

# Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials

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We did a meta-analysis of randomised controlled trials (RCTs) to assess the therapeutic role of antibiotics for acute sinusitis compared with placebo. Eligible studies were retrieved from PubMed and Scopus. 17 double-blind RCTs were included (three involving children). Acute sinusitis was diagnosed with clinical criteria in nine RCTs, imaging studies in six RCTs, and microbiological or laboratory methods in two RCTs. Amoxicillin was used in ten of 23 antibiotic treatment groups. To account for potential statistical heterogeneity between studies, a random-effects model was used for all analyses. Compared with placebo, antibiotics were associated with a higher rate of cure or improvement (2648 patients, odds ratio [OR] 1.64 [95% CI 1.35–2.00], data from 16 RCTs), or cure alone (1813 patients, OR 1.82 [1.34–2.46], 12 RCTs), but also with more adverse events (1963 patients, OR 1.87 [1.21–2.90], 12 RCTs). The rate of symptom resolution was faster with antibiotics in most RCTs. Disease complications, disease recurrence, and study withdrawals because of adverse events did not differ between compared treatments. In conclusion, use of antibiotics for acute sinusitis confers a small therapeutic benefit over placebo with a corresponding rise in the risk for adverse events. We suggest that antibiotics should be reserved for carefully selected patients with a higher probability for bacterial disease.

## Introduction

Paranasal sinusitis is a group of disorders characterised by a constellation of symptoms, including nasal congestion or obstruction, discharge (which can be purulent), postnasal drip, a feeling of facial pain or pressure, alterations in the sense of smell, fever, headache, cough, dental pain, and halitosis, among others. If sinusitis symptoms have a sudden onset and are present for no more than 4 weeks, then the disorder is defined as “acute”. The origin of sinusitis symptoms is an inflammatory reaction involving the mucous membranes of the nasal and paranasal cavities and the fluids within these cavities.<sup>1,2</sup> The combined term “acute rhinosinusitis”, which is used interchangeably with the term “sinusitis”, indicates that acute sinusitis usually develops in the context of preceding acute rhinitis (common cold),<sup>3</sup> and also that, in many cases of acute rhinitis, there is radiographic evidence of involvement of the paranasal sinuses.<sup>4,5</sup>

Acute sinusitis is commonly infectious in origin, although allergy and local irritants can produce similar symptoms.<sup>6</sup> The infectious agents involved in its aetiology are mostly viral, but a viral infection may evolve into a bacterial infection. Fungal pathogens might also be encountered in the immunocompromised host.<sup>7</sup> Among bacterial pathogens causing sinusitis, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most prevalent in adults.<sup>8</sup> *Moraxella catarrhalis* should also be considered, particularly in children.<sup>9</sup>

Acute bacterial sinusitis can complicate an estimated 0.5–2% of upper respiratory viral infections in adults,<sup>10,11</sup> although the proportion might be appreciably higher in young children.<sup>12</sup> However, in selected patients presenting to primary-care services with manifestations of acute sinusitis, bacterial disease can be diagnosed by either sinus puncture or radiological methods in approximately

50%.<sup>13–15</sup> Nevertheless, physicians tend to prescribe antibiotics in up to 98% of such cases.<sup>16,17</sup>

Acute sinusitis accounts for almost 3 million ambulatory-care visits annually in the USA.<sup>18,19</sup> Acute and chronic sinusitis taken together are estimated to affect 16% of the adult US population,<sup>20</sup> and represent the fifth leading cause for antibiotic prescriptions in the community.<sup>21</sup> The total annual health-care expenditures directly associated with this group of disorders have been calculated to be \$3.4 billion in the USA, of which a substantial proportion accounts for medication costs.<sup>22</sup>

Given the substantial disease burden caused by acute sinusitis, various professional societies and authoritative committees have issued recommendations regarding the selection of the appropriate antimicrobial agent in patients with sinusitis (table).<sup>19,23–27</sup> However, whether antibiotics should be prescribed in patients with acute sinusitis remains a controversial issue.<sup>28–30</sup> The US Food and Drug Administration has proposed that new antibiotics to be approved for acute bacterial sinusitis should show superiority over either an active agent or placebo,<sup>31,32</sup> partly because an appropriate non-inferiority margin is difficult to set. In this context, we aimed to further assess the effectiveness and safety of antibiotic treatment in patients with acute sinusitis by doing a meta-analysis of relevant randomised placebo-controlled trials.

## Methods

### Data sources

We searched PubMed database (July, 1965, to January, 2007) to identify relevant randomised controlled trials (RCTs). An updated search was done in May, 2008. The following search terms were used: “placebo AND

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(sinusitis OR rhinosinusitis OR sinus infection) AND (antibiotics OR anti-bacterial agents OR anti-infective agents OR anti-microbial agents OR drug therapy)". No limits were set for this search. We did a secondary search in the Scopus database to identify any additional article satisfying the inclusion criteria of our meta-analysis. We also hand-searched bibliographies of relevant articles.

### Study selection process

All retrieved articles were screened on the basis of title and abstract. Full-text papers were obtained for studies selected for further evaluation. We included in the meta-analysis RCTs done with a double-blind method that compared treatment with any antibiotic versus placebo for patients of any age with acute sinusitis of any location. The diagnosis of acute sinusitis in the included RCTs was required to be determined by either clinical criteria, or by positive radiological, microbiological, or laboratory tests in patients with appropriate clinical manifestations. With regard to clinical criteria, we

accepted those used in each of the reviewed RCTs if they explicitly stated that patients with a clinical diagnosis of acute sinusitis were exclusively enrolled. RCTs that assessed patients with mixed types of sinusitis (allergic, recurrent, or chronic sinusitis, or acute exacerbations of chronic sinusitis) or mixed types of upper respiratory tract infections were included if data on the subgroup of patients with acute sinusitis were specifically reported, or if a clinical diagnosis of acute sinusitis could be supported for more than two-thirds of the study population. A clinical diagnosis of acute sinusitis was inferred by the presence of at least two major criteria, or of at least one major and two minor criteria, or of nasal purulence at rhinoscopy in the appropriate clinical setting, as defined by Lanza and Kennedy.<sup>1</sup> Alternatively, sinusitis-like symptoms were required to be present and not improving after 7 days from onset, or to be worsening after 5 days from onset. We excluded RCTs published in languages other than English, Spanish, French, Italian, and German, and trials presented as abstracts in scientific conferences.

	Canada <sup>23</sup>	France <sup>24</sup>	Germany <sup>25</sup>	Spain <sup>26</sup>	USA <sup>28</sup>	UK <sup>27</sup>
<b>Treatment recommendations</b>						
First-line treatment	Amoxicillin	Amoxicillin-clavulanic acid; second and third-generation cephalosporins (except cefixime)	Amoxicillin;* aminopenicillin plus $\beta$ -lactamase inhibitor; second-generation cephalosporins; macrolides-ketolides; co-trimoxazole; clindamycin; doxycycline	..	Amoxicillin	Amoxicillin
Second-line treatment	Amoxicillin-clavulanic acid; cefuroxime	Fluoroquinolones	..	..	Amoxicillin-clavulanic acid (high-dose); fluoroquinolones (including gemifloxacin)	Amoxicillin-clavulanic acid;* fluoroquinolones
<b>Recommendations based on severity of symptoms and selected other factors</b>						
Mild symptoms	..	..	..	Symptomatic treatment;* amoxicillin (high-dose)	..	..
Moderate symptoms	..	..	..	Fluoroquinolones;* amoxicillin-clavulanic acid (high dose); telithromycin	..	..
Severe symptoms	..	..	Aminopenicillin plus $\beta$ -lactamase-inhibitor;* second-generation cephalosporins;* cefotaxime;* third-generation cephalosporins; fluoroquinolones (including ciprofloxacin)	Third-generation cephalosporins (intravenously)*; amoxicillin-clavulanic acid (intravenously)	..	..
Allergy to $\beta$ -lactams	First-line: doxycycline; co-trimoxazole. Second-line: macrolides; fluoroquinolones	Pristinamycin	..	..	First-line: co-trimoxazole; macrolides. Second-line: fluoroquinolones	Doxycycline; macrolides
Maxillary sinusitis of dental origin	..	..	..	Amoxicillin-clavulanic acid (high dose)*; moxifloxacin;* clindamycin or metronidazole with or without amoxicillin (high dose); levofloxacin	..	Amoxicillin plus metronidazole
*Treatment of choice. Fluoroquinolones include moxifloxacin and levofloxacin.						

Table: Treatment guidelines for adults with acute sinusitis in different countries

### Data extraction

For each study included in our meta-analysis, two investigators (KPG and DEK) independently extracted and tabulated data on study design, demographics of the study population, inclusion and exclusion criteria, duration of symptoms before treatment, number of randomised and clinically assessable patients, along with the duration and dosage of the compared regimens and the use of additional medications; data on the patient outcomes of cure or improvement, complications, recurrence, and adverse events were also recorded. Potential differences between the two reviewers were resolved in meetings of all investigators.

### Outcomes

The primary effectiveness outcome of the meta-analysis was cure or improvement, between days 7 to 15 from the beginning of treatment, in clinically assessable patients. Cure was defined as complete resolution of symptoms and signs related to acute sinusitis or presence of residual symptoms of the mildest degree only; improvement was defined as partial resolution of symptoms and signs related to acute sinusitis. The clinically assessable population comprised patients that satisfied the criteria for eligibility set in each of the included RCTs. Secondary effectiveness outcomes included cure alone, time to resolution of symptoms, complications (including secondary local infections that could be attributed to acute sinusitis and progression to severe or chronic disease), and recurrence (defined as reappearance of symptoms and signs of acute sinusitis after the course of treatment in a patient who had previously been classified as cured). The safety outcomes of the meta-analysis were total adverse events, and withdrawals because of adverse events.

### Quality assessment

The methodological quality of the included RCTs was assessed with the use of the Jadad criteria,<sup>31</sup> which include assessment of the randomisation and blinding procedures as well as the provision of data on study withdrawals. According to these criteria, the maximum score that can be assigned to an individual RCT is 5 points, and a score of at least 3 points is considered to denote high methodological quality.<sup>31</sup>

### Statistical analysis

Statistical analyses were done by use of Review Manager version 5.0 software (Cochrane Collaboration). Pooled odds ratios (ORs) and 95% CIs were determined by use of the DerSimonian-Laird random-effects model.<sup>34</sup> Statistical between-study heterogeneity was assessed by using the  $I^2$  test and the  $\chi^2$  test. Publication bias was assessed by use of a funnel plot.<sup>35</sup> Differences between subgroups were assessed on the basis of the  $\chi^2$  statistic. For all tests done, a p value of less than 0.05 was considered to denote statistical significance.

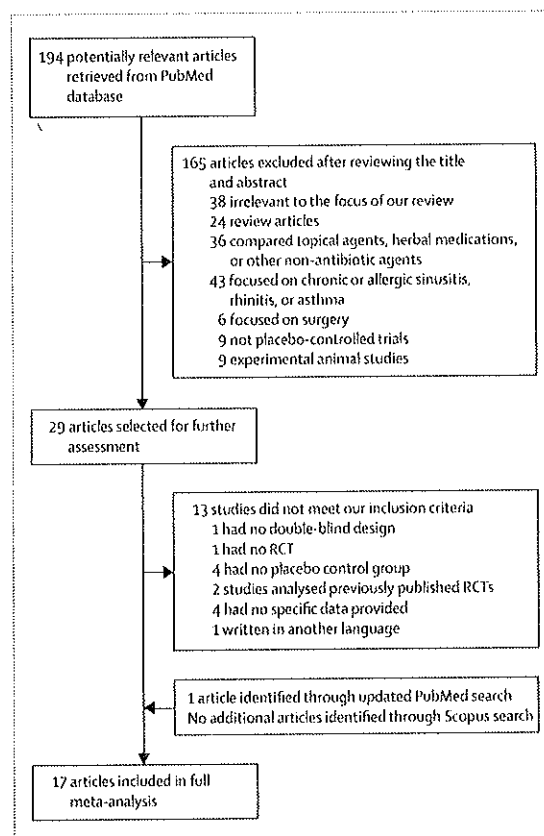


Figure 1: Flow diagram of the selection process of articles for inclusion in the meta-analysis

### Results

Figure 1 shows the process used to select potentially relevant studies for inclusion in our meta-analysis. We initially screened 194 publications retrieved from the PubMed database, of which 16 fulfilled the criteria for inclusion in this meta-analysis. No additional studies were included after a secondary search in the Scopus database. However, one additional RCT that was eligible for inclusion was identified through our updated PubMed search.

The main characteristics of the 17 overall RCTs included in the meta-analysis are shown in webtable 1.<sup>36-52</sup> All studies were randomised, double-blind, placebo-controlled trials, with a Jadad score of 4 or 5, and were done mainly in the USA and European countries. In total, 3291 outpatients (2915 adults and 376 children) were randomly assigned to receive study treatments in the clinical trials included in the meta-analysis.

With regard to the inclusion diagnostic criteria used, imaging studies of the paranasal sinuses, including plain radiography, computed tomography, and ultrasonography, were used for the verification of the clinical diagnosis of acute sinusitis in six of the 17 trials.<sup>37,44,47,49-51</sup> Bacteriological diagnostic methods were used in one trial,<sup>52</sup> laboratory

See Online for webtable 1

See Online for weblink 2

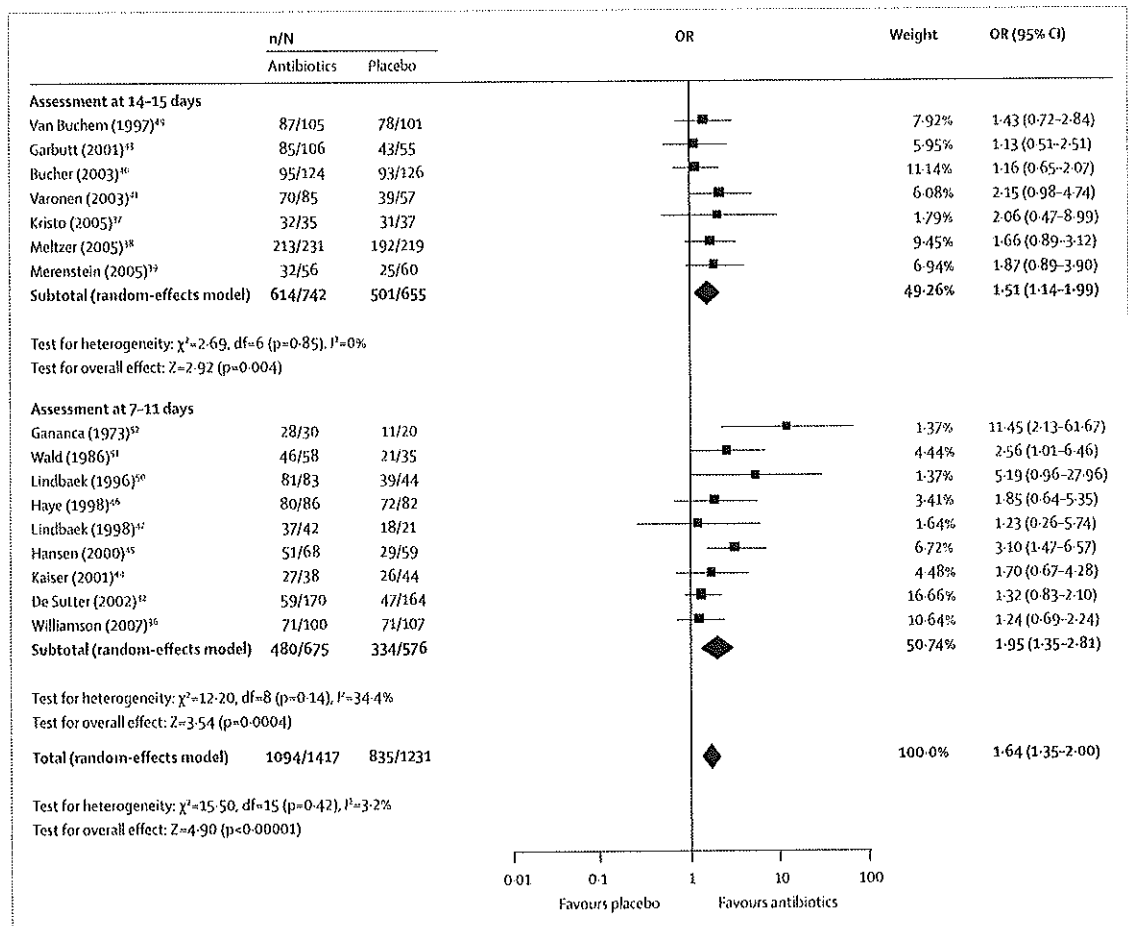
methods (measurement of inflammatory markers) in one trial,<sup>45</sup> and the remaining nine trials used clinical criteria alone for the diagnosis of acute sinusitis; a minimum duration of symptoms of at least 7 days was required in four trials (10 days in two trials,<sup>43,46</sup> 7 days in the other two trials<sup>38,39</sup>).

All study medications were given to patients orally. The most commonly compared antibiotic was amoxicillin in ten RCTs,<sup>36,38,39,41-43,47,49-51</sup> followed by phenoxymethylpenicillin in four RCTs,<sup>41,45,47,50</sup> amoxicillin-clavulanic acid in three RCTs,<sup>40,41,51</sup> whereas doxycycline was given in two RCTs,<sup>41,48</sup> azithromycin in two RCTs,<sup>44,46</sup> cefuroxime in one RCT,<sup>37</sup> and cefaclor in one RCT (weblink 1).<sup>52</sup> Of note, five RCTs had more than one antibiotic treatment group. Data on compliance to allocated treatment were scarce, and thus were not included in our analysis. The percentage of randomised patients in the antibiotic treatment groups that were judged as clinically assessable was 91.5%, which was similar to the respective percentage of patients randomly assigned to placebo (90.0%). The

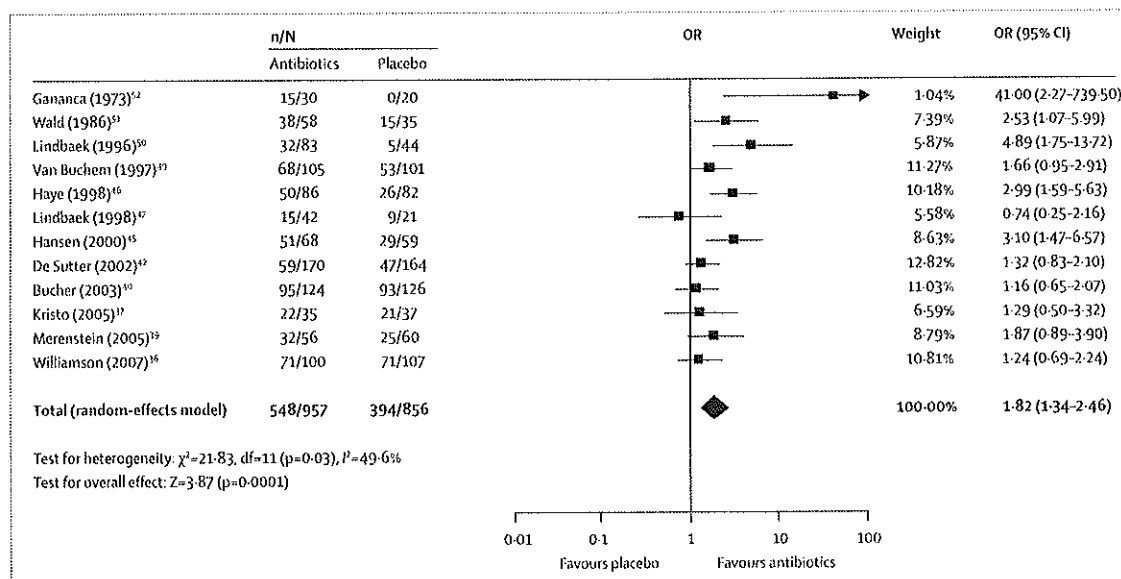
use of concomitant ancillary treatments, such as paracetamol, other analgesics, or decongestants, was not allowed in two of the included RCTs (data not shown).<sup>38,51</sup>

Weblink 2 shows the data on different outcomes that were extracted from each study and entered in the meta-analysis. A greater proportion of patients with acute sinusitis were cured or improved with antibiotic treatment compared with placebo (2648 patients, OR 1.64 [95% CI 1.35-2.00], data from 16 RCTs;<sup>36-47,49-52</sup> figure 2). For studies that reported on cure separately, more patients were cured with antibiotic treatment compared with placebo (1813 patients, OR 1.82 [CI 1.34-2.46], 12 RCTs;<sup>36,37,39,40,42,45-47,49-52</sup> figure 3). In the ten trials that specifically compared amoxicillin to placebo, cure or improvement was more likely in patients who received amoxicillin alone (1702 patients, OR 1.48 [1.17-1.89]).<sup>36,38,39,41-43,47,49-51</sup>

Eight of the included RCTs provided information on time to resolution of symptoms.<sup>36,39,41,42,45,47,48,50</sup> Three of these RCTs reported on the time to resolution of specific



**Figure 2:** Patients with acute sinusitis who were cured or improved with antibiotic treatment compared with placebo. Vertical line indicates no difference between compared treatments. 95% CIs are shown by horizontal lines. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. Pooled odds ratios (95% CI) are also shown. Reference 48 did not provide specific data on the outcome of cure or improvement and thus was not included in the analysis regarding this outcome.



**Figure 3:** Patients with acute sinusitis who were cured with antibiotic treatment compared with placebo. Vertical line indicates no difference between compared treatments. 95% CIs are shown by horizontal lines. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. Pooled odds ratios (95% CI) are also shown.

symptoms only, such as facial pain and purulent rhinorrhoea.<sup>42,45,48</sup> Although findings are not comprehensive, most of the relevant RCTs reported faster symptom resolution in patients receiving antibiotics than in those receiving placebo, although this was not always significant.<sup>39,41,42,45,48,50</sup>

More patients treated with antibiotics had any adverse event compared with those treated with placebo (1963 patients, OR 1.87 [1.21-2.90], 12 RCTs;<sup>37-39,41,43,45,46,48-52</sup> figure 4). The proportions of patients who withdrew from clinical trials because of adverse events was not significantly different between those treated with antibiotics and those with placebo (3013 patients, OR 1.42 [0.74-2.72], 17 RCTs).<sup>36-52</sup> Patients who were treated with antibiotics had a greater incidence of diarrhoea or other gastrointestinal disturbances than those treated with placebo (2403 patients, OR 2.28 [1.24-4.21], 14 RCTs).<sup>37-43,45-48,50-52</sup> No difference was found with regard to disease complications (1815 patients, OR 0.68 [0.22-2.09], nine RCTs)<sup>36,37,40-43,45,48,49</sup> or disease recurrence (1421 patients, OR 1.12 [0.79-1.59], six RCTs)<sup>38,40,41,43,46,49</sup> in patients treated with antibiotics compared with those treated with placebo.

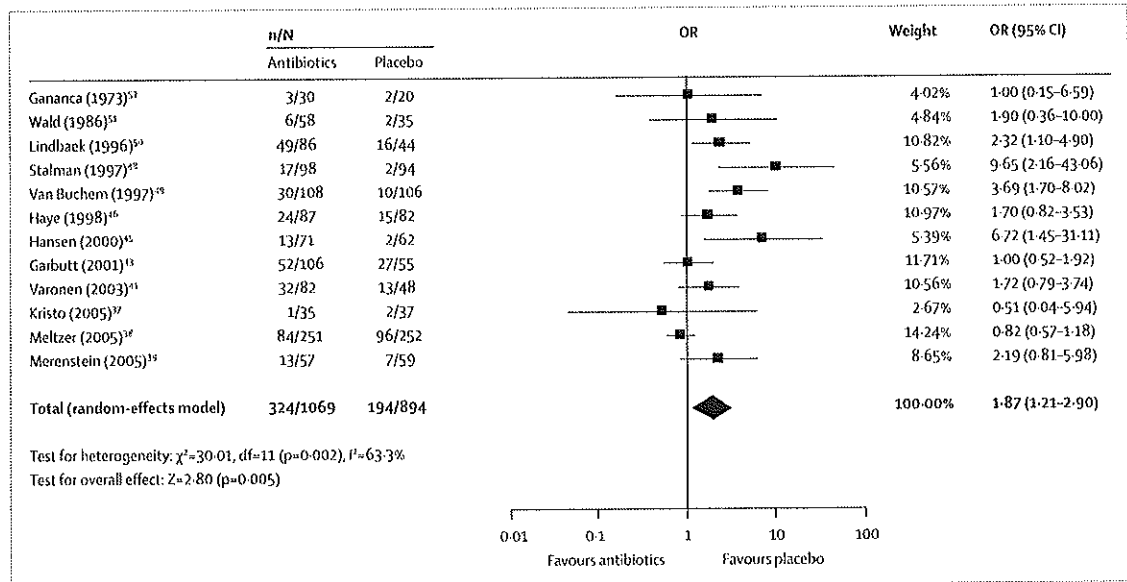
Results of our subgroup analyses are shown in figure 5. We found no differences in cure or improvement by age-group ( $p=0.95$ ), diagnostic criteria ( $p=0.30$ ), timing of assessment ( $p=0.43$ ; figure 2), or year of publication ( $p=0.21$ ).

With regard to the primary outcome of cure or improvement, characteristics of potential publication bias were detected in one of the included RCTs.<sup>53</sup> The enhanced therapeutic effect associated with antibiotic use in this RCT could alternatively be attributed to the particular

diagnostic method used (culture of purulent nasopharyngeal secretions), as has been shown in other trials that have used this method.<sup>44,53</sup> The statistical heterogeneity conferred by this trial was of a very mild degree ( $I^2=3.2\%$ ,  $p=0.42$  for the  $\chi^2$  test), and a subsequent sensitivity analysis that excluded this trial did not appreciably influence the findings of the meta-analysis with regard to cure or improvement of patients with acute sinusitis (2598 patients, OR 1.59 [95% CI 1.31-1.93], 15 RCTs).<sup>36-47,49-51</sup>

## Discussion

The main finding of our meta-analysis is that cure or improvement of patients with acute sinusitis, within a timeframe of 7-15 days from the initiation of treatment, was more likely with antibiotic treatment than with placebo. The association of antibiotic treatment with greater clinical success was consistent in the secondary analyses on the outcome of complete cure alone, and the comparison limited to amoxicillin versus placebo. No significant differences were detected in the comparisons between different subgroups of patients. However, in the subgroup analysis limited to children, only a small number of patients were included. No differences were shown between antibiotic and placebo treatment with regard to disease complications and recurrence. However, antibiotic treatment for acute sinusitis was associated with a higher number of patients with adverse events than with placebo. This seemed pronounced when gastrointestinal adverse events were separately considered. Study withdrawals because of adverse events did not differ between compared treatments. Of note,



**Figure 4:** Patients with acute sinusitis who presented adverse events with antibiotic treatment compared with placebo. Vertical line indicates no difference between compared treatments. 95% CIs are shown by horizontal lines. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. Pooled odds ratios (95% CI) are also shown.

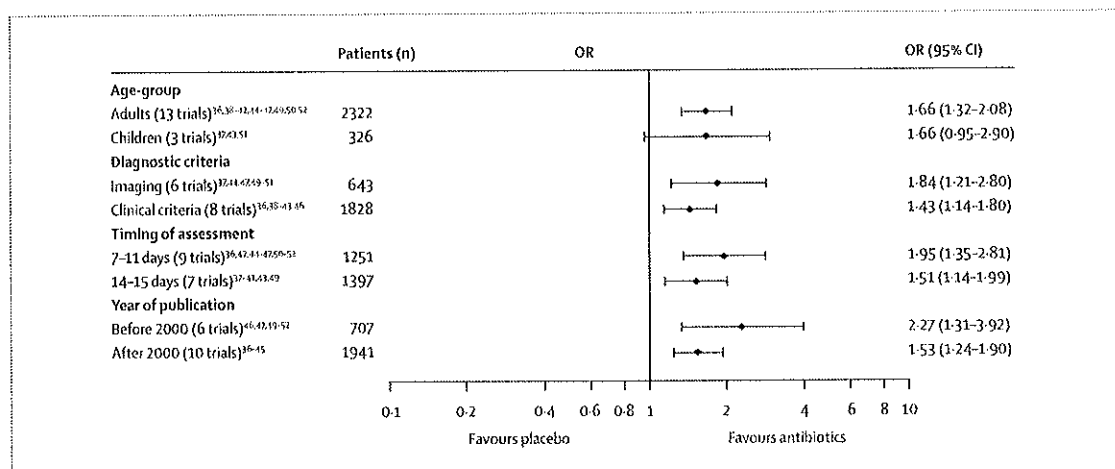
events in the latter analysis, and in the analysis of complications, were relatively rare.

Despite the consistency and statistical power of the association of antibiotic treatment with superior clinical success in acute sinusitis compared with placebo, the magnitude of the therapeutic effect does not seem to be large. Specifically, the overall crude proportion of cure or improvement in all patients assessed in the antibiotic treatment groups compared with placebo was 77.2% versus 67.8%. This apparently small difference might be related to various factors, such as the inclusion of a substantial number of patients without disease of bacterial origin, the high rate of spontaneous resolution of symptoms in acute bacterial sinusitis even in some patients not microbiologically cured, the persistence of symptoms caused by factors other than treatment failure, and the confounding effect of the administration of ancillary treatments.<sup>19,54-56</sup>

The potential inclusion of a substantial percentage of patients with acute sinusitis of non-bacterial cause might be attributed to the fact that none of the included studies was based on the standard of reference for the diagnosis of bacterial disease (ie, sinus puncture and quantitative culture of the aspirated specimen). Culture of endoscopic samples obtained from the middle meatus, which could be a reliable surrogate test for the diagnosis of bacterial disease in adult patients,<sup>37</sup> was also not used. The various diagnostic studies used in the RCTs analysed, such as culture of nasopharyngeal secretions, imaging modalities, and measurement of inflammatory markers, have generally shown moderate accuracy in differentiating between bacterial and viral causes of sinusitis.<sup>31,58-62</sup>

With regard to clinical criteria, no single symptom or sign can be reliably used for the diagnosis of acute bacterial sinusitis.<sup>61</sup> Moreover, the presence of any of the common clinical manifestations of the disease does not confidently predict a beneficial treatment effect of antibiotics.<sup>63</sup> Rather, the presence of a constellation of symptoms and signs should be considered in making a clinical diagnosis of acute bacterial sinusitis.<sup>64,65</sup> Additionally, the possibility of a bacterial cause of acute sinusitis is thought to increase substantially as symptoms persist for a longer duration of time.<sup>8</sup> A strategy of so-called "watchful waiting" for 7-10 days before initiation of antimicrobial treatment is a valid therapeutic option for acute sinusitis.<sup>10,66</sup> Despite these principles, bacterial sinusitis tends to be over-diagnosed by clinical criteria in nearly 50% of cases.<sup>61</sup>

In this meta-analysis, the therapeutic effect of antibiotics compared with placebo seemed greater in the subgroup of trials that used imaging criteria for the diagnosis of patients with acute sinusitis than in those that relied on clinical criteria alone. However, this difference did not reach significance. The predictive value of radiological abnormalities with regard to the effectiveness of antibacterial treatment for acute sinusitis might have been higher if only patients with radiological signs of complete opacification or air-fluid level in a paranasal sinus were considered, excluding those with mucosal thickening alone.<sup>67</sup> Radiological confirmation of a clinical diagnosis of acute sinusitis has been suggested as a discriminatory factor in selecting patients who are likely to show clinical benefit from antibacterial treatment.<sup>68</sup> However, in most primary health-care systems, radiological studies are not



**Figure 5: Subgroup analyses of patients with acute sinusitis who were cured or improved with antibiotic treatment compared with placebo**  
Vertical line indicates no difference between compared treatments. 95% CIs are shown by horizontal lines. Pooled odds ratios (ORs; 95% CI) are shown. Reference 48 did not provide specific data on the outcome of cure or improvement and thus was not included in the analysis regarding this outcome.

routinely done for the vast majority of patients with a clinical suspicion of acute sinusitis.<sup>69</sup>

A factor that might have confounded the effect of antibiotics compared with placebo for the treatment of acute sinusitis in the RCTs included in this meta-analysis is the use of ancillary therapies for symptomatic relief.<sup>56</sup> Although relevant data are inconclusive, there is evidence that analgesics,<sup>70</sup> topical decongestants,<sup>71</sup> nasal corticosteroids,<sup>38</sup> antihistamines,<sup>6</sup> and even saline irrigation,<sup>72</sup> may aid in the alleviation of sinonasal symptoms. In most studies included in our meta-analysis, additional symptomatic treatment, usually nasal vasoconstrictors and analgesics, was allowed, whereas the administration of nasal corticosteroids was part of the study experimental protocol in one of the included trials.<sup>36</sup> In three studies that reported detailed relevant data, use of ancillary treatments in the study population reached 50%,<sup>41,43,54</sup> and seemed higher for patients in the placebo groups than in those treated with antibiotics.

A characteristic of the RCTs included in this meta-analysis that should be pointed out is the exclusion of the most severely affected patients, or of patients with non-maxillary sinusitis. This was stated in 12 of the 17 RCTs.<sup>36,38,40-44,46-48,50,51</sup> Patients with disease of greater severity or sinusitis of the frontal, ethmoid, or sphenoid sinuses are the most likely to develop disease complications,<sup>73-75</sup> which could be prevented by antibacterial therapy. This should be taken into account when extrapolating the findings of this meta-analysis to clinical practice.

An important measure of effectiveness of antibiotic treatment for diseases with a high rate of spontaneous resolution, such as acute sinusitis, is the time to resolution of symptoms.<sup>56</sup> Although no pooled analysis could be done for this outcome, most of the included RCTs in which relevant data were reported concluded that the use of antibiotics was associated with faster rate

of symptom resolution. Additionally, the therapeutic benefit of antibiotics compared with placebo tended to be more pronounced (albeit not significantly) in the subgroup of trials that assessed the outcome of cure or improvement at an earlier timepoint in the course of acute sinusitis.

In this meta-analysis, no difference could be shown between antibiotic and placebo treatment for acute sinusitis in preventing disease recurrence. Recurrence was defined by clinical criteria, and thus it is expected to include both relapse of disease with the same bacterial strain or reinfection with a new strain. The apparent lack of effectiveness of antibiotics over placebo in preventing disease recurrence might be an epiphenomenon of the fact that the proportion of patients with disease of bacterial aetiology at baseline that were subsequently cured, and who are the most likely to suffer a relapse, might have been greater in the antibiotic treatment groups compared with the placebo groups, because of the effect of active treatment. Moreover, underlying allergic sinusitis might confound the assessment of recurrence if this is assessed by clinical criteria.<sup>6</sup> Conversely, antibiotics might alter the normal bacterial flora of the upper respiratory tract, which is thought to constitute a naturally occurring defence mechanism against reinfection.<sup>76</sup>

Complications of acute sinusitis, including progression to chronic disease, were not found to differ significantly between patients treated with antibiotics and those treated with placebo. The only serious complication reported, a brain abscess, developed in a patient treated with placebo, who subsequently required surgical treatment and recovered with a residual frontal syndrome.<sup>40</sup> The potential for development of serious complications in patients with acute bacterial sinusitis, such as local osteitis, periorbital infection, and intracranial infection via direct invasion or haematogenous spread,

should be considered in therapeutic decision-making. In patients admitted to hospital for sinusitis, intracranial complications can develop in 3–4%.<sup>77,78</sup> However, this figure is much lower in the community. In well-treated patients it can be lower than 1 in 10 000.<sup>79</sup> Nevertheless, sinusitis, because of its high incidence, might be the underlying cause in 5% of cases of community-acquired meningitis,<sup>80</sup> and, especially when frontal, in a much greater proportion of cases of brain abscess.<sup>81</sup>

Antibiotics given to patients with acute sinusitis were found to be associated with a higher incidence of adverse events compared with placebo. This difference seemed more pronounced when gastrointestinal adverse events were exclusively considered. The crude proportion of patients in the antibiotic treatment group who developed any adverse event was 30.3% versus 21.7% in placebo-treated patients. Data on the grade of severity of these adverse events were not systematically reported in the included RCTs. Study withdrawals because of adverse events, which could be used as a surrogate marker of severity of adverse events, were relatively rare, without significant difference between the treatment groups.

Apart from adverse events, other potential harms of unnecessary antibiotic treatment of acute sinusitis should also be considered.<sup>82</sup> At an individual level, antibiotic use carries the risk of subsequent infection with a drug-resistant pathogen.<sup>83,84</sup> At the community level, indiscriminate use of antibiotics contributes to an increase in the level of drug resistance in bacterial pathogens.<sup>85,86</sup> This is of particular concern, since antibiotics tend to be overused in routine clinical practice for the treatment of acute sinusitis,<sup>86</sup> which constitutes one of the leading causes for antibiotic prescriptions in the community.<sup>21</sup> Finally, the economic burden of inappropriate antibiotic use should also be considered.<sup>19</sup>

In interpreting all of the above aspects of antibiotic treatment in acute sinusitis, several potential limitations of this meta-analysis should be mentioned. First, various diagnostic inclusion criteria and definitions of outcomes and methods for assessing outcomes were used in the included RCTs. The heterogeneity in the diagnostic criteria used for identifying patients with acute sinusitis was substantial, particularly with regard to some of the included RCTs. Specifically, two RCTs done by the same group assessed patients with different types of radiological abnormalities.<sup>47,50</sup> Another RCT included patients with well-defined clinical criteria for the diagnosis of acute sinusitis, but with absence of radiological abnormalities.<sup>46</sup> Moreover, two RCTs included patients with mixed types of upper respiratory tract infections: one of these studies specifically reported treatment effectiveness data for the subgroup of patients with radiologically confirmed sinusitis,<sup>44</sup> whereas in the other study, most of the patients had characteristics that qualified for a diagnosis of acute sinusitis.<sup>42</sup>

With regard to the various methods used to assess outcomes, most of the included RCTs share the common

feature that they focused on the resolution of symptoms, partial or complete, over a relatively short time period after the completion of therapy. The exceptions include one RCT in which the primary outcome focused on the complete resolution of facial pain in particular,<sup>45</sup> and another RCT that reported specific data on secondary effectiveness outcomes regarding different types of symptoms or signs (webtable 2), but not on the primary effectiveness outcome.<sup>48</sup> For the latter RCT, we deemed it arbitrary to include any of the secondary effectiveness outcomes as a surrogate marker for cure or improvement. Furthermore, various methods for assessing clinical effectiveness were used in the trials, including symptom-scoring systems, physicians' clinical assessment, and patients' own assessment of symptoms recorded in diaries or questionnaires and reported at follow-up visits or telephone interviews.

Apart from their heterogeneity with regard to diagnostic criteria and outcome measures, the RCTs could also be thought of as complementary to each other by incorporating the various cases of patients with symptoms and signs of acute sinusitis that may be encountered in routine clinical practice, along with the variability in the physicians' clinical assessment and patients' own perception of their disease. It should also be emphasised that statistical between-studies heterogeneity was of a mild degree regarding the primary effectiveness outcome of the meta-analysis, while no significant differences were observed among the main subgroups of patients examined.

Another issue that should be discussed is the variability in the chronological and geographical characteristics of the studies included in this meta-analysis. RCTs that were published before 2000 tended to show a more pronounced treatment effect of antibiotics over placebo for acute sinusitis, which did not reach significance. If this effect was real, it could be attributed to various factors, such as differences in the inclusion criteria used, in the effectiveness of antibiotic treatment resulting from rising bacterial drug resistance,<sup>87</sup> and in methodological quality. However, the latter does not seem to be an issue because all of the included RCTs scored high on the Jadad scale. Finally, one relevant clinical trial, albeit without a large sample size,<sup>88</sup> was not included in our meta-analysis because it did not satisfy the pre-defined language criterion. On the basis of data from the abstract, the inclusion of this trial would not have influenced the findings of our meta-analysis.

In view of all the considerations discussed above, this meta-analysis provides strong evidence that antibiotics are more effective in the treatment of acute sinusitis than placebo. However, the clinical decision of whether to treat patients with presumed acute bacterial sinusitis with antibiotics seems to entail a trade-off between a rounded 10% added benefit in clinical outcomes from antibiotic use with an approximately equal rise in expected adverse events. However, adverse events are generally not of a severe degree. Moreover, not using

Search strategy  
and selection  
criteria

These are described  
in detail in the  
Methods section on  
page 543.

antibiotics might carry a risk for development of serious, although rare, disease complications. Still, the effect of antibiotic overuse on the increase of bacterial drug resistance should also be taken into consideration. On the basis of these findings, a universal policy for the prescribing of antibiotics for community cases of acute sinusitis cannot be proposed. Rather, clinicians should identify patients who are likely to have disease of bacterial cause and who could benefit from antibiotic treatment. In this regard, further studies that aim to better delineate the characteristics of this group of patients are required.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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