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Antibiotics to prevent complications following tooth extractions (Review)

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[Intervention Review]

Antibiotics to prevent complications following tooth extractions

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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.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotic 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

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antibiotic				
Local sign of infection Follow-up: mean 7 days	**118 per 1000**	**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	**69 per 1000**	**43 per 1000** (28 to 65)	**RR 0.62** (0.41 to 0.95)	1429 (9 studies)	⊕⊕⊕◯ **moderate**[2]	
Pain (dichotomous on 6-7th day) Follow-up: mean 6.5 days	**126 per 1000**	**76 per 1000** (40 to 140)	**RR 0.60** (0.32 to 1.11)	675 (3 studies)	⊕⊕◯◯ **low**[3,4]	
Pain score (VAS 7th day) Scale from: 1 to 100. Follow-up: mean 7 days	Mean pain score (VAS) in placebo groups was 15	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	**39 per 1000**	**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	**307 per 1000**	**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	**49 per 1000**	**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.

[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.

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; Karki 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)
- LILACS via BIREME (1982 to 25 January 2012) (Appendix 5).

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.*

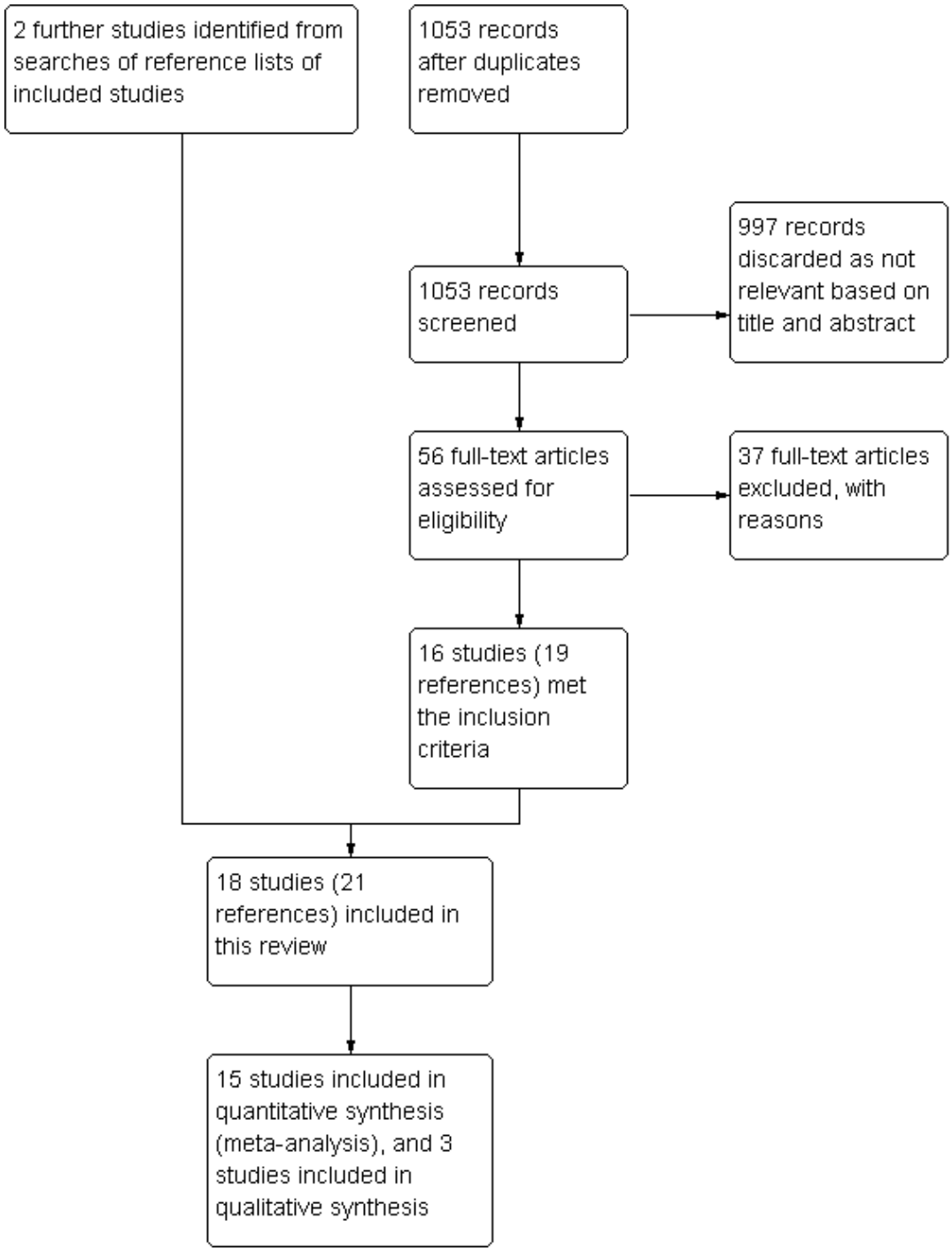
The handsearching was done as part of the Cochrane Worldwide Handsearching Programme. *See* the Cochrane Masterlist of Journals for details of the volumes and issues that have been searched to date.
Reference lists of all eligible trials and of existing reviews were checked for additional studies. The 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).

Figure 1. Study flow diagram.



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; Halpern 2007; Bezerra 2011), eight studies had three treatment arms (Bystedt 1981; Kaziro 1984; Happonen 1990; Sekhar 2001; Kaczmarzyk 2007; Lacasa 2007; López-Cedrún 2011; Pasupathy 2011) and one study (Bystedt 1980) had three subtrials, each with two or three arms. The data from these separately randomised subtrials were then combined and were unsuitable for inclusion in meta-analysis.

Characteristics of participants

The 18 included studies randomised more than 2456 participants to either an antibiotic or placebo. (One of the included trials (MacGregor 1980) used an unusual design and did not state exactly how many participants were randomised and analysed.) All of the included studies compared at least one antibiotic regimen with placebo in patients undergoing dental extraction. Fifteen trials described extraction procedures done using local anaesthesia, two trials used general anaesthesia (MacGregor 1980; Halpern 2007), and in one trial the method of anaesthesia was not stated (Mitchell 1986).

In all of the included studies the participants underwent extraction of third molars only, and in the majority of the studies only mandibular third molars were included (Bystedt 1980; MacGregor 1980; Bystedt 1981; Mitchell 1986; Barclay 1987; Happonen 1990; Ritzau 1992; Sekhar 2001; Bergdahl 2004; Arteagoitia 2005; 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 caries 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.
- Antibiotics given both pre- and post-operatively: Bystedt 1980; Bystedt 1981; Barclay 1987; Happonen 1990; Leon Arcila 2001; Kaczmarzyk 2007; Lacasa 2007.

The antibiotics selected for use in the studies were amoxicillin (Leon Arcila 2001; Bezerra 2011; López-Cedrún 2011; Pasupathy 2011), a combination of amoxicillin/clavulanate (Arteagoitia 2005; Lacasa 2007), azidocillin (Bystedt 1980; Bystedt 1981), clindamycin (Bystedt 1980; Halpern 2007; Kaczmarzyk 2007), doxycycline (Bystedt 1980), erythromycin (Bystedt 1980), metronidazole (Kaziro 1984; Barclay 1987; Ritzau 1992; Sekhar 2001; Bergdahl 2004; Pasupathy 2011), penicillin (MacGregor 1980; Halpern 2007), phenoxymethylpenicillin (Happonen 1990) and tinidazole (Mitchell 1986; Happonen 1990).

Details of specific dosage regimens are recorded in the Characteristics of included studies 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.

Fever in the first 24 hours was evaluated by Bystedt 1981; Happonen 1990; Arteagoitia 2005; Kaczmarzyk 2007 and Lacasa 2007, and three studies (Bystedt 1981; Kaczmarzyk 2007; Lacasa 2007) included swelling among outcomes.

Four studies investigated trismus among outcomes (Bystedt 1981; Happonen 1990; Kaczmarzyk 2007; Lacasa 2007), where Happonen 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; Krekmanov 1980; Krekmanov 1981; Krekmanov 1986; Lombardia Garcia 1987; Mitchell 1987; Abu-Mowais 1990; Lyall 1991; Samsudin 1994; Walkow 1995; Monaco 1999; Yoshii 2002; Delilbasi 2004; Foy 2004; Poeschl 2004; Graziani 2005; Sulejmanagić 2005; Uluibau 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 (Siddiqi 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

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; Happonen 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; López-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

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

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; Kaczmarzyk 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

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; Kaczmarzyk 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; Arteagoitia 2005; Lacasa 2007; Pasupathy 2011) were assessed as being at high risk of reporting bias. The trial by Arteagoitia 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; Arteagoitia 2005; Kaczmarzyk 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; Arteagoitia 2005; Kaczmarzyk 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.

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

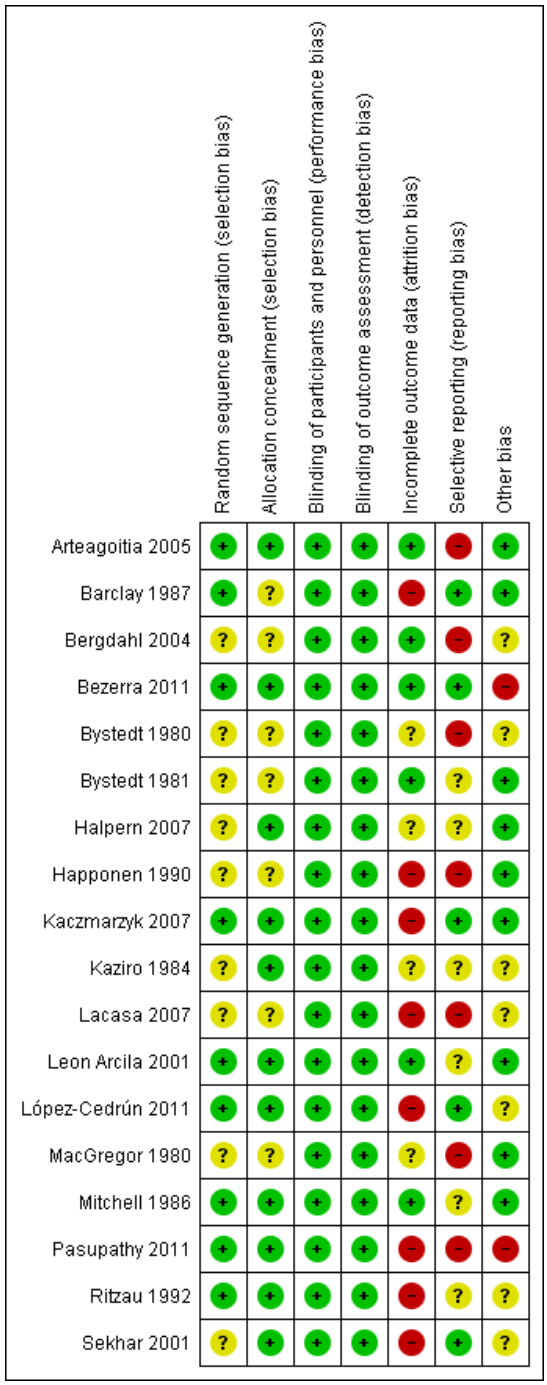
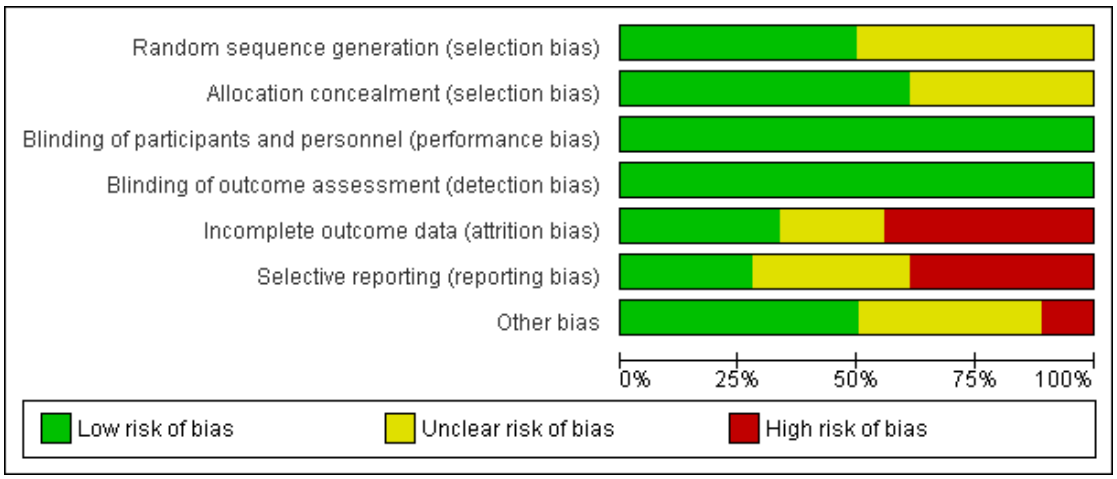


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic compared to placebo for preventing infectious complications after tooth extraction

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; Kaczmarzyk 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; Kaczmarzyk 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 (Bystedt 1981) (Analysis 1.3, Subgroup 1.3.3).
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. Statisitical heterogeneity was substantial (I^2 = 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 for the main comparison).

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.

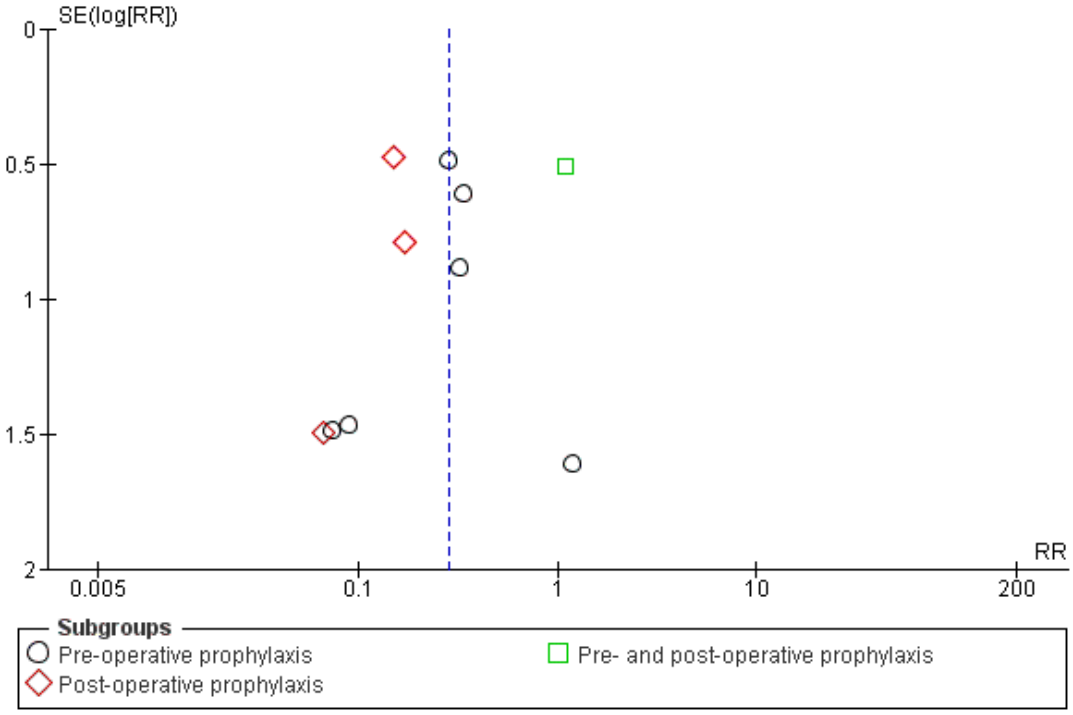
The quality of the body of evidence included in this review was evaluated using the GRADE system in Summary of findings for the main comparison. For most outcomes the quality of the evidence was moderate, because of high or unclear risk of bias in the studies. For the outcomes of fever and presence of 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).

Figure 4. Funnel plot of comparison: 1 Antibiotic versus placebo, outcome: 1.1 Local sign of infection.



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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

MacGregor 1980

Methods	Study design: RCT where participants paired based on number of lower molars extracted Conducted in: Leeds, England. 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.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (both participants and surgeons).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind (both participants and surgeons).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of patients allocated to treatment and assessed on day 4 not stated

MacGregor 1980 (*Continued*)

Selective reporting (reporting bias)	High risk	Planned report of pain swelling and trismus presented only in graphs. No estimates per group given
Other bias	Low risk	No other sources of bias identified.

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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned at random". Method of sequence generation not described

Bystedt 1980 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers of patients allocated to antibiotic or placebo not explicitly stated for each of the subtrials and numbers evaluated not stated for each subtrial for each outcome
Selective reporting (reporting bias)	High risk	All planned outcomes reported, but not for each randomised treatment group, and no estimates of variance given for pain
Other bias	Unclear risk	No description of characteristics of patients by randomised group at baseline

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: phenoxmethylpenicillin 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

Bystedt 1981 (*Continued*)

	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, II 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned at random". Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data. All randomised participants included in result analysis
Selective reporting (reporting bias)	Unclear risk	Data for swelling and trismus not reported, only comment that there was no difference
Other bias	Low risk	No other sources of bias identified.

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 4^{th} and 8^{th} post-op day, wound breakdown.
Notes	Data presented in graphs only. Extractions were done by 1 of 6 surgeons blinded to allocated treatment

Risk of bias

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) All outcomes	Low risk	Quote: "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	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

Kaziro 1984 (*Continued*)

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "allocated in accordance with a pre-determined randomisation code during pre-operative assessment"
Allocation concealment (selection bias)	Low risk	Quote: "drugs were individually packaged and allocated" -assumed allocation occurred at the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind".

Mitchell 1986 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in the outcome assessment
Selective reporting (reporting bias)	Unclear risk	Infection per socket and per patient reported. Pain swelling and trismus not reported
Other bias	Low risk	No other sources of bias identified.

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	

Barclay 1987 (*Continued*)

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

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 phenoxmethylpenicillin 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

Risk of bias

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) All outcomes	Low risk	Quote: "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	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

Happonen 1990 (*Continued*)

Other bias	Low risk	No other sources of bias identified.

Ritzau 1992

Methods	Study design: RCT. Conducted in: Denmark. Number of centres: 2. Recruitment period: between October 1987 and November 1988. 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random sequence ... generated by a computerized program"
Allocation concealment (selection bias)	Low risk	Quote: "the code was unknown to the investigators until the termination of collection of clinical data"

Ritzau 1992 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" and "metronidazole and placebo were manufactured in the shape of pills of identical size, shape, weight, and colour, packed and code numbered"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" and "metronidazole and placebo were manufactured in the shape of pills of identical size, shape, weight, and colour, packed and code numbered"
Incomplete outcome data (attrition bias) All outcomes	High risk	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
Selective reporting (reporting bias)	Unclear risk	Methods section states that planned outcome was alveolitis sicca dolorosa (ASD) and this was reported, but other clinically important outcomes were not reported
Other bias	Unclear risk	13% loss of participants post-randomisation and no baseline characteristics reported for each group. Biases possible

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 </= 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

Leon Arcila 2001 (*Continued*)

	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

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

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned using prepared randomizations in sealed envelopes". Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	Allocation concealed in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind, but dosing schedule different in each group. Outcome assessor was blinded to allocated treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double blind, but dosing schedule different in each group. Outcome assessor was blinded to allocated treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	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
Selective reporting (reporting bias)	Low risk	All planned outcomes reported.

Sekhar 2001 (*Continued*)

Other bias	Unclear risk	Percentage of patients in 2x daily metronidazole group who had bone removed appears to be significantly lower compared to other groups

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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "a randomised trial". Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind".

Bergdahl 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only "one patient had to be withdrawn because he had taken an oral antibiotic for other reasons two days after operation"
Selective reporting (reporting bias)	High risk	Pain, bad odour or taste as assessed by patients were not reported
Other bias	Unclear risk	Short duration of follow-up (4 days), unclear whether patients with acute pericoronitis prior to trial were treated with antibiotics

Arteagoitia 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 in-

	flammation (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

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

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

Bias	Authors' judgement	Support for judgement

Halpern 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". Method of sequence generation not described
Allocation concealment (selection bias)	Low risk	Quote: "Consecutively numbered, double-sealed envelopes were prepared containing the treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind. The surgeon and study subject were blinded to the true nature of the contents of the syringe"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind. The surgeon and study subject were blinded to the true nature of the contents of the syringe"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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
Selective reporting (reporting bias)	Unclear risk	Surgical site infections and acute osteitis planned and reported. No report of pain swelling or trismus
Other bias	Low risk	No other sources of bias identified.

Kaczmarzyk 2007

Methods	Study design: 3-arm RCT. Conducted in: Poland. Number of centres: 1. Recruitment period: between January 2005 and April 2006. 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

Kaczmarzyk 2007 (*Continued*)

	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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "group assignment for one patient, determined in advance by a random number table"
Allocation concealment (selection bias)	Low risk	Quote: "One hundred opaque and sequentially numbered envelopes were used for the concealment of allocation to trial groups"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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"
Incomplete outcome data (attrition bias) All outcomes	High risk	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

Kaczmarzyk 2007 (*Continued*)

		for the dichotomous outcomes incomplete outcome data could have resulted in bias
Selective reporting (reporting bias)	Low risk	Planned outcomes of post-operative inflammation (swelling, lymphadenopathy, trismus), pain, body temperature, and alveolar osteitis reported
Other bias	Low risk	No other sources of bias identified.

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 (NolotilTM 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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	High risk	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
Selective reporting (reporting bias)	High risk	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
Other bias	Unclear risk	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

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 breast-feeding, 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 dipyrone (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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	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
Allocation concealment (selection bias)	Low risk	Unclear who performed the coin toss and how the result was communicated to the surgeon. However bias unlikely to result from this design

Bezerra 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind - neither patient nor surgeon knew which treatment was given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind - neither patient nor surgeon knew which treatment was given
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/36 patients were not included in analysis. Due to low number and cross-over design, attrition bias is unlikely
Selective reporting (reporting bias)	Low risk	Duration of surgery, inflammatory/infectious events, pain scores, edema, maximum mouth opening, swelling of soft tissues, alveolitis reported
Other bias	High risk	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

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pharmacist held the randomisation code and the drug code (a random alpha numeric code)
Allocation concealment (selection bias)	Low risk	Quote: "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"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	High risk	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
Selective reporting (reporting bias)	Low risk	All planned outcomes reported.
Other bias	Unclear risk	Statistically significant difference in mean operating time between pre- and post-op antibiotic groups

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization table was prepared using a software program and a random allocating number was given to each patient"
Allocation concealment (selection bias)	Low risk	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"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple blind - neither the patient nor the surgeon nor the outcome evaluator were aware of the allocated treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple blind - neither the patient nor the surgeon nor the outcome evaluator were aware of the allocated treatment

Pasupathy 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	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
Selective reporting (reporting bias)	High risk	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.
Other bias	High risk	Trial is very clearly underpowered and this is likely to bias results towards the null hypothesis of no difference between interventions

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

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

Study	Reason for exclusion
Abu-Mowais 1990	Not double blind.
Ataoglu 2008	Not double blind.
Bargnesi 1985	Study of antibiotics used in conjunction with a range of small dental surgical procedures including but not limited to tooth extractions
Curran 1974	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	Washout period 4 weeks (translated from Spanish).
Delilbasi 2004	Not double blind.
Foy 2004	Not double blind.
Fridrich 1990	Not randomised or quasi-randomised.
Graziani 2005	Not double blind.

(*Continued*)

Grossi 2007	Not double blind.
Head 1984	Bacteraemia outcomes only.
Krekmanov 1980	Not double blind.
Krekmanov 1981	Not double blind.
Krekmanov 1986	Not double blind.
Laird 1972	This study compares 2 antibiotic regimens.
Limeres 2009	This study compares 2 antibiotic regimens.
Lombardia Garcia 1987	Not double blind.
Lopes 2011	Not double blind.
Luaces-Rey 2010	This study compares 2 antibiotic regimens.
Lyall 1991	Not double blind.
MacGregor 1973	Topical antibiotic.
Mitchell 1987	No blinding described.
Monaco 1999	Not double blind.
Monaco 2009	Not double blind.
Olusanya 2011	This study compares 2 antibiotic regimens.
Osborn 1979	From translator: "it is clear that this study is double blinded but it is unclear how participants were allocated to treatment groups. Random not mentioned"
Poeschl 2004	Not double blind.
Reekie 2006	Topical antibiotic therapy.
Rood 1979	Not randomised.
Samsudin 1994	Not randomised or quasi and not double blind.
Siddiqi 2010	Washout period only 3 weeks (communication from author).
Stavropoulos 2006	Authors considered only topical antibiotic therapy.
Sulejmanagić 2005	Not randomised or quasi-randomised and not double blind.

(*Continued*)

Swanson 1989	Topical antibiotic therapy.
Uluibau 2005	Not double blind.
Walkow 1995	Abstract only, no mention of blinding and no subsequent trial report found
Yoshii 2002	No blinding described.

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

Arteagoitia 2011

Trial name or title	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)
Methods	Double-blind placebo-controlled trial.
Participants	Patients with bony impactions of mandibular third molars undergoing extraction under locoregional anaesthesia
Interventions	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
Outcomes	Infection.
Starting date	26 June 2009.
Contact information	Atreagoitia M Stomatology Department, University of the Basque Country, Leioa, Spain
Notes	

DATA AND ANALYSES

Comparison 1. Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local sign of infection	10		Risk Ratio (Random, 95% CI)	0.29 [0.16, 0.50]
1.1 Pre-operative prophylaxis	7		Risk Ratio (Random, 95% CI)	0.29 [0.15, 0.54]
1.2 Post-operative prophylaxis	4		Risk Ratio (Random, 95% CI)	0.15 [0.07, 0.31]
1.3 Pre- and post-operative prophylaxis	2		Risk Ratio (Random, 95% CI)	1.09 [0.40, 2.94]
2 Dry socket	9		Risk Ratio (Random, 95% CI)	0.62 [0.41, 0.95]
2.1 Pre-operative prophylaxis	6		Risk Ratio (Random, 95% CI)	0.75 [0.42, 1.33]
2.2 Post-operative prophylaxis	2		Risk Ratio (Random, 95% CI)	0.18 [0.01, 3.70]
2.3 Pre- and post-operative prophylaxis	3		Risk Ratio (Random, 95% CI)	0.52 [0.27, 0.99]
3 Pain (dichotomous on 6th-7th day)	3	675	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.32, 1.11]
3.1 Pre-operative prophylaxis	1	61	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.53, 1.76]
3.2 Post-operative prophylaxis	2	554	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.14, 1.82]
3.3 Pre- and post-operative prophylaxis	1	60	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.13, 0.98]
4 Pain score (VAS 7th day)	4		Mean Difference (Random, 95% CI)	-8.17 [-11.90, -4.45]
4.1 Pre-operative prophylaxis	3		Mean Difference (Random, 95% CI)	-7.41 [-16.18, 1.36]
4.2 Pre- and post-operative prophylaxis	3		Mean Difference (Random, 95% CI)	-8.30 [-13.18, -3.42]
5 Fever (6th-7th day)	4	816	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.06, 1.99]
6 Swelling (7th day)	3	334	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.65, 1.30]
6.1 Pre-operative prophylaxis	3	165	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.69, 1.83]
6.2 Post-operative prophylaxis	1	64	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.24, 1.02]
6.3 Pre- and post-operative prophylaxis	2	105	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.53, 2.17]
7 Trismus (7th day)	2	175	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.71]
8 Adverse effects	5	930	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.10, 3.59]

ADDITIONAL TABLES

Table 1. Studies of reasons for tooth extraction

Author	Country	% for caries	% for periodontitis
Da'ameh 2006	Afghanistan	59.2	35.3
Akhter 2008	Bangladesh	67.5	18.5
Jovino-Silveira 2005	Brazil	63.3	13.1

Table 1. Studies of reasons for tooth extraction (*Continued*)

Chrysanthakopoulos 2011	Greece	45.6	32.1
Anand 2010	India	44.6	33.2
Aida 2009	Japan	43.6	37.1
Baqain 2007	Jordan	63.8	22.9
Al-Shammari 2006	Kuwait	43.7	37.4
Byahatti 2011	Libya	55.9	34.4
Danielson 2011	Nigeria	32.6	45
Trovik 2000	Norway	40	24
Chestnutt 2000	Scotland	51	21
McCaul 2001	Scotland	54.7	16.7
Lesolang 2009	South Africa	47.9	22.6
Richards 2005	Wales	59	29.1

Table 2. Kaziro 1984 outcome data (from graphs)

	Antibiotic group	**Placebo group**
Infection- wound breakdown	5%	27%
Pain - Day 8	60% pain free	22% pain free
Swelling - Day 8	80% minimal swelling	66% minimal swelling

Table 3. Raw outcome data - Local signs of infection

Infection (%)		
	Antibiotic	Placebo
Pre-operative prophylaxis		
Mitchell 1986	4/25 (16%)	14/25 (56%)
Sekhar 2001	1/44 (2%)	0/17

Table 3. Raw outcome data - Local signs of infection (*Continued*)

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

Table 4. Raw outcome data - Dry socket

Dry socket		
	Antibiotic	Placebo
Pre-operative prophylaxis		
Ritzau 1992	6/135 (4.4%)	7/135 (5.2%)
Bergdahl 2004*	10/59 (16.9%)	13/60 (21.6%)
Kaczmarzyk 2007	1/31 (3.2%)	2/13 (15.4%)
Halpern 2007	0/59	0/59
Bezerra 2011	0/34	0/34

Table 4. Raw outcome data - Dry socket (*Continued*)

López-Cedrún 2011	0/39	0/20
Post-operative prophylaxis		
Arteagoitia 2005	0/259	2/231 (0.9%)
López-Cedrún 2011	0/44	0/20
Pre- and post-operative prophylaxis		
Bystedt 1981	2/40 (5%)	2/20 (1%)
Barclay 1987*	8/45 (17.8%)	17/50 (34%)
Kaczmarzyk 2007	2/28 (7.1%)	2/14 (14.3%)
Mean incidence dry socket per group	29/773 (3.8%)	45/656 (6.9%)

* Participants in both these studies had some pericoronitis in the recent past and were therefore at higher risk of infection.

Table 5. Raw outcome data - VAS pain scores

Mean (SD) VAS pain scores		
	Antibiotic	Placebo
Pre-operative prophylaxis		
Kaczmarzyk 2007	9.51 (28.83) n = 31	10.14 (19.54) n = 13
López-Cedrún 2011	10.92 (16.89) n = 39	5.75 (12.26) n = 20
Bezerra 2011	15.9 (23.6) n = 34	31.2 (29.5) n = 34
Pre- and post-operative prophylaxis		
Barclay 1987*	6.33 (12.58) n = 45	14.79 (23.09) n = 50
Kaczmarzyk 2007	3.92 (9.79) n = 28	10.14 (19.54) n = 14

Table 5. Raw outcome data - VAS pain scores (*Continued*)

López-Cedrún 2011	15.02 (23.44) n = 44	5.75 (12.26) n = 20

*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.

FEEDBACK

Comment from Dr John Curran, 11 February 2013

Summary

Very good review. Unfortunately the difficulty of designing a randomised trial still exists partly due to ethical requirements and logistics -e.g. with third molar surgery assessment of difficulty and surgical ability are hard to measure. Post-operative assessment also needs to be done sooner than the 7 days used in the review. Little has changed in but I believe that in patient age groups most prevalent in the North America context the incidence of infection is even lower than reported -i.e. antibiotic usage should be highly selective.

Reply

Thank you for your interest in our work and for your comment.
I absolutely agree that real incidence of infectious complications in a population similar to study groups is likely to be lower, and for that reason we did not really recommend for regular antibiotic prophylaxis. Unfortunately because of the lack of studies on patients at higher risk, no evidence is available on cases for which antibiotic prophylaxis is (anecdotally) recommended.

Contributors

Summary: John Curran.
Reply: Giovanni Lodi.

WHAT'S NEW

Date	Event	Description
24 April 2013	Feedback has been incorporated	Comment from Dr John Curran.

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.

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Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis [adverse effects]; Anti-Bacterial Agents [adverse effects; *therapeutic use]; Controlled Clinical Trials as Topic; Dry Socket [prevention & control]; Molar, Third [*surgery]; Pain, Postoperative [prevention & control]; Tooth Extraction [*adverse effects]; Tooth, Impacted [*surgery]

MeSH check words

Humans