xylometazoline 1% nose drops and paracetamol or ibuprofen were allowed
Outcomes	Clinical outcomes reported at day 10 in 384 out of 408 people randomised (in 189 out of 202 participants in the amoxicillin group and 195 of 206 participants in the placebo group). Patients were considered as "cured "if all the symptoms that the patient had included is the list of "most important item affecting my health scored 0 (absent) or 1 (very mild present) after 10 days of treatment. Other primary outcomes were duration of general illness (as noted in the diary), duration of pain (as noted in the diary), duration of purulent rhinorrhoea (as noted in the diary). Secondary outcomes were mean change in severity score (between day 1 and day 10 of the various symptoms), incidence of unfavourable evolution, incidence of side effects, intake of analgesics stopped and duration of sick leave
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

De Sutter 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	Assignment via a computer-generated random number list to receive antibiotics or placebo
Allocation concealment (selection bias)	Low risk	The randomisation list was kept at the pharmacy of the University Hospital. The randomisation list was accessible to the participating family physician only in case of a serious adverse event. The trial medication was supplied in numbered uniform cardboard boxes
Blinding (performance bias and detection bias) All outcomes	Low risk	Capsules had the same size, colour and shape for active and placebo treatment. To assess effectiveness of masking: patients and family physician guessed their treatment group at day 10. Data were encoded and entered without knowledge of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 patients were excluded after randomisation because they did not meet the inclusion criteria (7 complaints > 30 days, 1 allergy to penicillin). Post-randomisation drop-out rate: 24/408 (5.9%) due to loss of follow-up or withdrawal without knowing if they were cured or not. Drop-out balance: 13 out of the amoxicillin group (2 concurrent pathology, 1 allergic reaction, 1 gastrointestinal side effect, 9 lost to follow-up) and 11 out of the placebo group (4 suspected allergic reaction, 7 lost to follow-up). The ratio of participants with missing data to participants with events was 0.18. 2 patients in the amoxicillin group (1 clinical exacerbation, 1 complete recovery) and 8 in the placebo group (7 clinical exacerbation, 1 complete recovery) withdrew with a "known" illness course. 15 patients in the amoxicillin group and 19 in the placebo group got an open antibiotic therapy after 10 days follow-up. Sensitivity analysis performed
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined

De Sutter 2002 (*Continued*)

Other bias	Low risk	With the available information, we cannot detect reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). This trial was financed by a grant by Eurogenerics NV, Brussels. Patients were recruited from 68 General Practices, which means an average of 5.6 patients per practice

Varonen 2003

Methods	RCT. Clinical diagnosis: patients with an upper respiratory tract infection and having at least 3 main symptoms (nasal obstruction, nasal discharge, headache, postnasal drip, cough, sinus pain, unilateral facial pain, maxillary toothache, hyposmia, anosmia, malaise or fever) and 1 clinical sign (purulent secretion in the nasal cavity, discharge in the pharynx and tenderness in sinus tapping). Completion of a questionnaire (12 symptoms (3-steps scale), duration of symptoms, double sickening). Recording of history and clinical findings. Performance of ultrasound examination, nasal samples and sinus radiography (occipitomental, Waters' view). Follow-up with diary for 2 weeks (12 symptoms (3-steps scale), possible self-medication, side effects, overall estimate whether they thought they continued to have sinusitis). Telephone interview after 2 weeks (subjective symptoms, severity, possible side effects, patients' estimate of recovery or recurrence). Check of patient records after 1 year to register recurrent or chronic sinusitis. Proportion of patients without known or reported clinical outcome: 4.7% after 14 days
Participants	Patients were recruited by 35 physicians in 9 health centres. Mean age 40.6 in antibiotic group and 38.1 in placebo group; 44 men, 103 women, 2 not known. Finland. Exclusion criteria were acute maxillary sinusitis symptoms lasting over 30 days, antibiotics during the previous month, allergy to study medications, pregnancy, breastfeeding, exacerbation of a diagnosed chronic maxillary sinusitis, previous paranasal sinus surgery, clinical suspicion of dental or frontal sinusitis or pansinusitis, suspicion of a severe complication and previous sinus surgery
Interventions	Four treatment arms. Group 1: amoxicillin 750 mg 2 times daily for 7 days. Group 2: penicillin V 1500 IU 2 times daily for 7 days. Group 3: doxycycline 100 mg 2 times daily for 7 days. Group 4 (doubled): placebo 2 times daily for 7 days. Concomittant use of xylometazoline, paracetamol or anti-inflammatory agents were allowed if the physician considered them necessary
Outcomes	Clinical outcomes reported at 2 weeks in 142 out of 149 people randomised (originally, 150 patients were randomised, but 1 patient was excluded for pregnancy after randomisation; 2 participants were lost because treatment data were missing; 85 out of 88 participants in the antibiotic group and 57 out of 59 participants in the placebo group). Primary outcome was the recovery rate after 2 weeks, according to the telephone interview.

	Secondary outcomes were incidence of side effects, subjective symptom score (at day 3, at day 10), duration of sinusitis, use of additional medication, frequency of chronic or recurrent sinusitis during 1 year follow-up, number of physician consultations during 1 year follow-up)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The treatments were previously randomised in blocks of 20 consecutive patients at the Military Pharmacy in Helsinki
Allocation concealment (selection bias)	Low risk	The study medications were coded with 6-number individual codes. The senior researcher kept the code and was the primary contact in the case of adverse effects or severe complications. All study centres also had the code in a closed envelope to be opened only if the senior researcher could not be reached
Blinding (performance bias and detection bias) All outcomes	Low risk	The medication bottles were identically sealed. Physicians, patients and the main researcher remained blinded to the treatments until the recruitment was ended. The result of the ultrasound was not disclosed to the patient. The main researcher did not know the patient's history, treatment or the result of the ultrasound examination while interviewing the patient 14 to 16 days after inclusion
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors report that the data were analyzed by intention-to-treat in main outcomes. 1 patient was excluded from the trial after randomisation because of pregnancy. Post-randomisation drop-out rate: 7/149 (4.7%) due to missing treatment data, loss of follow-up or withdrawal without knowing if they were cured or not. Drop-out balance: 2 participants were lost because treatment data were missing, 3 out of the antibiotic group and (side effects), 2 out of the placebo group (1 not reached by phone, 1 side effects). The ratio of participants with missing data to participants with events: 0.

Varonen 2003 (*Continued*)

		07. The authors analyzed the data by intention-to-treat in main outcomes. Withdrawals (trial medication or other antibiotics) were analyzed as treatment failures. Duration of sinusitis was analyzed only in patients who recovered fully during the 2-week follow-up
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined
Other bias	Low risk	With the available information, we cannot detect reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). Stakes, the National Research and Development Centre for Welfare and Health covered the administrative and travel costs of this study. Leiras-Schering and SmithKline Beecham provided the study medication. Patients were recruited from 9 health centres, which means an average of 15.8 patients per centre

Bucher 2003

Methods	RCT. Clinical diagnosis: participants presented a history of repeated purulent nasal discharge and maxillary or frontal unilateral or bilateral pain for at least 48 hours, but less than 1 month, and presence of pus under rhinoscopy (this last criterion was withdrawn after the first winter season). Registration of medical history for rhinosinusitis-like symptoms, number of days during which rhinosinusitis restricted activities at home or work, previous upper respiratory tract infections, clinical examination, questionnaire (rating of severity), radiograph maxillary and frontal sinus (occipitomental view), blood sampling (white blood cell count and CRP level) at inclusion. Follow-up by telephone interview by study nurse at day 14 and 28 (questions about rhinosinusitis-related symptoms, adverse effects, use of other drugs or other visits to physicians). Clinical examination, number of tablets taken and 2nd questionnaire at day 7. Proportion of the participants without known or reported clinical outcome: 0.8% on day 8
Participants	Patients were recruited by 24 general practices and in the internal medicine and otolaryngology outpatient clinics of the University Hospital Basel (only walk-in patients and not referred patients). Mean age 37; 115 men, 136 women, 1 not known. Switzerland. Exclusion criteria were age younger than 18, an upper respiratory tract infection or use of antibiotics for any reason within the previous 4 weeks, an upper respiratory tract infection or intermittent fever that persisted for more than 4 weeks, pathologic

	features or malformation of nasal cavities or the pharynx, immunosuppressive treatment, human immunodeficiency virus infection, allergy to amoxicillin-clavulanate, pregnancy or breastfeeding and no fluency in one of the national languages. After 2000, an extra exclusion criterion was introduced because of a brain abscess in the placebo group: patients with a CPR-level greater than 100 mg/L, a CRP-level between 50 and 99 mg/L (if clinical worsening), or an increase in CRP-level higher than 100 mg/L occurred 3 days after inclusion were rejected from the trial
Interventions	2 treatment arms. Group 1: amoxicillin 875 mg and clavulanic acid 125 mg 2 times daily for 6 days. Group 2: placebo 2 times daily for 6 days. Decongestant therapy (xylometazoline hydrochloride spray) and acetaminophen tablets (500 mg with a maximal dose of 6 tablets a day) were provided. Steam inhalation was allowed
Outcomes	Clinical outcomes reported at day 7 and day 14 in 247 and 250 respectively out of 252 patients randomised (in 122 and 124 respectively out of 125 participants in the amoxicillin/clavulanic acid group and in 125 and 126 respectively out of 127 participants in the placebo group). Patients were considered as cured if they had no days without restrictions due to rhinosinusitis since the previous interview. The primary outcomes were the number of days (since the previous interview) during which rhinosinusitis restricted activities at home or work) and the time to cure in a rating of 1 on a 10-point, equal distance scale for the severity of restricted activity at home or work. Secondary outcomes were the number of days during which rhinosinusitis restricted activities at home or work, the frequency of adverse effects and the recurrence rate of rhinosinusitis at 28 days
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer random number generator was used. Stratified randomisation: general practice or outpatient clinic as stratification unit, patients randomised in blocks of 6
Allocation concealment (selection bias)	Low risk	Tablets were provided in identical, numbered containers. The allocation sequence was performed by a statistician who was not involved in the final analysis
Blinding (performance bias and detection bias) All outcomes	Low risk	Tablets of equal size, colour and taste. All study physicians and the study nurse were blinded to the treatment given to each patient. Data were entered by the study nurse. Randomisation code was kept at the 24-hour emergency call centre in Basel

Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate: 2/252 (0.8%) due to loss of follow-up (1 patient) or adherence problems (1 patient). 1 patient with a serious adverse event was by the authors considered as a drop-out but included in this review as a failure. The ratio of participants with missing data to participants with events: 0.01. Intention-to-treat principle was followed (all patients were included in the analysis, except the one patient that never started treatment). The authors did not mention how they imputed information from the patients who were lost to follow-up at certain time points. 11 patients in the amoxicillin/clavulanic acid group and 19 in the placebo group (1 serious adverse event, 1 lost to follow-up) received open antibiotic therapy. 24 patients in the amoxicillin/clavulanic acid group and 15 in the placebo group took fever tablets as instructed
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined
Other bias	Low risk	In this study, the inclusion criteria changed (omission of the criterion "presence of pus at rhinoscopy") after the first winter season and the exclusion criteria changed after one serious adverse effect in 2000 (CPR-level greater than 100 mg/L, CRP-level between 50 and 99 mg/L (if clinical worsening), or an increase in CRP higher than 100 mg/L occurred 3 days after inclusion). With the available information, we cannot detect other reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). Dr. Bucher has received honorarium for presentations and financial support for participation in scientific meetings from GlaxoSmithKline. Patients were recruited from 24 general practices and 2 outpatient clinics, which means an average of 9.6 patients per practice

Merenstein 2005

Methods	RCT. Clinical diagnosis: patients presenting with at least 1 cardinal feature described by the clinical prediction rule (purulent nasal discharge predominating on 1 side, local facial pain predominating on one side, purulent nasal discharge on both sides and pus in the nasal cavity) and having symptoms for at least 7 days. Follow-up by telephone interviews on days 3, 7 and 14 (12 follow-up questions (clinical improvement) and asking for patients' visits for sinusitis). Proportion of patients without known or reported clinical outcome: 14% at day 14
Participants	Patients were recruited by 2 physicians and 1 nurse practitioner in 1 suburban primary care office. Mean age 35.1 in the amoxicillin group and 32.6 in the placebo group; 42 men, 93 women. USA. Exclusion criteria were antibiotic treatment within the past month in the history, allergy to penicillin, sinus surgery in history, compromised immunity, pneumonia in history and streptococcal pharyngitis in history
Interventions	2 treatment arms. Group 1: amoxicillin 500 mg 2 tablets twice daily for 10 days. Group 2: placebo 2 tablets twice daily for 10 days
Outcomes	Clinical outcomes reported at day 14 in 116 out of 135 people randomised (in 56 out of 67 participants in the amoxicillin group and 60 out of 68 participants in the placebo group). The primary outcome was improvement (yes or no) at day 14. Secondary outcomes were the day of improvement and side effects (diarrhea, nausea, emesis, abdominal pain, rash, hot flashes, jittery, dizziness, dry mouth, vaginal infection)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We used stratified randomisation with each physician representing the strata and patients were randomised in block sizes of 6. A computer random-number generator was used to create the permuted blocks. A biostatistician who was not employed by Georgetown University performed the allocation sequence
Allocation concealment (selection bias)	Low risk	Prior to the start of the trial, envelopes containing amoxicillin or placebo were prepared by the pharmacy and each envelope was labelled with a study ID. The envelopes given to each patient contained 40 capsules, either placebo or amoxicillin with instructions to take twice daily for 10 days. The randomisation codes were sent to the Pharmacy Department at Georgetown and were kept in a locked cabinet. Patients were con-

		secutively enrolled over the 18-month enrolment period
Blinding (performance bias and detection bias) All outcomes	Low risk	The envelopes were opaque and the pills within were identical in appearance, size, shape, colour and taste. All study physicians, patients and research co-ordinators were blinded to the treatment given to each patient. Through this process allocation concealment was achieved over the entire course of the enrolment period; neither physician nor patient could determine which treatment the next patient would receive
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate: 19/135 (14%) due to loss of follow-up (only baseline data collected). Drop-out balance: 11 patients in the intervention group, 8 patients in the placebo group. The ratio of participants with missing data to participants with events: 0.33. The authors state that the primary analyses were performed using the intention-to-treat principle. The drop-outs were counted as "not improved" in the intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined. The analysis of the subgroups was not announced in the section "methods"
Other bias	Low risk	With the available information, we cannot detect reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). None of the authors report any conflict of interests. This study was part of the Carpicorn Research Network of Georgetown University. This project was supported by a grant from the American Academy of Family Physicians and the American Academy of Family Physicians Foundation "Joint AAFP/F-AAFP Grant Awards Program. Support was also pro-

		vided by the Capitol Area Primary Care Research Network. Patients were recruited from 1 general practice

Meltzer 2005

Methods	RCT. Clinical diagnosis: patients presenting with signs and symptoms of acute rhinosinusitis for ≥ 7 days but ≤ 28 days and major symptom score ≥ 5 but ≤ 12 at screening and baseline visits with no more than 3 of the 5 symptoms rated severe at the baseline visit. Registration of major symptom score (rhinorrhoea, postnasal drip, nasal congestion/stuffiness, sinus headache, facial pain/pressure/tenderness on palpation over the nasal sinuses), total symptom score, vital signs, nasal examination, clinical laboratory test and physical examination. Follow-up by telephone call on day 3 and 4 and by diary (symptom recording, 2 times daily). Treatment visits on days 8, 15 an 29: evaluation of major symptom score, total symptom score, examination and treatment compliance. Proportion of patients without known or reported clinical outcome 2.6% on day 15 and 5.2% on day 29 (13 lost to follow-up at day 15 (treatment phase), 13 at day 29 (follow-up phase))
Participants	Patients were recruited by 71 medical centres. Mean age 35.9 in amoxicillin group, 34.4 in placebo group; 170 men, 329 women. 14 countries. Exclusion criteria were signs or symptoms suggestive for fulminant bacterial sinusitis (fever ≥ 101°F/38.3°C, persistent severe unilateral facial or tooth pain, facial swelling, dental involvement, or a worsening of symptoms after initial improvement), chronic rhinosinusitis (or sinus or nasal surgery for this condition within 6 months before screening), otitis or atrophic rhinitis, nasal polyps noted on anterior rhinoscopic examination, symptomatic seasonal allergic rhinitis (after pollen exposure during the study), an allergy to corticosteroids, any other condition that would interfere with study evaluations, unstable asthma or with a history of exacerbations within 30 days before screening or forced expiratory volume in 1 second (FEV1) < 65% of predicted within 3 months before screening
Interventions	Originally, there were 4 treatment arms. For this review, we only looked at 2 treatment arms. Group 1: amoxicillin 500 mg 3 times daily and placebo nasal spray 2 times daily for 10 days. Group 2: placebo 3 times daily for 10 days and placebo nasal spray 2 times daily for 10 days. The use of certain concomitant medication was forbidden (nasal saline, nasal cromolyn sodium ipratropium bromide, corticosteroids (excluding oral inhaled corticosteroids for mild to moderate persistent asthma), antihistamines, decongestants, leukotriene pathway modifiers, analgesics, nonsteroidal anti-inflammatory drugs)
Outcomes	Clinical outcomes reported at day 15 and day 29 in 486 and 473 respectively out of 499 participants randomised (in 245 and 242 respectively out of 251 participants in the amoxicillin group and in 241 and 231 respectively out of 248 participants in the placebo group). The primary outcome measure was the mean AM/PM major symptom score over days 2 to 15 of the treatment phase. Secondary outcome measures were mean major symptom score, total symptom score, individual scores for each symptom (average weekly and for days 2 to 15 and 16 to 29), global response to treatment (at visit 4 or last treatment visit (scale 0 (complete relief) to 4 (no relief)) evaluated by the investigator and the subject, time to onset of action (the first day of active treatment on which

	major symptom score was statistically significantly different from placebo and sustained thereafter), evaluation of the proportion of subjects presenting with symptoms suggestive of fulminant bacterial rhinosinusitis or worsening or no improvement of symptoms by day 3 or 4 (Kaplan Meier), adverse effects in relation to treatment (mild, moderate, severe, life-threatening) and the proportion of subjects, as assessed by the physician, who met disease criteria for recurrence/relapse during the follow-up phase
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in a 1:1:1:1 ratio to 4 treatment arms, according to a computer-generated code, stratified on the basis of duration of rhinosinusitis symptoms before baseline (7 to 14 days and 15 to 28 days)
Allocation concealment (selection bias)	Low risk	The study was conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice. The randomisation schedule for blinding of treatments was maintained by the sponsor and was disclosed only after the study completion and database closure. A set of sealed envelopes corresponding to the individual subject supplies, which contained the identification of the test drug, was provided to each site to enable the investigator to identify the treatment assignment of an individual subject, in the event of an emergency that requires this knowledge, without compromising the blinding of other study subjects. These envelopes were returned to the sponsor and open envelopes were accompanied by a written explanation
Blinding (performance bias and detection bias) All outcomes	Low risk	A double-dummy blinding technique was used during the treatment phase. Participants units were numbered from 0001 to 3000. All study drugs dispensed were labelled with the study number, packaging requisition number, treatment unit number and the investigational use statement with the instructions for proper storage conditions. Placebo for amoxicillin was identical in appearance to the active compound. Mometasone furoate nasal spray

		placebo was identical in appearance to the active compound
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Post-randomisation drop-out rate: 13/499 (2.6%) at day 15, 26/499 (5.2%) at day 29 due to loss of follow-up (13 lost to follow-up after treatment phase, 13 during follow-up phase). Drop-out balance: 9 out of the amoxicillin group (6 after treatment phase, 3 during follow-up phase), 17 out of the placebo group (7 after treatment phase, 10 during follow-up phase). We could not calculate the ratio of patients with missing data to participants with events, because the primary outcome was not "cure" but a difference in symptom scores. Discontinuation of treatment: 49/499 (10.5%, 20 out of the amoxicillin group, 29 out of the placebo group) due to adverse events, treatment failure, lost to follow-up, wish to discontinue, noncompliance with the protocol. (We used the numbers of the table, because there was a discrepancy between the text and the table). The authors state that the analyses are based on intent-to-treat population
Selective reporting (reporting bias)	High risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined. The outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis
Other bias	Low risk	With the available information, we cannot detect reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). E. Meltzer received grant support form Schering-Plough for this study and is a consultant on the speakers' bureau and has received grants from numerous pharmaceutical companies. H. Staudinger and C. Bachert have disclosed no conflict of interest. Patients were recruited from 71 medical centres, which means an average of 6.8

		patients per practice (instead of 16 as foreseen)

Williamson 2007

Methods	RCT (factorial design). Clinical diagnosis: patients presenting with uncomplicated acute illness (< 28 days) and at least 2 symptoms and 1 clinical sign of sinusitis (according to the Berg and Carenfelt criteria: purulent nasal discharge predominating on 1 side, local facial pain predominating on one side, purulent nasal discharge on both sides, pus in the nasal cavity). At inclusion: baseline questionnaire including clinical signs and confirmation of entry criteria completed by GPs, basic physical examination of temperature recording, sinus tenderness and anterior nasal cavity inspection (anterior rhinoscopy), recording of symptom duration and pain severity, collection of baseline demographic details. Follow-up with diary for 14 days (11 symptom variables, 7-point Likert scale), questionnaire on other variables (clinical features and satisfaction), and a telephone call during the first week to encourage adherence and improve the quality of the diary returns. Proportion of patients without known or reported clinical outcome: 12.9% on day 14
Participants	Patients were recruited by 74 physicians (primary care, 40 participating practices at the start, 18 extra practices recruited during the study because of low recruitment year) . Mean age 43 in amoxicillin group and 42 in placebo group; 66 men, 174 women. UK. Exclusion criteria were < 2 of the Berg and Carendfelt criteria (low probability of sinusitis), history of recurrent sinusitis (>= 2 attacks of acute sinusitis in the previous 12 months), significant morbidities (poorly controlled diabetes or heart failure), pregnant or breastfeeding, allergies, a history of adverse reactions to either medications and receiving antibiotics or steroids in the previous month
Interventions	Originally, there were 4 treatment arms. For this review, we only looked at 2 treatment arms. Group 1: amoxicillin 500 mg 3 times daily for 7 days, budesonide or placebo nose spray in each nostril once daily for 10 days. Group 2: placebo 3 times daily for 7 days, budesonide or placebo nose spray in each nostril once daily for 10 days
Outcomes	Clinical outcomes reported at day 14 in 209 out of 240 people randomised (in 101 out of 113 participants in the amoxicillin group and in 108 out of 127 participants in the placebo group). Patients were considered as cured if they scored all their symptoms 0 in the diary. The secondary outcome was the total symptom severity score. Subgroup analysis of the pain and unwell group
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	4 recruited cases per family physician, 1 block randomised pack of 4 physicians and 2 physicians per practice. The packs were made up using random number tables.

		Randomisation: at the level of the patient. Each pack contained an auditable sequence of the 4 possible combinations of the 2 interventions. Physicians were instructed to use the packs in sequence
Allocation concealment (selection bias)	Low risk	An independent person to the trial team was employed for distribution using the random sequence and trial code. The code break was kept in a sealed envelope in a locked filing cabinet at the university throughout the study period. All drug containers and all trial materials were identifiable only by the randomisation code number. Blind-sequenced trial packs. Sealed opaque numbered packages with physician instructions and either active or placebo drugs that were distributed in batches in randomised blocks of 4
Blinding (performance bias and detection bias) All outcomes	Low risk	Neither the antibiotic nor the nasal steroid spray: not recognisable as active or placebo medication, identical in taste and appearance. No significant difference in patient's belief in the effectiveness of the treatment allocated (0 to 5 scales) for the antibiotic tablet versus placebo tablet (P = 0.07), or for steroid spray versus placebo spray (P = 0.25). The single code break envelope was not opened until after all data collection was completed and all variables had been entered into the database. All outcome assessments were recorded on a central database and checked and verified when necessary by a research fellow blinded to treatment grouping
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate: 31/240 (12.9%) due to loss to follow-up. Drop-out balance: 12 out of the amoxicillin group and 19 out of the placebo group. 2 additional patients withdrew (1 in the amoxicillin group and 1 in the placebo group) because of ongoing symptoms. In our review they are considered as failures. The authors remark that patients who had pus on examination and were male were more likely to be lost to follow-up. The ratio of participants with missing data to participants

		with events: 0.23. The authors performed a sensitivity analysis in 2 ways: with imputation of data (assuming those lost to follow-up were still symptomatic at day 14) and with and without the additional telephone information obtained. They found no significant difference in results
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined
Other bias	Low risk	There was no significant imbalance of participant characteristics at baseline, except for temperature (slightly higher temperature in the placebo group but the difference was too small to have any clinical importance). With the available information, we cannot detect other reasons for bias (no design-specific risks of bias, the study was not stopped early, no imbalance of participant characteristics at baseline, blinding was not broken due to side effects, no bias due to increased or different diagnostic activity). This study was supported by the UK Department of Health. Dr. Little reported receiving consultancy fees for 2 half days from Abbott Pharmaceuticals regarding complications of respiratory tract infections. No other authors reported financial disclosures. The UK Department of Health did not participate in the design and conduct of the study, in the collection, analysis and interpretation of the data, or in the preparation, review, or approval of the manuscript. Family physicians received $50 per patient recruited for their time from government funding but patients received no reimbursement. Patients were recruited from 58 general practices, which means an average of 3.6 patients per practice

Garbutt 2012

Methods	RCT. Clinical diagnosis: patients presenting with a history of maxillary pain or tenderness in the face or teeth, purulent nasal secretions and rhinosinusitis symptoms for 7 days or more and 28 days or less that were not improving or worsening, or rhinosinusitis symptoms lasting for less than 7 days that had significantly worsened after initial improvement. Symptoms had to be moderate, severe or very severe. At inclusion: brief interview with research assistant, SNOT-16 questionnaire, registration of demographic and disease-related information, signs and symptoms. Telephone interview later that day to standardise the mode of data collection. Follow-up with telephone interview 3, 7, 10 and 28 days after treatment initiation (structured questionnaire, trained research assistants). Proportion of patients without known or reported clinical outcome: 6.6% on day 28
Participants	10 offices of primary care. Median age 32 in the amoxicillin group, 31 in the placebo group; 60 men, 106 women. US. Exclusion criteria were allergy to penicillin or amoxicillin, prior antibiotic treatment within 4 weeks, complications of sinusitis, a comorbidity that may impair their immune response, cystic fibrosis, requiring an antibiotic for a concurrent condition, pregnancy and patients who rated their symptoms as very mild or mild
Interventions	2 treatment arms. Group 1: amoxicillin 500 mg 3 times daily for 10 days. Group 2: placebo 3 times daily for 10 days. All patients (except if contraindications) received a 5 to 7 day supply of the following symptomatic treatments to be used as needed: acetaminophen for pain or fever at a dose of 500 mg every 6 hours, guaifenesin to thin secretions at a dose of 600 mg every 12 hours, 10mg/5mL of dextromethorphan hydrobromide and 100 mg/ 5 mL of guaifenesin for cough at a dose of 10 mL every 4 to 6 hours, pseudoephedrine-sustained action for nasal congestion at a dose of 120 mg every 12 hours, and 0.65% saline spray using 2 puffs per nostril as needed
Outcomes	Clinical outcomes reported at day 3 in 155 out of 166 people randomised (in 81 out of 85 participants in the amoxicillin group and in 74 out of 81 participants in the placebo group). Primary outcome was the effect of treatment on disease-specific quality of life at day 3 (measured using the Sinonasal Outcome Test (SNOT) - 16). Secondary outcomes were significant improvement ("symptom change", based on symptom scores (6-point scale), reporting their symptoms a lot better or absent), change in functional status, recurrent sinus infection, satisfaction with treatment, adverse effects of treatment, treatment compliance and adequacy of blinding. Patients were recruited from 10 primary care offices, which means an average of 15.5 patients per practice
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation scheme. Computer-generated random numbers were used to determine how the 2 study drugs were allocated to the consecutively numbered study treatment packages. Randomi-

		sation occurred when the research assistant assigned the treatment package
Allocation concealment (selection bias)	Low risk	Randomisation was performed in advance by the investigational pharmacist who did not participate in patients' enrolment or outcome assessment
Blinding (performance bias and detection bias) All outcomes	Low risk	The tablets were similar in appearance and taste and dispensed in the same fashion. Research assistants were blinded to group assignment. The percentage of participants who guessed their treatment assignment correctly did not differ by study group (36% in amoxicillin group and 37% in placebo group, P = 0.2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post-randomisation drop-out rate: 11/166 (6.6%) due to missing data. Drop-out balance: 4 out of the amoxicillin group and 7 out of the placebo group. Discontinuation of treatment rate: 23/166 (13.9%) (11 out of 85 participants in the amoxicillin group and 12 out of 81 participants in the placebo group) due to failure to improve (2 in the amoxicillin group and 6 in the placebo group), worsening symptoms (3 in the amoxicillin group and 4 in the placebo group), improved symptoms (4 in the amoxicillin group), adverse events (1 in the amoxicillin group) and unknown reasons (1 in the amoxicillin group and 2 in the placebo group). Treatment with other antibiotics: 16/166 (9.6%) (5 in the amoxicillin group and 11 in the placebo group, P = 0.09). Intention to treat analysis
Selective reporting (reporting bias)	Low risk	The study protocol is described in the section "methods". The primary and secondary endpoints were predefined. Sensitivity analysis for participants who completed 10 days of treatment with the study drug and those with symptoms for 7 days or more and 28 days or less. Findings were consistent with the primary analysis
Other bias	Low risk	Approval by the institutional review board at Washington University. Written consent obtained from each participant. This study

		was funded by grant U01-AI064655-01A1 from the National Institute of Allergy and Infectious Diseases. This institute did not have a role in the design and conduct of the study; in the collection, management, analysis or interpretation of the data; or in the preparation, review or approval of the manuscript

CRP: C-reactive protein
RCT: randomised controlled trial

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

Study	Reason for exclusion
Axelsson 1970	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by radiology)
Gananca 1973	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs and bacteriologic criteria)
Gananca 1977	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs and bacteriologic criteria)
Hadley 2010	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, radiologic and bacteriologic criteria)
Hansen 2000a	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs and raised values of either C-reactive protein (CRP) or the erythrocyte sedimentation (ESR) rate)
Hansen 2000b	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs and raised values of either C-reactive protein (CRP) or the erythrocyte sedimentation (ESR) rate)
Haye 1998	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs but exclusion of patients with radiographically confirmed empyema)
Lacroix 2002	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and positive bacterial cultures)

(*Continued*)

Lindbaek 1996	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by computed tomography)
Lindbaek 1998	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by computed tomography)
Pessey 1999	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by radiology)
Rantanen 1973	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by radiology)
van Buchem 1997a	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by radiology)
van Buchem 1997b	Randomised, double-blind, placebo controlled trial but diagnostic criteria of acute sinusitis did not fulfil the inclusion criteria of this review (clinical symptoms and signs, confirmed by radiology)

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall treatment effect	8	1687	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [1.02, 1.53]
2 Cure at 1 week	4	856	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.81, 1.41]
3 Cure at 10 days	4	1048	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.92, 1.52]
4 Cure at 2 weeks	3	467	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.99, 2.23]
5 Cure at 1 week, with Garbutt data	5	1011	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.93, 1.54]
6 Cure at 10 days with Garbutt data	5	1203	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.90, 1.46]
7 Influence of missing data: overall treatment effect if drop-outs are successes	8	1785	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [1.02, 1.52]
8 Influence of missing data: overall treatment effect if drop-outs are failures	8	1785	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [1.02, 1.51]
9 Influence of missing data: overall treatment effect if drop-outs have the same cure rate as the control group	8	1785	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [1.02, 1.51]
10 Influence of missing data: cure at 1 week if drop-outs are successes	4	901	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
11 Influence of missing data: cure at 1 week if drop-outs are failures	4	901	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.84, 1.44]
12 Influence of missing data: cure at 1 week if drop-outs have the same cure rate as the control group	3	632	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.79, 1.50]
13 Influence of missing data: cure at 10 days if drop-outs are successes	3	840	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.94, 1.66]
14 Influence of missing data: cure at 10 days if drop-outs are failures	3	840	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.94, 1.65]
15 Influence of missing data: cure at 10 days if drop-outs have the same cure rate as the control group	3	840	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.93, 1.65]
16 Influence of missing data: cure at 2 weeks if drop-outs are successes	4	1026	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.98, 1.73]

17 Influence of missing data: cure at 2 weeks if drop-outs are failures	4	776	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.99, 1.84]
18 Influence of missing data: cure at 2 weeks if drop-outs have the same cure rate as the control group	4	776	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.99, 1.86]
19 Resolution of purulent secretions at endpoint	3	660	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.13, 2.22]
20 Side effects: in general	7	1371	Odds Ratio (M-H, Fixed, 95% CI)	2.10 [1.60, 2.77]
21 Diarrhoea	4	816	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [1.18, 2.78]
22 Treatment failure	8	2175	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.36, 0.66]
23 Overall treatment effect (with Young 2008 data concerning Stalman)	8	1687	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [1.04, 1.56]

Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Overall treatment effect.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 1 Overall treatment effect

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bucher 2003	95/124	93/126		13.0 %	1.16 [0.65, 2.07]
De Sutter 2002	73/189	59/195		21.5 %	1.45 [0.95, 2.21]
Kaiser 2001	76/133	75/132		19.5 %	1.01 [0.62, 1.65]
Merenstein 2005	32/56	25/60		6.2 %	1.87 [0.89, 3.90]
Norrelund 1978	40/71	33/64		9.2 %	1.21 [0.62, 2.39]
Stalman 1997	56/94	55/92		13.6 %	0.99 [0.55, 1.78]
Varonen 2003	70/85	39/57		5.0 %	2.15 [0.98, 4.74]
Williamson 2007	75/101	80/108		12.0 %	1.01 [0.54, 1.88]
Total (95% CI)	**853**	**834**		**100.0 %**	**1.25 [1.02, 1.53]**

Total events: 517 (Antibiotics), 459 (Placebo)

Heterogeneity: Chi^2 = 5.28, df = 7 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 2.16 (P = 0.031)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Cure at 1 week.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Cure at 1 week

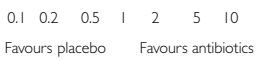
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Norrelund 1978	40/71	33/64		15.5 %	1.21 [0.62, 2.39]
Williamson 2007	53/101	52/108		24.4 %	1.19 [0.69, 2.05]
Bucher 2003	36/122	38/125		27.1 %	0.96 [0.56, 1.65]
Kaiser 2001	76/133	75/132		33.0 %	1.01 [0.62, 1.65]
Total (95% CI)	**427**	**429**		**100.0 %**	**1.07 [0.81, 1.41]**

Total events: 205 (Antibiotics), 198 (Placebo)

Heterogeneity: $Chi^2 = 0.48$, df = 3 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Cure at 10 days.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 3 Cure at 10 days

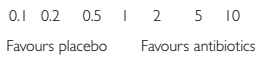
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Williamson 2007	71/101	71/108		18.3 %	1.23 [0.69, 2.21]
Stalman 1997	56/94	56/92		20.5 %	0.95 [0.53, 1.70]
Kaiser 2001	77/135	76/134		29.3 %	1.01 [0.63, 1.64]
De Sutter 2002	73/189	59/195		31.9 %	1.45 [0.95, 2.21]
Total (95% CI)	**519**	**529**		**100.0 %**	**1.18 [0.92, 1.52]**

Total events: 277 (Experimental), 262 (Control)

Heterogeneity: $Chi^2 = 1.86$, df = 3 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 Cure at 2 weeks.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 4 Cure at 2 weeks

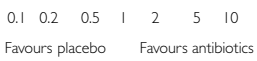
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Varonen 2003	70/85	39/57		21.4 %	2.15 [0.98, 4.74]
Merenstein 2005	32/56	25/60		26.9 %	1.87 [0.89, 3.90]
Williamson 2007	75/101	80/108		51.7 %	1.01 [0.54, 1.88]
Total (95% CI)	**242**	**225**		**100.0 %**	**1.48 [0.99, 2.23]**

Total events: 177 (Antibiotics), 144 (Placebo)

Heterogeneity: $Chi^2 = 2.71$, df = 2 (P = 0.26); $I^2 = 26\%$

Test for overall effect: Z = 1.92 (P = 0.055)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 Cure at 1 week, with Garbutt data.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 5 Cure at 1 week, with Garbutt data

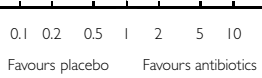
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Garbutt 2012	60/81	41/74		10.2 %	2.30 [1.17, 4.52]
Norrelund 1978	40/71	33/64		13.9 %	1.21 [0.62, 2.39]
Williamson 2007	53/101	52/108		21.9 %	1.19 [0.69, 2.05]
Bucher 2003	36/122	38/125		24.3 %	0.96 [0.56, 1.65]
Kaiser 2001	76/133	75/132		29.6 %	1.01 [0.62, 1.65]
Total (95% CI)	**508**	**503**		**100.0 %**	**1.20 [0.93, 1.54]**

Total events: 265 (Antibiotics), 239 (Placebo)

Heterogeneity: Chi^2 = 4.68, df = 4 (P = 0.32); I^2 =14%

Test for overall effect: Z = 1.39 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 Cure at 10 days with Garbutt data.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 6 Cure at 10 days with Garbutt data

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Garbutt 2012	63/81	59/74		10.9 %	0.89 [0.41, 1.93]
Williamson 2007	71/101	71/108		16.3 %	1.23 [0.69, 2.21]
Stalman 1997	56/94	56/92		18.2 %	0.95 [0.53, 1.70]
Kaiser 2001	77/135	76/134		26.1 %	1.01 [0.63, 1.64]
De Sutter 2002	73/189	59/195		28.4 %	1.45 [0.95, 2.21]
Total (95% CI)	**600**	**603**		**100.0 %**	**1.15 [0.90, 1.46]**

Total events: 340 (Experimental), 321 (Control)

Heterogeneity: $Chi^2 = 2.32$, df = 4 (P = 0.68); $I^2 = 0.0\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Antibiotics versus placebo, Outcome 7 Influence of missing data: overall treatment effect if drop-outs are successes.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 7 Influence of missing data: overall treatment effect if drop-outs are successes

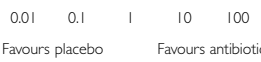
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bucher 2003	96/125	94/127		12.4 %	1.16 [0.65, 2.06]
De Sutter 2002	86/202	70/206		22.8 %	1.44 [0.96, 2.15]
Kaiser 2001	78/135	77/134		18.7 %	1.01 [0.62, 1.64]
Merenstein 2005	43/67	33/68		6.7 %	1.90 [0.95, 3.79]
Norrelund 1978	42/73	37/67		9.4 %	1.10 [0.56, 2.14]
Stalman 1997	60/98	57/94		12.9 %	1.02 [0.57, 1.83]
Varonen 2003	74/89	42/60		4.8 %	2.11 [0.97, 4.63]
Williamson 2007	87/113	99/127		12.3 %	0.95 [0.52, 1.74]
Total (95% CI)	**902**	**883**		**100.0 %**	**1.24 [1.02, 1.52]**

Total events: 566 (Antibiotics), 509 (Placebo)

Heterogeneity: Chi^2 = 5.82, df = 7 (P = 0.56); I^2 =0.0%

Test for overall effect: Z = 2.15 (P = 0.032)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Antibiotics versus placebo, Outcome 8 Influence of missing data: overall treatment effect if drop-outs are failures.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 8 Influence of missing data: overall treatment effect if drop-outs are failures

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bucher 2003	95/125	93/127		12.3 %	1.16 [0.66, 2.04]
De Sutter 2002	73/202	59/206		20.7 %	1.41 [0.93, 2.14]
Kaiser 2001	76/135	75/134		18.3 %	1.01 [0.63, 1.64]
Merenstein 2005	32/67	25/68		7.2 %	1.57 [0.79, 3.13]
Norrelund 1978	40/73	33/67		8.6 %	1.25 [0.64, 2.43]
Stalman 1997	56/98	55/94		13.4 %	0.95 [0.53, 1.68]
Varonen 2003	70/89	39/60		5.5 %	1.98 [0.95, 4.13]
Williamson 2007	75/113	80/127		14.1 %	1.16 [0.68, 1.97]
Total (95% CI)	**902**	**883**		**100.0 %**	**1.24 [1.02, 1.51]**
Total events: 517 (Antibiotics), 459 (Placebo)					
Heterogeneity: Chi^2 = 4.05, df = 7 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 2.14 (P = 0.032)					
Test for subgroup differences: Not applicable					

Analysis 1.9. Comparison 1 Antibiotics versus placebo, Outcome 9 Influence of missing data: overall treatment effect if drop-outs have the same cure rate as the control group.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 9 Influence of missing data: overall treatment effect if drop-outs have the same cure rate as the control group

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bucher 2003	96/125	94/127		12.3 %	1.16 [0.65, 2.06]
De Sutter 2002	77/202	62/206		21.6 %	1.43 [0.95, 2.16]
Kaiser 2001	77/135	76/134		18.7 %	1.01 [0.63, 1.64]
Merenstein 2005	37/67	28/68		7.1 %	1.76 [0.89, 3.48]
Norrelund 1978	41/73	35/67		9.1 %	1.17 [0.60, 2.28]
Stalman 1997	58/98	56/94		13.3 %	0.98 [0.55, 1.75]
Varonen 2003	73/89	41/60		5.0 %	2.11 [0.98, 4.55]
Williamson 2007	84/113	94/127		12.9 %	1.02 [0.57, 1.81]
Total (95% CI)	**902**	**883**		**100.0 %**	**1.24 [1.02, 1.51]**
Total events: 543 (Antibiotics), 486 (Placebo)					
Heterogeneity: Chi^2 = 5.16, df = 7 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 2.14 (P = 0.033)					
Test for subgroup differences: Not applicable					

Analysis 1.10. Comparison 1 Antibiotics versus placebo, Outcome 10 Influence of missing data: cure at 1 week if drop-outs are successes.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 10 Influence of missing data: cure at 1 week if drop-outs are successes

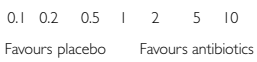
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Norrelund 1978	42/73	37/67		15.6 %	1.10 [0.56, 2.14]
Bucher 2003	39/125	40/127		26.1 %	0.99 [0.58, 1.68]
Williamson 2007	65/113	71/127		27.1 %	1.07 [0.64, 1.78]
Kaiser 2001	78/135	77/134		31.2 %	1.01 [0.62, 1.64]
Total (95% CI)	**446**	**455**		**100.0 %**	**1.03 [0.79, 1.35]**

Total events: 224 (Antibiotics), 225 (Placebo)

Heterogeneity: $Chi^2 = 0.08$, $df = 3$ ($P = 0.99$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.25$ ($P = 0.81$)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Antibiotics versus placebo, Outcome 11 Influence of missing data: cure at 1 week if drop-outs are failures.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 11 Influence of missing data: cure at 1 week if drop-outs are failures

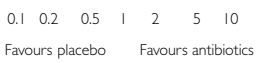
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Norrelund 1978	40/73	33/67		15.4 %	1.25 [0.64, 2.43]
Williamson 2007	53/113	52/127		25.7 %	1.27 [0.76, 2.12]
Bucher 2003	36/125	38/127		26.5 %	0.95 [0.55, 1.63]
Kaiser 2001	76/135	75/134		32.5 %	1.01 [0.63, 1.64]
Total (95% CI)	**446**	**455**		**100.0 %**	**1.10 [0.84, 1.44]**

Total events: 205 (Antibiotics), 198 (Placebo)

Heterogeneity: $Chi^2 = 0.86$, df = 3 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Antibiotics versus placebo, Outcome 12 Influence of missing data: cure at 1 week if drop-outs have the same cure rate as the control group.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 12 Influence of missing data: cure at 1 week if drop-outs have the same cure rate as the control group

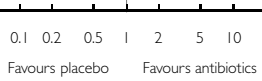
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Norrelund 1978	41/73	35/67		22.6 %	1.17 [0.60, 2.28]
Bucher 2003	37/125	39/127		38.5 %	0.95 [0.55, 1.63]
Williamson 2007	59/113	61/127		38.8 %	1.18 [0.71, 1.96]
Total (95% CI)	**311**	**321**		**100.0 %**	**1.09 [0.79, 1.50]**

Total events: 137 (Antibiotics), 135 (Placebo)

Heterogeneity: $Chi^2 = 0.40$, df = 2 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Antibiotics versus placebo, Outcome 13 Influence of missing data: cure at 10 days if drop-outs are successes.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 13 Influence of missing data: cure at 10 days if drop-outs are successes

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
De Sutter 2002	86/202	70/206		46.9 %	1.44 [0.96, 2.15]
Stalman 1997	60/98	57/94		26.6 %	1.02 [0.57, 1.83]
Williamson 2007	83/113	90/127		26.5 %	1.14 [0.65, 2.00]
Total (95% CI)	**413**	**427**		**100.0 %**	**1.25 [0.94, 1.66]**

Total events: 229 (Experimental), 217 (Control)

Heterogeneity: Chi^2 = 1.04, df = 2 (P = 0.60); I^2 =0.0%

Test for overall effect: Z = 1.53 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Antibiotics versus placebo, Outcome 14 Influence of missing data: cure at 10 days if drop-outs are failures.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 14 Influence of missing data: cure at 10 days if drop-outs are failures

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Stalman 1997	56/98	56/94		28.3 %	0.90 [0.51, 1.61]
Williamson 2007	71/113	71/127		28.7 %	1.33 [0.79, 2.24]
De Sutter 2002	73/202	59/206		43.1 %	1.41 [0.93, 2.14]
Total (95% CI)	**413**	**427**		**100.0 %**	**1.25 [0.94, 1.65]**

Total events: 200 (Experimental), 186 (Control)

Heterogeneity: Chi^2 = 1.60, df = 2 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Antibiotics versus placebo, Outcome 15 Influence of missing data: cure at 10 days if drop-outs have the same cure rate as the control group.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 15 Influence of missing data: cure at 10 days if drop-outs have the same cure rate as the control group

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Stalman 1997	58/98	56/94		27.4 %	0.98 [0.55, 1.75]
Williamson 2007	79/113	84/127		28.0 %	1.19 [0.69, 2.05]
De Sutter 2002	77/202	62/206		44.6 %	1.43 [0.95, 2.16]
Total (95% CI)	**413**	**427**		**100.0 %**	**1.24 [0.93, 1.65]**

Total events: 214 (Experimental), 202 (Control)

Heterogeneity: Chi^2 = 1.11, df = 2 (P = 0.58); I^2 =0.0%

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 1.16. Comparison 1 Antibiotics versus placebo, Outcome 16 Influence of missing data: cure at 2 weeks if drop-outs are successes.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 16 Influence of missing data: cure at 2 weeks if drop-outs are successes

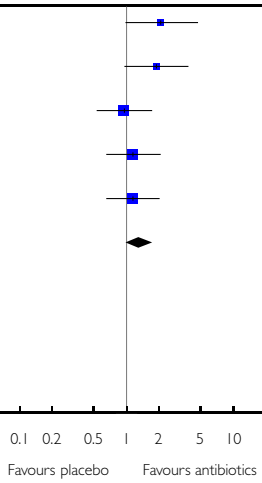
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Varonen 2003	74/89	42/60		10.0 %	2.11 [0.97, 4.63]
Merenstein 2005	43/67	33/68		13.8 %	1.90 [0.95, 3.79]
Williamson 2007	87/113	99/127		25.3 %	0.95 [0.52, 1.74]
Bucher 2003	95/124	93/126		25.4 %	1.16 [0.65, 2.07]
Bucher 2003	96/125	94/127		25.5 %	1.16 [0.65, 2.06]
Total (95% CI)	**518**	**508**		**100.0 %**	**1.30 [0.98, 1.73]**

Total events: 395 (Antibiotics), 361 (Placebo)

Heterogeneity: $Chi^2 = 3.99$, df = 4 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 1.85 (P = 0.064)

Test for subgroup differences: Not applicable



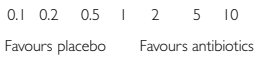
Analysis 1.17. Comparison 1 Antibiotics versus placebo, Outcome 17 Influence of missing data: cure at 2 weeks if drop-outs are failures.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 17 Influence of missing data: cure at 2 weeks if drop-outs are failures

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Varonen 2003	70/89	39/60		14.1 %	1.98 [0.95, 4.13]
Merenstein 2005	32/67	25/68		18.4 %	1.57 [0.79, 3.13]
Bucher 2003	95/125	93/127		31.5 %	1.16 [0.66, 2.04]
Williamson 2007	75/113	80/127		36.0 %	1.16 [0.68, 1.97]
Total (95% CI)	**394**	**382**		**100.0 %**	**1.35 [0.99, 1.84]**
Total events: 272 (Antibiotics), 237 (Placebo)					
Heterogeneity: Chi^2 = 1.84, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.93 (P = 0.054)					
Test for subgroup differences: Not applicable					



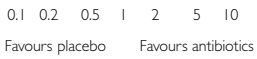
Analysis 1.18. Comparison 1 Antibiotics versus placebo, Outcome 18 Influence of missing data: cure at 2 weeks if drop-outs have the same cure rate as the control group.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 18 Influence of missing data: cure at 2 weeks if drop-outs have the same cure rate as the control group

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Varonen 2003	73/89	41/60		13.4 %	2.11 [0.98, 4.55]
Merenstein 2005	37/67	28/68		19.0 %	1.76 [0.89, 3.48]
Bucher 2003	96/125	94/127		33.0 %	1.16 [0.65, 2.06]
Williamson 2007	84/113	94/127		34.6 %	1.02 [0.57, 1.81]
Total (95% CI)	**394**	**382**		**100.0 %**	**1.35 [0.99, 1.86]**
Total events: 290 (Antibiotics), 257 (Placebo)					
Heterogeneity: Chi^2 = 3.08, df = 3 (P = 0.38); I^2 =3%					
Test for overall effect: Z = 1.87 (P = 0.062)					
Test for subgroup differences: Not applicable					



Analysis 1.19. Comparison 1 Antibiotics versus placebo, Outcome 19 Resolution of purulent secretions at endpoint.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 19 Resolution of purulent secretions at endpoint

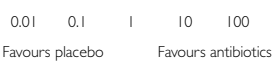
Study or subgroup	Antibiotic n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
De Sutter 2002	140/187	116/179		55.8 %	1.62 [1.03, 2.54]
Norrelund 1978	30/71	18/64		20.5 %	1.87 [0.91, 3.84]
Stalman 1997	66/84	56/75		23.7 %	1.24 [0.60, 2.60]
Total (95% CI)	**342**	**318**		**100.0 %**	**1.58 [1.13, 2.22]**

Total events: 236 (Antibiotic), 190 (Placebo)

Heterogeneity: $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 2.65 (P = 0.0081)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Antibiotics versus placebo, Outcome 20 Side effects: in general.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 20 Side effects: in general

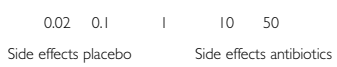
Study or subgroup	Antibiotica n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
De Sutter 2002	55/189	37/195		35.8 %	1.75 [1.09, 2.82]
Garbutt 2012	13/81	10/74		12.2 %	1.22 [0.50, 2.99]
Kaiser 2001	32/133	14/132		14.8 %	2.67 [1.35, 5.28]
Merenstein 2005	13/56	7/60		7.2 %	2.29 [0.84, 6.24]
Norrelund 1978	31/71	17/64		14.0 %	2.14 [1.04, 4.43]
Stalman 1997	17/94	2/92		2.3 %	9.94 [2.22, 44.37]
Varonen 2003	32/82	13/48		13.9 %	1.72 [0.79, 3.74]
Total (95% CI)	**706**	**665**		**100.0 %**	**2.10 [1.60, 2.77]**

Total events: 193 (Antibiotica), 100 (Placebo)

Heterogeneity: $Chi^2 = 6.86$, df = 6 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 5.29 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1 Antibiotics versus placebo, Outcome 21 Diarrhoea.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 21 Diarrhoea

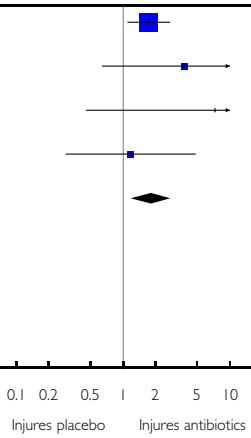
Study or subgroup	Experimental n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
De Sutter 2002	55/189	37/195		82.7 %	1.74 [1.09, 2.78]
Merenstein 2005	4/56	1/60		5.7 %	3.73 [0.63, 22.24]
Stalman 1997	2/94	0/92		2.3 %	7.31 [0.45, 117.80]
Varonen 2003	6/82	3/48		9.3 %	1.18 [0.29, 4.77]
Total (95% CI)	**421**	**395**		**100.0 %**	**1.81 [1.18, 2.78]**

Total events: 67 (Experimental), 41 (Control)

Heterogeneity: $Chi^2 = 1.99$, df = 3 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 2.74 (P = 0.0061)

Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1 Antibiotics versus placebo, Outcome 22 Treatment failure.

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 22 Treatment failure

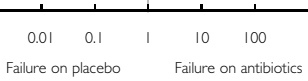
Study or subgroup	Antibiotic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Kaiser 2001	1/135	14/134		8.9 %	0.16 [0.06, 0.45]
Varonen 2003	6/89	10/60		8.7 %	0.36 [0.12, 1.03]
Stalman 1997	3/98	7/94		6.0 %	0.41 [0.12, 1.47]
Garbutt 2012	5/85	11/81		9.1 %	0.42 [0.15, 1.16]
Bucher 2003	11/125	19/127		16.6 %	0.56 [0.26, 1.19]
De Sutter 2002	16/202	26/206		23.7 %	0.60 [0.32, 1.14]
Meltzer 2005	18/251	27/248		25.7 %	0.64 [0.35, 1.17]
Williamson 2007	1/113	1/127		1.2 %	1.12 [0.07, 18.17]
Total (95% CI)	**1098**	**1077**		**100.0 %**	**0.49 [0.36, 0.66]**

Total events: 61 (Antibiotic), 115 (Placebo)

Heterogeneity: $Chi^2 = 6.55$, df = 7 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 4.54 (P < 0.00001)

Test for subgroup differences: Not applicable

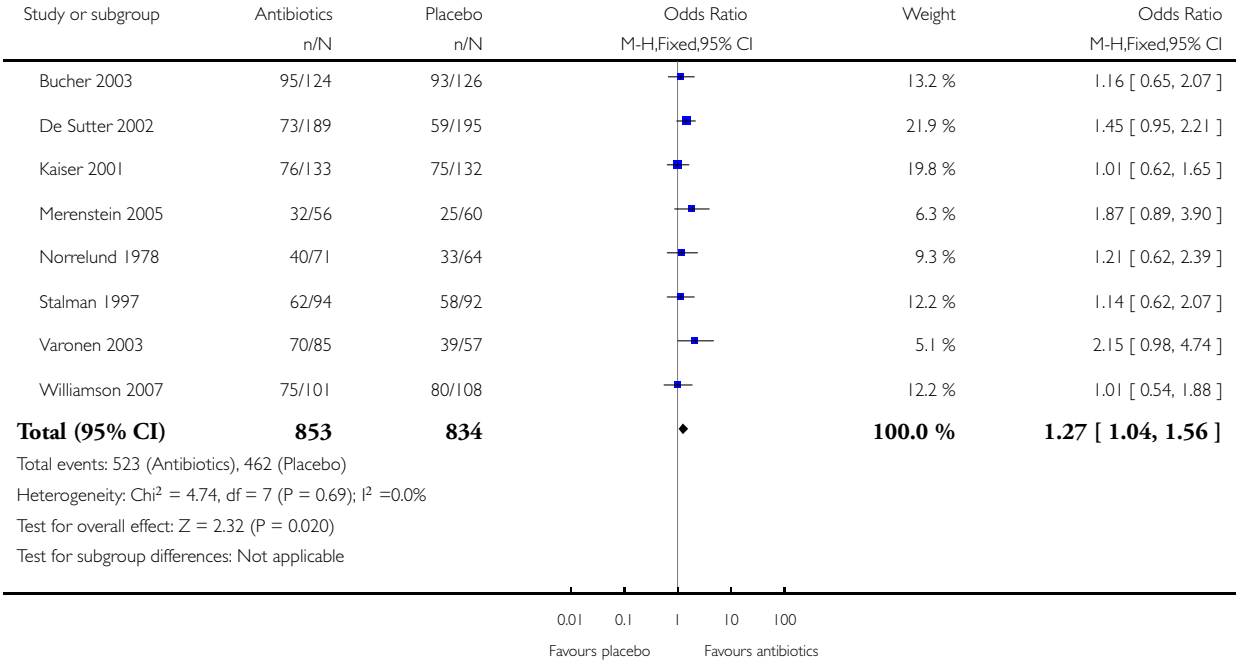


Analysis 1.23. Comparison 1 Antibiotics versus placebo, Outcome 23 Overall treatment effect (with Young 2008 data concerning Stalman).

Review: Antibiotics for clinically diagnosed acute rhinosinusitis in adults

Comparison: 1 Antibiotics versus placebo

Outcome: 23 Overall treatment effect (with Young 2008 data concerning Stalman)



ADDITIONAL TABLES

Table 1. Collected information from placebo controlled studies

Study	Comparisons	Allowed concomitant medication	Diagnostic method	Day assessed	Drop-outs	Definition of cure	Number cured/ total with known outcome	Number cured or improved/ total with known outcome	Side effects
Norrelund 1978 Denmark 135 participants ana-	Pivampicillin (700 mg twice daily for 6 days) ver-	Otrivin (xylometazoline hydrochloride) 0.1%	At least 3 symptoms *(feeling of malaise; headache,*	Day 8	5 (3.6%)	Reduction in symptom score of > 2/3 at con-	Placebo: 33/64 Antibiotic: 40/71	Placebo: 36/64 Antibiotic 53/71	Placebo: 17/64 (2/3 from gastrointesti-

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

lyzed 19 general practitioners	sus placebo	10 mL, 4 times daily	*particularly behind the eyes, behind the bridge of the nose or corresponding to the maxilla; irritative cough)*, including at least 1 of the main symptoms *(yellow or yellowish-green or possibly blood-stained nasal discharge on blowing the nose; good nasal passage together with a nasal voice)*			trol visit			nal tract) pivampicillin: 31/71 (all from the gastrointestinal tract)
Kaiser 2001 Switzerland 265 participants analyzed Outpatient clinic of the University of Geneva Hospital	Azithromycin (500 mg orally once daily for 3 days) versus placebo	Ibuprofen offered; nasal drops containing xylometazoline offered	Presentation with common cold or acute sinusitis, a history of rhinorrhoea of less than 4 weeks and a confirmed URTI at physical examination, including	Day 8	4 (1.5%)	Definition 1: reduction of more than 80% of the mean baseline symptom score (diary evaluated at day 7) Definition 2: clinical evaluation	Definition 1: Placebo: 77/132 Antibiotics: 93/133 Definition 2: Placebo: 75/132 Antibiotics: 76/133		Placebo: 14/132 (gastrointestinal disturbances) azithromycin: 32/133 (gastrointestinal disturbances) No side effect necessitated with-

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

			rhinoscopy						drawal of treatment
Stalman 1997 The Netherlands 186 participants analyzed 12 family practices	Doxycycline (100 mg twice daily for 1 day (1st), once daily for 9 days) versus placebo	Xylometazoline 0.1% 3 times daily if complaints; steam inhalation for 15 minutes 3 times daily if complaints; paracetamol 500 mg if needed	Symptoms of upper respiratory tract infections for at least 5 days, 3 main symptoms or 2 main symptoms *(complaints after a common cold or influenza; purulent nasal discharge; pain in the maxillary sinuses on bending forward)* and 1 other symptom *(predominantly unilateral maxillary pain, toothache, or pain when chewing)*	Day 10	6 (3.1%)	Meeting all primary and secondary outcome events (noted in diary, evaluated at control visit, day 10 and day 42)	Day 10: Placebo: 56/92* Antibiotics: 56/94*	Day 10: Placebo: 79/92 Antibiotics: 80/94	Placebo: 2/92 (nausea 2) doxycycline: 17/94 (nausea 9, vomiting 5, abdominal pain 5, diarrhea 2, rash 2, dizziness 1) + 2 lost to follow-up because of vomiting and abdominal pain
De Sutter 2002 Belgium 384 participants analyzed 69 family practices	Amoxicillin (500 mg three times daily for 10 days) versus placebo	Xylometazoline 1% nose drops allowed; paracetamol or ibuprofen allowed	Presentation with a respiratory tract infection and having purulent rhinorrhoea	Day 10	24 (5.9%)	If all the symptoms that the patient had included is the list of "most important item	Placebo: 59/195$ Antibiotics: 73/189$		Placebo: 37/195 (diarrhea) amoxicillin: 55/189 (diarrhea) Other side

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

						affecting my health" scored 0 (absent) or 1 (very mild present) after 10 days of treatment			effects: no difference (skin rash, abdominal pain, vomiting)
Bucher 2003 Switzerland 250 participants analyzed 24 general practices and 2 outpatient clinics	Amoxicillin/ clavulanic acid (875/ 125 mg twice daily for 6 days) versus placebo	Xylometazoline hydrochloride spray and acetaminopher received by all patients; steam inhalation allowed	A history of repeated purulent nasal discharge and maxillary or frontal unilateral or bilateral pain for at least 48 hours but less than 1 month and presence of pus under rhinoscopy (this last criterion was withdrawn after the first winter season)	Day 7 Day 14 (Day 28)	2 (0.8%)	Time to cure (0 days (since the previous interview) during which rhinosinusitis restricted activities at home or work) alternative definition: rating of 1 on a 10-point, equal-distance scale for degree of restriction at home or work at day 7: clinical evaluation by physician at day 14 and day 28: telephone interview by	Day 7: Placebo: 38/125 Antibiotics: 36/122 Day 14: Placebo: 93/126 Antibiotics: 95/124		Diarrhoea: OR 3.89 (95% CI, 2. 09-7.25) at 7 days and OR 1.71 (95% CI, 0.91-3. 23) at 14 days (no exact numbers available) Vaginal discharge or pruritus and abdominal pain: no significant differences 4 possibly drug related adverse events of moderate or severe intensity: 2 in amoxicillin-

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

						study nurse			clavulanate group (diarrhea) and 2 in the placebo group (diarrhea and vomiting)
Varonen 2003 Finland 142 participants analyzed 9 primary care sites	Amoxicillin (750 mg twice daily for 7 days) versus penicillin V (1500 IU twice daily for 7 days) versus doxycycline 100 mg twice daily for 7 days) versus placebo	Xylometazoline, paracetamol or anti-inflammatory agents: if physician considered them as necessary, use recorded	Upper respiratory tract infections + clinical diagnosis of acute maxillary sinusitis (at least 3 symptoms and 1 clinical sign) *(symptoms: nasal obstruction, nasal discharge, headache, postnasal drip, cough, sinus pain, unilateral facial pain, maxillary toothache, hyposmia, anosmia, malaise, fever; clinical signs: purulent secretion in the nasal cavity, discharge*	Days 14-16	7 (4.7%)	Frequency of recovery at follow-up, according to the telephone interview (executed by the researcher)	Placebo: 39/57 Antibiotics: 70/85		Placebo: 12/47 + 1 loss of follow-up due to side effects (13/48) (diarrhea 6%, stomach pain 12%, headache 4%, rash 0%, vaginal discharge 0%, fatigue 6%) Antibiotics: 29/79 + 3 loss of follow-up due to side effects (32/82) (diarrhea 7%, stomach pain 22%, headache 6%, rash 2%, vaginal discharge 4%,

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

			in the pharynx and tenderness in sinus tapping)						fatigue 6%)
Merenstein 2005 USA 116 participants analyzed 1 suburban primary care office	Amoxicillin (500 mg 2 tablets twice daily for 10 days) versus placebo		At least 1 cardinal feature *(purulent nasal discharge predominating on 1 side, local facial pain predominating on one side, purulent nasal discharge on both sides, pus in the nasal cavity)* and symptoms for at least 7 days	Day 14	19 (14.3%)	Improved or not improved by the end of 2 weeks ("what day were you entirely improved?"), evaluated during telephone interviews	Placebo: 25/60 Antibiotics: 32/56		Placebo: 7/60 (diarrhea 1, nausea 5, emesis 0, abdominal pain 1, rash 0, hot flashes 1, jittery 1, dizziness 0, dry mouth 0, vaginal infection 0) Amoxicillin: 13/56 (diarrhea 4, nausea 4, emesis 1, abdominal pain 2, rash 2, hot flashes 0, jittery 0, dizziness 3, dry mouth 1, vaginal infection 2) No drop-outs due to side effects
Meltzer 2005 Calif, Belgium and NJ 486 participants analyzed (omission	Amoxicillin (500 mg 3 times daily for 10 days) versus placebo	Concomitant medications that would interfere with study evaluation, anal-	Signs and symptoms of acute rhinosinusitis for $\geq$ 7 days but $\leq$ 28 days	Day 15	13 (2.6%)	No definition of cure Primary outcome measure: difference in	No significant difference (no numbers nor P values available)		No exact number available or calculable 19 loss of follow-up due to ad-

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

of groups with monometasone furoate nasal spray) 71 medical centres in 14 countries		gesics and NSAIDs were not permitted	and major symptom score ≥ 5 but ≤ 12 at screening and baseline visits with no more than 3 of the 5 symptoms *(rhinorrhoea, postnasal drip, nasal congestion/stuffiness, sinus headache and facial pain/pressure/tenderness on palpation over the paranasal sinuses)* rated severe (baseline visit)			mean AM/PM MSS over days 2 to 15 of the treatment phase			verse events: MFNS twice daily 7, MFNS once daily 1, amoxicillin 5, placebo 6 Treatment-emergent adverse events (mostly headache and epistaxis) was similar among the treatment groups: MFNS twice daily 36%, MFNS once daily 35%, amoxicillin 33.5%, placebo 38% More in detail: placebo: 7/252 nausea, 10/252 diarrhea, 3/252 abdominal pain

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

									amoxicillin: 9/251 nausea, 7/251 diarrhea, 3/251 abdominal pain
Williamson 2007 UK 209 participants analyzed 58 family practices (74 family physicians)	Amoxicillin (500 mg three times daily for 7 days) and budesonide (200 μg once daily for 10 days) versus budesonide (200 μg once daily for 10 days) amoxicillin (500 mg 3 times daily for 7 days) versus placebo		Uncomplicated acute illness (< 28 days), symptoms of sinusitis (*Berg and Carenfelt criteria: purulent nasal discharge predominating on 1 side, local facial pain predominating on one side, purulent nasal discharge on both sides, pus in the nasal cavity)* (inclusion if 2 symptoms and 1 clinical sign)	Day 10	31 (12.9%)	Symptom resolution (scoring 0 for all symptoms in the diary)	Placebo: 71/108 Antibiotics: 71/101		No information available
Garbutt 2012 US 155 participants analyzed 10 offices of primary	Amoxicillin 500 mg 3 times daily for 10 days versus placebo	Acetaminopher for pain or fever at a dose of 500 mg every 6 hours,	A history of maxillary pain or tenderness in the face or teeth, purulent	Day 3 Day 7 Day 10 (Day 28)	11 (6.6%)	No definition of cure Primary outcome measure: mean change in SNOT-		Day 3: Placebo: 25/74 Antibiotics: 30/81 Day 7:	No difference in reporting adverse effects from the study med-

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

care		guaifenesin to thin secretions at a dose of 600 mg every 12 hours, 10mg/5mL of dextromethorphan hydrobromide and 100mg/5mL of guaifenesin for cough at a dose of 10 mL every 4 to 6 hours, pseudoephedrine sustained action for nasal congestion at a dose of 120 mg every 12 hours, and 0.65% saline spray using 2 puffs per nostril Use as needed, supplied for 5 to 7 days to all patients except when contraindications present	nasal secretions and rhinosinusitis symptoms for 7 days or more and 28 days or less that were not improving or worsening, or rhinosinusitis symptoms lasting for less than 7 days that had significantly worsened after initial improvement. Symptoms had to be moderate, severe or very severe			16 scores "Significant improvement": symptoms a lot better or absent since enrolment		Placebo: 41/74 Antibiotics: 60/81 Day 10: Placebo: 59/74 Antibiotics: 63/81	ication: Placebo: 10/74 Antibiotics: 5/81 1 participant of the antibiotic group discontinued intervention because of adverse effects Headache: placebo: 17/74 antibiotics: 18/81 Excessive tiredness: placebo: 16/74 antibiotics: 9/81 Nausea (7%), diarrhea (9%), abdominal pain (5%), vaginitis (6% of women), no differences between the treatment groups

* Stalman 1997 only mentioned the total cure rate for both groups and stated that there was no difference between both groups. We used the same percentages in both groups for pooling.
$ We added data from 50 patients with a known course of illness but with lack of data about the main outcome, based on follow-up data from diaries and physical examination.
AM/PM MSS: major symptom score
MFNS: mometasone furoate nasal spray
NSAIDs: non-steroidal anti-inflammatory drugs
URTI: upper respiratory tract infection

APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)

1 exp Sinusitis/
2 sinusit*.tw.
3 Rhinitis/
4 rhinit*.tw.
5 rhinosinusit*.tw.
6 nasosinusit*.tw.
7 ((suppurative or purulent) adj2 (nasal discharge or rhinitis or rhinorrhoea or rhinorrhoea)).tw.
8 or/1-7
9 exp Anti-Bacterial Agents/
10 antibacterial*.tw.
11 antibiotic*.tw.
12 exp Amoxicillin/
13 amoxicillin*.tw,nm.
14 Ampicillin/
15 ampicillin*.tw,nm.
16 Azithromycin/
17 azithromycin.tw,nm.
18 Cefaclor/
19 cefaclor.tw,nm.
20 exp Cefadroxil/
21 cefadroxil.tw,nm.
22 cefatrizine.tw,nm.
23 Cefuroxime/
24 cefuroxim*.tw,nm.
25 Cephalexin/
26 cephalexin*.tw,nm.
27 Cephalosporins/
28 cephalosporin*.tw,nm.
29 Ciprofloxacin/
30 ciprofloxacin*.tw,nm.
31 Clarithromycin/
32 clarithromycin*.tw,nm.
33 Clindamycin/

34 clindamycin*.tw,nm.
35 Doxycycline/
36 doxycyclin*.tw,nm.
37 Erythromycin/
38 erythromycin*.tw,nm.
39 Fluoroquinolones/
40 fluoroquinolone*.tw,nm.
41 levofloxacin.tw,nm.
42 Lincomycin/
43 lincomycin*.tw,nm.
44 Macrolides/
45 macrolide*.tw,nm.
46 Minocycline/
47 minocyclin*.tw,nm.
48 Miocamycin/
49 (miocamycin* or miokamycin*).tw,nm.
50 moxifloxacin*.tw,nm.
51 norfloxacin.tw,nm.
52 Norfloxacin/
53 Ofloxacin/
54 ofloxacin.tw,nm.
55 Penicillins/
56 penicillin*.tw,nm.
57 Quinolones/
58 quinolone*.tw,nm.
59 Spiramycin/
60 spiramycin.tw,nm.
61 telithromycin.tw,nm.
62 tetracyclines/ or tetracycline/
63 tetracycline*.tw,nm.
64 Trimethoprim-Sulfamethoxazole Combination/
65 trimethoprim-sulfamethoxazole combination.tw,nm.
66 cotrimoxazole*.tw,nm.
67 or/9-66
68 8 and 67

Appendix 2. EMBASE search strategy

#21 #12 AND #20 970
#20 #15 NOT #19 689539
#19 #16 NOT #18 3410992
#18 #16 AND #17 720081
#17 'human'/de AND [embase]/lim8013828
#16 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de AND [embase]/lim4131073
#15 #13 OR #14 772533
#14 crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR placebo*:ab,ti OR (doubl* NEXT/1 blind*):ab,ti OR allocat*:ab,ti OR random*:ab,ti OR trial:ti AND [embase]/lim729924
#13 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim256908
#12 #6 AND #11 9078
#11 #7 OR #8 OR #9 OR #10 824686

#10 amoxicillin:ab,ti OR ampicillin*:ab,ti OR azithromycin:ab,ti OR cefaclor:ab,ti OR cefadroxil:ab,ti OR cefatrizine:ab,ti OR cefuroxim*:ab,ti OR cephalexin*:ab,ti OR cephalosporin*:ab,ti OR ciprofloxacin*:ab,ti OR clarithromycin*:ab,ti OR clindamycin:ab,ti OR doxycyclin*:ab,ti OR erythromycin*:ab,ti OR fluoroquinolone*:ab,ti OR levofloxacin*:ab,ti OR lincomycin*:ab,ti OR macrolide*:ab,ti OR minocyclin*:ab,ti OR miocamycin*:ab,ti OR miokamycin*:ab,ti OR moxifloxacin*:ab,ti OR norfloxacin*:ab,ti OR ofloxacin*:ab,ti OR penicillin*:ab,ti OR quinolone*:ab,ti OR spiramycin*:ab,ti OR telithromycin*:ab,ti OR tetracyclin*:ab,ti OR trimethoprim*:ab,ti OR cotrimoxazol*:ab,ti AND [embase]/lim147653
#9 'amoxicillin'/de OR 'ampicillin'/de OR 'azithromycin'/de OR 'cefaclor'/de OR 'cefadroxil'/de OR 'cefuroxime'/de OR 'cefalexin'/de OR 'cephalosporin'/de OR 'ciprofloxacin'/de OR 'clarithromycin'/de OR 'clindamycin'/de OR 'doxycycline'/de OR 'erythromycin'/de OR 'lincomycin'/de OR 'macrolide'/de OR 'quinolone derivative'/de OR 'minocycline'/de OR 'miokamycin'/exp OR 'norfloxacin'/de OR 'ofloxacin'/de OR 'penicillin derivative'/de OR 'spiramycin'/de OR 'tetracycline derivative'/de OR 'cotrimoxazole'/de AND [embase]/lim269822
#8 antibiotic*:ab,ti AND [embase]/lim188472
#7 'antibiotic agent'/exp AND [embase]/lim744001
#6 #1 OR #2 OR #3 OR #4 OR #5 44104
#5 ((suppurative OR purulent) NEAR/2 ('nasal discharge' OR rhinitis OR rhinorrhea OR rhinorrhoea)):ab,ti AND [embase]/lim252
#4 rhinit*:ab,ti OR rhinosinusit*:ab,ti OR nasosinusit*:ab,ti AND [embase]/lim21609
#3 'rhinitis'/de OR 'rhinosinusitis'/de AND [embase]/lim13895
#2 sinusit*:ab,ti AND [embase]/lim10058
#1 'sinusitis'/exp AND [embase]/lim19971

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 10, 2012

Date	Event	Description
7 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

An De Sutter (ADS) wrote the first draft of the protocol.

James Young (JY) developed the methodology for the individual patient data meta-analysis (IPDMA).

Marieke Lemiengre (ML) wrote the first draft of the review.

ADS, Mieke van Driel (MVD), JY and Dan Merenstein (DM) commented on the draft and suggested changes which consequently led to a new version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Ghent University, Belgium.

Salary

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Rhinitis [*drug therapy]; Sinusitis [*drug therapy]; Time Factors

MeSH check words

Adult; Humans