Antibiotics to prevent complications following tooth extractions

Review information

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What's new

Abstract
Background
The most frequent indications for tooth extractions are dental caries and periodontal infections, and these extractions are generally done by general dental practitioners. Antibiotics may be prescribed to patients undergoing extractions to prevent complications due to infection.

Objectives
To determine the effect of antibiotic prophylaxis on the development of infectious complications following tooth extractions.

Search methods
The following electronic databases were searched: the Cochrane Oral Health Group's Trials Register (to 25 January 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 1), MEDLINE via OVID (1948 to 25 January 2012), EMBASE via OVID (1980 to 25 January 2012) and LILACS via BIREME (1982 to 25 January 2012). There were no restrictions regarding language or date of publication.

Selection criteria
We included randomised double-blind placebo-controlled trials of antibiotic prophylaxis in patients undergoing tooth extraction(s) for any indication.
Data collection and analysis
Two review authors independently assessed risk of bias for the included studies and extracted data. We contacted trial authors for further details where these were unclear. For dichotomous outcomes we calculated risk ratios (RR) and 95% confidence intervals (CI) using random-effects models. For continuous outcomes we used mean differences (MD) with 95% CI using random-effects models. We examined potential sources of heterogeneity. The quality of the body of evidence has been assessed using the GRADE tool.

Main results
This review included 18 double-blind placebo-controlled trials with a total of 2456 participants. Five trials were assessed at unclear risk of bias, thirteen at high risk, and none at low risk of bias. Compared to placebo, antibiotics probably reduce the risk of infection in patients undergoing third molar extraction(s) by approximately 70% (RR 0.29 (95% CI 0.16 to 0.50) P < 0.0001, 1523 participants, moderate quality evidence) which means that 12 people (range 10-17) need to be treated with antibiotics to prevent one infection following extraction of impacted wisdom teeth. There is evidence that antibiotics may reduce the risk of dry socket by 38% (RR 0.62 (95% CI 0.41 to 0.95) P = 0.03, 1429 participants, moderate quality evidence) which means that 38 people (range 24-250) need to take antibiotics to prevent one case of dry socket following extraction of impacted wisdom teeth. There is also some evidence that patients who have prophylactic antibiotics may have less pain (MD -8.17 (95% CI -11.90 to -4.45) P < 0.0001, 372 participants, moderate quality evidence) overall 7 days after the extraction compared to those receiving placebo, which may be a direct result of the lower risk of infection. There is no evidence of a difference between antibiotics and placebo in the outcomes of fever (RR 0.34, 95% CI 0.06 to 1.99), swelling (RR 0.92, 95% CI 0.65 to 1.30) or trismus (RR 0.84, 95% CI 0.42 to 1.71) 7 days after tooth extraction.

Antibiotics are associated with an increase in generally mild and transient adverse effects compared to placebo (RR 1.98 (95% CI 1.10 to 3.59) P = 0.02) which means that for every 21 people (range 8-200) who receive antibiotics, an adverse effect is likely.

Authors’ conclusions
Although general dentists perform dental extractions because of severe dental caries or periodontal infection, there were no trials identified which evaluated the role of antibiotic prophylaxis in this group of patients in this setting. All of the trials included in this review included healthy patients undergoing extraction of impacted third molars, often performed by oral surgeons. There is evidence that prophylactic antibiotics reduce the risk of infection, dry socket and pain following third molar extraction and result in an increase in mild and transient adverse effects. It is unclear whether the evidence in this review is generalisable to those with concomitant illnesses or immunodeficiency, or those undergoing the extraction of teeth due to severe caries or periodontitis. However, patients at a higher risk of infection are more likely to benefit from prophylactic antibiotics, because infections in this group are likely to be more frequent, associated with complications and be more difficult to treat. Due to the increasing prevalence of bacteria which are resistant to treatment by currently available antibiotics, clinicians should consider carefully whether treating 12 healthy patients with antibiotics to prevent one infection is likely to do more harm than good.

Plain language summary
Antibiotics to prevent complications following tooth extractions
Tooth extraction is a surgical treatment to remove teeth that are affected by decay or gum disease (performed by general dentists). The other common reason for tooth extraction, performed by oral surgeons, is to remove wisdom teeth that are poorly aligned/developed (also known as impacted wisdom teeth) or those causing pain or inflammation.

The risk of infection after extracting wisdom teeth from healthy young people is about 10%; however, it may be up to 25% in patients who are already sick or have low immunity. Infectious complications include swelling, pain, pus drainage, fever, and also dry socket (this is where the tooth socket is not filled by a blood clot, and there is severe pain and bad odour). Treatment of these infections is generally simple and involves patients receiving antibiotics and drainage of infection from the wound.

This review looks at whether antibiotics, given to dental patients as part of their treatment, prevent infection after tooth extraction. There were 18 studies considered, with a total of 2456 participants who received either antibiotics (of different kinds and dosages) or placebo, immediately before and/or just after tooth extraction. There were concerns about aspects of the design and reporting of all the studies. In all of the studies healthy people had extractions of impacted wisdom teeth done by oral surgeons.

This review provides evidence that antibiotics administered just before and/or just after surgery reduce the risk of infection, pain and dry socket after wisdom teeth are removed by oral surgeons, but that using antibiotics also causes more (generally brief and minor) side effects for these patients. Additionally, there was no evidence that antibiotics prevent fever, swelling or problems with restricted mouth opening in patients who have had wisdom teeth removed.

There was no evidence to judge the effects of preventative antibiotics for extractions of severely decayed teeth, teeth in diseased gums, or extractions in patients who are sick or have low immunity to infection. Undertaking research in these groups of people may not be possible or ethical. However, it is likely that in situations where patients are at a higher risk of infection that preventative antibiotics may be beneficial, because infections in this group are likely to be more frequent and more difficult to treat.

Another concern, which cannot be assessed by clinical trials, is that widespread use of antibiotics by people who do not have an infection is likely to contribute to the development of bacterial resistance.
The conclusion of this review is that antibiotics given to healthy people to prevent infections, may cause more harm than benefit to both the individual patients and the population as a whole.

**Background**

**Description of the condition**

Tooth extraction is a very common surgical procedure, and is most frequently done by general dental practitioners. In spite of the steady decrease in routine extraction of permanent teeth registered in the last decades (Thomas 1994; Sleeman 1995; McCaul 2001), general dental practitioners from European countries may extract up to seven teeth per week (McCaul 2001). An estimated 17% of patients undergo extractions over a 5-year period (Worthington 1999), with the highest tooth extraction rate per patient being among patients in the sixth and seventh decade of life (Chrysanthakopoulos 2011). The main reasons for extraction of permanent teeth are still caries and periodontal disease, in variable proportions according to age of patients, country and year of publication (Additional Table 1). Wisdom teeth failing to erupt or erupting only partially represent a distinct category of dental elements named impacted (third molar) teeth. In fact, impacted wisdom teeth are extracted either because of local inflammatory problems, or in order to avoid possible future complications (although a recent Cochrane review did not find sufficient evidence to support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults (Mettes 2012)).

The main objective for a successful surgery is to minimise, as much as possible, patient discomfort in the post-operative period after tooth extraction. Symptoms such as pain, swelling, trismus, fever and dry socket are complications which are unpleasant for patients and could generate difficulty in chewing, in speaking, in performing oral hygiene, and alteration of other activities of daily living, resulting in days off from work or study. All these complications depend on inflammatory response, but they can be due to subsequent infection, for example if surgical trauma is in a contaminated area (where severe caries or periodontitis is present) or where more complex and aggressive procedures are performed (e.g. ostectomy).

Signs of post-extraction infectious complications include abscess, pain, fever, swelling, trismus. Another complication of putative bacterial origin is alveolar osteitis (dry socket), a painful condition which follows the dissolution of the blood clot which occurs as a result of bacterial invasion. The overall incidence of post-operative infections is relatively low (Jaafar 2000; Bouloux 2007; Bortoluzzi 2010), however antibiotics are frequently prescribed in a prophylactic way, particularly in case of complicated surgeries and patients with systemic conditions potentially causing immunodeficiency, such as HIV infection, diabetes and cancer (Epstein 2000).

**Description of the intervention**

There are a range of antibiotics which are effective in treating dental infections. These include penicillin, amoxicillin, erythromycin, clindamycin, doxycycline and metronidazole which are usually administered orally, between one and four times daily. Alternatively antibiotics can also be administered by parenteral or local routes.

**How the intervention might work**

The oral environment contains a range of bacteria which have the potential to cause painful infections in wounds. Antibiotics are effective in treating such infections and are also likely to act to prevent the development of painful wound infections. The optimal timing of the dose or doses is unclear. Antibiotics could be administered as a large single dose prior to the extraction, or a course of antibiotics taken over the post-operative period, or some combination of these. Adverse effects, such as diarrhoea or allergy due to antibiotics are also possible.

**Why it is important to do this review**

In 2010, a systematic review showed that both long duration and multiple courses of antibiotics prescribed in general medical practice were consistently associated with the development of bacterial resistance to those antibiotics in that individual and that the greater the number of antibiotic courses prescribed, the higher the chance of resistant bacteria development (Costelloe 2010). Dental prescribing accounts for a significant proportion of total antibacterial prescribing in primary care (7% to 9%) (Dar-Odeh 2010; Kariki 2011). In addition, antibiotics used in dental practice can cause potentially serious adverse drug reactions and interactions (Hersh 1999). According to the European Commission, overuse and misuse of antibiotics are the main causes of microbial resistance to drugs. For this reason in 2011 an action plan to tackle microbial resistance to drugs was presented; the first aim of such plan is to make sure that antimicrobials are used appropriately both in humans and animals. Better evidence is needed about the use of antibiotic prophylaxis in patients undergoing tooth extraction in order to determine appropriate use (EU Commission 2011).

This systematic review will summarise the evidence of the effects of systemic antibiotics prescribed to prevent infectious complications following tooth extraction. A separate Cochrane systematic review evaluating interventions to manage dry socket following tooth extraction will be published in 2012 (Daly 2008).

**Objectives**

- To assess the effects of antibiotic prophylaxis on the incidence of infectious complications following tooth extraction.
- To assess the effects of antibiotic prophylaxis following tooth extraction in immunosuppressed patients (e.g. HIV infection, AIDS, diabetes, transplants) or patients with other conditions (e.g. bone diseases).
- To assess the effects of antibiotic prophylaxis in particular procedures, such as extraction of impacted teeth or wisdom teeth.

**Methods**
Criteria for considering studies for this review

Types of studies
Randomised controlled trials with a double-blind design (participants and assessors) were included. Cross-over studies were included providing the interval (or washout period) between interventions was at least 6 weeks.

Types of participants
Anyone undergoing a tooth extraction, including extraction of impacted teeth.

Types of interventions
Active
1) Any regimen of systemic antibiotic prophylaxis (i.e. prescribed in absence of infection) administered before or after tooth extraction. Topical antibiotic therapy was not included.

Control
1) Placebo.

Types of outcome measures
Primary outcomes
- Post-surgical complications of putative infectious nature, including: alveolar osteitis (dry socket), pain, fever, swelling, trismus.

Secondary outcomes
- Other post-surgical complications.
- Any adverse effect related to antibiotics.

Trials which reported the outcomes of endocarditis incidence, bacteriaemia or serum markers of infection only, were not considered for inclusion in this review.

Search methods for identification of studies
For the identification of studies included or considered for this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database. The search strategy used a combination of controlled vocabulary and free text terms and was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011) (Higgins 2011).

We searched the following electronic databases:
- The Cochrane Oral Health Group's Trials Register (to 25 January 2012) (Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 1) (Appendix 2)
- MEDLINE via OVID (1948 to 25 January 2012) (Appendix 3)
- EMBASE via OVID (1980 to 25 January 2012) (Appendix 4)

Details of the MEDLINE search are provided in Appendix 3. We linked the search of EMBASE to the Cochrane Oral Health Group filter for identifying RCTs (Appendix 4), and the search of LILACS to the Brazilian Cochrane Center filter (Appendix 5).

Handsearching
The following journals were identified as being important to handsearch for this review:
- British Journal of Oral and Maxillofacial Surgery
- British Dental Journal
- International Journal of Oral and Maxillofacial Surgery
- Journal of the American Dental Association
- Journal of Dental Research
- Journal of Dentistry
- Oral Surgery, Oral Pathology, Oral Medicine, Oral Radiology and Endodontics.

The handsearching was done as part of the Cochrane Worldwide Handsearching Programme. See the Cochrane Masterlist of Journals for details of the volumes and issues that have been searched to date.

Reference lists of all eligible trials and of existing reviews were checked for additional studies. The first named authors of all included trials were contacted in an attempt to identify unpublished studies and to obtain further information about the trials.

There were no restrictions on language or date of publication.

Data collection and analysis

Selection of studies
The title and abstract of each article resulting from the different search strategies were examined independently by two
review authors (Giovanni Lodi (GL) and Susan Furness (SF)). Where studies appeared to meet the inclusion criteria for this review or where there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. The full report was then assessed by at least two review authors to determine whether studies met the inclusion criteria. Any disagreements were resolved by discussion. Studies rejected at this or subsequent stages were recorded in the Characteristics of excluded studies table where the reason(s) for exclusion were recorded. A flow chart to summarise the results of the search was prepared (Figure 1).

Data extraction and management

All studies which met the inclusion criteria for this review underwent risk of bias assessment and data extraction using a specially designed data extraction form. Data were extracted by at least two review authors independently and were also entered into a spreadsheet. Any disagreement was discussed and agreement reached. When necessary authors were contacted for clarification or missing information.

For each trial the following data were recorded.

- Year of publication, country of origin, number of centres, source of study funding, recruitment period.
- Details of the participants including demographic characteristics and criteria for inclusion and exclusion, type of teeth being extracted and reasons, numbers randomised to each treatment group.
- Details of the type of antibiotic, dose, mode of administration, time of administration relative to the extraction procedure and duration of antibiotic treatment.
- Details of other concomitant treatments - type of anaesthetic, mouthrinses, pain management.
- Details of the outcomes reported, including method of assessment, and time(s) assessed.
- Description of operators.
- Sample size calculation.

Assessment of risk of bias in included studies

Each of the trials included in this review was assessed for risk of bias using The Cochrane Collaboration's risk of bias assessment tool (Higgins 2011). The following six domains were assessed for each trial: random sequence generation, allocation concealment, blinding, completeness of outcome data, risk of selective outcome reporting and risk of other bias.

A description of what was reported to have occurred was included for each domain in each trial, together with a judgement of low, unclear or high risk of bias. For example criteria, used for risk of bias judgements for allocation concealment as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) are described below.

1) Method of allocation concealment. Criteria for the judgement of low risk of bias: when the randomisation schedule is concealed from the researcher recruiting participants to the trial by means of either:
   - central allocation (including telephone, web-based and pharmacy-controlled randomisations); or
   - sequentially numbered drug containers of identical appearance; or
   - sequentially numbered, opaque, sealed envelopes.

   When this information is not reported, the domain was judged as unclear.

2) Protection against performance and detection bias (blindness of the study). One of the inclusion criteria for this review is that trials be double blind. This is interpreted as meaning that neither the participants nor the researchers assessing the outcomes of the trial were aware of the allocated treatment, unless further information is given.

3) Incomplete outcome data. Criteria for the judgement of low risk of bias for this domain are:
   - no missing outcome data; or
   - less than 20% of randomised participants excluded from the analysis and numbers of trial participants excluded balanced in numbers across intervention groups, with similar reasons for missing data across groups;
   and
   
   for dichotomous outcome data, the proportion of missing outcomes compared with observed event rate not great enough to have a clinically relevant impact on the effect estimate.

Overall risk of bias

A summary assessment of the risk of bias was undertaken (Higgins 2011) as follows:

1) low risk of bias: all of the domains judged to be at low risk of bias
2) unclear risk of bias: one or more domains judged to be at unclear risk of bias
3) high risk of bias: one or more domains judged to be at high risk of bias.

Risk of bias assessment of the studies was carried out without blinding the name of authors, institutions and journal. Data about the study, its eligibility, validity, design and outcome information, were recorded by each review author on an extraction form. In case of disagreement, consensus was achieved by discussion.

Measures of treatment effect

The primary measure of intervention effect was reduction in incidence of infectious complications, such as alveolar osteitis (dry socket), pain, fever, swelling or trismus between the control and intervention group. Dichotomous data are expected for these. Other dichotomous data may include the incidence of adverse effects.

For each intervention, data on the number of patients of intervention and control group who experienced the event (outcome)
and the total number of patients, were sought and summarised. Dichotomous data were analysed by calculating risk ratios and 95% confidence intervals.

Where pooling of data from both parallel and cross-over studies was appropriate we used the generic inverse variance method to enter the data into Review Manager (RevMan) software (Higgins 2011).

**Dealing with missing data**

Missing data were obtained from tables and graphs if possible. Where data were missing or unclear we attempted to contact the authors of the studies to request clarification or additional data.

**Assessment of heterogeneity**

We assessed heterogeneity by inspection of the point estimates and confidence intervals on the forest plots. We assessed the variation in treatment effects by means of Cochran's test for heterogeneity and quantified by the $I^2$ statistic. We considered heterogeneity statistically significant if the P value was < 0.1. A rough guide to the interpretation of the $I^2$ statistic given in the Cochrane Handbook for Systematic Reviews of Interventions is: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, 75% to 100% considerable heterogeneity (Higgins 2011).

**Assessment of reporting biases**

Only a proportion of research projects conducted are ultimately published in an indexed journal and become easily identifiable for inclusion in systematic reviews. Reporting biases arise when the reporting of research findings is influenced by the nature and direction of the findings of the research. We attempted to minimise potential reporting biases including publication bias, time lag bias, multiple (duplicate) publication bias and language bias in this review.

If there had been more than ten studies in one outcome we planned to construct a funnel plot. If there were asymmetry in the funnel plot indicating possible publication bias we planned to undertake statistical analysis using the methods introduced by Egger 1997 (continuous outcome) and Rücker 2008 (dichotomous outcome).

We attempted to avoid time lag bias, multiple (duplicate) publication bias and language bias by conducting a detailed sensitive search, including searching for ongoing studies. There were no restrictions on language, and we found translators for potentially relevant trials published in other languages.

**Data synthesis**

We only conducted a meta-analysis if there were studies of similar comparisons reporting the same outcome measures. We combined risk ratios for dichotomous data, and mean differences for continuous data, using random-effects models provided there were more than three studies in the meta-analysis.

We combined the treatment effects from cross-over trials with those from parallel group trials where appropriate, using the data from both periods of the cross-over studies (Elbourne 2002). We used the generic inverse variance method incorporated in RevMan for all analyses that included cross-over trials using appropriate methods as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Elbourne 2002; Higgins 2011).

**Subgroup analysis and investigation of heterogeneity**

Whenever possible, subgroup analyses were undertaken based on time of administration (pre- or post-procedure) and the presence or absence of patients with systemic conditions (HIV, diabetes, etc).

**Sensitivity analysis**

A sensitivity analysis was undertaken, excluding studies at high risk of bias.

**Presentation of main results**

A summary of findings table was developed for the main outcomes of this review using GRADEPro software. We used the mean risk in the placebo groups of the included studies as the assumed risk for each outcome and calculated the corresponding risk using the risk ratio (or mean difference) estimate obtained from the meta-analysis. The quality of the body of evidence was assessed with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, the risk of publication bias and the magnitude of the effect. The quality of the body of evidence for each of the main outcomes was categorised as high, moderate, low or very low.

**Results**

**Description of studies**

**Results of the search**

A total of 1053 references were identified by the electronic searches. The titles and abstracts were scanned by two review authors (Susan Furness (SF) and Giovanni Lodi (GL)) and 997 references were excluded as not relevant to this review. Full text copies of 56 potentially eligible papers were retrieved and after close reading, 37 studies were excluded (see Characteristics of excluded studies table). Two further studies were identified from searches of reference lists of included studies. Finally 21 references to 18 studies met the inclusion criteria for this review (Figure 1).

**Included studies**

Characteristics of trial design and setting
For a summary of the characteristics of each of the included studies see Characteristics of included studies table.

Of the 18 included studies, three were conducted in Spain (Arteagoitia 2005; Lacasa 2007; López-Cedrún 2011), three in Sweden (Bystedt 1980; Bystedt 1981; Bergdahl 2004), three in the UK (MacGregor 1980; Kaziro 1984; Mitchell 1986), two in India (Pasupathy 2011; Sekhar 2001) and one study was conducted in each of Brazil (Bezerra 2011), Colombia (Leon Arcila 2001), Denmark (Ritzau 1992), Finland (Happonen 1990), Poland (Kaczmarzyk 2007), New Zealand (Barclay 1987), and United States of America (Halpern 2007).

Seventeen studies used parallel group designs and one was a split-mouth cross-over trial (Bezerra 2011) where participants each had two extraction procedures, which were separated by a period of at least 45 days. Nine studies had two treatment arms (MacGregor 1980; Mitchell 1986; Barclay 1987; Ritzau 1992; Leon Arcila 2001; Bergdahl 2004; Arteagoitia 2005; Happonen 1990; Ritzau 1992; Sekhar 2001; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; Pasupathy 2011). Fourteen studies included participants with impacted teeth only (Bystedt 1980; MacGregor 1980; Bystedt 1981; Kaziro 1984; Mitchell 1986; Barclay 1987; Happonen 1990; Leon Arcila 2001; Sekhar 2001; Arteagoitia 2005; Kaczmarzyk 2007; Halpern 2007; Bezerra 2011; Pasupathy 2011), two studies included participants with either impacted or partially impacted teeth (Ritzau 1992; López-Cedrún 2011), one study included participants with only partially impacted teeth (Bergdahl 2004), and one study included participants with "teeth needing surgical extraction" (Lacasa 2007).

In one trial (Barclay 1987) the participants had a history of non-acute pericoronitis, and in another (Bergdahl 2004) 41% of participants had pericoronitis at some stage and were entered into the trial "after objective and subjective symptoms of pericoronitis had ceased", thus participants of both these studies were likely to be at higher risk of infectious complications. Recent episodes of local infection were reason for exclusion in two other studies (Sekhar 2001; Lacasa 2007). In the remaining trials, participants were considered healthy at baseline and systemic conditions, including those causing immunosuppression, were often reason for exclusion from the trial (see Characteristics of included studies).

None of the trials assessed the effect of antibiotic prophylaxis in patients who required extraction of one or more teeth due to carries or periodontal disease, even though these indications are the most common reasons for tooth extraction.

Characteristics of interventions
In 16 trials the antibiotics were administered orally, one study (Halpern 2007) used intravenous penicillin or clindamycin and one study (MacGregor 1980) administered penicillin intramuscularly.

The antibiotic interventions were classified into three groups, based on the time of administration relative to the extraction (studies with three or more arms may be included in more than one group).

- **Antibiotics given pre-operatively only** (30 minutes to 2 hours prior to procedure): MacGregor 1980; Mitchell 1986; Ritzau 1992; Sekhar 2001; Bergdahl 2004; Halpern 2007; Kaczmarzyk 2007; Lacasa 2007; Bezerra 2011; López-Cedrún 2011.
- **Antibiotics given post-operatively only**: Kaziro 1984; Sekhar 2001; Arteagoitia 2005; López-Cedrún 2011.


Details of specific dosage regimens are recorded in the Characteristics of included studies table for each study.

Characteristics of outcomes
Four studies (Bystedt 1981; Ritzau 1992; Bergdahl 2004; Arteagoitia 2005) reported the development of dry socket. Ritzau 1992 with a follow-up at 7 days, Arteagoitia 2005 with a follow-up at 7 days and 8 weeks, Bergdahl 2004 with a follow-up between 2 and 4 days after surgery, and Bystedt 1981 with a follow-up at 2, 5 and 7 days.

Five studies (Bystedt 1981; Happonen 1990; Arteagoitia 2005; Kaczmarzyk 2007; Lacasa 2007) investigated pain. Arteagoitia 2005 with a follow-up at 48 hours and 6 days, Bystedt 1981 with a follow-up at 2, 5 and 7 days, Happonen 1990 had a follow-up at 6 days, Kaczmarzyk 2007 with a follow-up at 1, 2 and 7 days and Lacasa 2007 with a follow-up at 1, 3 and
7 days.


Four studies investigated trismus among outcomes (Bystedt 1981; Happen 1990; Kaczmarzyk 2007; Lacasa 2007), where Happen 1990 had a follow-up at 6 days.

Bystedt 1981 reported that there were no non-infectious complications following extraction, and Kaczmarzyk 2007 stated that gastric complications in the antibiotic group following extraction was the reason that 3 of the 100 participants in this trial were excluded from the analysis. The other studies did not report other complications following extraction.

Adverse effects were reported per participant by only 5 of the 18 trials included in this review (Bystedt 1981; Barclay 1987; Arteagoitia 2005; Kaczmarzyk 2007; Lacasa 2007).

**Excluded studies**

For the main reason for excluding each study see Characteristics of excluded studies table.

A total of 37 studies were listed as excluded from this review after the full text of the paper was reviewed by two or more authors. Twenty-two studies because they were not double blind (Curran 1974; Krekmann 1980; Krekmann 1981; Krekmann 1986; Lombardia Garcia 1987; Mitchell 1987; Abu-Mowais 1990; Lyall 1991; Samsudin 1994; Walkow 1995; Monaco 1999; Yoshii 2002; Delibasi 2004; Foy 2004; Poeschl 2004; Graziani 2005; Sulejmanagić 2005; Ulubau 2005; Grossi 2007; Ataoglu 2008; Monaco 2009; Lopes 2011). Four studies were excluded because two antibiotic regimens were compared directly with no placebo-controlled group (Laird 1972; Limeres 2009; Luaces-Rey 2010; Olusanya 2011) and three trials were excluded because interventions were not randomly allocated (Osborn 1979; Rood 1979; Fridrich 1990). Two cross-over trials were excluded because the washout period between interventions was less than 6 weeks (Siddi 2010; de Moura 2011) and four trials because they evaluated topical antibiotics only (MacGregor 1973; Swanson 1989; Reekie 2006; Stavropoulos 2006). One trial was excluded because it evaluated antibiotics in conjunction with a range of dental surgical procedures not just extractions (Bargnesi 1985) and one because it presented data on bacteraemia outcomes only (Head 1984).

**Risk of bias in included studies**

**Allocation (selection bias)**

Sequence generation

Nine studies were assessed as being at low risk of bias for this domain. Four studies reported that randomisation was generated by computer (Ritzau 1992; Leon Arcila 2001; Arteagoitia 2005; Pasupathy 2011), two studies used random number tables (Barclay 1987; Kaczmarzyk 2007), two used predetermined random codes (Mitchell 1986; López-Cedrún 2011) and one used a coin toss (Bezerra 2011). The remaining nine studies gave no details about the method of sequence generation and were assessed at unclear risk of bias for this domain (Bystedt 1980; MacGregor 1980; Bystedt 1981; Kaziro 1984; Happen 1990; Sekhar 2001; Bergdahl 2004; Halpern 2007; Lacasa 2007).

Allocation concealment

Eleven studies described adequate allocation concealment (Kaziro 1984; Mitchell 1986; Ritzau 1992; Leon Arcila 2001; Sekhar 2001; Arteagoitia 2005; Halpern 2007; Kaczmarzyk 2007; Bezerra 2011; Lopez-Cedrún 2011; Pasupathy 2011) and were assessed at low risk of bias for this domain. For the remaining seven studies allocation concealment was not reported and these studies were assessed as at unclear risk of bias for this domain.

Overall eight trials were considered to be at low risk of selection bias (Mitchell 1986; Ritzau 1992; Leon Arcila 2001; Arteagoitia 2005; Kaczmarzyk 2007; Bezerra 2011; López-Cedrún 2011; Pasupathy 2011) and for the remaining 10 studies the risk of selection bias was unclear.

**Blinding (performance bias and detection bias)**

The inclusion criteria for this review specified that trials be double blind. Where trials only reported 'double blind' with no further details we interpreted this as meaning that both the participant and the person who assessed the outcomes (either the surgeon or the patient) were blinded to the allocated treatment. Consequently all included trials were assessed as being at low risk of performance and detection bias.

**Incomplete outcome data (attrition bias)**

Most of the included trials had relatively low rates of participants excluded from the analysis due to loss to follow-up or withdrawal from the trials. However, these trials also reported low event rates for the outcomes of interest, which meant that even small numbers of patients excluded could have introduced a bias.

Three trials reported that all the randomised participants were included in the analysis (Bystedt 1981; Mitchell 1986; Leon Arcila 2001) and in two trials attrition was less than 1% (Bergdahl 2004; Arteagoitia 2005). In the split-mouth study by Bezerra 2011, two participants were lost to follow-up but this was not considered to introduce a risk of attrition bias due to the study design. These six trials were assessed as being at low risk of attrition bias.

Three trials (Bystedt 1980; MacGregor 1980; Kaziro 1984) did not report the number of randomised participants included in the analysis and these trials were published more than 25 years ago and we were unable to obtain this information. In the study by Halpern 2007 there were more drop-outs in the placebo group than the antibiotic group and it was unclear whether this could have introduced a bias. These four trials were assessed as being at unclear risk of attrition bias.
Three trials (Barclay 1987; Sekhar 2001; López-Cedrún 2011) reported overall exclusion of participants from outcome evaluation of 10%, 8% and 17% respectively, and noted that losses were unequally distributed between antibiotic and placebo groups. A further five trials (Happonen 1990; Ritzau 1992; Kaczmarszyk 2007; Lacasa 2007; Pasupathy 2011) reported between 5% and 14% of participants were excluded from the outcome evaluation and did not describe the reasons or the treatment group from which participants were excluded. These eight trials were all assessed as being at high risk of attrition bias.

Selective reporting (reporting bias)
Selective reporting is difficult to assess in the absence of a trial protocol. We based our assessment on three factors: whether the trial report contained in the results section, data on all the outcome measures described in the methods section of the report; whether planned outcome measures included those that would reasonably be expected in such a trial; and whether both point estimates and variances were reported.

Five trials (Barclay 1987; Sekhar 2001; Kaczmarszyk 2007; Bezerra 2011; López-Cedrún 2011) reported complete data on all the outcomes that were listed in their methods sections and were consequently assessed as being at low risk of reporting bias.

The authors in Bystedt 1981 evaluated swelling and trismus but did not report these data, stating only that there was no difference between the groups. In Kaziro 1984 planned outcomes were reported only in graphical form as percentages in each group. A further four trials (Mitchell 1986; Ritzau 1992; Leon Arcila 2001; Halpern 2007) reported the planned single outcome but did not report pain, swelling or trismus which we consider to be important outcomes following this procedure. These six trials were assessed as being at unclear risk of reporting bias.

The remaining seven trials (Bystedt 1980; MacGregor 1980; Happonen 1990; Bergdahl 2004; Arteagotia 2005; Lacasa 2007; Pasupathy 2011) were assessed as being at high risk of reporting bias. The trial by Arteagotia 2005 planned to measure pain scores on a VAS but these were not reported. Bergdahl 2004 did not report data on three of the outcomes listed in the methods of the report, and Lacasa 2007 listed eight planned outcomes of which one was reported fully, one (pain) was reported as a mean for each group without an estimate of variance and the remaining six outcomes were not reported at all. Bystedt 1980 reported planned outcomes as point estimates without estimates of variance, but not for each group to which participants were randomised in the three subtrials in this report, and MacGregor 1980 reported pain, swelling, and trismus for all participants combined, in graphical form only, making it impossible to determine the effects of the interventions on these outcomes. Happonen 1990 did not report the pain measured by VAS at 7 days despite stating that pain was the main reason given for participants to be unable to work. Pasupathy 2011 did not report the outcomes of pain swelling or trismus but it would appear that these data were collected.

Other potential sources of bias
For nine of the included studies there were no other sources of bias identified (MacGregor 1980; Bystedt 1981; Mitchell 1986; Barclay 1987; Happonen 1990; Leon Arcila 2001; Arteagotia 2005; Kaczmarszyk 2007; Halpern 2007). Two trials were assessed as at high risk of other bias (Bezerra 2011; Pasupathy 2011). The trial by Bezerra 2011 was a split-mouth study in which participants each underwent two extraction procedures a minimum of 45 days apart. The trial report states that “the mean pain scores were lower on the last assessment [day 14] compared with the first [baseline] in both groups” suggesting that there may have been a period effect. The power calculation reported in Pasupathy 2011 suggests that this trial is underpowered which is likely to bias results towards the null hypothesis of no difference between antibiotic and placebo.

In the remaining seven trials risk of other bias was unclear.

Overall risk of bias
None of the trials included in this review were assessed as at low risk of bias for all the domains (Figure 2; Figure 3). Five trials (Bystedt 1981; Kaziro 1984; Mitchell 1986; Leon Arcila 2001; Halpern 2007) were assessed as at unclear risk of bias because there was insufficient information in the trial report or available from the authors to determine risk of bias in at least one domain. The remaining 13 trials (Bystedt 1980; MacGregor 1980; Barclay 1987; Happonen 1990; Ritzau 1992; Sekhar 2001; Bergdahl 2004; Arteagotia 2005; Kaczmarszyk 2007; Lacasa 2007; Bezerra 2011; López-Cedrún 2011; Pasupathy 2011) were assessed as at high overall risk of bias because each of these trials was at high risk of bias in one or more domains.

Effects of interventions
Three of the trials which met the inclusion criteria for this review did not report data in a form that was suitable for inclusion in meta-analysis (Bystedt 1980; MacGregor 1980; Kaziro 1984). The trial by MacGregor 1980 compared a single dose of intramuscular penicillin with placebo, followed up participants for 4 days and reported only that there were no significant differences between antibiotic and placebo with regard to pain, swelling and trismus but provided no data to substantiate this claim. The authors of Bystedt 1980 conducted three independent subtrials but reported data combining all of these trials. We were unable to draw any conclusions based on the data presented in this paper. In Kaziro 1984 the authors did not report the number of participants included in the outcome assessments but used graphs to report the percentage of participants with infections, pain and swelling. There were fewer patients in the antibiotic group who reported infections or pain but there were no estimates of variance so the statistical significance (if any) cannot be determined from this report (Additional Table 2).

The results from the remaining 15 trials are described below in subgroups depending on the time(s) the antibiotics were administered (either pre-operatively, post-operatively or both pre- and post-operatively). Subgroup analysis based on the
immune state of patients was not possible, as studies on immunosuppressed patients, or those with underlying health conditions which may have influenced their immune system, were not identified by our searches.

Where there were few trials reporting an outcome, the subgroups were indicated by footnotes but in these cases separate subgroup estimates were not reported (Analysis 1.5; Analysis 1.7; Analysis 1.8).

**Local sign of infection**

**Pre-operative antibiotics**

Seven trials reported the outcome of surgical site infection diagnosed clinically (Mitchell 1986; Sekhar 2001; Halpern 2007; Lacasa 2007; Bezerra 2011; López-Cedrún 2011; Pasupathy 2011). Antibiotics were administered intravenously in one study (Halpern 2007) immediately prior to the procedure, and in the other six trials antibiotics were administered orally 1-2 hours prior to surgery. The pooled estimate showed a statistically significant reduction in infection in the antibiotic groups with risk ratio (RR) 0.29 (95% confidence interval (CI) 0.15 to 0.54) \( P = 0.0001 \).

**Post-operative antibiotics**

Four trials were included in this group (Sekhar 2001; Arteagoitia 2005; Lacasa 2007; López-Cedrún 2011). There were no infections in either the antibiotic or the placebo group in the trial by Sekhar, and the pooled estimate for the other three trials showed fewer infections in the antibiotic groups (RR 0.15 (95% CI 0.07 to 0.31) \( P < 0.00001 \)).

**Pre- and post-operative antibiotics**

Two trials (Happonen 1990; Leon Arcila 2001) administered antibiotic or placebo both before and after the tooth extraction procedure and there was no difference between the infections reported in each group (RR 1.09 (95% CI 0.40 to 2.94) \( P = 0.87 \)).

Overall the pooled estimate from all 10 trials which reported the outcome of infection showed that the use of antibiotics reduced the risk of infection by approximately 70% (RR 0.29 (95% CI 0.16 to 0.50) \( P < 0.0001 \)). In individual trials the rate of infections in the placebo group varied between 0 and 56% with a mean event rate of 12.5% (Additional Table 3).

**Dry socket**

**Pre-operative antibiotics**

Six trials in this group reported this outcome and in two of these (Halpern 2007; López-Cedrún 2011) there were no dry sockets identified in either group. The pooled estimate for the other four trials (Ritzau 1992; Bergdahl 2004; Kaczmarszyk 2007; Bezerra 2011) showed no evidence of a difference between pre-operative antibiotics and placebo (RR 0.75 (95% CI 0.42 to 1.33) \( P = 0.32 \)) with no statistical heterogeneity.

**Post-operative antibiotics**

Two trials administering antibiotics after the tooth extraction reported this outcome. The trial by López-Cedrún 2011 again reported no dry sockets in either group and the remaining trial (Arteagoitia 2005) showed no evidence of a difference (RR 0.18 (95% CI 0.01 to 3.70) \( P = 0.27 \)).

**Pre- and post-operative antibiotics**

In three trials (Bystedt 1981; Barclay 1987; Kaczmarszyk 2007) antibiotics or placebo were administered prior to the tooth extraction and continued for 5 days post-operatively. The pooled estimate showed a reduction in the risk of dry socket (RR 0.52 (95% CI 0.27 to 0.99) \( P = 0.04 \)) with no statistical heterogeneity.

The pooled estimate for all nine trials that reported the outcome of dry socket is RR 0.62 (95% CI 0.41 to 0.95) \( P = 0.03 \) with no statistical heterogeneity. This is a reduction in the risk of dry socket from a mean of 6.9% in the placebo groups to 3.8% in the antibiotic groups (Additional Table 4).

**Pain (present or absent) days 6-7 or mean VAS score day 7**

**Pre-operative antibiotics**

One trial in this outcome group reported pain as either present or absent and found no difference between the antibiotic and placebo groups (Analysis 1.3, Subgroup 1.3.1).

Likewise the three trials which reported mean pain score (visual analogue scale (VAS)) in each group at 7 days showed no difference between antibiotic and placebo mean difference (MD) -7.41 (95% CI -16.18 to 1.36) \( P = 0.10 \) (Analysis 1.4, Subgroup 1.4.1). There was moderate statistical heterogeneity in this analysis which may be due to the different study designs included or different antibiotics used in these trials.

**Post-operative antibiotics**

Two trials (Sekhar 2001; Arteagoitia 2005) in this group reported pain as a dichotomous outcome and also found no difference between antibiotic and placebo RR 0.51 (95% CI 0.14 to 1.82) \( P = 0.30 \) with substantial statistical heterogeneity (I\(^2\) = 75%) (Analysis 1.3, Subgroup 1.3.2). This heterogeneity might be attributed to the different antibacterial spectrum of the two drugs. Arteagoitia 2005 used amoxicillin/clavulanic acid, which has a broad spectrum, and Sekhar 2001 used metronidazole which is active only against anaerobic bacteria.

**Pre- and post-operative antibiotics**

Only one study reported the dichotomous pain outcome in this group and found a benefit favouring the antibiotic group (
In the four trials which reported the mean pain score at day 7 (Barclay 1987; Kaczmarzyk 2007; Bezerra 2011; López-Cedrún 2011), there was a reduction in pain in the antibiotic groups MD -8.17 (95% CI -11.90 to -4.45) P < 0.001 with no statistical heterogeneity (Analysis 1.4) (Additional Table 5).

**Fever day 7**

Results from four trials (Bystedt 1981; Happonen 1990; Arteagoitia 2005; Lacasa 2007) which included a combined total of 816 participants reported fever as a dichotomous outcome at day 7. The time of administration of antibiotics varied: pre-operative administration in Lacasa 2007, post-operative administration in Arteagoitia 2005 and both pre- and post-operative administration in Bystedt 1981 and Happonen 1990. In two of these trials there were no cases of fever in either group. The pooled estimate for the other two trials (Happonen 1990; Arteagoitia 2005) showed no evidence of a difference in post-operative fever between antibiotic and placebo groups RR 0.34 (95% CI 0.06 to 1.99) P = 0.23. Statistical heterogeneity was substantial (I² = 60%) and this is likely due to the different antibiotics and the varied times the antibiotics were administered.

**Swelling day 7**

Pre-operative antibiotics

Three trials (Sekhar 2001; Kaczmarzyk 2007; López-Cedrún 2011) including a total of 165 participants, comparing pre-operative antibiotics with placebo, found no evidence of a difference in swelling after 7 days between the antibiotic and placebo groups RR 1.13 (95% CI 0.69 to 1.83) P = 0.63 (Analysis 1.6, Subgroup 1.6.1).

Post-operative antibiotics

Only one trial in this group (Sekhar 2001) reported the outcome of swelling and found no difference between antibiotic and placebo groups (Analysis 1.6, Subgroup 1.6.2).

Pre- and post-operative antibiotics

There was no evidence of a difference in swelling after 7 days in the two trials (Kaczmarzyk 2007; López-Cedrún 2011) which reported this outcome RR 1.07 (95% CI 0.53 to 2.17) P = 0.85 (Analysis 1.6, Subgroup 1.6.3).

The pooled estimate for all groups in all three trials (combined total of 334 participants) showed no evidence of a difference between antibiotic and placebo groups for the outcome of swelling (RR 0.92 (95% CI 0.65 to 1.30) P = 0.63).

**Trismus (dichotomous) day 7**

The presence or absence of trismus was reported in only two trials (175 participants) in this review (Kaczmarzyk 2007; Pasupathy 2011) and found no evidence of a difference between antibiotic and placebo groups (RR 0.84 (95% CI 0.42 to 1.71) P = 0.64).

**Adverse effects**

Adverse effects were reported per participant by only 5 of the 18 trials included in this review. In a total of 930 participants there were twice as many people experiencing adverse effects in the antibiotic groups RR 1.98 (95% CI 1.10 to 3.59) P = 0.02. Reported adverse effects were generally mild and required no further treatment. However, in one trial (Kaczmarzyk 2007) 3% of participants taking a 5-day course of clindamycin developed gastric complications and were excluded from the trial.

**Discussion**

**Summary of main results**

This review included 18 double-blind placebo-controlled trials with a total of 2456 participants undergoing extraction of third molar (wisdom) teeth. None of the included studies were of patients undergoing tooth extraction in general dental practice, for the removal of severely decayed teeth. Thirteen of the included trials were at high risk of bias and the remaining five were at unclear risk of bias. There is evidence that antibiotics, administered to prevent infection in patients undergoing wisdom tooth extraction, reduce the risk of infection by approximately 70% (risk ratio (RR) 0.29 (95% confidence interval (CI) 0.16 to 0.50) P < 0.0001), and reduce the risk of dry socket by about one third (RR 0.62 (95% CI 0.41 to 0.95) P = 0.03). There is also evidence that patients who have antibiotics have overall less pain 7 days after the extraction compared to those receiving placebo, mean difference (MD) -8.17 (95% CI -11.90 to -4.45) which may be a direct result of the lower risk of infection (Summary of findings table 1).

There is no evidence of a difference between antibiotics and placebo in the outcomes of fever (RR 0.34, 95% CI 0.06 to 1.99), swelling (RR 0.92, 95% CI 0.65 to 1.30) or trismus (RR 0.84, 95% CI 0.42 to 1.71) 7 days after tooth extraction. However, antibiotics are associated with an increase in generally mild and transient adverse effects compared to placebo (RR 1.98 (95% CI 1.10 to 3.59) P = 0.02).

While antibiotic prophylaxis is shown to reduce the risk of infection and dry socket, these outcomes still occur in some healthy people who take antibiotic prophylaxis associated with the extraction of impacted third molars. It is interesting to note that the rate of infection in the placebo groups in the included trials varied between nil (Leon Arcila 2001; Sekhar 2001) and 56% (Mitchell 1986) with a mean of 11.8% across the placebo groups of the included studies (Additional Table 3). Based on the evidence presented in this review the use of prophylactic antibiotics will reduce infection to a mean of 3%, which means that approximately 12 (range 10 to 17) people would need to receive antibiotic prophylaxis to prevent one infection.
The incidence of dry socket in the placebo group varied between nil (Halpern 2007; López-Cedrún 2011) and 34% (Barclay 1987) with a mean of 6.9%. This means that approximately 38 (range 24 to 250) healthy people would need to be treated with prophylactic antibiotics to prevent one case of dry socket (Additional Table 4). However using prophylactic antibiotics is likely to result in at least one adverse effect for every 21 people treated (range 8 to 200), though adverse effects reported in the trials were generally mild and transient.

Overall completeness and applicability of evidence

We conducted a comprehensive search including both electronic and handsearching through reference lists. We identified 18 randomised double-blind placebo-controlled trials including a combined total of approximately 2500 participants. Trials were conducted in different countries but included healthy patients in their 20s, undergoing extraction of impacted teeth (mainly of the lower jaw), thus making the results of our review quite sound regarding effectiveness of antibiotic prophylaxis of infectious complications in healthy young people undergoing wisdom tooth extractions, actually a very large proportion of surgical tooth extractions.

However, we identified no trials of patients attending general dental practices for the extraction of teeth due to caries or periodontitis. Identified trials did not include patients with depressed immune systems, patients with other illnesses, young children or elderly patients who required tooth extractions. Indeed, it is unlikely to be feasible or ethical to conduct placebo-controlled trials in this group of patients. The results of this review may or may not be generalisable to this group who would be expected to be at higher risk of infection. However, on the basis of the results of this review, it is likely that in subjects at higher risk of infectious complications, antibiotic prophylaxis may be more effective and the number of people needed to receive antibiotics to prevent one infection likely to decrease.

Another limit to generalisability of our results regards the clinical skill of the operators, as those in the included studies were mainly oral surgery specialists working in referral centres. Whether results would be similar for general dental practitioners is unclear.

Adverse effect frequency and severity can be important determinants in deciding about a preventive treatment. As for many medical areas, quality and quantity of information about adverse effects of interventions in these trials were inadequate (Ioannidis 2009). However, on the basis of the drop-out rates, and the adverse effects in the five trials which reported adverse effects per patient, it seems likely that adverse effects were generally mild and well tolerated.

This review cannot provide any information on the extent to which the use of prophylactic antibiotics in association with tooth extraction in healthy people may have on the subsequent development of strains of bacteria resistant to antibiotics in common use in these situations (EU Commission 2011).

Quality of the evidence

Although this review was restricted to double-blind placebo-controlled trials none of the included trials were at low risk of bias (unclear (5 trials) or high (13 trials)). The most common sources of bias were missing outcome data and selective reporting. In trials such as many of those included in this review, where the outcome events are uncommon even in the placebo group, losses to follow-up can potentially cause misleading results.

The quality of the body of evidence included in this review was evaluated using the GRADE system in Summary of findings table 1. For most outcomes the quality of the evidence was moderate, because of high or unclear risk of bias in the studies. For the outcomes of fever and presence of pain on day 6-7, there was also heterogeneity between studies, so the quality of the body of evidence for these outcomes was graded as low.

We found no evidence concerning the use of prophylactic antibiotics in patients undergoing extraction for severe caries or periodontitis.

Potential biases in the review process

Data from some of the studies included in the present review, namely older ones, could not be entered in the meta-analysis because of the poor reporting that prevented data extraction. This may have introduced a reporting bias into this review. The funnel plot for the primary outcome of infection (Figure 4) shows no evidence of publication bias (note the points on the plot are not independent because two of the trials (Lacasa 2007; López-Cedrún 2011) are included in two subgroups).

There were some post hoc changes from the protocol for this review, and we acknowledge that such changes can potentially introduce a bias into the review process (see Differences between protocol and review). The inclusion criteria for the review were amended so that only randomised, double-blind placebo-controlled trials were included. The protocol planned to only include trials where the important clinical outcome of infection was reported. In this review we made it more explicit that trials which only reported other or intermediate outcomes (endocarditis incidence, bacteraemia or serum marker of infection) would be excluded. We think that these changes have resulted in higher quality clinically relevant trials being included in our review.

Agreements and disagreements with other studies or reviews

A systematic review on the same subject was published in 2007 (Ren 2007). This review included a different group of studies, because of different inclusion criteria (they considered mandibular third molar extractions only and did not limit the review to double-blind studies). Ren 2007 concluded that antibiotic administration was effective in preventing wound infection, although they reported a higher number needed to treat: "on average 25 patients needed to be treated with systemic antibiotics to prevent 1 case of extraction wound infection" in this group of healthy patients.

Authors' conclusions
Implications for practice
There is moderate quality evidence that the use of prophylactic antibiotics reduces the risk of infectious complications following third molar extraction. There is no clear evidence that timing of antibiotic administration (pre-operative, post-operative or both) is important. The numbers of healthy people undergoing third molar extraction who need to be treated with antibiotics to prevent one infection range between 10 and 17, and to prevent a case of dry socket between 24 and 250 people would need to receive prophylactic antibiotics. The size of the benefit is not enough to recommend a routine use of this practice, due to the increased risk of mild adverse effects for the patients and also the potential for contributing to the development of bacterial resistance.

Implications for research
Future trials should investigate prophylactic antibiotics effectiveness in patients at high risk of infective complications, such as immunocompromised subjects and patients who have experienced infective complications following previous extractions. Trials on patients undergoing extractions for severe caries or periodontal disease are also needed. Future studies should also measure the outcomes of symptoms and clinical assessment using standardised measures and timepoints, and report these according to CONSORT guidelines.

Acknowledgements
Our thanks to Luisa Fernandez-Mauleffinch who translated two papers from Spanish to English, and to Annette Blumle who translated a paper from German to English. Our thanks to Jo Leese for her contributions to the plain language summary of this review.

Contributions of authors
- Conceiving, designing and co-ordinating the review: Giovanni Lodi (GL).
- Screening search results and retrieved papers against inclusion criteria: GL, Susan Furness (SF), Lara Figini (LF).
- Appraising quality of papers: GL, SF.
- Extracting data from papers: GL SF, Andrea Sardella (AS).
- Writing to authors of papers for additional information: GL, SF.
- Data management for the review and entering data into RevMan: GL, SF, LF.
- Analysis and interpretation of data: GL, SF, AS.
- Preparing the summary of findings table: SF.
- Providing a clinical perspective: GL, Antonio Carrassi (AC), Massimo Del Fabbro (MD).
- Writing the text of the review: GL, SF.
- Preparing the plain language summary: GL.
- Providing comments on a draft of the review: AS, MD.

Declarations of interest
None known.

Differences between protocol and review
Quasi-randomised studies are no longer eligible for inclusion in this review because less biased evidence is available from randomised controlled trials.

It was decided to include only double-blind placebo-controlled studies because we believed that these studies were likely to provide the best evidence to inform practice.

We clarified excluded outcomes by specifically excluding trials where the outcome was endocarditis incidence, bacteraemia or serum marker of infection only.

Published notes
Characteristics of studies
Characteristics of included studies
Bystedt 1980
**Methods**

Study design: RCT.
Conducted in: Sweden.
Number of centres: 1.
Recruitment period: not stated.

**Participants**

Inclusion criteria: healthy outpatients requiring surgical removal of impacted third molar of mandible.
Exclusion criteria: history of significant gastric, hepatic or renal disease, those taking any other medication except analgesia during study period.
Age group: mean 29 years, range 17-79 years.
Number randomised: 140 in 3 separate subtrials.
Number evaluated: unclear, reported as percentage of combined groups.

**Interventions**

Comparison A: 1 hour pre-op + 7 days post-op azidocillin versus placebo.
Comparison B: 90 min pre-op + 7 days post-op erythromycin or clindamycin versus placebo.
Comparison C: 180 min pre-op + 7 days post-op doxycycline versus placebo.

Study  A (n = 40): either azidocillin 750 mg 1 hour pre-op + 750 mg bid for 7 days post-op or matching placebo.
Study  B (n = 60): either erythromycin stearate 500 mg or clindamycin 300 mg or placebo 90 min pre-op followed by 250 mg erythromycin or 150 mg clindamycin or placebo 4x daily for 7 days.
Study  C (n = 40): either 200 mg doxycycline or placebo 180 min pre-op plus either 100 mg doxycycline or placebo once daily for 7 days.
All participants had 0.5-1 g acetylsalicylic acid as needed for pain.

**Outcomes**

Capillary serum antibiotic levels, dental alveolar blood antibiotic levels, bone antibiotic levels, evaluated on day 2. Duration of operation, pain, trismus, swelling, wound healing, side effects evaluated on days 2, 5 and 7 post-op.

**Notes**

**Risk of bias table**

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<th>Authors’ judgement</th>
<th>Support for judgement</th>
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### MacGregor 1980

**Methods**

Study design: RCT where participants paired based on number of lower molars extracted.


Number of centres: 1.

Recruitment period: not stated.

**Participants**

Inclusion criteria: Caucasian patients requiring removal of 1 or 2 mandibular third molars under endotracheal anaesthesia. M3 had to be fully developed with an identifiable occlusal plane.

Exclusion criteria: patients who wear artificial dentures, who could not attend 4th day appointment or those whose operation had "undue haemorrhage". Patients who required antibiotics for other reasons (e.g. endocarditis) were also excluded.

Age group: not stated.

Number randomised: not stated.

Number evaluated: not stated.

**Interventions**

Comparison: pre-op penicillin versus placebo.

Group A: benzyl penicillin 300 mg + procaine penicillin 300 mg intramuscular 30 min pre-operatively.

Group B: placebo injection IM 30 min pre-operatively.

Procedures performed by 2 surgeons with attempts to standardise methods.

**Outcomes**

Pain, swelling and trismus on day 4 in graphs only.

**Risk of bias table**

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### Bystedt 1981
| Methods | Study design: 3-arm RCT.  
Conducted in: Sweden.  
Number of centres: 1.  
Recruitment period: unclear.  
Funding source: unspecified. |
|---|---|
| Participants | Inclusion criteria: healthy outpatients, referred for surgical removal of an impacted third molar of the mandible.  
Exclusion criteria: not specified.  
Age group: range 17-30 years.  
Group A: randomised 20; analysed 20.  
Group B: randomised 20; analysed 20.  
Group C: randomised 20; analysed 20. |
| Interventions | **Comparison: pre- + post-op penicillin versus pre- + post-op azidocillin versus placebo.**  
Group A: phenoxymethylpenicillin 800 mg 1 hour before operation and then twice a day (at 9.00 AM and 9.00 PM) for 7 days.  
Group B: azidocillin 750 mg 1 hour before operation and then twice a day (at 9.00 AM and 9.00 PM) for 7 days.  
Group C: placebo 1 hour before operation and then twice a day (at 9.00 AM and 9.00 PM) for 7 days.  
Aspirin 0.5-1.0 g was provided to all participants as a rescue analgesic to be taken when needed. No other medications except analgesics were allowed during the investigation period. |
| Outcomes | Pain was measured on the day of operation and on days 2, 5, and 7 on a 3-grade scale (I none or insignificant, II pain requiring no analgesic, III severe pain requiring analgesic).  
Trismus was measured on the day of operation and on days 2, 5, and 7 measuring the ability to open the mouth, using a vernier gauge.  
Extraoral swelling was measured according to the method described by Lökken 1975.  
Dry socket diagnosis was made clinically on the basis of severe mandibular pain accompanied by necrotic debris or a denuded alveolus.  
Wound healing (evidence of loose of periosteal flap and alveolitis).  
Side effects: patients were questioned at each examination regarding side effects such as fever, indisposition or diarrhoea. |
| Notes | Only usable data that can be extracted by the paper are those on dry socket, subjects with no complications and adverse effects. Groups A and B have been considered together in the analysis.  
All operations were carried out by the same surgeons under local anaesthesia. |
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<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No missing data. All randomised participants included in result analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Data for swelling and trismus not reported, only comment that there was no difference.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

### Kaziro 1984

#### Methods
- Study design: RCT.
- Conducted in: UK.
- Number of centres: 1.
- Recruitment period: not stated.

#### Participants
- Inclusion criteria: patients with impacted mandibular wisdom teeth.
- Exclusion criteria: not described.
- Age group: not stated.
- Number randomised: 118.
- Number evaluated: unclear.

#### Interventions
- **Comparison**: post-op metronidazole versus arnica versus placebo.
  - Group A (n = 41): metronidazole 400 mg 1 tablet twice daily post-operatively.
  - Group B (n = 39): arnica 200 tablets 1 tablet twice daily post-operatively.
  - Group C (n = 38): placebo 1 tablet twice daily post-operatively.
  - Tablets were taken for 3 days.
  - All participants had 2 Codis (aspirin plus codeine) tablets 3x daily for pain.

#### Outcomes
- Pain, trismus, oedema, wound healing on 4th and 8th post-op day, wound breakdown.

#### Notes
- Data presented in graphs only. Extractions were done by 1 of 6 surgeons blinded to allocated treatment.
Bias | Authors' judgement | Support for judgement
--- | --- | ---
Random sequence generation (selection bias) | Unclear risk | Quotes: "randomised allocation" "randomly divided". Method of sequence generation not described.
Allocation concealment (selection bias) | Low risk | Code was kept by pharmacist at Royal London Homeopathic hospital.
Blinding of participants and personnel (performance bias) | Low risk | Quote: "Double blind".
Blinding of outcome assessment (detection bias) | Low risk | Quote: "Double blind".
Incomplete outcome data (attrition bias) | Unclear risk | Numbers of patients included in outcome assessments reported as percentage only.
Selective reporting (reporting bias) | Unclear risk | All planned outcomes reported, but data only presented in graphs.
Other bias | Unclear risk | No description of characteristics of patients by randomised group at baseline.

Mitchell 1986

Methods
Study design: parallel group RCT.
Conducted in: Newcastle, UK.
Number of centres: 1.
Recruitment period: not stated.

Participants
Inclusion criteria: inpatients, aged 18-30 years, attending hospital for removal of 1 or more third molars.
Exclusion criteria: those with a significant medical history or acute infection were excluded.
Age group: mean 24 years, range 17-33 years.
Number randomised: 50 participants (89 teeth).
Number evaluated: 50.

Interventions
Comparison: pre-op tinidazole versus placebo.
Group A (n = 25 participants, 45 teeth): tinidazole 500 mg orally 12 hours pre-operatively.
Group B (n = 25 participants, 44 teeth): placebo oral 12 hours pre-operatively.
All patients had ibuprofen as required while in hospital and access to analgesics as required after discharge.

Outcomes
Infected socket, onset of painful socket increasing in severity, within first 7 days. Other signs of infection or dry socket, type of bone removal.

Notes
4 surgeons conducted the extractions, using a standardised technique.
1 clinician blinded to intervention assessed all patients both pre- and post-operatively.
Antibiotics to prevent complications following tooth extractions

### Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;allocated in accordance with a pre-determined randomisation code during pre-operative assessment&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;drugs were individually packaged and allocated&quot; -assumed allocation occurred at the pharmacy.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All randomised participants included in the outcome assessment.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Infection per socket and per patient reported. Pain swelling and trismus not reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

### Barclay 1987

#### Methods

- **Study design**: RCT.
- **Conducted in**: New Zealand.
- **Number of centres**: 1.
- **Recruitment period**: unclear.
- **Funding source**: metronidazole and placebo tablets were supplied by May and Baker New Zealand Ltd.

#### Participants

- **Inclusion criteria**: "patients with a history of non-acute pericoronitis, and therefore likely to experience a high prevalence of dry socket". Patients had to meet 2 or more of the following criteria: a history of 2 or more episodes of previously diagnosed pericoronitis; the expression of pus from beneath a pericoronal flap in the absence of significant symptoms; radiographic enlargement of the follicular space distal to the third molar in the absence of significant symptoms; crater-like radiographic defect as described by Howe (Howe 1985).
- **Exclusion criteria**: pregnancy.
- **Age group**: mean 23 years, range 16-48 years.
- **Group A**: randomised 50; analysed 45.
- **Group B**: randomised 50; analysed 50.

#### Interventions

- **Comparison**: pre + post-op metronidazole versus placebo.
  - **Group A**: metronidazole 400 mg 1 hour before the intervention and then 3 times a day for 8 times.
  - **Group B**: placebo 1 hour before the intervention and then 3 times a day for 8 times.
  - All patients were given the same post-operative instructions, and were given 6 analgesic tablets (codeine phosphate and paracetamol).

#### Outcomes

- **Dry socket**: continuous dull pain from an empty, or partially empty socket, or from the region of the socket. Pain: marked by patient on a 10 mm line (VAS). Outcomes were recorded at 2 and 7 days post-operatively.

### Notes

Risk of bias table
### Bias Assessment

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Assigned to one of two groups by a table of random numbers&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Double blind. Quote: &quot;None of the patients, nor the several operators, were aware of the active or placebo nature of the individual medication&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Double blind. Quote: &quot;None of the patients, nor the several operators, were aware of the active or placebo nature of the individual medication&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>10% of antibiotic group not included in the analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Planned outcomes of dry socket, pain (VAS), adverse effects and compliance were reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

*Happonen 1990*
### Methods

- **Study design:** 3-arm RCT.
- **Conducted in:** Finland.
- **Number of centres:** 1.
- **Recruitment period:** unclear.
- **Funding source:** unclear.

### Participants

- **Inclusion criteria:** healthy consecutive students seeking treatment for impacted, not on any drugs, with the exception of oral contraceptives.
- **Exclusion criteria:** hypersensitivity to penicillin or codeine.
- **Age group:** mean 24 years.
- **Group A:** randomised unclear; analysed 44.
- **Group B:** randomised unclear; analysed 47.
- **Group C:** randomised unclear; analysed 45.
- 8 of the patients enrolled (total 144) were not included in the analysis, but it is unclear in which group they were allocated.

### Interventions

- **Comparison:** pre-+ post-op penicillin versus pre-+ post-op tinidazole versus placebo.
- **Group A:** 1 tablet of phenoxymethylpenicillin 660 mg 1 hour before operation and then 3 times a day for 14 times.
- **Group B:** 1 tablet of tinidazole 500 mg 1 hour before operation and then 3 times a day for 14 times.
- **Group C:** 1 tablet of placebo 1 hour before operation and then 3 times a day for 14 times.
- A 1 minute mouth rinse of 0.2% chlorhexidine was given before surgery.
- 3 tablets of a preparation containing aminophenazon (300 mg), phenobarbital (50 mg) codeine (30 mg) and caffeine (100 mg) was provided to all participants as a rescue analgesic to be taken when needed.

### Outcomes

- **Time of onset and resolution of post-operative swelling,** as well as **time of maximum swelling,** as recorded by patients.
- **Post-operative pain** every hour during the day of the surgery, and at intervals of 4 and 6 hours on the first and second post-operative day respectively. **Number of analgesics was also reported.**
- **Maximal opening of the mouth** was measured before and after surgery (sixth day).
- **Patients were visited on the sixth post-operative day** and **signs of infection,** **fever,** **swelling** and **tender lymph nodes** were recorded by the clinicians.

### Notes

- **Group A and B** were considered together in the present review.
- All operations were carried out under local anaesthesia, by 1 surgeon, using a standardised procedure, 1 tooth being operated at a time.
### Bias  | Authors' judgement | Support for judgement
--- | --- | ---
Random sequence generation (selection bias) | Unclear risk | Quote: "randomly assigned". Method of sequence generation not described.
Allocation concealment (selection bias) | Unclear risk | Not mentioned.
Blinding of participants and personnel (performance bias) | Low risk | Quote: "Double blind".
Blinding of outcome assessment (detection bias) | Low risk | Quote: "Double blind".
Incomplete outcome data (attrition bias) | High risk | 8 out of 144 patients were lost at follow-up (5%), and it is unclear which groups these were from. No specific ITT approach is adopted.
Selective reporting (reporting bias) | High risk | Planned outcomes of duration of swelling, infection, fever reported. Pain (VAS) reported only in graph for first 13 hours, no data at day 7, yet this was the main reason given for time off work.
Other bias | Low risk | No other sources of bias identified.

#### Ritzau 1992

**Methods**
- Study design: RCT.
- Conducted in: Denmark.
- Number of centres: 2.
- Funding source: unclear.

**Participants**
- Inclusion criteria: healthy subjects scheduled for surgical removal of an impacted (partially or totally) mandibular third molar.
- Exclusion criteria: any medical condition that might interfere with the study, acute pericoronitis, patients who had taken antibiotics within 48 hours before surgery were also excluded.
- Age group: not stated.
- A total of 312 subjects were randomised in 2 groups.
- Group A: randomised unclear; analysed 135.
- Group B: randomised unclear; analysed 135.
- 42 subjects did not complete the study: 4 did not comply with the protocol, 4 withdrew voluntarily, 1 had intercurrent disease, 11 were lost to follow-up for various reasons, 22 did not present for surgery after have been enrolled.

**Interventions**
- **Comparison: pre-op metronidazole versus placebo.**
- Group A: 2 tablets with a total dose of 1000 mg metronidazole no later than 30 min before surgery.
- Group B: 2 tablets of placebo no later than 30 min before surgery.

**Outcomes**
- Follow-up examination was scheduled for a week after surgery when sutures were to be removed. Alveolitis sicca dolorosa (dry socket) was diagnosed when 2 criteria were simultaneously present: 1 severe pain irradiating from the empty socket towards the ipsilateral ear, and 2 disintegration (partial or total) of the socket coagulum.

**Notes**

Risk of bias table
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;random sequence ... generated by a computerized program&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;the code was unknown to the investigators until the termination of collection of clinical data&quot;.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;double-blind&quot; and &quot;metronidazole and placebo were manufactured in the shape of pills of identical size, shape, weight, and colour, packed and code numbered&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;double-blind&quot; and &quot;metronidazole and placebo were manufactured in the shape of pills of identical size, shape, weight, and colour, packed and code numbered&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>22/312 randomised participants did not have surgery. 20/290 (7%) patients who did undergo surgery were excluded from the outcome evaluation, but allocated treatment not stated. No specific ITT approach is reported, attrition rate is higher than event rate (4.8%) and bias in these results is considered to be likely.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Methods section states that planned outcome was alveolitis sicca dolorosa (ASD) and this was reported, but other clinically important outcomes were not reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>13% loss of participants post-randomisation and no baseline characteristics reported for each group. Biases possible.</td>
</tr>
</tbody>
</table>

*Sekhar 2001*
## Methods
Study design: RCT.
Conducted in: India.
Number of centres: 1.
Recruitment period: not stated.
Funding source: not stated.

## Participants
Inclusion criteria: patients aged 19-36 requiring removal of lower wisdom teeth under local anaesthesia.
Exclusion criteria: pre-existing abscess or cellulitis, acute pericoronitis, pre-existing conditions associated with third molars, xerostomia. Those requiring antibiotic prophylaxis for other reasons, immunocompromised patients, pregnancy, diabetes, cancer or renal failure and those who had received antibiotics in 2 weeks prior to start of study.
Age group: mean 30 years.
Number randomised: 151 (53, 61 & 37 in Groups A, B, C respectively).
Number evaluated: 125 (44, 47 & 34 in Groups A, B, C respectively).

## Interventions
Comparison: pre-op versus post-op metronidazole versus placebo.
Group A: metronidazole 1 g 1 hour pre-op.
Group B: metronidazole 400 mg 8 hourly for 5 days.
Group C: placebo – frequency of administration not specified.
All participants had a prescription for ibuprofen 400 mg to be taken as required for pain relief.

## Outcomes
Pain (4 point scale) measured on days 2 and 6 post-op, inter-incisal mouth opening (mm) whether there was purulent discharge from wound, dry socket on day 6.

## Notes
Surgeons performing the extractions were either consultants, post-graduate trainees or house officers.

Risk of bias table
### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;randomly assigned using prepared randomizations in sealed envelopes&quot;. Method of sequence generation not described.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation concealed in sealed envelopes.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Described as double blind, but dosing schedule different in each group. Outcome assessor was blinded to allocated treatment.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Described as double blind, but dosing schedule different in each group. Outcome assessor was blinded to allocated treatment.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>26/151 (17%) (9, 14 and 3 from groups A, B and C) of those randomised were excluded because they did not return for follow-up evaluation. Those excluded were more likely to have had bone removed and had longer mean operating times. Given low event rate this attrition could have resulted in biased outcome estimates.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All planned outcomes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Percentage of patients in 2x daily metronidazole group who had bone removed appears to be significantly lower compared to other groups.</td>
</tr>
</tbody>
</table>

#### Leon Arcila 2001

**Methods**

Study design: RCT.

Conducted in: University of Valley, Colombia.

Number of centres: 1.

Recruitment period: 1 September 1998 to 1 September 2000.

**Participants**

Inclusion criteria: patients aged 14-53 years, ASA1, with good oral hygiene, bacterial plaque index $\leq 30\%$, no oral cavity infections or inflammation or pericoronitis, who required extraction of third molars.

Exclusion criteria: allergy to penicillin.

Age group: not stated.

Number randomised: 102.

Number evaluated: 102.

**Interventions**

Comparison: pre- + post-op amoxicillin versus placebo.

Group A (n = 49): amoxicillin 1 gm orally 1 hour pre-operatively and 6 hours post-operatively.

Group B (n = 53): placebo 1 hour pre-op and 6 hours post-operatively.

**Outcomes**

Infection.

**Notes**

All patients had a single extraction - 38 upper teeth and 64 lower teeth.

Additional information supplied by author in response to email request.
### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Quote: &quot;Participants were randomised using a computer&quot; (email from author).</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Quote: &quot;One of the researchers allocated the treatment. Surgeon, patient and statistician did not know such information&quot; (email from author).</td>
</tr>
<tr>
<td>(selection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>(performance bias)</td>
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<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
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<tr>
<td>(detection bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>Quote: &quot;No drop outs or losses to follow up. Everybody was included&quot; (email from author).</td>
</tr>
<tr>
<td>(attrition bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear risk</td>
<td>Infection was the only planned outcome.</td>
</tr>
<tr>
<td>(reporting bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

### Bergdahl 2004

#### Methods
- Study design: RCT.
- Conducted in: Sweden.
- Number of centres: 1.
- Recruitment period: unclear.
- Funding source: unspecified.

#### Participants
- Inclusion criteria: healthy subjects, not taking any other drugs apart from oral contraceptives, who needed removal of unilateral or bilateral mandibular third molar teeth. Only partially impacted teeth, which had partly broken through the mucosa, with a communication to the oral cavity, requiring surgical flap, were included in the study.
- Exclusion criteria: subjects with teeth completely covered with mucosa.
- Age group: mean 29 years, range 17-65 years.
- Group A: randomised 60; analysed 59.
- Group B: randomised 60; analysed 60.

#### Interventions
- **Comparison:** pre-op metronidazole versus placebo.
- Group A: metronidazole 1600 mg as a single dose 45 min before the intervention.
- Group B: placebo as a single dose 45 min before the intervention.
- All patients were given the same post-operative instructions, and were given 20 analgesic tablets (paracetamol 500 mg with codeine 30 mg).

#### Outcomes
- Dry socket assessed 4 days post-op.

#### Notes
- Patients with acute pericoronitis were operated on after objective and subjective symptoms of pericoronitis had ceased.
- Sample size calculation reported.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;a randomised trial&quot;. Method of sequence generation not described.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;double blind&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;double blind&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Only &quot;one patient had to be withdrawn because he had taken an oral antibiotic for other reasons two days after operation&quot;.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Pain, bad odour or taste as assessed by patients were not reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Short duration of follow-up (4 days), unclear whether patients with acute pericoronitis prior to trial were treated with antibiotics.</td>
</tr>
</tbody>
</table>

Arteagotia 2005
### Methods
- **Study design:** RCT.
- **Conducted in:** Spain.
- **Number of centres:** 1.
- **Recruitment period:** between March 2001 and February 2003.
- **Funding source:** financed by the Health Research Fund FIS/GRAN dossier number 00/0585. The trial patients' insurance was taken out by the Basque Health Department, Basque Health Service/Osakidetza, Osakidetza, pursuant to the conditions laid down in RD 561/1993. The antibiotic and placebo were supplied free of charge by Géminis (Novartis generics). Chlorhexidine was supplied free of charge by LACER.

### Participants
- **Inclusion criteria:** patients needing a third molar extraction under local anaesthesia.
- **Exclusion criteria:** patients with any bacterial endocarditis risk factors, pregnant and breastfeeding women, patients with acute infections 10 days prior to the intervention, those who had to take antibiotics and those with a history of allergy or intolerance to the drugs used.
- **Age group:** mean 24 years, range 18-60 years.
- **Group A:** randomised 233; analysed 233 (ITT analysis).
- **Group B:** randomised 261; analysed 261 (ITT analysis).

### Interventions
- **Comparison:** post-op amoxicillin/clavulanate versus placebo.
- **Group A:** amoxicillin/clavulanic acid 500/125 mg oral 3 times a day for 4 days after the procedure.
- **Group B:** placebo oral 3 times a day for 4 days after the procedure.
- All patients had irrigation of the alveolus with 0.12% chlorhexidine digluconate, and chlorhexidine mouthwashes were used for 3 days.

### Outcomes
- Fever (oral temperature >37.88 after 24 hours for no other justifiable cause); intraoral abscess diagnosed via fluctuation pus drainage; dry socket defined as absence of clot with necrotic remains present in the alveolus accompanied by severe mandibular pain; severe pain persisting or increasing 48 hours after surgery accompanied by intraoral inflammation (moderate or severe) and/or intraoral erythema (moderate or severe); severe pain after 7th day accompanied by intraoral inflammation (moderate or severe) and/or intraoral erythema (moderate or severe) for no other justifiable reason which improves with antibiotic treatment. Lack of inflammatory complications. Diagnosis of post-operative infection and inflammatory complication was performed by the main researcher, according to previously published clinical criteria.

### Notes
- All extractions were performed by maxillofacial surgeons, under locoregional anaesthetic of the inferior alveolar and buccal nerves with Ultracain.

### Risk of bias table
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;The simple randomizations was performed using C4-SDP program and , which was used as the patient's number&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Each of enrolled patients was assigned the corresponding blinded random successive treatment number&quot;.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double-blinded&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double-blinded&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>2 participants lost to follow-up from each group but intention-to-treat analysis was performed.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Planned outcomes of pain inflammation and erythema measured qualitatively and reported but VAS pain scores measured and not reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

*Lacasa 2007*
### Methods

Study design: 3-arm RCT.  
Conducted in: Spain.  
Number of centres: 1.  
Recruitment period: between January and December 2002.  
Funding source: the trial was supported by a grant from GlaxoSmithKline S.A., Tres Cantos, Madrid, Spain.

### Participants

Inclusion criteria: adult patients (>18 years of age) who were going to have third mandibular molar surgery.  
Exclusion criteria: patients were excluded if they had a recent local infection prior to surgery (<15 days), had known or suspected allergy to beta-lactams, known or suspected allergy to metamizol, history of renal failure, blood dyscrasia or chronic liver disease of any type, antecedents of recent and/or symptomatic peptic ulcer, or were on antiaggregants or corticosteroids prior (<15 days) to entry. Female patients of child-bearing potential had to have a negative urine pregnancy test prior to enrolment.  
Age group: mean 29 years.  
Group A: randomised 75; analysed (day 7) 62.  
Group B: randomised 75; analysed (day 7) 68.  
Group C: randomised 75; analysed (day 7) 69.

### Interventions

Comparison: pre-op versus post-op amoxicillin/clavulanate versus placebo.  
Group A: 2 amoxicillin/clavulanate 1000/62.5 mg matching placebo tablets (2000/125 mg) in a single dose before surgery, plus 2 amoxicillin/clavulanate 1000/62.5 mg matching placebo tablets (2000/125 mg, BID) for 5 days.  
Group B: 2 active amoxicillin/clavulanate 1000/62.5 mg tablets (2000/125 mg) in a single dose before surgery followed by 2 matching placebo tablets (2000/125 mg, BID) for 5 days.  
Group C: 2 matching placebo tablets (2000/125 mg) in a single dose before surgery followed by 2 active amoxicillin/clavulanate 1000/62.5 mg tablets (2000/125 mg, BID) for 5 days.  
All patients were matched to receive the same analgesic drug throughout the study period with identical dosage. Metamizol (Nolotil™ capsules) was used, 1 capsule every 8 hours, for a minimum of 48 hours, since it is much less anti-inflammatory than other analgesics. Patients were able to continue receiving analgesia afterwards (according to the investigator’s judgement), depending on the presence of pain.

### Outcomes

The main study variables and subjective well being were evaluated on days 1, 3 and 7.  
Infection was defined by any of the following: (1) presence of purulent discharge in the extraction socket and/or excessive swelling with fluctuation, with or without pain; (2) presence of a local abscess; (3) onset of facial or cervical cellulitis plus other signs suggesting infection such as pain, increased heat, erythema and/or fever; (4) presence of osteitis of dental alveolus defined as absence of the haematic clot of the orifice and presence of a putrid smell and intense neuralgic type pain.  
Other inflammatory outcomes were recorded individually, and in a composite way using an inflammation score tabular display with a maximum permitted score of 10. They included swelling, trismus, pain, dysphagia, fever.

### Notes

Only groups A and C were considered for the present review.  
2 of the authors are employees of the funding company.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;randomised&quot;. Method of sequence generation not described.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>It is unclear whether authors used any ITT analysis. 3/225, 9/225 and 26/225 participants are lost to follow-up at days 1, 3 and 7 respectively. Given the low rate of infection this attrition could have introduced a bias.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>According to the methods the planned outcomes were infection, inflammation, swelling, trismus, pain, dysphagia, fever and adverse effects. Data are reported for infection, and means without variance estimates for pain, but no other outcome data reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Statistically significant difference in duration of operation between the placebo and pre-emptive groups. 2 of the authors are employed by the company that funded the trial.</td>
</tr>
</tbody>
</table>

*Kaczmarzyk 2007*
**Methods**

- Study design: 3-arm RCT.
- Conducted in: Poland.
- Number of centres: 1.
- Funding source: unclear.

**Participants**

- Inclusion criteria: healthy volunteers, needing surgical extraction of a retained lower third molar, which was not the cause of inflammation (mainly due to orthodontic recommendations) that required bone removal.
- Exclusion age under 18 or over 60, pregnancy, allergy to clindamycin, lactose intolerance (lactose was the main component of the placebo), episodes of diarrhoea after antibiotic therapy in the interview, any digestive diseases, inflammation in the area of the tooth to be extracted, and any antibiotic or analgesic intake within the previous 7 days.
- Age group: mean 24 years.
- Group A: randomised unclear; analysed 31.
- Group B: randomised unclear; analysed 28.
- Group C: randomised unclear; analysed 27.
- Of the 100 patients enrolled 9 did not check in for the follow-up examination, 3 were disqualified due to complications and 2 resigned during the trial without stating any reason.

**Interventions**

- **Comparison:** pre-op versus pre- + post-op clindamycin versus placebo.
- Group A: single-dose group: patients receiving 600 mg clindamycin hydrochloride orally 60 min pre-operatively, followed by a 300 mg placebo every 8 hours for 5 days.
- Group B: 5-day group: patients receiving 600 mg clindamycin hydrochloride orally 60 min pre-operatively, followed by a dose of 300 mg clindamycin hydrochloride every 8 hours for 5 days.
- Group C: placebo group: patients receiving 600 mg placebo orally 60 min prior to surgery, followed by a dose of 300 mg placebo every 8 hours for 5 days.
- Only groups B and C were considered for the present review.

**Outcomes**

- On the first, second and seventh post-operative day the following outcomes were evaluated: trismus (on a 4-grade scale), facial swelling (on a 4-grade scale), submandibular lymphadenopathy (on a 4-grade scale), body temperature, pain (on a 100-mm VAS), alveolar osteitis (clinical diagnosis of this complication was given in the case of the presence of a necrotic grey clot in a bare bony socket, foetor ex ore, accompanied by pain in this area).

**Notes**

- Risk of bias table
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;group assignment for one patient, determined in advance by a random number table&quot;.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;One hundred opaque and sequentially numbered envelopes were used for the concealment of allocation to trial groups&quot;.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;The patients, the surgeon performing the qualification, operative procedure and follow-up examination, and the statistician were not aware of who received which study intervention&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;The patients, the surgeon performing the qualification, operative procedure and follow-up examination, and the statistician were not aware of who received which study intervention&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>14 out of 100 patients were lost at follow-up (14%). No specific ITT approach is adopted and it is unclear which groups these were from. Due to low event rates for the dichotomous outcomes incomplete outcome data could have resulted in bias.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Planned outcomes of post-operative inflammation (swelling, lymphadenopathy, trismus), pain, body temperature, and alveolar osteitis reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

*Halpern 2007*
### Methods

- **Study design:** RCT.
- **Conducted in:** US.
- **Number of centres:** 1.
- **Recruitment period:** between 1 June 2002 and 1 July 2005.
- **Funding source:** supported in part by the Oral and Maxillofacial Surgery Foundation Research Grant and Massachusetts General Hospital (MGH) Center for Applied Clinical Investigation.

### Participants

- **Inclusion criteria:** patients needing a third molar extraction under intravenous sedation or general anaesthesia in the office-based ambulatory setting.
- **Exclusion criteria:** subjects with pre-existing conditions that could affect wound healing or predispose them to inflammatory complications, including previous radiation therapy to the maxillofacial region, human immunodeficiency virus infection, organ or marrow transplant candidates or recipients, diabetes, or organ failure (kidney, heart, liver); subjects requiring antibiotic prophylaxis for endocarditis, were currently on oral steroid therapy, were allergic to the antibiotics proposed for use in this study, deferred intravenous sedation or general anaesthesia; had local pathology, e.g. cysts or tumour, associated with M3s that was not incidental to the removal of the M3; acute inflammation in the area of the planned extraction characterized by frank purulence, erythema, induration, or trismus; supernumerary teeth to be removed; or deferred study participation.
- **Age group:** mean 25 years.
- **Group A:** randomised 60; analysed 59.
- **Group B:** randomised 62; analysed 59.

### Interventions

- **Comparison:** pre-op IV penicillin (or clindamycin) versus placebo.
- **Group A:** solution of penicillin (15,000 units per kilogram) or, for penicillin-allergic subjects, clindamycin (600 mg) administered intravenously within 1 hour before the intervention.
- **Group B:** placebo solution (10 cc saline 0.9%) administered intravenously within 1 hour before the intervention.
- **Post-operative analgesia:** consisted of the use of 1 or 2 acetaminophen (500 mg) and hydrocodone (5 mg) tablets administered orally every 3 to 4 hours.

### Outcomes

- **Dry socket** (a new onset or increasing pain more than 36 hours after the operation, with a loss of the blood clot in the extraction site as evidenced by exposed bone, gentle probing or irrigation of the wound duplicating the pain, and significant pain relief after application of an anodyne dressing; all elements needed to be present to make the diagnosis).
- **Surgical site infection** (visual evidence of frank purulence in one or more of the extraction sites and a Gram’s stain demonstrating white blood cells present).
- **Any post-operative inflammatory complications** (dry socket or surgical site infection).
- **Assessed on day 7 post-operatively (range 5-14).**

### Notes

**Risk of bias table**
### Bias

<table>
<thead>
<tr>
<th>Bias</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;randomized&quot;. Method of sequence generation not described.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Consecutively numbered, double-sealed envelopes were prepared containing the treatment assignment&quot;.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind. The surgeon and study subject were blinded to the true nature of the contents of the syringe&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind. The surgeon and study subject were blinded to the true nature of the contents of the syringe&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>1/60 and 3/62 participants lost to follow-up in the antibiotic and placebo groups, but low event rates mean that data from these participants could have changed the outcome.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Surgical site infections and acute osteitis planned and reported. No report of pain swelling or trismus.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other sources of bias identified.</td>
</tr>
</tbody>
</table>

### Pasupathy 2011

#### Methods

- Study design: RCT.
- Conducted in: India.
- Number of centres: 1.
- Recruitment period: unclear.
- Funding source: not stated.

#### Participants

- Inclusion criteria: patients with mandibular mesioangularly impacted third molars requiring extraction.
- Exclusion criteria: infections (space infections, acute pericoronitis), medically compromised, pregnant, allergic to either penicillin or metronidazole, those who have taken antibiotics in the 2 months prior to surgery.
- Age group: mean 29 years, range 18-48 years.
- Number randomised: 98.
- Number evaluated: 89.

#### Interventions

- **Comparison: pre-op amoxicillin versus pre-op metronidazole versus placebo.**
  - Group A: amoxicillin 1 g orally 1 hour prior to surgery.
  - Group B: metronidazole 800 mg orally 1 hour prior to surgery.
  - Group C: placebo.
  - All patients received ibuprofen 600 mg 3x daily for pain.

#### Outcomes

- Surgical wound infection, purulent discharge, fever, restricted mouth opening on day 7 post-op.

#### Notes

Sample size: reported that estimated sample size required was 107 in each group. Trial recruited ~30 per group.
<table>
<thead>
<tr>
<th><strong>Bias</strong></th>
<th><strong>Authors’ judgement</strong></th>
<th><strong>Support for judgement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “randomization table was prepared using a software program and a random allocating number was given to each patient”.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Sealed envelopes with the allotted number were used and were dispensed by 1 of our post graduate trainees throughout the study according to the allotted randomization number”.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Triple blind – neither the patient nor the surgeon nor the outcome evaluator were aware of the allocated treatment.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Triple blind – neither the patient nor the surgeon nor the outcome evaluator were aware of the allocated treatment.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>9/98 (9%) of randomised patients excluded from the analysis, due to either not returning for follow-up (n = 8) or use of antibiotic (n = 1). Allocated treatment group not described for these 9. Given low event rate this attrition is likely to have introduced bias.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Surgical wound infection, purulent discharge, reported for each group. Fever, pain and trismus is not reported per treatment group, although it seems likely that these data were collected.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Trial is very clearly underpowered and this is likely to bias results towards the null hypothesis of no difference between interventions.</td>
</tr>
</tbody>
</table>

*López-Cedrún 2011*
### Methods
- **Study design:** RCT.
- **Conducted in:** Spain.
- **Number of centres:** 1.
- **Recruitment period:** not stated.

### Participants
- **Inclusion criteria:** at least 1 mandibular impacted or partially erupted third molar requiring extraction.
- **Exclusion criteria:** aged >60 or <18 years, infectious or systemic diseases, immunosuppressive treatment, smoking, peptic ulcer, pregnancy, lactation, known or suspected allergy to ibuprofen or beta-lactam antibiotics, carious or non-impacted third molars, pericoronitis, or patients in whom excessive technical difficulty was expected.
- **Age group:** mean 22 years, range 18-46 years.
- **Number randomised:** 134.
- **Number evaluated:** 123.

### Interventions
- **Comparison:** pre-op versus post-op amoxicillin versus placebo.
  - **Group A:** amoxicillin 4x 500 mg 2 hours prior to surgery plus 15 placebo tablets taken 3x daily for 5 days.
  - **Group B:** 4 placebo tablets 2 hours pre-op plus 15 placebo tablets taken 3x daily for 5 days.
  - **Group C:** 4 placebo tablets 2 hours pre-op plus 15 amoxicillin 500 mg to be taken 3x daily for 5 days.

### Outcomes
- **Intraoral swelling, maximal mouth opening, pain (100 point VAS) dysphagia, fever, purulent wound discharge, alveolar osteitis (dry socket), side effects of treatment at 7 days post-op.**

### Notes
- All procedures were performed by the same surgeon.
- Additional information supplied by author in response to email request.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Pharmacist held the randomisation code and the drug code (a random alpha numeric code).</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;A set of opaque sealed envelopes contained the drug code for every patient. One envelope was opened for every patient and the patient was provided with the coded tablet pack that matched the number in the envelope&quot;.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Quote: &quot;Double blind&quot;.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>11/134 (8%) were excluded from the analysis. 3, 0, 1 were excluded from pre-op, post-op and placebo groups due to technical difficulty of the procedure and 2,1, 4 due to inadequate follow-up. Due to the low event rate for infection it is probable that this attrition introduced a bias to the outcome.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>All planned outcomes reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Statistically significant difference in mean operating time between pre- and post-op antibiotic groups.</td>
</tr>
</tbody>
</table>

**Bezerra 2011**

**Methods**
- Study design: RCT cross-over.
- Conducted in: Brazil.
- Number of centres: 1.
- Recruitment period: January to November 2008.

**Participants**
- Inclusion criteria: healthy patients with no periodontal disease requiring removal of 4 third molars, with similar degrees of impaction between sides of mouth.
- Exclusion criteria: tobacco use, orthodontic bands on second molars, pregnancy or breastfeeding, chronic systemic disorders, allergies to antibiotics, history of adverse effects from antibiotics and use of antibiotics in 3 months prior to entering trial.
- Age group: mean 21 years, range 18-31 years.
- Number randomised: 36.
- Number evaluated: 34.

**Interventions**
- **Comparison: pre-op amoxicillin versus placebo.**
  - Group A: amoxicillin 2 x 500 mg administered orally 1 hour pre-op.
  - Group B: placebo (2 tablets) identical in appearance administered 1 hour pre-op.
  - Standard post-operative treatment was Nimesulid (NSAID) 100 mg every 12 hours for 4 days and dipyprone (NSAID) 500 mg 6 hourly for 2 days.

**Outcomes**
- Soft tissue edema/ulcer, pain (1-10 VAS), edema, limitation of mouth opening, infection (purulent secretion, alveolitis (pain + partially/totally disintegrated clot), fever at 3, 7 and 14 days post-op.

**Notes**
- Email from author 13/2/2012 stating duration of washout period at least 45 days.
- Additional outcome data provided.
### Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Drugs/placebo placed into transparent, sterile boxes with code number. Patient chose one box for first procedure and a coin toss decided which side of mouth was done first.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Unclear who performed the coin toss and how the result was communicated to the surgeon. However bias unlikely to result from this design.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Double blind – neither patient nor surgeon knew which treatment was given.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Double blind – neither patient nor surgeon knew which treatment was given.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>2/36 patients were not included in analysis. Due to low number and cross-over design, attrition bias is unlikely.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Duration of surgery, inflammatory/infectious events, pain scores, edema, maximum mouth opening, swelling of soft tissues, alveolitis reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Indications of a significant period effect with regard to the outcome of pain. This is likely to bias this outcome towards no difference between active and placebo.</td>
</tr>
</tbody>
</table>

### Footnotes

ITT = intention-to-treat; RCT = randomised controlled trial; VAS = visual analogue scale.

### Characteristics of excluded studies

**Abu-Mowais 1990**

**Reason for exclusion**

Not double blind.

**Ataoglu 2008**

**Reason for exclusion**

Not double blind.

**Bargnesi 1985**

**Reason for exclusion**

Study of antibiotics used in conjunction with a range of small dental surgical procedures including but not limited to tooth extractions.

**Curran 1974**

**Reason for exclusion**

Described as double blind but control group received no treatment. Patients not blinded to treatment, and asked not to inform outcome assessors.

**de Moura 2011**

**Reason for exclusion**

Washout period 4 weeks (translated from Spanish).

**Dellibasi 2004**

**Reason for exclusion**

Not double blind.

**Foy 2004**
<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>Not double blind.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fridrich 1990</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not randomised or quasi-randomised.</td>
</tr>
<tr>
<td><strong>Graziani 2005</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Grossi 2007</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Head 1984</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Bacteraemia outcomes only.</td>
</tr>
<tr>
<td><strong>Krekmanov 1980</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Krekmanov 1981</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Krekmanov 1986</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Laird 1972</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>This study compares 2 antibiotic regimens.</td>
</tr>
<tr>
<td><strong>Limeres 2009</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>This study compares 2 antibiotic regimens.</td>
</tr>
<tr>
<td><strong>Lombardia Garcia 1987</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Lopes 2011</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>Luaces-Rey 2010</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>This study compares 2 antibiotic regimens.</td>
</tr>
<tr>
<td><strong>Lyall 1991</strong></td>
<td></td>
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<tr>
<td>Reason for exclusion</td>
<td>Not double blind.</td>
</tr>
<tr>
<td><strong>MacGregor 1973</strong></td>
<td></td>
</tr>
<tr>
<td>Reason for exclusion</td>
<td>Topical antibiotic.</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------</td>
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<tr>
<td>Mitchell 1987</td>
<td>No blinding described.</td>
</tr>
<tr>
<td>Monaco 1999</td>
<td>Not double blind.</td>
</tr>
<tr>
<td>Monaco 2009</td>
<td>Not double blind.</td>
</tr>
<tr>
<td>Olusanya 2011</td>
<td>This study compares 2 antibiotic regimens.</td>
</tr>
<tr>
<td>Osborn 1979</td>
<td>From translator: &quot;it is clear that this study is double blinded but it is unclear how participants were allocated to treatment groups. Random not mentioned&quot;.</td>
</tr>
<tr>
<td>Poeschl 2004</td>
<td>Not double blind.</td>
</tr>
<tr>
<td>Reekie 2006</td>
<td>Topical antibiotic therapy.</td>
</tr>
<tr>
<td>Rood 1979</td>
<td>Not randomised.</td>
</tr>
<tr>
<td>Samsudin 1994</td>
<td>Not randomised or quasi and not double blind.</td>
</tr>
<tr>
<td>Siddiqi 2010</td>
<td>Washout period only 3 weeks (communication from author).</td>
</tr>
<tr>
<td>Stavropoulos 2006</td>
<td>Authors considered only topical antibiotic therapy.</td>
</tr>
<tr>
<td>Sulejmanagić 2005</td>
<td>Not randomised or quasi-randomised and not double blind.</td>
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<tr>
<td>Swanson 1989</td>
<td>Topical antibiotic therapy.</td>
</tr>
<tr>
<td>Uluibau 2005</td>
<td>Not double blind.</td>
</tr>
<tr>
<td>Walkow 1995</td>
<td>Topical antibiotic therapy.</td>
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### Reason for exclusion

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<thead>
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<th>Reason for exclusion</th>
<th>Abstract only, no mention of blinding and no subsequent trial report found.</th>
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</thead>
</table>

#### Yoshii 2002

<table>
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<tr>
<th>Reason for exclusion</th>
<th>No blinding described.</th>
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### Footnotes

#### Characteristics of studies awaiting classification

#### Characteristics of ongoing studies

**Arteagoitia 2011**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Efficacy of amoxicillin/clavulanic acid 2000/125 mg in preventing infection after extraction of impacted mandibular third molar totally covered by bone (EUDRACT 2008-005663-34).</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Double-blind placebo-controlled trial.</td>
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<tr>
<td>Participants</td>
<td>Patients with bony impactions of mandibular third molars undergoing extraction under locoregional anaesthesia.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Amoxicillin/clavulanic acid 2000/125 mg 1 hour pre-op plus post-op twice daily for 4 days versus placebo. All patients received 0.2% chlorhexidine rinses.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Infection.</td>
</tr>
<tr>
<td>Starting date</td>
<td>26 June 2009.</td>
</tr>
<tr>
<td>Contact information</td>
<td>Arteagoitia M Stomatology Department, University of the Basque Country, Leioa, Spain.</td>
</tr>
</tbody>
</table>

### Notes

#### Summary of findings tables

1. Antibiotic compared to placebo for preventing infectious complications after tooth extraction
Antibiotics compared to placebo for preventing infectious complications after tooth extraction

**Patient or population:** Patients undergoing tooth extraction  
**Settings:** Oral surgery referral centre  
**Intervention:** Antibiotic  
**Comparison:** Placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Local sign of infection**  
Follow-up: mean 7 days | Placebo: 118 per 1000 (19 to 59)  
Antibiotic: 34 per 1000 (19 to 59) | RR 0.29 (0.16 to 0.50) | 1523 (10 studies) | ⊕⊕⊕⊕ moderate | 1 |
| **Dry socket**  
Follow-up: mean 7 days | Placebo: 69 per 1000 (28 to 65)  
Antibiotic: 43 per 1000 (28 to 65) | RR 0.62 (0.41 to 0.95) | 1429 (9 studies) | ⊕⊕⊕ moderately | 2 |
| **Pain (dichotomous on 6-7th day)**  
Follow-up: mean 6.5 days | Placebo: 126 per 1000 (40 to 140)  
Antibiotic: 76 per 1000 (40 to 140) | RR 0.60 (0.32 to 1.11) | 675 (3 studies) | ⊕⊕⊕ moderate | 3,4 |
| **Pain score (VAS 7th day)**  
Scale from: 1 to 100  
Follow-up: mean 7 days | Placebo: Mean pain score (VAS) in placebo groups was 15  
Antibiotic: The mean pain score (VAS 7th day) in the intervention groups was 8.17 lower (11.9 to 4.45 lower) |  | 372 (4 studies) | ⊕⊕⊕ moderate | 5 |
| **Fever (6th-7th day)**  
Follow-up: mean 6.5 days | Placebo: 39 per 1000 (2 to 78)  
Antibiotic: 13 per 1000 (2 to 78) | RR 0.34 (0.06 to 1.99) | 816 (4 studies) | ⊕⊕⊕ low | 6,7 |
| **Swelling (7th day)**  
Follow-up: mean 7 days | Placebo: 307 per 1000 (200 to 399)  
Antibiotic: 282 per 1000 (200 to 399) | RR 0.92 (0.65 to 1.30) | 334 (3 studies) | ⊕⊕⊕ moderate | 8 |
| **Adverse effects**  
Follow-up: mean 7 days | Placebo: 49 per 1000 (54 to 175)  
Antibiotic: 96 per 1000 (54 to 175) | RR 1.98 (1.10 to 3.59) | 930 (5 studies) | ⊕⊕⊕ moderate | 9 |

*The basis for the assumed risk (e.g. the mean control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

| CI: confidence interval; RR: risk 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.

**Footnotes**

1. 10 double-blind placebo-controlled trials - 7 trials at high risk of bias and 3 trials at unclear risk of bias.
2. 9 double-blind placebo-controlled trials - 7 trials at high risk of bias and 2 trials at unclear risk of bias.
3. 3 double-blind placebo-controlled trials - 2 trials at high risk of bias and 1 trial at unclear risk of bias.
4. Substantial heterogeneity $I^2 = 57\%$ $P = 0.07$.
5. 4 double-blind placebo-controlled trials - all at high risk of bias.
6. 4 double-blind placebo-controlled trials - 3 at high risk of bias and 1 at unclear risk of bias.
7. Substantial heterogeneity $I^2 = 60\%$ ($P = 0.11$).
8. 3 double-blind placebo-controlled trials at high risk of bias.
9. 5 double-blind placebo-controlled trials - 4 at high risk of bias and 1 at unclear risk of bias.
## Additional tables

### 1 Studies of reasons for tooth extraction

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>% for caries</th>
<th>% for periodontitis</th>
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<tr>
<td>Da’ameh 2006</td>
<td>Afghanistan</td>
<td>59.2</td>
<td>35.3</td>
</tr>
<tr>
<td>Akhter 2008</td>
<td>Bangladesh</td>
<td>67.5</td>
<td>18.5</td>
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<td>Jovino-Silveira 2005</td>
<td>Brazil</td>
<td>63.3</td>
<td>13.1</td>
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<td>Chrysanthakopoulos 2011</td>
<td>Greece</td>
<td>45.6</td>
<td>32.1</td>
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<td>Anand 2010</td>
<td>India</td>
<td>44.6</td>
<td>33.2</td>
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<tr>
<td>Aida 2009</td>
<td>Japan</td>
<td>43.6</td>
<td>37.1</td>
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<tr>
<td>Baqain 2007</td>
<td>Jordan</td>
<td>63.8</td>
<td>22.9</td>
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<td>Al-Shammari 2006</td>
<td>Kuwait</td>
<td>43.7</td>
<td>37.4</td>
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<td>Byahatti 2011</td>
<td>Libya</td>
<td>55.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Danielson 2011</td>
<td>Nigeria</td>
<td>32.6</td>
<td>45</td>
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<tr>
<td>Trovik 2000</td>
<td>Norway</td>
<td>40</td>
<td>24</td>
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<tr>
<td>Chestnutt 2000</td>
<td>Scotland</td>
<td>51</td>
<td>21</td>
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<tr>
<td>McCaul 2001</td>
<td>Scotland</td>
<td>54.7</td>
<td>16.7</td>
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<td>Lesolang 2009</td>
<td>South Africa</td>
<td>47.9</td>
<td>22.6</td>
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<td>Richards 2005</td>
<td>Wales</td>
<td>59</td>
<td>29.1</td>
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### 2 Kaziro 1984 outcome data (from graphs)

<table>
<thead>
<tr>
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<th>Antibiotic group</th>
<th>Placebo group</th>
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<tr>
<td>Infection- wound breakdown</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td>Pain - Day 8</td>
<td>60% pain free</td>
<td>22% pain free</td>
</tr>
<tr>
<td>Swelling - Day 8</td>
<td>80% minimal swelling</td>
<td>66% minimal swelling</td>
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</table>

### 3 Raw outcome data - Local signs of infection
### Infection (%)

<table>
<thead>
<tr>
<th></th>
<th>Antibiotic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-operative prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchell 1986</td>
<td>4/25 (16%)</td>
<td>14/25 (56%)</td>
</tr>
<tr>
<td>Sekhar 2001</td>
<td>1/44 (2%)</td>
<td>0/17</td>
</tr>
<tr>
<td>Lacasa 2007</td>
<td>4/75 (5%)</td>
<td>6/38 (16%)</td>
</tr>
<tr>
<td>Halpern 2007</td>
<td>0/59</td>
<td>5/59 (8%)</td>
</tr>
<tr>
<td>Bezerra 2011</td>
<td>0/34</td>
<td>0/34</td>
</tr>
<tr>
<td>López-Cedrún 2011</td>
<td>0/39</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Pasupathy 2011</td>
<td>2/60 (3%)</td>
<td>3/29 (10%)</td>
</tr>
<tr>
<td><strong>Post-operative prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sekhar 2001</td>
<td>0/47</td>
<td>0/17</td>
</tr>
<tr>
<td>Arteagoitia 2005</td>
<td>5/259 (2%)</td>
<td>30/231 (13%)</td>
</tr>
<tr>
<td>Lacasa 2007</td>
<td>2/72 (3%)</td>
<td>6/37 (16%)</td>
</tr>
<tr>
<td>López-Cedrún 2011</td>
<td>0/44</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td><strong>Pre- and post-operative prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happonen 1990</td>
<td>11/91 (12%)</td>
<td>5/45 (11%)</td>
</tr>
<tr>
<td>Leon Arcila 2001</td>
<td>0/49</td>
<td>0/53</td>
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<tr>
<td><strong>Mean incidence of infection per group</strong></td>
<td>29/898 (3.4%)</td>
<td>74/625 (12.5%)</td>
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</table>

### Footnotes

#### 4 Raw outcome data - Dry socket

<table>
<thead>
<tr>
<th></th>
<th>Antibiotic</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>Pre-operative prophylaxis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ritzau 1992</td>
<td>8/135 (4.4%)</td>
<td>7/135 (5.2%)</td>
</tr>
<tr>
<td>Bergdahl 2004*</td>
<td>10/59 (16.9%)</td>
<td>13/60 (21.6%)</td>
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<tr>
<td>Kaczmarzyk 2007</td>
<td>1/31 (3.2%)</td>
<td>2/13 (15.4%)</td>
</tr>
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<td>Halpern 2007</td>
<td>0/59</td>
<td>0/59</td>
</tr>
<tr>
<td>Bezerra 2011</td>
<td>0/34</td>
<td>0/34</td>
</tr>
<tr>
<td>López-Cedrún 2011</td>
<td>0/39</td>
<td>0/20</td>
</tr>
<tr>
<td><strong>Post-operative prophylaxis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Arteagoitia 2005</td>
<td>0/259</td>
<td>2/231 (0.9%)</td>
</tr>
<tr>
<td>López-Cedrún 2011</td>
<td>0/44</td>
<td>0/20</td>
</tr>
<tr>
<td><strong>Pre- and post-operative prophylaxis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bystedt 1981</td>
<td>2/40 (5%)</td>
<td>2/20 (1%)</td>
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<tr>
<td>Barclay 1987*</td>
<td>8/45 (17.8%)</td>
<td>17/50 (34%)</td>
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<tr>
<td>Kaczmarzyk 2007</td>
<td>2/28 (7.1%)</td>
<td>2/14 (14.3%)</td>
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<td><strong>Mean incidence dry socket per group</strong></td>
<td>29/773 (3.8%)</td>
<td>45/656 (6.9%)</td>
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### Footnotes

* Participants in both these studies had some pericoronitis in the recent past and were therefore at higher risk of infection.
5 Raw outcome data - VAS pain scores

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<th>Mean (SD) VAS pain scores</th>
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<th>Placebo</th>
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<td>10.92 (16.89)</td>
<td>5.75 (12.26)</td>
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<td>n = 39</td>
<td>n = 20</td>
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<td>Bezerra 2011</td>
<td>15.9 (23.6)</td>
<td>31.2 (29.5)</td>
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<td>n = 34</td>
<td>n = 34</td>
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<tr>
<td>Pre- and post-operative prophylaxis</td>
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<td></td>
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<tr>
<td>Barclay 1987*</td>
<td>6.33 (12.58)</td>
<td>14.79 (23.09)</td>
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<td>n = 45</td>
<td>n = 50</td>
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<td>Kaczmarzyk 2007</td>
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<td>10.14 (19.54)</td>
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<td>n = 28</td>
<td>n = 14</td>
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<td>15.02 (23.44)</td>
<td>5.75 (12.26)</td>
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<td>n = 44</td>
<td>n = 20</td>
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</table>

Footnotes

*Participants in this study had some pericoronitis in the recent past and were therefore at higher risk of infection.
SD = standard deviation; VAS = visual analogue scale.

References to studies

Included studies

**Arteagoitia 2005**

**Barclay 1987**

**Bergdahl 2004**

**Bezerra 2011**
*Published and unpublished data*


**Bystedt 1980**

**Bystedt 1981**
Antibiotics to prevent complications following tooth extractions

**Halpern 2007**

**Happonen 1990**

**Kaczmarzyk 2007**

**Kaziro 1984**


**Lacasa 2007**

**Leon Arcila 2001**
*Published and unpublished data*

**López-Cedrún 2011**
*Published and unpublished data*

**MacGregor 1980**


**Mitchell 1986**

**Pasupathy 2011**

**Ritzau 1992**

**Sekhar 2001**

**Excluded studies**

**Abu-Mowais 1990**

**Ataoğlu 2008**
Ataoğlu H, Oz GY, Candirli C, Kızıloğlu D. Routine antibiotic prophylaxis is not necessary during operations to remove third
Antibiotics to prevent complications following tooth extractions

Bargnesi 1985

Curran 1974

Delilbasi 2004

de Moura 2011

Foy 2004

Fridrich 1990

Graziani 2005

Grossi 2007

Head 1984

Krekmanov 1980

Krekmanov 1981

Krekmanov 1986

Laird 1972

Limeres 2009

Lombardía García 1987
0062 Antibiotics to prevent complications following tooth extractions

Lopes 2011

Luaces-Rey 2010

Lyall 1991

MacGregor 1973

Mitchell 1987

Monaco 1999

Monaco 2009

Olusanya 2011

Osborn 1979

Poeschl 2004

Reekie 2006

Rood 1979

Samsudin 1994

Siddiqi 2010

Stavropoulos 2006

Sulejmanagić 2005
Swanson 1989

Uluibau 2005

Walkow 1995

Yoshii 2002
Yoshii T, Hamamoto Y, Muraoka S, Furudoi S, Komori T. Differences in postoperative morbidity rates, including infection and dry socket, and differences in the healing process after mandibular third molar surgery in patients receiving 1-day or 3-day prophylaxis with lenampicillin. Journal of Infection & Chemotherapy 2002;8(1):87-93.

Studies awaiting classification
Ongoing studies
Arteagoitia 2011

Other references
Additional references
Aida 2009

Akhter 2008

Al-Shammari 2006

Anand 2010

Baqain 2007

Bortoluzzi 2010

Bouloux 2007

Byahatti 2011

Chestnutt 2000

Chrysanthakopoulos 2011
Costelloe 2010

Da’ameh 2006

Daly 2008

Danielson 2011

Dar-Odeh 2010

Egger 1997

Elbourne 2002

Epstein 2000

EU Commission 2011

Hersh 1999

Higgins 2011

Howe 1985

Ioannidis 2009

Jaafar 2000

Jovino-Silveira 2005

Karki 2011

Lesolang 2009

Lökken 1975

McCaul 2001

Mettes 2012

Ren 2007

Richards 2005

Rucker 2008

Sleeman 1995

Thomas 1994

Trovik 2000

Worthington 1999

Other published versions of this review
Classification pending references

Data and analyses

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
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<td><strong>1 Antibiotic versus placebo</strong></td>
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<tr>
<td>1.1 <strong>Local sign of infection</strong></td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.29 [0.16, 0.50]</td>
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<td>1.1.1 Pre-operative prophylaxis</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.29 [0.15, 0.54]</td>
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<td>1.1.2 Post-operative prophylaxis</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.15 [0.07, 0.31]</td>
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<td>1.1.3 Pre- and post-operative prophylaxis</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>1.09 [0.40, 2.94]</td>
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<tr>
<td>1.2 <strong>Dry socket</strong></td>
<td>9</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.62 [0.41, 0.95]</td>
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<td>1.2.1 Pre-operative prophylaxis</td>
<td>6</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.75 [0.42, 1.33]</td>
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<td>1.2.2 Post-operative prophylaxis</td>
<td>2</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.18 [0.01, 3.70]</td>
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<td>1.2.3 Pre- and post-operative prophylaxis</td>
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<td>Risk Ratio(IV, Random, 95% CI)</td>
<td>0.52 [0.27, 0.99]</td>
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<td>1.3 <strong>Pain (dichotomous on 6th-7th day)</strong></td>
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<td>Risk Ratio(M-H, Random, 95% CI)</td>
<td>0.60 [0.32, 1.11]</td>
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<td>1.3.1 Pre-operative prophylaxis</td>
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<td>Risk Ratio(M-H, Random, 95% CI)</td>
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<td>1.3.2 Post-operative prophylaxis</td>
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<td>Risk Ratio(M-H, Random, 95% CI)</td>
<td>0.51 [0.14, 1.82]</td>
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<td>1.3.3 Pre- and post-operative prophylaxis</td>
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<td>60</td>
<td>Risk Ratio(M-H, Random, 95% CI)</td>
<td>0.36 [0.13, 0.98]</td>
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</tbody>
</table>
1.4 Pain score (VAS 7th day)  
Mean Difference (IV, Random, 95% CI)  
-8.17 [-11.90, -4.45]  
1.4.1 Pre-operative prophylaxis  
Mean Difference (IV, Random, 95% CI)  
-7.41 [-16.18, 1.36]  
1.4.2 Pre- and post-operative prophylaxis  
Mean Difference (IV, Random, 95% CI)  
-8.30 [-13.18, -3.42]  
1.5 Fever (6th-7th day)  
Risk Ratio (M-H, Random, 95% CI)  
0.34 [0.06, 1.99]  
1.6 Swelling (7th day)  
Risk Ratio (M-H, Random, 95% CI)  
0.92 [0.65, 1.30]  
1.6.1 Pre-operative prophylaxis  
Risk Ratio (M-H, Random, 95% CI)  
1.13 [0.69, 1.83]  
1.6.2 Post-operative prophylaxis  
Risk Ratio (M-H, Random, 95% CI)  
0.50 [0.24, 1.02]  
1.6.3 Pre- and post-operative prophylaxis  
Risk Ratio (M-H, Random, 95% CI)  
1.07 [0.53, 2.17]  
1.7 Trismus (7th day)  
Risk Ratio (M-H, Random, 95% CI)  
0.84 [0.42, 1.71]  
1.8 Adverse effects  
Risk Ratio (M-H, Random, 95% CI)  
1.98 [1.10, 3.59]

Figures

Figure 1

Caption
Study flow diagram.

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

**Figure 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
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<tr>
<td>Antunes et al. 2005</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
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<td>Barros et al. 2007</td>
<td>![Low risk of bias]</td>
<td>![Low risk of bias]</td>
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<td>Patzak et al. 2011</td>
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<td>Ritzau et al. 2002</td>
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</tbody>
</table>
Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 4 (Analysis 1.1)

Caption
Funnel plot of comparison: 1 Antibiotic versus placebo, outcome: 1.1 Local sign of infection.

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Internal sources
- MAHSC, UK
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- The University of Manchester, UK

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Feedback

Appendices

1 Cochrane Oral Health Group's Trials Register search strategy
   ((extract* or remov* or exodontia or "impacted teeth" or "impacted tooth" or "oral surg*" or (tooth and surg*) or (teeth and surg*) or ("third molar*" and surg*)) AND (antibiotic* or erthromycin* or metronidaz* or tetracycline* or clindamycin* or teicoplanin* or vancomycin* or floxacillin* or gentamicin* or cephalaxin* or "anti biotic*" or anti-biotic* or penicillin* or antibacterial* or anti-bacterial* or "anti bacterial*" or "anti bacterial" or erthromycin* or cephalexin* or "anti biotic"" or anti-biotic* or penicillin* or antibacterial* or anti-bacterial* or "anti bacterial*" or "anti bacterial" or erthromycin* or vancomycin* or sulfonamide* or clindamycin* or augmentin* or flagyl* or amoxy* or amoxil* or co-amox* or antifungal* or anti-fungal* or "anti fungal*" or vancomycin* or fluocacinil* or floxacinil* or gentamycin* or cephalaxin*))

2 CENTRAL search strategy
   #1 MeSH descriptor Tooth extraction explode all trees
   #2 exodontia in All Text
   #3 (tooth in All Text near/4 extract* in All Text) or (teeth in All Text near/4 extract* in All Text) or ("third molar*" in All Text near/4 extract* in All Text) or (3rd in All Text and (molar* in All Text near/4 extract* in All Text) ) or "dental extract*" in All Text or (tooth in All Text near/4 remov* in All Text) or (teeth in All Text near/4 remov* in All Text) or ("third molar*" in All Text near/4 remov* in All Text) or ("3rd molar*" in All Text near/4 remov* in All Text) or (tooth in All Text near/4 surg* in All Text) or (teeth in All Text near/4 surg* in All Text) or (tooth in All Text near/4 surg* in All Text) or (teeth in All Text near/4 surg* in All Text)
(teeth in All Text near/4 surg* in All Text) or ("third molar*" in All Text near/4 surg* in All Text) or ("3rd molar*" in All Text near/4 surg* in All Text))

#4 (#1 or #2 or #3)

#5 MeSH descriptor Molar explode all trees

#6 MeSH descriptor Tooth, impacted this term only

#7 ("wisdom tooth" in All Text or "wisdom teeth" in All Text or (third in All Text near/3 molar in All Text))

#8 "impacted tooth" in All Text

#9 "impacted teeth" in All Text

#10 (#5 or #6 or #7 or #8 or #9)

#11 (extract* in All Text or remov* in All Text) or surg* in All Text)

#12 (#10 and #11)

#13 (#4 or #12)

#14 MeSH descriptor Anti-Bacterial Agents explode all trees

#15 MeSH descriptor Antibiotic prophylaxis this term only

#16 MeSH descriptor Erythromycin explode all trees

#17 MeSH descriptor Metronidazole this term only

#18 MeSH descriptor Tetracyclines this term only

#19 MeSH descriptor Clindamycin this term only

#20 MeSH descriptor Teicoplanin this term only

#21 MeSH descriptor Vancomycin this term only

#22 MeSH descriptor Floxacillin this term only

#23 MeSH descriptor Gentamicins this term only

#24 MeSH descriptor Cephalexin this term only

#25 (antibiot* in All Text or "anti biot*" in All Text or anti-biot* in All Text)

#26 (penicillin* in All Text or erythromycin* in All Text or metronidazol* in All Text or cephalosporin* in All Text)

#27 (sulphonamide* in All Text or tetracycline* in All Text or clindamycin* in All Text or clindamicin* in All Text or augmentin* in All Text or flagyl* in All Text or amoxyl* in All Text or amoxil* in All Text or co-amox* in All Text or antifungal* in All Text or anti-fungal* in All Text or "anti fungal*" in All Text or teicoplanin* in All Text or vancomycin* in All Text or vancomicon* in All Text or flucloxacillin* in All Text or floxacillin* in All Text or gentamicin* in All Text or gentamycin* in All Text or cephalaxin* in All Text)

#28 (antibacterial in All Text or anti-bacterial in All Text or "anti bacterial" in All Text)

#29 (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28)

#30 (#13 and #29)

3 MEDLINE via OVID search strategy

1. exp TOOTH EXTRACTION/

2. exodontia.mp.

3. (tooth adj4 extract$) or (teeth adj4 extract$) or ("third molar$" adj4 extract$) or ("3rd molar$" adj4 extract$) or "dental extract$" or (tooth adj4 remov$) or (teeth adj4 remov$) or ("third molar$" adj4 remov$) or ("3rd molar$" adj4 remov$) or (tooth adj4 surg$) or (teeth adj4 surg$) or ("third molar$" adj4 surg$) or ("3rd molar$" adj4 surg$)).mp.

4. 1 or 2 or 3

5. MOLAR/

6. TOOTH IMPACTED/

7. ("wisdom tooth" or "wisdom teeth" or (third adj3 molar$) or (3rd adj3 molar$)).mp.

8. "impacted tooth".mp.


10. (5 or 6 or 7 or 8 or 9) and (extract$ or remov$ or surg$).mp.

11. 10 or 4

12. exp ANTIBIOTICS/

13. ANTIBIOTIC PROPHYLAXIS/

14. ERYTHROMYCIN/

15. METRONIDAZOLE/

16. TETRACYCLINES/

17. CLINDAMYCIN/

18. TEICOPLANIN/

19. VANCOMYCIN/

20. FLOXACILIN/

21. GENTAMICINS/

22. CEPHALEXIN/

23. (Antibiot$ or "anti biot$" or anti-biot$).mp.

24. (penicillin$ or erythromycin$ or Metronidazol$ or Cephalosporin$).mp.

25. (antibacterial or anti-bacterial or "anti bacterial"$).mp.

26. (sulphonamide$ or tetracycline$ or clindamycin$ or clindamicin$ or augmentin$ or flagyl$ or amoxyl$ or amoxil$ or co-amox$ or antifungal$ or anti-fungal$ or teicoplanin$ or vancomycin$ or vancomicon$ or flucloxacillin or floxacillin or gentamicin$ or gentamycin$ or cephalaxin$).mp.

27. or/12-26

28. 27 and 11
The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

4 EMBASE via OVID search strategy
1. exp TOOTH EXTRACTION/
2. exodontia.ti,ab.
3. ((tooth adj4 extract$) or (teeth adj4 extract$) or ("third molar$" adj4 extract$) or ("3rd molar$" adj4 extract$) or "dental extract$" or (tooth adj4 remov$) or (teeth adj4 remov$) or ("third molar$" adj4 remov$) or ("third molar$" adj4 remov$) or (tooth adj4 surg$) or (teeth adj4 surg$) or ("third molar$" adj4 surg$) or ("3rd molar$" adj4 surg$)).ti,ab.
4. 1 or 2 or 3
5. exp TOOTH/
6. ("wisdom tooth" or "wisdom teeth" or (third adj3 molar$) or (3rd adj3 molar$)).ti,ab.
7. "impacted tooth".ti,ab.
8. "impacted teeth".ti,ab.
9. or/5-8
10. (extract$ or remov$ or surg$).ti,ab.
11. 9 and 10
12. 4 or 11
13. exp ANTIBIOTIC AGENT/
14. ANTIBIOTIC PROPHYLAXIS/
15. METRONIDAZOLE/
16. (Antibiot$ or "anti biot$" or anti-biot$).ti,ab.
17. (penicillin$ or erythromycin$ or Metronidazol$ or Cephalosporin$).ti,ab.
18. (antibacterial or anti-bacterial or "anti bacterial").ti,ab.
19. (sulphonamide$ or tetracycline$ or clindamycin$ or clindamicin$ or anti-fungal$ or "anti fungal$" or teicoplanin$ or vancomycin$ or vancomycin$ or fluclaxacillin or floxacinil or gentamicin$ or gentamycin$ or cephalexin$).ti,ab.
20. or/13-19
21. 12 and 20

The above subject search was linked to the Cochrane Oral Health Group filter for EMBASE via OVID:
1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

5 LILACS via BIREME search strategy
(Mh Tooth extraction or Mh Extracción Dental or Mh Extração Dentária or (Tw tooth or Tw teeth or Tw molar$ or Tw dental) and (Tw extrac$ or Tw remov$ or Tw surg$)) [Words] and (Mh Anti-Bacterial Agents or Mh Agentes Antibacterianos or Mh Antibiotic Prophylaxis or Profilaxis Antibiótica or Mh Antibioticoprofilaxia or antibiot$ or "anti biot$" or anti-biot$ or antibacte$
0062 Antibiotics to prevent complications following tooth extractions

or anti-bacteria or "anti bacter" or penicillin or erythromycin or metronidazole or cephalosporin or sulphonamide or tetracycline or clindamycin or clindamycin or augmentin or flagyl or azithromycin or co-amoxiclav or teicoplanin or vancomycin or fluclaxacin or clindamycin or gentamicin or gentamycin or cephalaxin

The above subject search was linked to the Brazilian Cochrane Center filter for LILACs via BIREME:

Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw double$ OR Tw doble$ OR Tw duplo$ OR Tw treb$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw masca$)) OR Mh placebos OR Mh placebo$ OR (Tw random$ OR Tw rando$ OR Tw caus$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct ANIMAL AND NOT (Ct HUMAN AND Ct ANIMAL))

**Graphs**

1 - Antibiotic versus placebo

1.1 Local sign of infection

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Pre-operative prophylaxis</td>
<td>Mitchell 1985</td>
<td>-1.25</td>
<td>0.013</td>
<td>16.2%</td>
<td>0.29 (0.11, 0.75)</td>
<td>1986</td>
</tr>
<tr>
<td></td>
<td>Solness 2001</td>
<td>0.1603</td>
<td>0.003</td>
<td>2.0%</td>
<td>1.17 (0.66, 2.75)</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>Hitzmann 2007</td>
<td>-2.39</td>
<td>0.05</td>
<td>25.4%</td>
<td>0.09 (0.01, 0.161)</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Lacaze 2007</td>
<td>-1.0854</td>
<td>0.014</td>
<td>14.0%</td>
<td>0.34 (0.10, 1.13)</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Paspage 2011</td>
<td>-1.7325</td>
<td>0.184</td>
<td>6.3%</td>
<td>0.32 (0.06, 0.32)</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Decres 2011</td>
<td>0</td>
<td>0</td>
<td>3.4%</td>
<td>0.97 (0.00, 13.35)</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Lopes-Castagn 2011</td>
<td>-2.69</td>
<td>0.08</td>
<td>2.4%</td>
<td>0.29 (0.15, 0.64)</td>
<td>2011</td>
</tr>
<tr>
<td>Subtotal (55%) CI</td>
<td></td>
<td></td>
<td>50.3%</td>
<td>0.29 (0.15, 0.64)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Heterogeneity</td>
<td>Tau² = 0.00, Chi² = 2.23, df = 5 (P = 0.81); I² = 0%</td>
<td>Test for overall effect: Z = 3.03 (P = 0.0001)</td>
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</tbody>
</table>

1.1 Post-operative prophylaxis

<table>
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<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio IV, Random, 95% CI</th>
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<tr>
<td>1.2 Pre-operative prophylaxis</td>
<td>Solness 2001</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antero 2005</td>
<td>-1.6062</td>
<td>0.075</td>
<td>18.9%</td>
<td>0.16 (0.06, 0.38)</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>Lacaze 2007</td>
<td>-1.7644</td>
<td>0.078</td>
<td>9.8%</td>
<td>0.17 (0.04, 0.61)</td>
<td>2007</td>
</tr>
<tr>
<td></td>
<td>Lopes-Castagn 2011</td>
<td>-2.70</td>
<td>0.08</td>
<td>3.4%</td>
<td>0.07 (0.00, 1.23)</td>
<td>2011</td>
</tr>
<tr>
<td>Subtotal (55%) CI</td>
<td></td>
<td></td>
<td>32.1%</td>
<td>0.15 (0.07, 0.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity</td>
<td>Tau² = 0.00, Chi² = 0.22, df = 2 (P = 0.89); I² = 0%</td>
<td>Test for overall effect: Z = 4.51 (P = 0.0001)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

1.3 Pre- and post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4 Pre-operative prophylaxis</td>
<td>Hippomen 1990</td>
<td>0.0043</td>
<td>0.0576</td>
<td>17.6%</td>
<td>0.99 (0.40, 2.94)</td>
<td>1990</td>
</tr>
<tr>
<td></td>
<td>Leon Aranda 2001</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Subtotal (55%) CI</td>
<td></td>
<td></td>
<td>17.6%</td>
<td>1.00 (0.40, 2.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity</td>
<td>Tau² = 0.00, Chi² = 0.22, df = 2 (P = 0.89); I² = 0%</td>
<td>Test for overall effect: Z = 0.17 (P = 0.87)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.5 Total (95% CI) | 100.0% | 0.29 (0.16, 0.50) | Test for overall effect: Z = 4.37 (P = 0.0001) |

Favours antibiotic Favours placebo

(1) Administered Intravenously

58 / 61
## 1.2 Dry socket

### 1.2.1 Pre-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rittou 1992</td>
<td>-0.1542</td>
<td>0.5429</td>
<td>15.9%</td>
<td>0.06 [0.30, 2.44]</td>
<td>1992</td>
<td></td>
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</tr>
<tr>
<td>Bergdahl 2004</td>
<td>-0.2460</td>
<td>0.3766</td>
<td>52.8%</td>
<td>0.70 [0.37, 1.64]</td>
<td>2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holperm 2007 (T)</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaczmarzyk 2007</td>
<td>-1.5622</td>
<td>1.1793</td>
<td>3.4%</td>
<td>0.20 [0.02, 2.12]</td>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>López-Casión 2011</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td>2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bezares 2011</td>
<td>0</td>
<td>1.4044</td>
<td>2.4%</td>
<td>1.00 [0.69, 1.56]</td>
<td>2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>54.5%</td>
<td>0.75 [0.42, 1.33]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Q = 1.28$, df = 3 ($\chi^2 = 0.73$), $p = 0.90$%  
Test for overall effect: $Z = 0.99$ ($p = 0.32$)

### 1.2.2 Post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aragó 2005</td>
<td>-1.7234</td>
<td>1.5468</td>
<td>2.0%</td>
<td>0.10 [0.01, 3.70]</td>
<td>2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>López-Casión 2011</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td>2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>2.0%</td>
<td>0.10 [0.01, 3.70]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable  
Test for overall effect: $Z = 1.11$ ($p = 0.27$)

### 1.2.3 Pre- and post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bestetti 1981</td>
<td>-0.6931</td>
<td>0.8818</td>
<td>5.1%</td>
<td>0.50 [0.00, 3.29]</td>
<td>1981</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barclay 1987</td>
<td>-0.6334</td>
<td>0.3703</td>
<td>52.2%</td>
<td>0.92 [0.29, 3.08]</td>
<td>1987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaczmarzyk 2007</td>
<td>-0.6361</td>
<td>0.5446</td>
<td>5.3%</td>
<td>0.50 [0.00, 3.19]</td>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td>43.5%</td>
<td>0.52 [0.27, 0.98]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Q = 0.00$, df = 2 ($\chi^2 = 1.00$), $p = 0.90$%  
Test for overall effect: $Z = 2.01$ ($p = 0.04$)

### 1.3 Pain (dichotomous on 0th-7th day)

#### 1.3.1 Pre-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Total Events</th>
<th>Placebo Events</th>
<th>Total Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slezar 2001</td>
<td>60</td>
<td>44</td>
<td>17</td>
<td>31.7%</td>
<td>0.97 [0.53, 1.76]</td>
<td>2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>31.7%</td>
<td>0.97 [0.53, 1.76]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable  
Test for overall effect: $Z = 0.11$ ($p = 0.91$)

#### 1.3.2 Post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Total Events</th>
<th>Placebo Events</th>
<th>Total Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slezar 2001</td>
<td>47</td>
<td>17</td>
<td>17</td>
<td>29.1%</td>
<td>0.83 [0.44, 1.47]</td>
<td>2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aragó 2005</td>
<td>259</td>
<td>14</td>
<td>231</td>
<td>18.8%</td>
<td>0.25 [0.09, 0.67]</td>
<td>2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>47.9%</td>
<td>0.51 [0.14, 1.82]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.64$, $Q = 3.98$, df = 1 ($\chi^2 = 0.05$), $p = 75$%  
Test for overall effect: $Z = 1.04$ ($p = 0.30$)

#### 1.3.3 Pre- and post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Total Events</th>
<th>Placebo Events</th>
<th>Total Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Year</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bestetti 1981</td>
<td>50</td>
<td>40</td>
<td>20</td>
<td>20.5%</td>
<td>0.36 [0.13, 0.98]</td>
<td>1981</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>20.5%</td>
<td>0.36 [0.13, 0.98]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>50</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.23$, $Q = 7.05$, df = 3 ($\chi^2 = 0.07$), $p = 57$%  
Test for overall effect: $Z = 1.62$ ($p = 0.10$)

Test for subgroup differences: $Q = 3.04$, df = 2 ($\chi^2 = 0.22$), $p = 34.3$%
### 1.4 Pain score (VAS 7th day)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaczmarek 2007</td>
<td>-0.63 (6,915)</td>
<td>7.6%</td>
<td>0.63 (0.9, 12.9)</td>
<td>2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Cedrón 2011</td>
<td>-1.4 (5.081)</td>
<td>17.2%</td>
<td>4.1 (13.0, 4.8)</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borzella 2011</td>
<td>-1.53 (4.838)</td>
<td>15.8%</td>
<td>-1.53 (24, 30)</td>
<td>8.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>41.6%</strong></td>
<td><strong>7.41 (16.18, 13.56)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>41.6%</strong></td>
<td><strong>7.41 (16.18, 13.56)</strong></td>
</tr>
</tbody>
</table>

#### Heterogeneity
- Test for overall effect: $Z = 1.06$ (P = 0.10)
- Test for subgroup differences: $I^2 = 43.4$, df = 2 (P = 0.11), P = 0.04

#### 1.5 Fever (6th 7th day)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Events</th>
<th>Total</th>
<th>Placebo</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacer 2007 (1)</td>
<td>0.60</td>
<td>60</td>
<td>82</td>
<td>0.01</td>
<td>0.08</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteaga 2009 (2)</td>
<td>297</td>
<td>73</td>
<td>20</td>
<td>0.32</td>
<td>0.11</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borrell 2011 (3)</td>
<td>0.40</td>
<td>40</td>
<td>20</td>
<td>0.19</td>
<td>0.17</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siakana 2014 (4)</td>
<td>0.63</td>
<td>63</td>
<td>20</td>
<td>0.37</td>
<td>0.34</td>
<td>0</td>
<td>0.34 (0.06, 1.99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Total
- 458
- 358
- 100%
- 0.34 (0.06, 1.99)

#### Heterogeneity
- Test for overall effect: $Z = 0.20$ (P = 0.23)
- Test for subgroup differences: $I^2 = 0.00$, df = 1 (P = 0.88), P = 0.00

#### 1.6 Swelling (7th day)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Events</th>
<th>Total</th>
<th>Placebo</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaczmarek 2007</td>
<td>2.04</td>
<td>44</td>
<td>17</td>
<td>29.2%</td>
<td>1.16</td>
<td>0.61, 2.21</td>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Cedrón 2011</td>
<td>0.31</td>
<td>31</td>
<td>14</td>
<td>6.3%</td>
<td>0.03</td>
<td>0.05, 2.21</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>52.2%</strong></td>
<td><strong>1.13 (0.69, 1.83)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Total
- 40
- 15
- 100%
- 0.43 (0.06, 0.63)

#### Heterogeneity
- Test for overall effect: $Z = 1.30$ (P = 0.09)
- Test for subgroup differences: $I^2 = 1.11$, df = 2 (P = 0.57), P = 0.00

#### 1.2 Post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Events</th>
<th>Total</th>
<th>Placebo</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaczmarek 2007</td>
<td>0.04</td>
<td>28</td>
<td>2</td>
<td>13</td>
<td>0.39</td>
<td>0.32, 5.99</td>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Cedrón 2011</td>
<td>0.08</td>
<td>44</td>
<td>20</td>
<td>18.6%</td>
<td>0.08</td>
<td>0.04, 2.21</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>24.9%</strong></td>
<td><strong>1.07 (0.53, 2.17)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Total
- 10
- 8
- 100%
- 0.18 (0.05)

#### Heterogeneity
- Not applicable

#### 1.3 Pre- and post-operative prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Events</th>
<th>Total</th>
<th>Placebo</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaczmarek 2007</td>
<td>0.00</td>
<td>28</td>
<td>2</td>
<td>13</td>
<td>0.39</td>
<td>0.32, 5.99</td>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Cedrón 2011</td>
<td>0.00</td>
<td>44</td>
<td>20</td>
<td>18.6%</td>
<td>0.08</td>
<td>0.04, 2.21</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>24.9%</strong></td>
<td><strong>1.07 (0.53, 2.17)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Total
- 10
- 8
- 100%
- 0.18 (0.05)

#### Heterogeneity
- Test for overall effect: $Z = 1.30$ (P = 0.09)
- Test for subgroup differences: $I^2 = 1.11$, df = 2 (P = 0.57), P = 0.00
1.7 Trismus (7th day)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Kaczmarek 2007 (1)</td>
<td>7</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Pasupathy 2011 (2)</td>
<td>5</td>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>Kaczmarek 2007 (3)</td>
<td>6</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>119</strong></td>
<td><strong>56</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 18

Heterogeneity: Tau² = 0.04, Chi² = 0.44, df = 2 (P = 0.80), I² = 0%

Test for overall effect: Z = 0.47 (P = 0.64)

(1) Preoperative antibiotics
(2) Pre-operative antibiotics
(3) Pre- and post-operative antibiotics

1.8 Adverse effects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Kaczmarek 2007 (1)</td>
<td>0</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Lakska 2007 (2)</td>
<td>1</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td>Arbeagalia 2005 (3)</td>
<td>14</td>
<td>259</td>
<td>2</td>
</tr>
<tr>
<td>Laxso 2007 (4)</td>
<td>10</td>
<td>83</td>
<td>2</td>
</tr>
<tr>
<td>Byrdet 1981 (5)</td>
<td>0</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Barclay 1987 (6)</td>
<td>20</td>
<td>45</td>
<td>14</td>
</tr>
<tr>
<td>Kaczmarek 2007 (7)</td>
<td>3</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>540</strong></td>
<td><strong>390</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 48

Heterogeneity: Tau² = 0.07, Chi² = 4.60, df = 4 (P = 0.34), I² = 11%

Test for overall effect: Z = 2.27 (P = 0.02)

(1) Pre-operative antibiotics
(2) Pre-operative antibiotics
(3) Post-operative antibiotics
(4) Post-operative antibiotics
(5) Pre- and post-operative antibiotics
(6) Pre- and post-operative antibiotics
(7) Pre- and post-operative antibiotics