Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery (Review)

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TABLE OF CONTENTS

[Intervention Review]

Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

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ABSTRACT

Background

Orthognathic surgery (OS) is a term that refers to many elective surgical techniques to correct facial deformity; the associated malocclusion and functional disorders related to the stomatognathic system. Whilst such surgery is classed as "clean-contaminated", the usefulness of and the most appropriate regimen for antibiotic prophylaxis in these patients are still debated.

Objectives

To assess the effects of antibiotic prophylaxis for preventing surgical site infection (SSI) in people undergoing orthognathic surgery.

Search methods

In June 2014, we searched the Cochrane Wounds Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE; and EBSCO CINAHL. We also searched Google Scholar and performed manual searches in journals relevant to the topic, conference proceedings and lists of references of potentially included articles. We did not restrict the search and study selection with respect to language, date of publication or study setting.

Selection criteria

We included randomised controlled trials (RCTs) involving people undergoing orthognathic surgery comparing one regimen of antibiotic prophylaxis with any other regimen or placebo. The primary outcome was SSI, and secondary outcomes were systemic infections, adverse events, duration of hospital stay and health-related quality of life. Two review authors screened articles independently.

Data collection and analysis

Data were abstracted independently by two review authors, and agreement was checked. Risk of bias was assessed using the Cochrane risk of bias tool. Antibiotic regimens were classified as preoperative (one dose before surgery), short-term (before or during surgery and/or during the same day of surgery) and long-term (before or during surgery and longer than one day after surgery) antibiotic prophylaxis. Random-effects meta-analyses using inverse variance methods were undertaken when possible. We report risk ratios (RRs) and their corresponding 95% confidence intervals (CIs).

Main results

A total of 11 trials were included in this review. Most of the studies had an unclear risk of bias prompting us to downgrade the quality of evidence for our outcomes. Seven of these trials provided evidence for the main comparison and the primary outcome and these were pooled. Overall, long-term antibiotic prophylaxis probably reduces the risk of SSI (plausible effects range between a 76% to a 0.26% relative reduction in SSI with long-term antibiotic prophylaxis) (472 participants; RR 0.42, 95% CI 0.24 to 0.74; moderate-quality evidence). There is uncertainty surrounding the relative effects of short-term antibiotics compared with a single dose (220 participants; RR 0.34, 95% CI 0.09 to 1.22; low-quality evidence). No reports described adverse effects associated with the drugs in those trials that reported in this outcome. None of these trials assessed or reported data regarding other outcomes, and information was insufficient to show whether a specific antibiotic is better than another.

Authors' conclusions

For people undergoing orthognathic surgery, long term antibiotic prophylaxis decreases the risk of SSI compared with short-term antibiotic prophylaxis and the is uncertainty of whether short-term antibiotic prophylaxis decreases SSi risk relative to a single pre-operative dose of prophylactic antibiotics.

PLAIN LANGUAGE SUMMARY

Antibiotics for preventing infection after jaw surgery

Many people undergo surgery of the jaws each year to correct malformations. Whilst a risk of infection following surgery has been noted, no agreement has been reached regarding how useful antibiotics are for infection prevention and what type and dose of antibiotic should be used.

We conducted a comprehensive search for studies on this topic. We collected data from all studies addressing this question and summarised them to determine whether antibiotics could prevent infection after surgery, whether this treatment has any adverse effects, whether it reduces the number of days that patients need to be in the hospital and whether it improves overall health status.

We found 11 studies. Overall, long-term antibiotics reduce the risk of SSI, and there is uncertainty regarding the effects of receiving one dose of antibiotics preoperatively versus short term antibiotics. There was no investigation of side effects of antibiotics in these studies, but in the studies where side effects were investigated, no side effects were found. None of the other effects of interest to clinicians or patients were measured in the studies, and information was insufficient to show whether any single antibiotic is better than any other.

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

Short-term antibiotic prophylaxis compared with long-term antibiotic prophylaxis in patients undergoing orthognathic surgery

Patient or population: patients undergoing orthognathic surgery
Intervention: short-term antibiotic prophylaxis
Comparison: long-term antibiotic prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Short-term	Long-term				
Surgical site infection Follow-up: 2 to 36 weeks	168 per 1000[a]	71 per 1000 (41 to 125)	**RR 0.42** (0.24 to 0.74)	472 (7 studies)	⊕⊕⊕◯ moderate[b]	This outcome was measured using different definitions. We accepted all authors' definitions
Systemic infection	Not reported				-	This outcome was not reported in any of the trials
Adverse events	Not reported				-	This outcome was not reported in any of the trials
Duration of hospital stay	Not reported				-	This outcome was not reported in any of the trials
Health-related quality of life	Not reported				-	This outcome was not reported in any of the trials

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

[a] Assumed risk based on control arms of included trials.
[b] Most of these trials were judged to have unclear risk of bias in the domains of allocation concealment and blinding.

BACKGROUND

Description of the condition

Orthognathic surgery (OS) is the surgical correction of a deformity of the jaw (ortho meaning 'straight,' and gnath meaning 'jaws'). It is a general term that includes many elective surgical techniques to correct facial deformity, the associated malocclusion and functional disorders related to the stomatognathic system (set of anatomical features in the head that focus on the mouth, functions of which include chewing, breathing, speaking and swallowing) (Obwegeser 2007). The first orthognathic surgery was performed In 1847 by Hullihen (Hullihen 1849). This surgery involves carrying out total, or partial, osteotomies (cutting of bone) on the maxilla, the mandible and other facial bones to position the skeleton correctly and to correct functional problems (Moore 2001).

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS 2008), conditions that indicate the need for orthognathic surgery include difficulty chewing or biting food; difficulty swallowing; chronic jaw or jaw joint (TMJ) pain and headache; excessive wear of the teeth; open bite; unbalanced facial appearance from the front or side; facial injury or birth defects; receding chin; protruding jaw; inability to make the lips meet without straining; chronic mouth breathing and dry mouth; and serious breathing problems while sleeping (sleep apnoea). The consequences of these conditions depend on the degree of deformity and can vary from very mild to severe. Dentofacial deformities may provoke functional problems such as physical pain, physical disability, cosmetic dissatisfaction and difficulties with speaking, breathing and chewing. Patients can improve significantly after orthognathic surgery with regard to their psychological discomfort, social disability and self-confidence, as when functional limitations decrease, quality of life is improved (Choi 2010; Lee 2008; Rustemeyer 2011).

Although few data are available to estimate the number of OS procedures performed each year around the world, statistics from oral and maxillofacial surgery training programs reported to the American Dental Association and the American Association of Oral and Maxillofacial Surgeons show a gradual increase in the number of these procedures performed between 1996 and 2007. In 2007 it was reported that a total of 8755 OS procedures were performed in the United States of America (Sullivan 2011). The average age of patients undergoing orthognathic surgery in 2008 was 26.7 years, and a great majority of these patients were between 15 and 30 years of age (Venugoplan 2012). Female patients accounted for 56.2% of those undergoing the procedure (Venugoplan 2012). Whites constituted 71.9%, blacks 4.9%, Hispanics 12.6%, Asian/Pacific Islanders 5.6%, Native Americans 0.4% and other groups 4.6%, respectively (Venugoplan 2012).

Specific postoperative complications related to orthognathic surgery include haemorrhage, temporary or permanent sensory and motor problems affecting the face and mouth (V2 and V3 nerve dysfunction), deviation of the nasal septum, bone infection (osteomyelitis), connection of the mouth to a sinus cavity (oroantral fistula), sinusitis and loss or degradation of results obtained by surgery (postoperative relapse) (Chow 2007). In addition, patients can suffer more general surgical complications, such as pain, swelling and surgical site infection (SSI).

SSIs are divided into incisional SSIs and organ/space SSIs (Horan 1992). Incisional SSIs are further classified into those involving only the skin and subcutaneous tissue, and those involving deep soft tissues of the incision (called deep incisional SSIs (e.g. fascial and muscle layers)). Organ/space SSIs involve any part of the anatomy (e.g. organs, spaces) other than the incision that was opened or manipulated during the operative procedure (Horan 1992). The SSIs seen with OS are organ/space infections.

The proportion of patients developing SSI after OS is estimated to be about 7% (Alpha 2006; Barrier 2009; Chow 2007). The pathogens most commonly associated with SSI after OS are anaerobic bacteria, which have been observed in 50% of pus samples of SSI after OS, and streptococci, which have been observed in 43% of cases (Chow 2007). Studies show that risk factors that may be associated with a higher incidence of SSI after OS include longer surgery; short-term antibiotic prophylaxis; extraction of a third molar during surgery; greater number of osteotomies performed; older age; smoking; poor oral hygiene; and a compromised immune system (Alpha 2006; Barrier 2009; Cheynet 2001; Chow 2007; Fridrich 1999; Laskin 2003; Manor 1999; Theodossy 2006). SSI following orthognathic surgery can cause localised pain, swelling, surface redness (erythema), pus formation and restricted movement. Throughout the body, these infections cause fever, swollen lymph nodes (lymphadenopathy), general discomfort, toxic reactions and an elevated white blood cell count (Topazian 2002).

A multi-centre, retrospective study assessed the cost of and factors influencing orthognathic surgery in a single region in the UK. The average total treatment cost for people who experienced complications after orthognathic surgery, including infected bone plates, was EUR 6815.94, whereas the cost for those who had no complications was EUR 5962.61. Average ward stay costs were EUR 1421.49 and EUR 1295.64, respectively (Kumar 2008).

Description of the intervention

Surgical antibiotic prophylaxis is defined as the use of antibiotics to prevent infection at a surgical site (Munckhof 2005).

The original experiments to evaluate efficacy, which were performed 40 years ago in animal models, concluded that the most effective period for prophylaxis is within three hours of the time at which bacteria gain access to the tissues (Burke 1961). Since then, many studies have been performed on people undergoing surgery, and they have led to wide acceptance of antibiotic prophylaxis as a part of surgical practice (Dellinger 1994). A non-systematic re-

view of the literature indicated that intravenous antibiotics should be given ≤ 30 minutes preoperatively to patients undergoing all categories of surgery except caesarean section (Mangram 1999).
A classification system that ranks procedures according to their potential risk for infectious complications guides the administration of surgical antibiotic prophylaxis. This system ranks surgical procedures as clean, clean-contaminated and contaminated. In clean-contaminated surgery, the respiratory, digestive or genitourinary tract is penetrated, thus antibiotic prophylaxis is recommended. Orthognathic surgery is classified as clean-contaminated surgery because the upper digestive tract is penetrated (Gottrup 2005; Mangram 1999).
Although researchers have investigated the effectiveness of penicillin (Jansisyanont 2008), amoxicillin (Baqain 2004), clindamycin (Baqain 2004; Lindeboom 2003), a combination of amoxicillin and clavulanic acid (Jansisyanont 2008; Zijderveld 1999) and a combination of levofloxacin and cefazolin (Yoda 2000) against placebo and/or each other, no single antibiotic regimen is currently recommended to prevent infection after OS; also, lack of agreement regarding type of antibiotic and dosing schedule is ongoing.

How the intervention might work

The aim of surgical antibiotic prophylaxis is to prevent SSI (Salmeron-Escobar 2006) in patients at greatest risk of infection and/or when a clean-contaminated surgery and implant insertions are being performed (Munckhof 2005).
The risk of infection is increased in orthognathic surgery because of the use of titanium plates and screws to fix bones together. Bacteria and other micro-organisms organise in thin, but robust, layers of mucilage that adhere to the surface of implants, such as plates and screws. Consequently, implants stimulate the adherence and multiplication of micro-organisms and increase infection rates (Mangram 1999).
The role of bacterial biofilms from the surface of implants in the development of SSI is well recognised (Costerton 1999; Deacon 1996; Lee 2010; Mombelli 2011; Murdoch 2001; Peel 2011; Southwood 1985). Many experimental studies have confirmed the pro inflammatory and bone-remodeling effects of toxins present on orthopaedic implant surfaces, which are also capable of causing osteolytic (dissolving of bone) and immune responses (Bi 2002; Greenfield 2005; Gristina 1985; Ragab 1999; Xing 2006). Therefore, it seems reasonable to believe that the oral biofilm and its toxins, adhered to the surface of titanium plates and screws used for stabilisation of maxillary osteotomy segments, could be a source of local or regional infectious complications. In consequence, antibiotic prophylaxis could be useful for preventing these infections.
Many studies show that antibiotic prophylaxis may reduce the risk of infection in orthognathic surgery, but the best route of administration is still not clear (Baqain 2004; Bentley 1999; Danda 2010; Fridrich 1994; Jansisyanont 2008; Lindeboom 2003). Nonetheless, two main types of regimens can be differentiated: first, short-term antibiotic prophylaxis administered any time before or after surgery for up to 24 hours after the surgical intervention; and second, long-term antibiotic prophylaxis that is continued for longer than 24 hours (SIGN 2008). In patients undergoing OS, prophylaxis with broad-spectrum antibiotics has been recommended (Baqain 2004; Bentley 1999; Fridrich 1994; Zijderveld 1999).

Why it is important to do this review

The usefulness of antibiotic prophylaxis in orthognathic surgery is still debated, as is the most appropriate regimen. Some study authors advocate that perioperative morbidity can be kept to a minimum with adherence to general surgical principles (Fridrich 1994; Laskin 2003; Waddell 1994), that prophylactic antibiotics have questionable value in preventing infection and that their deployment could lead to the development of super-infections (i.e. infections resistant to antibiotics) (Kunitake 1986; Peterson 1976). On the other hand, it has been reported that the use of prophylactic antibiotics may significantly reduce the postoperative infection rate after orthognathic surgery (Zijderveld 1999). Many attempts have been made to determine the effects of antibiotic prophylaxis in patients undergoing orthognathic surgery (Baqain 2004; Danda 2010; Jansisyanont 2008; Zallen 1971; Zijderveld 1999); therefore the literature identified in a systematic review must be summarised so that the beneficial and adverse effects of antibiotic prophylaxis for orthognathic surgery can be determined and the best evidence provided to clinicians.

OBJECTIVES

To assess the effects of antibiotic prophylaxis for preventing SSI in people undergoing OS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) conducted in people undergoing OS. Quasi-randomised and non-randomised trials, observational studies, narrative reviews, commentaries and letters to editors were excluded.

Types of participants

People of any age undergoing OS in any setting.

Types of interventions

- Intervention: any type of antibiotic (penicillin and its derivatives, cephalosporins, etc.), with any regimen or mode of administration (short-term or long term; oral, endovenous or intramuscular; preoperative or perioperative regimen).
- Comparison: placebo, or another antibiotic, or another regimen of antibiotic.

Types of outcome measures

Studies had to report any of the following outcomes to be included:

Primary outcomes

Occurence of postoperative SSI (i.e. infection of organs/spaces in relation with OS) as defined by Centers for Disease Control and Prevention (CDC) criteria (Horan 1992), or the authors' definition of SSI. We did not differentiate between superficial and deep-incisional infection.

Secondary outcomes

- Systemic infection: defined as a systemic inflammatory response syndrome associated with a postoperative SSI consecutive to OS. It is a secondary, not a primary, outcome because it is very unlikely to occur. OS is a scheduled procedure, and surgeons do not perform it in patients at high risk of infection.
- Length of hospital stay (LOS): defined as the number of days from the day of admission to the day of discharge of participants undergoing OS.
- Participant health-related quality of life (HRQoL): measured using a standardised generic questionnaire such as EQ-5D (standardised measure of health outcomes) (EuroQol 1990), Short Form (SF)-36 (Ware 1992), SF-12 (Müller-Nordhorn 2004) or SF-6 (Brazier 2002) or wound-specific questionnaires such as the Cardiff wound impact schedule (Price 2004). We did not include ad hoc measures of quality of life, which are unlikely to be validated and are not common to multiple trials.
- Adverse events (e.g. gastrointestinal complications, allergic reactions due to antibiotic administration): Gastrointestinal adverse events were defined as any abnormal or harmful effects in the gastrointestinal tract related to the use of antibiotic prophylaxis. Allergic reactions were defined as any hypersensitive reactions of the immune system related to the use of antibiotic prophylaxis. Information regarding any other adverse events reported by trial authors was collected.

RCTs that evaluate any of these outcomes were included, irrespective of the scale used for assessment. If possible, outcomes were evaluated at one week, at one month and up to three months after surgery.

Search methods for identification of studies

Electronic searches

In June 2014 we searched the following electronic databases to identify reports of relevant randomised clinical trials.

- The Cochrane Wounds Group Specialised Register (up to 05 June 2014);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 5);
- Ovid MEDLINE (1946 to May Week 4 2014);
- Ovid MEDLINE (in-Process & Other Non-Indexed Citations, June 04 2014);
- Ovid EMBASE (1980 to 2014 June 04);
- EBSCO CINAHL (1982 to 05 June 2014).

We used the following search strategy in Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor: [Orthognathic Surgery] explode all trees 8
#2 MeSH descriptor: [Orthognathic Surgical Procedures] explode all trees 61
#3 MeSH descriptor: [Osteotomy, Le Fort] explode all trees 63
#4 (orthognathic near/5 surg*):ti,ab,kw 197
#5 ((maxillary next osteotom*) or "Le Fort" or (mandibular near/5 osteotom*) or (vertical next ramus next osteotom*) or genioplast*):ti,ab,kw 210
#6 #1 or #2 or #3 or #4 or #5 343
#7 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees 1226
#8 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 9253
#9 (antibiotic* or cephalosporin* or cefazolin or cefuroxime or amoxicillin* or amoxycillin* or clindamicin or clindamycin or penicillin* or levofloxacin):ti,ab,kw 20956
#10 #7 or #8 or #9 24784
#11 #6 and #10 22
We adapted this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 1, Appendix 2 and Appendix 3 respectively. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We combined the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2011). We did not restrict the search and study selection with respect to language, date of publication or study

setting. If an article published in a language other than English was identified, relevant data were extracted by a translator.
We searched the following ongoing trials databases up to February 2013.

- Current Controlled Trials (http://www.controlled-trials.com/).
- ClinicalTrials.gov (http://www.clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/).
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)

Searching other resources

We examined reference lists of relevant articles that were identified by the electronic searches for other pertinent articles to include in the review. We also searched in Google Scholar to detect unpublished or grey literature.
To account for any delay in indexing in the electronic databases mentioned above, we also searched the last six months of the following journals, up to February 2013.

- *Journal of Oral and Maxillofacial Surgery*.
- *International Journal of Oral and Maxillofacial Surgery*.
- *British Journal of Oral and Maxillofacial Surgery*.
- *Journal of Craniofacial Surgery*.
- *Head & Neck: Journal for the Sciences & Specialties of the Head and Neck*.

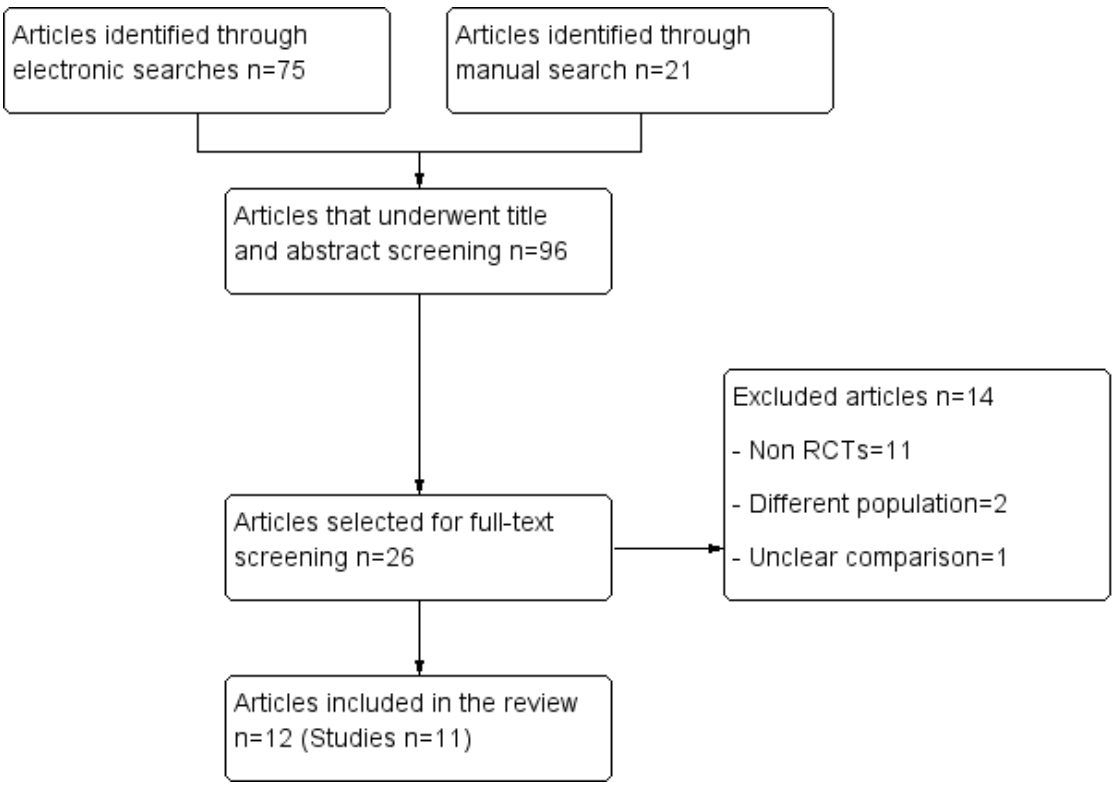
Finally, we handsearched the last five years of the online abstract indexes of conference proceedings of the annual meetings of the *American Association of Oral and Maxillofacial Surgeons* and the *International Association for Dental Research* up to February 2013.

Data collection and analysis

Selection of studies

In a first screening, the title and the abstract of all potentially relevant articles were listed and were evaluated using a pre established selection criteria form. This process was done independently by two review authors who followed instructions especially designed for this stage, which were widely inclusive. All articles selected for full-text screening by either review author were retrieved. The full text of all articles that potentially met the eligibility criteria were assessed independently by two review authors. Disagreements were resolved by discussion, and, if no consensus was reached, a third review author acted as arbiter. We include a study flow diagram, as recommended by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati 2009), to illustrate the results of all searching activity and the process of screening and selecting studies for inclusion in the review (Figure 1). Articles that were published in a different language were evaluated by reviewers fluent in that language, with previous experience in systematic reviews.

Figure 1. Flow diagram.



Data extraction and management

Two review authors extracted the data from all selected studies independently, using a standardised form of Microsoft Excel Office for Mac 2011 created for this purpose. We extracted data regarding the characteristics of the studies relevant for this review, such as the characteristics of the population (sex, age, and selection criteria for enrolment in the trial), surgery (type and number of osteotomies, if reported), intervention and comparison (antibiotic type and regimen), and outcomes (definitions and results of the trial). Discrepancies between the data were reviewed by the two review authors, and, if needed, a third review author acted as arbiter. If data for the outcomes of interest were missing, we contacted the trial authors to obtain the information. A standard form was to be designed to request trial authors to provide specific data needed for the review, and the fields required were highlighted in each case. We planned to liaise with the Wounds Group should any translations be required.

Assessment of risk of bias in included studies

The risk of bias of the included studies was evaluated using the Cochrane risk of bias tool (Higgins 2011). All domains of this tool were used (sequence generation, allocation concealment, blinding of participants, personnel and outcome, incomplete outcome data, selective outcome reporting and other sources of bias), and the instructions published in the *Cochrane Handbook for Systematic Reviews of Interventions* were followed in assessing each domain and in performing the evaluation of the overall risk of bias. This evaluation was performed by two review authors independently, based on the full text of the trials. Disagreements between the review authors were discussed, and consensus had to be reached for a study to be classified as having low, high or unclear risk of bias. As allocation concealment was judged to be the most critical risk of bias domain for this review, a trial would have been classified as having overall HIGH risk of bias if either the allocation concealment domain or two or more other domains were judged to have been at high risk of bias. The same criteria were applied to classify a trial as having unclear risk of bias. Otherwise, the trial was to be classified as having low risk of bias. As it has been shown that blinding to study author and/or affiliation of the study is not associated with the overall results of evaluations (Moher 1999), the review authors were not blinded to these characteristics of the

trials.

Measures of treatment effect

The measures of treatment effect that were to be used for evaluating the outcome in each trial include the following.

- SSI: Rate of infection at the surgical site was analysed as dichotomous, and risk ratios (RRs) and 95% confidence intervals (CIs) were calculated. We expected studies to report how the presence of SSI was judged and two review authors with clinical expertise determined whether this definition was consistent with the CDC definition.
- Systemic infection: We planned to analyse data as dichotomous, and RRs and 95% CIs would have been calculated; however, no data were available that would permit the review authors to do this.
- Length of hospital stay (days): We planned to analyse data as continuous, using mean difference (MD) with 95% CI. If the data were presented as median and were likely skewed, we would not have pooled the data. Data were insufficient for evaluation of this outcome.
- Adverse events: When trials reported adverse events in sufficient detail (e.g. the number of participants who experienced at least one adverse event), we analysed these data dichotomously.

Unit of analysis issues

We used the participant as the unit of analysis. No unit of analysis issues were anticipated, nor were any found.

Dealing with missing data

Each trial was analysed with regards to the presence and proportion of missing data, and it was judged that the amount of missing data was not substantial enough to change the direction of the results. Therefore, it was not necessary to impute missing data, and only complete case data were used.

Assessment of heterogeneity

The Chi^2 test was used to determine the presence of statistical heterogeneity, using a level of significance of 0.1. Quantification of inconsistency across studies was done using the I^2 statistic, and its interpretation was based on recommendations of The Cochrane Collaboration (Deeks 2011), that is, an I^2 between 0% and 40% might be considered as unimportant heterogeneity amongst the trials; 30% to 60% might represent moderate heterogeneity; 50% to 90% might represent substantial heterogeneity; and 75% to 100% might represent considerable heterogeneity. Clinical heterogeneity was assessed qualitatively by considering participants, setting and intervention characteristics with the help of experts. Methodological heterogeneity was evaluated using the domains of the risk of bias tool (Higgins 2011). Exploration of heterogeneity was based on subgroup analyses (detailed below).

Assessment of reporting biases

Efforts were made to detect reporting biases, if possible, in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). Outcome reporting biases were explored by looking for published protocols of the trials included in the systematic review (where available). If a sufficient number of studies had been identified, publication bias was to have been explored using funnel plots for all outcomes and tested using the Egger test (Egger 1997).

Data synthesis

We present a narrative overview of the included trials. When appropriate, we present meta-analyses of outcome data using RevMan 5.3. The decision to pool data in a meta-analysis depended on the availability of outcome data and assessment of between-trial heterogeneity. Because of anticipated and observed clinical heterogeneity between primary studies, random-effects meta-analysis was planned and performed. Participants were analysed in the arms to which they were randomly assigned, in accordance with the intention-to-treat principle.

For analytical purposes, we classified the antibiotic regimens according to time and duration of antibiotic prophylaxis as follows.

- Preoperative dose only: antibiotic was administered only once before the OS.
- Short-term prophylaxis: antibiotic was administered before and during surgery, and during the same day of surgery.
- Long-term prophylaxis: antibiotic was administered before, during and longer than one day after surgery.

In studies that included more than one arm of any of the categories, data from those arms were combined. The main findings are presented in a 'Summary of findings' table (Rosenbaum 2010).

Subgroup analysis and investigation of heterogeneity

We anticipated that two factors could cause heterogeneity across results of the trials, and these would be explored through subgroup analyses. The number of osteotomies was the predictor of greatest interest. Based on previous findings (Chow 2007), the *a priori* hypothesis for this factor is that trials in which participants had a lower number of osteotomies would show greater treatment effect in favour of antibiotic prophylaxis than trials in which participants underwent a greater number of osteotomies. Other sources of heterogeneity that would have been investigated, if possible, include mode of administration of the antibiotic and duration of surgery. However, as statistical heterogeneity between studies was low and we detected no important clinical source of heterogeneity; we did not perform any subgroup analysis.

Sensitivity analysis

We had planned to perform a sensitivity analysis by excluding trials with high risk of bias. As the allocation concealment was judged to be the most critical risk of bias domain for this review, a trial would have been classified as having high risk of bias if either the allocation concealment domain or two or more other domains were judged to have high risk of bias. The same criteria were applied to classify a trial as having unclear risk of bias. Otherwise, the trial was to be classified as having low risk of bias. None of the trials was classified as having high risk of bias, thus no sensitivity analysis was performed.

We also planned to perform sensitivity analyses if data imputation was needed, if a meta-analysis showed a trial with an effect that was different from the others in an important way (outlier) and if this trial had clinical features that made it different from the others. None of these scenarios were faced, thus no sensitivity analyses were performed.

Assessment of the quality of the evidence

After this entire process was performed, we graded the quality of the evidence (confidence in the estimates) for each outcome (post-operative SSI; LOS; HRQoL; adverse events) using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach. We used the five criteria of this approach: limitations in study design of studies that contribute to the outcome, inconsistency, imprecision, indirectness and publication bias (Guyatt 2008). As mentioned above, we included a GRADE summary of findings table in the results section.

RESULTS

Description of studies

We included a total of 11 studies. See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The search resulted in 96 references that underwent screening. After two screening stages, a total of 11 studies (Baqain 2004; Bentley 1999; Danda 2010; Fridrich 1994; Jansisyanont 2008; Kang 2009; Lindeboom 2003; Ruggles 1984; Samman 2010; Tan 2011; Zijderveld 1999), reported in 12 articles, were included in this review. Details of the results of each search and screening stage can be found in Figure 1.

Included studies

See Characteristics of included studies for further details.

Setting

Of the 11 studies included, six were undertaken in Asia (Baqain 2004; Danda 2010; Jansisyanont 2008; Kang 2009; Samman 2010; Tan 2011), three in North America (Bentley 1999; Fridrich 1994; Ruggles 1984) and two in Europe (Lindeboom 2003; Zijderveld 1999). Six of the trials were performed in academic settings (e.g. universities) (Baqain 2004; Danda 2010; Jansisyanont 2008; Lindeboom 2003; Ruggles 1984; Samman 2010), one was performed in a hospital setting (Bentley 1999), two were performed in collaboration between a university and a hospital (Fridrich 1994; Kang 2009) and two were performed at a University Hospital (Tan 2011; Zijderveld 1999).

Participants

The trials recruited between 30 (Bentley 1999; Fridrich 1994) to 160 (Samman 2010) participants. Most trials recruited a higher proportion of females than males; only two studies recruited more males (Fridrich 1994; Ruggles 1984). Most study participants were young adults. In all but one study (Jansisyanont 2008), the mean age of participants was younger than 30 years. In two studies, neither the sex nor the age distribution of recruited participants was reported (Bentley 1999; Samman 2010).

The mean duration of OS ranged from 2.5 hours (Lindeboom 2003) to 7.5 hours (Tan 2011); no information regarding duration of surgery was provided in five trials (Danda 2010; Fridrich 1994; Ruggles 1984; Samman 2010; Zijderveld 1999). The type and number of osteotomies varied according to the details reported. Some study authors described the bone in which it was performed (i.e. mandibular/ maxillary osteotomy) (Danda 2010, Fridrich 1994; Kang 2009; Ruggles 1984; Tan 2011), whereas others specifically described the type of surgery performed (i.e. LeFort I, bilateral sagittal split osteotomy, etc) (Baqain 2004; Bentley 1999; Jansisyanont 2008; Lindeboom 2003; Zijderveld 1999). Seven studies reported different combinations of osteotomies performed and the total number of participants who received these combinations, without distinguishing the arm to which the participants belonged (Danda 2010; Fridrich 1994; Jansisyanont 2008; Kang 2009; Lindeboom 2003; Tan 2011; Zijderveld 1999). Two studies reported the combination of osteotomies and the numbers of participants who received these combinations per arm (Baqain 2004; Bentley 1999), and one study reported the number of each single type of osteotomy performed, without considering its combinations and the arms in which each was performed (Ruggles 1984). One study did not report any information regarding the type or number of osteotomies performed (Samman 2010).

Interventions

Most of the trials were parallel two-arm studies (Baqain 2004; Bentley 1999; Danda 2010; Fridrich 1994; Kang 2009; Lindeboom 2003; Ruggles 1984; Tan 2011). One study had

three arms (Zijderveld 1999), and two studies had four arms (Jansisyanont 2008; Samman 2010). Six trials assessed the effects of preoperative and perioperative antibiotic prophylaxis versus the effects of preoperative, perioperative and postoperative prophylaxis (Baqain 2004; Bentley 1999; Fridrich 1994; Jansisyanont 2008; Kang 2009; Ruggles 1984); two trials assessed the effects of a single preoperative dose of antibiotic prophylaxis versus preoperative and perioperative antibiotic prophylaxis (Danda 2010; Lindeboom 2003); one trial assessed the effects of preoperative antibiotic prophylaxis versus no prophylaxis (Zijderveld 1999); one trial compared the effects of two different antibiotics up to the second day postoperatively (Tan 2011); and one trial compared four different regimens of the same antibiotic (Samman 2010).

In five trials, participants received penicillin (Bentley 1999; Fridrich 1994; Jansisyanont 2008; Ruggles 1984; Samman 2010). Other antibiotics administered were amoxicillin (Baqain 2004; Jansisyanont 2008; Tan 2011), ampicillin (Danda 2010; Tan 2011), amoxicillin plus clavulanic acid (Jansisyanont 2008; Zijderveld 1999), clindamycin (Lindeboom 2003), cefpiramide (Kang 2009) and cefuroxime (Zijderveld 1999).

Outcomes

All studies measured the outcome SSI. Three studies used the CDC criteria to diagnose a postoperative infection (Baqain 2004; Jansisyanont 2008; Kang 2009); one study used the CDC criteria but modified them by eliminating one criterion (Danda 2010); in five studies, a definition and criteria determined by the authors were used (Baqain 2004; Lindeboom 2003; Ruggles 1984; Tan 2011; Zijderveld 1999; see details of measurement criteria in Characteristics of included studies); and two studies did not provide details on how this outcome was measured (Fridrich 1994; Samman 2010).

Only two studies measured the occurrence of adverse reactions to antibiotics (Lindeboom 2003; Tan 2011), and none of the studies measured systemic infection, duration of hospital stay or HRQoL.

Follow-up

In four studies, participants were followed-up for up to one month (Baqain 2004; Bentley 1999; Danda 2010; Zijderveld 1999). The shortest follow-up was two weeks (Kang 2009), and the longest follow-up was six months (Samman 2010).

Excluded studies

A total of 14 studies that underwent full-text screening were excluded from this review (see Characteristics of excluded studies). Most of these studies were excluded because they were not RCTs (Bystedt 1987; Danda 2011; Fenner 1950; Fridrich 1999; Martis 1984; Paterson 1970; Peterson 1976; Schubert 1990; Spaey 2005; Tan 2011; Yrastorza 1976). Two studies were excluded because although the participants underwent maxillofacial surgery the results were not available separately for participants who underwent OS (Dumbach 1987; Sixou 2006). One study was excluded because no description of what participants in the control arm received was reported (Xiaoyi 1996).

Risk of bias in included studies

The risk of bias assessment is illustrated in Figure 2 and Figure 3.

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

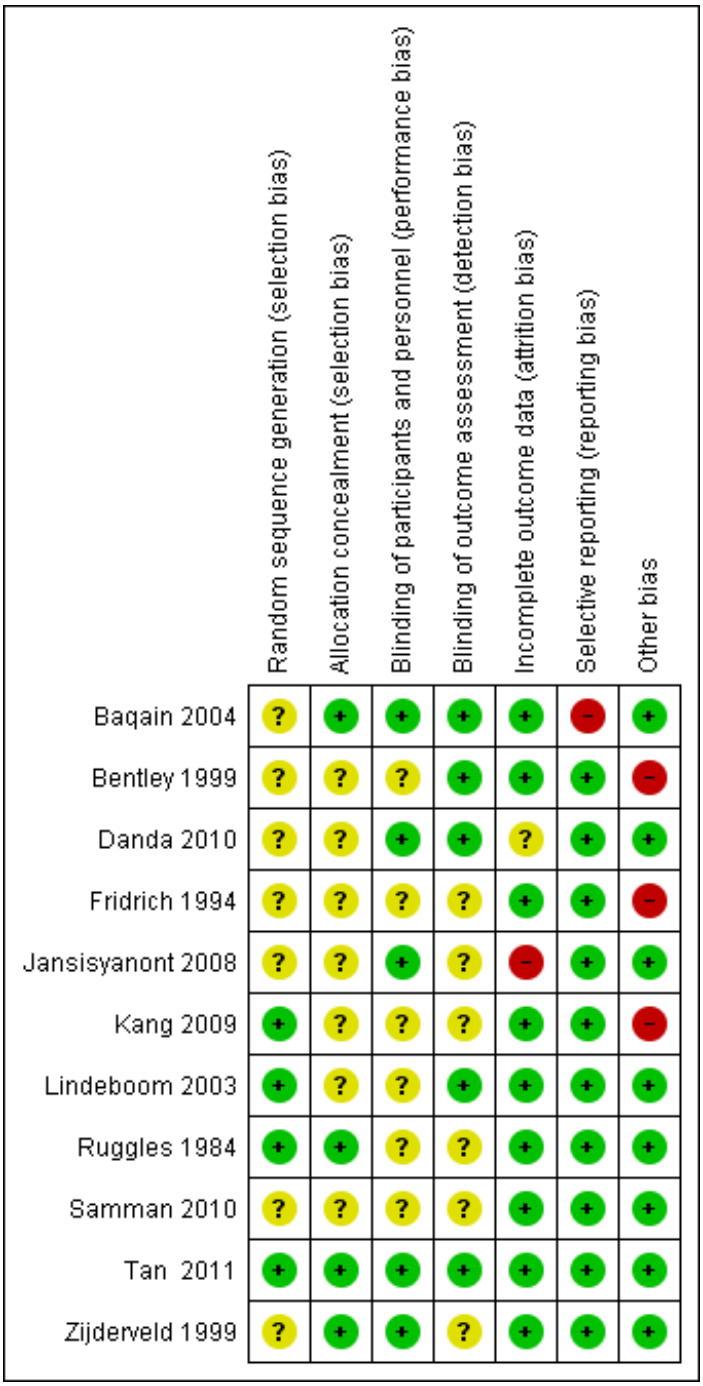


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

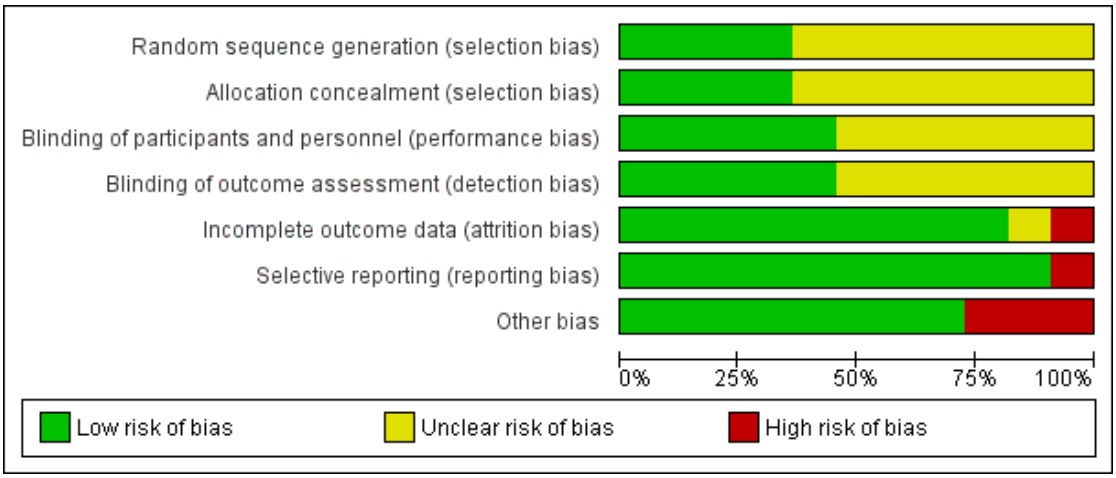


Figure 2 shows the assessment of risk of bias per study and domain. In only one study all domains were judged as having low risk of bias (Tan 2011). In many of the studies, the information reported did not allow a judgement as to whether the risk of bias related to sequence generation, allocation concealment and/or blinding was high or low (Bentley 1999; Fridrich 1994; Kang 2009; Lindeboom 2003; Samman 2010; Tan 2011). Five studies had one domain judged to have high risk of bias (Baqain 2004; Bentley 1999; Fridrich 1994; Jansisyanont 2008; Kang 2009).

Figure 3 shows the risk of bias assessment per domain, across studies. The domain judged to have the lowest risk of bias was selective reporting, whereas the domain judged to have the highest risk of bias was other bias.

Random sequence generation

The generation of the randomisation sequence was described on only four of the studies (Kang 2009; Lindeboom 2003; Ruggles 1984; Tan 2011). Although the other seven studies described allocating patients to the intervention and comparison groups randomly, they authors did not provide details regarding the sequence generation, and therefore were judged as having an unclear risk of bias.

Allocation

Allocation concealment was described in only four of the 11 studies (Baqain 2004; Ruggles 1984; Tan 2011; Zijderveld 1999). In all other studies, no information regarding this design feature was provided, thus those studies were judged as having an unclear risk of bias.

Blinding

Blinding in relation to performance bias and detection bias was assessed separately. With respect to performance bias, blinding was described in five of the studies (Baqain 2004; Danda 2010; Jansisyanont 2008; Tan 2011; Zijderveld 1999). In relation to detection bias, blinding was described in five studies (Baqain 2004; Bentley 1999; Danda 2010; Lindeboom 2003; Tan 2011). The other studies did not provide any information and thus were judged as having an unclear risk of bias.

Incomplete outcome data

One study had high risk of bias with regard to this domain (Jansisyanont 2008), as 15 participants were excluded from the analysis, and this is a high number compared with the overall number of events. One study had an unclear risk of bias because no information regarding losses to follow-up was provided, nor were details given regarding whether the number of participants accounted for in the results section was the same as the number of participants enrolled (Danda 2010). All other studies were judged as having low risk of bias.

Selective reporting

Most of the studies were judged to have low risk of bias. Even though the only outcome measured in most of them was SSI, it is uncommon to find trials in this area measuring duration of hospital stay or quality of life, thus selective reporting was not suspected. One trial was judged as having high risk of bias because the study authors did not report explicitly in the results section the number of participants with postoperative infection, and instead reported in the discussion section the number of participants who required extra antibiotics (Baqain 2004).

Other potential sources of bias

We detected other potential sources of bias in three studies. In two of the trials (Fridrich 1994; Kang 2009) a co-intervention applied to patients in both arms after the surgery (drainage tubes) could have increased the risk of SSI in patients receiving shorter term regimens of antibiotics. One trial was stopped early (Bentley 1999). More details can be found in the risk of bias table for each of these studies, provided in Characteristics of included studies.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Comparison 1. Short-term compared with long-term antibiotic prophylaxis

Surgical site infection

A total of seven studies (472 participants) provided data for this comparison and outcome (Baqain 2004; Bentley 1999; Fridrich 1994; Jansisyanont 2008; Kang 2009; Ruggles 1984; Samman 2010). Participants who received long-term antibiotic prophylaxis were less likely to develop an SSI than those who received short-term prophylaxis (risk ratio (RR) 0.42, 95% confidence interval (CI) 0.24 to 0.74; Analysis 1.1). Heterogeneity was low (I^2 0%), with all of the trials individually showing the same direction of the effect (or no effect) and with overlapping confidence intervals.

We performed a *post hoc* sensitivity analysis by excluding one study (Baqain 2004) from the analysis. The authors of this study reported the number of participants who required additional antibiotics, which, according to clinical experts, could be considered as a proxy for postoperative infection. However, as no explicit report of infection was provided, we explored whether the results changed when this study was left out of the meta-analysis. Exclusion of Baqain 2004 from the meta analysis did not change the result (RR 0.41, 95% CI 0.22 to 0.75) (Analysis 2.1).

Other outcomes

The trials did not report on systemic infection, adverse events, duration of hospital stay or HRQoL.

Comparison 2. Preoperative compared with short-term antibiotic prophylaxis

Surgical site infection

In all, two studies (220 participants) provided data for this comparison and outcome (Danda 2010; Lindeboom 2003) and the results of these trials were pooled (I^2 0%). Whilst participants who received short-term antibiotic prophylaxis were less likely to develop an SSI than those who received a single, preoperative dose, this result is rather uncertain and no difference is also a plausible result (RR 0.24, 95% CI 0.09 to 1.22; Analysis 3.1). No evidence of statistical heterogeneity was found.

Adverse events

One study (70 participants) reported on this outcome (Lindeboom 2003). None of the participants suffered any types of adverse events

Other outcomes

No trials for this comparison reported on systemic infection, duration of hospital stay or HRQoL.

Comparison 3. Amoxicillin compared with ampicillin

Surgical site infection

One study (42 participants) reported on this comparison (Tan 2011). In this study, both antibiotics were administered in a long-term regimen. Only nine people in this small study developed an SSI and therefore the results are highly uncertain (RR 0.5, 95% CI 0.14 to 1.74; Analysis 4.1).

Adverse events

Tan 2011 reported that none of the participants suffered any types of adverse events.

Other outcomes

No trials for this comparison reported on systemic infection, duration of hospital stay or HRQoL.

Comparison 4. Amoxicillin and clavulanic acid compared with cefuroxime

Surgical site infection

One small study (35 participants; 5 SSIs) reported on this comparison (Zijderveld 1999) and therefore the results are highly uncertain (RR of SSI with amoxicillin/clavulanic acid relative to cefuroxime 0.63, 95% CI 0.12 to 3.32; Analysis 5.1). Both antibiotics were administered preoperatively.

Other outcomes

No trials for this comparison reported on systemic infection, adverse events, duration of hospital stay or HRQoL.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Preoperative antibiotic prophylaxis compared with short-term antibiotic prophylaxis in patients undergoing orthognathic surgery						
Patient or population: patients undergoing orthognathic surgery **Intervention:** preoperative antibiotic prophylaxis **Comparison:** short-term antibiotic prophylaxis						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Preoperative	**Short-term**				
Surgical site infection Follow-up: 4 to 12 weeks	**82 per 1000**[a]	**28 per 1000** (8 to 101)	**RR 0.34** (0.09 to 1.22)	220 (2 studies)	⊕⊕◯◯ **low**[b,c]	This outcome was measured using different definitions. We accepted all authors' definitions
Adverse events Follow-up: up to 12 weeks	0 per 35 See comment	0 per 35 See comment	Not estimable	70 (1 study)	⊕⊕◯◯ **low**[d,e]	No adverse events were reported in any of arms of the trial
Systemic infection	Not reported				-	This outcome was not reported in any of the trials
Duration of hospital stay	Not reported				-	This outcome was not reported in any of the trials
Health-related quality of life	Not reported				-	This outcome was not reported in any of the trials

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

[a] Assumed risk based on control arms of included trials.
[b] Most of the trials were judged to have unclear risk of bias in the domains of allocation concealment and blinding.
[c] The 95% CI of the pooled estimate suggests both benefit and harm.
[d] The trial was judged to have unclear risk of bias in the domains of allocation concealment and blinding.
[e] The number of participants included in this analysis is below the optimal information size.

DISCUSSION

Summary of main results

The results of this review suggest that patients who receive long-term antibiotic prophylaxis (compared with short-term prophylaxis) experience a reduction in the absolute risk of developing a SSI (from 168 SSIs per 1000 surgeries with short-term antibiotics to 71 SSIs per 1000 surgeries with long-term antibiotics). The quality of the evidence was downgraded due to risk of bias of included studies and overall the evidence is of moderate quality (see the Summary of Findings Table). There was no evidence of a difference between all antibiotic comparisons and insufficient evidence to show if one antibiotic was any better than another or whether rates of adverse effects differed. Furthermore the results were uncertain for people who receive short-term antibiotic prophylaxis (compared with a single pre-operative dose). Whilst participants who received short-term antibiotic prophylaxis were less likely to develop an SSI than those who received a single, preoperative dose, no difference is also a plausible result. The evidence for this outcome was low quality (downgraded for risk of bias of included studies and imprecision)."

Overall completeness and applicability of evidence

The studies included in this review provided information regarding only two of the five outcomes of interest. All studies reported on SSI, and two studies reported on adverse events. No data were provided on the incidence of systemic infection, duration of hospital stay and HRQoL.

The studies included a broad sample of participants (given the characteristics of patients who undergo OS) who were treated in different settings and with different regimens of antibiotic prophylaxis. This and the fact that the results were very similar among trials favour the applicability of the evidence to many populations and settings.

Quality of the evidence

We found moderate-quality evidence for SSIs in the comparison of short-term versus long-term antibiotic prophylaxis. We downgraded the quality of the evidence because of serious limitations in risk of bias, as most of the trials were judged to have an unclear risk of bias in the domains of allocation concealment and blinding, and this decreases our confidence in the estimates of effects.

We found low-quality evidence for the comparison of preoperative versus short-term antibiotic prophylaxis. For both outcomes-SSIs and adverse events-the quality of the evidence was downgraded because of serious limitations in risk of bias and imprecision. For the outcome SSI, the confidence interval of the pooled estimate of effect suggests uncertainty over the possibility of harm or benefit. For the outcome adverse events, it was not possible to pool an estimate of effect, because although investigators collected data on adverse events, no adverse events were observed. However, the number of participants included for this outcome was low.

Potential biases in the review process

This systematic review adhered in a rigorous manner to all of the steps recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.

We were not able to assess publication bias using a funnel plot. Our broad searching strategy, however, minimises the likelihood of publication bias for the other comparisons and outcomes.

We were not able to perform the subgroup analyses that we had planned because the number of trials in each comparison were insufficient. However, the low statistical heterogeneity makes it unnecessary to perform such analyses.

Finally, we would have liked to confirm some information with the authors of the included trials; however, contact efforts were unfruitful in all cases. The main issue we would have liked to clarify was the number of participants who were reported to receive additional antibiotics versus the number of participants diagnosed with SSI in the trial by Baqain 2004; a sensitivity analysis excluding this trial did not result in a change in the pooled estimate.

Agreements and disagreements with other studies or reviews

Two systematic reviews on this topic were published in the literature (Danda 2011; Tan 2011). Some differences are evident between those reviews and ours, particularly differences regarding the criteria used to classify the interventions. Danda 2011 classified studies based on the presence of a placebo comparator and blinding in three categories. They performed a meta-analysis in which arms were classified as short-term and extended-term, with the shorter-term regimen considered the 'control.' This led to short-term prophylaxis classified as short-term when the comparison was long-term but classified as extended-term when the comparison was preoperative prophylaxis. In addition, review authors identified a smaller number of trials than were included in our review. The systematic review performed by Tan 2011 excluded some of the trials that we included for lack of details regarding the medical conditions of study participants, and, according to the review authors, lack of specified criteria used to define the outcomes. However, the findings of both studies tend to agree with ours, as the review authors observed that participants who received antibiotic prophylaxis for a longer time were less likely to develop postoperative infection. This finding was determined to be statistically significant in one review (Danda 2010) and non-significant in the other (Tan 2011).

AUTHORS' CONCLUSIONS

Implications for practice

Based on the results of this systematic review and the quality of the evidence found, clinicians who consider administering antibiotic prophylaxis to patients undergoing OS, should bear in mind that there is probably a benefit when administering long-term prophylaxis instead of short-term. It must be considered, also, that the only outcome for which evidence of benefit was found is the incidence of SSI, and that other outcomes of importance have not been measured in clinical trials.

Available evidence regarding the use of a single preoperative dose versus short-term antibiotic prophylaxis and regarding the use of a specific antibiotic versus another is not conclusive, thus the decision amongst these options lays in clinical experience, awaiting publication of additional evidence.

Implications for research

This systematic review has uncovered the need to perform randomised clinical trials in which other outcomes that are important for clinical decision-making are assessed and/or reported, such as systemic infection, duration of hospital stay and HRQoL. It is also necessary to perform trials in which the number of patients is sufficient enough to detect differences in such outcomes. There is a need for improvement in the conducting and/or reporting of trials in this area, particularly in those areas related with the randomisation method, allocation concealment and blinding.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Baqain 2004

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 34 **Setting:** Oral and Maxillofacial Surgery Department, Faculty of Dentistry, University of Jordan, Amman, Jordan **Sex:** 32.35% male **Age:** mean 27 years (range 18-48 years) **Inclusion criteria:** "Patients listed to undergo orthognathic operations" **Exclusion criteria:** use of antibiotics in the month before the operation, lactose intolerance (because the placebo was lactose-based) and previous orthognathic operations
Interventions	**Long-term group:** amoxicillin 1 g intravenously at induction, followed by 500 mg intravenously 3 hours postoperatively and amoxicillin 500 mg orally every 8 hours for 5 days Participants allergic to penicillin were given clindamycin 300 mg intravenously at induction and 150 mg 3 hours postoperatively, and continued taking clindamycin 150 mg orally every 6 hours for a total of 5 days **Short-term group:** amoxicillin 1 g intravenously at induction, followed by 500 mg intravenously 3 hours postoperatively and placebo orally every 8 hours for 5 days Participants allergic to penicillin were given clindamycin 300 mg intravenously at induction and 150 mg 3 hours postoperatively and placebo for the following 5 days
Outcomes	**SSI:** measured up to 30 days after surgery. Seven variables from a previously validated system (according to study authors, 4 references given) were used to audit postoperative infection, including the following • Facial swelling (score 0-3 for null, minor, moderate and gross swelling) • Pain was scored on a visual analogue scale (VAS) (0-4 for nil, mild, moderate, severe and excruciating). The remaining 5 criteria were scored as presence or absence • Extraoral erythema 0 or 5 • Wound exudate 0 or 10 • Isolation of pathogen 0 or 10 • Pyrexia 0 or 10 • Wound dehiscence 0 or 10 The total achievable score for severe infection per participant was 52. Study authors reported the sum of scores across participants, per group
Notes	No report described adverse reactions to drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	List of random numbers was prepared by the clinical pharmacist (no explanation how)

Baqain 2004 (*Continued*)

Allocation concealment (selection bias)	Low risk	List of random numbers was kept by the clinical pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Dispensed capsules were unmarked, so that neither the participant nor the assessor knew the regimen that was being administered
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Dispensed capsules were unmarked so that neither the participant nor the assessor knew the regimen
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	High risk	No explicit report described the infected number or proportion of participants. Only the numbers of participants who required extra antibiotics were reported in the discussion section of the article
Other bias	Low risk	No other biases were detected

Bentley 1999

Methods	Randomised controlled trial
Participants	**Number of patients enrolled:** 30 **Setting:** Oral and Maxillofacial Surgery Service at Montreal General Hospital, Montreal, Canada **Sex:** not reported **Age:** not reported **Inclusion criteria:** healthy male and female patients who were to undergo intraoral or combined intraoral and extraoral orthognathic surgical procedures, including those requiring autogenous bone grafts **Exclusion criteria:** not reported
Interventions	**Arm 1, 5-day regimen:** 2 million units aqueous penicillin G intravenously (TV) immediately preoperatively, 1 million units lV every 3 hours intraoperatively, and then 1 million units IV postoperatively 3 hours after the last intraoperative dose. Then, aqueous penicillin G, 1 million units IV every 6 hours for 8 doses, then a suspension of benzathine penicillin V 300 mg given orally every 6 hours for 8 doses **Arm 2, 1 day-regimen:** 2 million units aqueous penicillin G intravenously (TV) immediately preoperatively, 1 million units lV every 3 hours intraoperatively, and then 1 million units IV postoperatively 3 hours after the last intraoperative dose. Then placebo and oral placebo according to the same schedule
Outcomes	**SSI:** measured daily in the hospital and at 1, 2 and 4 postoperative weeks Criteria for an infected wound were based on the Centers for Disease Control and Prevention definition of infection, that is, infection must occur at the operative site

Bentley 1999 (*Continued*)

	within 30 days of surgery and must be based on the existence of any 1 of the following conditions • Purulent drainage from an incision or drain • Serosanguineous drainage and a wound culture positive for a known pathogen. • Wound spontaneously dehisces or is deliberately opened by the surgeon when the participant has fever or localised pain or tenderness, unless wound culture is negative • Surgeon's diagnosis of infection
Notes	No use of plates, only wire fixation No report about adverse reactions to drugs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 2 groups, no explanation how
Allocation concealment (selection bias)	Unclear risk	No information was provided about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information was provided about blinding of participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were not aware of the randomisation codes until 4 weeks after the last surgical procedure was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported and details per participant provided
Other bias	High risk	The trial was stopped early because of harm (33.4% increased risk of infection), which may overestimate the treatment effect

Danda 2010

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 150 **Setting:** Department of Oral and Maxillofacial Surgery, College of Dental Surgery, Saveetha University, Chennai, India **Sex:** 38% male **Age:** mean 24 years (15-37 years) **Inclusion criteria:** not reported

Danda 2010 (*Continued*)

	Exclusion criteria: patients who had received antibiotics 1 month before surgery; patients who had a history of allergy to ampicillin; signs of active infection; immunocompromised patients
Interventions	**Arm 1, single dose:** saline solution intravenously every 6 hours for 24 hours and ampicillin 1 g intravenously at induction **Arm 2, single day:** ampicillin 500 mg intravenously every 6 hours for 24 hours and ampicillin 1 g intravenously at induction
Outcomes	**SSI:** measured 1, 2, 3 and 4 postoperative days until discharge and then at the 2nd, 3rd and 4th week postoperatively Criteria for infection were based on any of the following conditions • Purulent discharge from an incision • Serosanguineous drainage and a wound culture positive for a known pathogen • Clinician diagnosis of infection
Notes	No report about adverse reactions to drugs was provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 2 groups, with no explanation how
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participant and assessor were blinded to the antibiotic protocol
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both participant and assessor were blinded to the antibiotic protocol
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about withdrawals was provided, and reporting does not allow us to judge whether losses to follow-up occurred
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	Low risk	No other biases were detected

Fridrich 1994

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 30 **Setting:** Department of Hospital Dentistry, Division of Oral and Maxillofacial Surgery, University Iowa Hospitals and Clinics, Iowa City, USA **Sex:** 53.33% male **Age:** mean 27.2 years (15-55 years) **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	**Arm 1, 1 week:** penicillin G 2 million U IV preoperatively and continued every 4 hours until the IV was discontinued on postoperative day 1. 500 mg penicillin VK was continued 4 times daily for 1 week Cefazolin or clindamycin was used in allergic participants in comparable doses, intervals and duration **Arm 2, 1 day:** penicillin G 2 million U IV, preoperatively and continued every 2 hours until participants reached the recovery room, where the final dose was given Cefazolin or clindamycin was used in allergic participants in comparable doses, intervals and duration
Outcomes	**SSI:** measured up to 8 weeks after the surgery. No further details provided
Notes	No report described adverse reactions to drugs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 2 groups, with no explanation how
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of assessors was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned previously in the methods section were reported with sufficient details

Fridrich 1994 (*Continued*)

Other bias	High risk	Both groups used drainage tubes, which in arm 2 may increase the rate of infection because participants were not using antibiotic coverage

Jansisyanont 2008

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 122 **Setting:** Faculty of Dentistry, Chulalolongkorn University, Thailand **Sex:** mean 26.52 years (17.10-47.60 years) **Age:** 34.42% male **Inclusion criteria:** not reported **Exclusion criteria:** patients with metabolic disease or low resistance to infection; need for a bone graft for correction of dentofacial deformities; patients who sustained perioperative complications that made antibiotic usage crucial, such as unfavourable fractures or excessive bleeding that could cause a large haematoma; patients who had received an antibiotic within 4 weeks of surgery; patients who had been treated by a distraction osteogenesis device or surgically assisted rapid palatal expansion; patients who had a history of allergy to penicillin
Interventions	**Arm 1, short-term amoxicillin-clavulanic acid:** 1.2 g of intravenous amoxicillin-clavulanic acid 30 minutes preoperatively and every 8 hours during the operation. then 1 more single dose 8 hours postoperatively (33 participants) **Arm 2, short-term penicillin:** 2 million units of aqueous penicillin G (IV) 30 minutes preoperatively, which was continued every 4 hours during surgery. then 1 more single dose 4 hours after surgery (29 participants) **Arm 3, long-term amoxicillin-clavulanic acid:** 1.2 g of intravenous amoxicillin-clavulanic acid 30 minutes preoperatively and every 8 hours during the operation, followed by a 625-mg tablet amoxicillin-clavulanic acid orally every 8 hours postoperatively for 5 days (28 participants) **Arm 4, long-term penicillin:** 2 million units of aqueous penicillin G (IV) 30 minutes preoperatively, which was continued every 4 hours during surgery. then postoperative antibiotic of 500 mg oral amoxicillin every 8 hours for 5 days (32 participants)
Outcomes	**SSI:** measured daily at the hospital and at 1, 2, 4, 6, 8 and 12 weeks The criteria for postoperative infection were based on the definition of the infection provided by the Centers for Disease Control and Prevention. The infection had to be present at the surgical site within 42 days (6 weeks) of surgery. A diagnosis of infection was made if the following were present • Purulent discharge from the surgical site • Serosanguineous drainage and a wound culture proved positive for a known pathogen • Elevation of temperature to greater than 38.5°C after more than 48 hours and after participants had been ruled out from other causes of infection by complete blood count, chest x-ray and urinary analysis • Pain or tenderness, localised swelling and redness of the wound margin and

Jansisyanont 2008 (*Continued*)

	surrounding tissue
Notes	No report described adverse reactions to drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 2 groups, with no explanation how
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind. It is likely that participants were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of surgeons and personnel was provided. Study authors mentioned only that the study was double-blind, and it cannot be inferred who was the second party blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Mention is made of 15 participants excluded from the analysis for different reasons. Six participants were excluded because of intraoperative complications, and 1 was lost
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	Low risk	No other biases were detected

Kang 2009

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 56 **Setting:** Department of Oral and Maxillofacial Surgery, College of Dentistry, Yonsei University, Seoul; Korea National Health Insurance Corporation Ilsan Hospital Gyeonggi; Wonju Christian Hospital, Kangwon, South Korea **Sex:** 40% male **Age:** arm 1: mean 23.9 years (SD 5.84); arm 2: mean 24.3 years (SD 6.33) **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	**Arm 1, short term:** 1.0 g of a third-generation cephalosporin (cefpiramide) intravenously 30 minutes before surgery (28 participants)

	Arm 2, long term: 1.0 g of Cefpiramide 30 minutes before surgery, as well as twice daily until 3 days after surgery (28 participants)
Outcomes	**SSI:** measured every day during the first 3 days and at the end of the first and second weeks after surgery for any postoperative infection Postoperative wound infection was defined by at least 1 of the following criteria • Purulent drainage from the surgical site with or without laboratory confirmation • At least 1 of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness or heat and a superficial incision deliberately opened by surgeon, unless the incision is culture-negative • Abscess or other evidence of infection is found on direct examination, during reoperation or by histopathological or radiological examination • Diagnosis of SSI by the surgeon or attending physician
Notes	Both groups used a closed intraoral suction, which in arm 2 may increase the rate of infection because participants are not using postoperative antibiotic coverage No report described adverse reactions to drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation codes were generated using Microsoft Excel
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of participants was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	High risk	Both groups used drainage tubes, which in arm 2 may increase the rate of infection because participants were not using postoperative antibiotic coverage

Lindeboom 2003

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 70 **Setting:** Medical Center and Academic Center for Dentistry, University of Amsterdam, The Netherlands **Sex:** 25.71% male **Age:** mean 29.9 years (19-54 years) **Inclusion criteria:** 70 consecutive patients who underwent a bilateral sagittal ramus osteotomy of the mandible. All participants were Angle Class II retrognathia patients, and all had received preoperative orthodontic treatment to optimise the shape of the dental arches **Exclusion criteria:** patients who had received antibiotics within 2 weeks before surgery; history of allergy to clindamycin; signs and symptoms of active infection; additional surgical procedures (i.e. chin or maxillary osteotomies) indicated; and participants suffering from severe underlying illness associated with compromised host defences
Interventions	**Arm 1:** single dose of 600 mg clindamycin and saline solution intravenously 15 minutes before surgery (35 participants) **Arm 2:** 4 doses of 600 mg clindamycin and saline solution intravenously (1 every 6 hours for 24 hours; 35 participants)
Outcomes	**SSI:** After surgery and until hospital discharge, all participants were observed daily and at 1, 2, and 4 weeks and at 3 months. A postoperative infection was defined as the presence of purulent drainage (spontaneously or by incision), accompanied by pain or tenderness, localised swelling, redness and heat or fever (38.5°C) or an increase in localised swelling, after an initial postoperative decrease in oedema, together with pain, discomfort, induration and increased body temperature (38.5°C) Early infection was defined as infection occurring within 1 week postoperatively **Drug adverse reactions:** All undesirable reactions such as skin rashes or gastrointestinal disorders occurring in connection with the antibiotic prophylaxis were noted
Notes	Both groups used chlorhexidine and were seen by a dental hygienist preoperatively and postoperatively. Bethamethasone 8 mg preoperatively and 4 mg postoperatively, and, during the next 3 days, in a slow, tapering fashion was administered to both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A list of random numbers was used
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding of participants was provided

Lindeboom 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	One clinician was blinded to the antibiotic protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	Low risk	No other biases were detected

Ruggles 1984

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 40 **Setting:** Medical University of South Carolina, College of Dental Medicine, Department of Oral and Maxillofacial Surgery, USA **Sex:** 77.5% male **Age:** mean 23 years (19 to 39 years) **Inclusion criteria:** not reported **Exclusion criteria:** history of allergy to penicillin or other beta-lactam antibiotics, a compromised immune defense and a history of receiving antibiotic therapy within 14 days before the planned surgery
Interventions	**Arm 1, 2 days:** intramuscular dose of 600,000 units procaine penicillin G and 400,000 units aqueous penicillin G 1 hour preoperatively. Two million units aqueous penicillin G was administered intravenously over 30 minutes every 3 hours during the operation, and another 2 million units aqueous penicillin G was administered intravenously over 30 minutes 3 hours after the last intraoperative dose was given. Aqueous penicillin G intravenously over 30 minutes every 4 hours for a total of 12 doses postoperatively (2 days of antibiotic prophylaxis, 20 participants) **Arm 2, 1 day:** intramuscular dose of 600,000 units procaine penicillin G and 400,000 units aqueous penicillin G 1 hour preoperatively. Two million units aqueous penicillin G was administered intravenously over 30 minutes every 3 hours during the operation, and another 2 million units aqueous penicillin G was administered intravenously over 30 minutes 3 hours after the last intraoperative dose was given. Then placebo was administered (20 participants)
Outcomes	**SSI:** All participants were observed postoperatively. Not reported how many days or weeks The diagnosis of postoperative infection was made when 3 of the following criteria were met • Elevation of body temperature for longer than 72 hours or a sudden elevation of body temperature following return to normal after surgery • Increasing oedema, indurations and erythema of wound margins and surrounding tissues

Ruggles 1984 (*Continued*)

	• Unusual pain associated with the surgical site • Elevated total leucocyte count with an associated increase in immature forms of polymorph nuclear neutrophils • Drainage of purulent exudates from the surgical site
Notes	No report described adverse reactions to drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number table was used to divide the 40 participants into 2 groups of 20
Allocation concealment (selection bias)	Low risk	The code was not revealed to the investigators until 6 weeks after the last surgical procedure was performed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of assessors was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	Low risk	No other biases were detected

Samman 2010

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 160 **Setting:** Department of Oral and Maxillofacial Surgery, University of Hong Kong, Hong Kong, China **Sex:** not reported **Age:** not reported **Inclusion criteria:** not reported **Exclusion criteria**: not reported
Interventions	**Arm 1:** penicillin, 1 intravenous dose at induction **Arm 2:** penicillin, 2 IV doses 6 hours apart **Arm 3:** penicillin, 8 IV doses over 2 days **Arm 4:** penicillin, 8 IV doses over 2 days with additional 5 days of oral penicillin

Samman 2010 (*Continued*)

Outcomes	**SSI:** followed for 6 months and assessed for incidence of clinically significant postoperative infection
Notes	This is an abstract from a conference No report described adverse reactions to drugs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 4 groups, with no explanation how
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding of participants and personnel was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of assessors was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up are reported
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	Low risk	No other biases were detected

Tan 2011

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 42 **Setting:** University of Hong Kong/Hospital, China **Sex:** 33.33% male **Age:** mean 26 years (18-34 years, SD 4,2) **Inclusion criteria:** patients who underwent bimaxillary OS **Exclusion criteria:** History of any type of previous surgery to the head and neck area, including previous OS; patients who were having distraction osteogenesis as part of the OS; history of malignancy of the head and neck region and/or history of radiation to the head and neck region; known hypersensitivity to amoxicillin, ampicillin or other beta-lactamic antibiotics; known history of lactose intolerance; patients who had used any antibiotics in the 14 days before surgery; patients with compromised host defences (e.g.

	diabetes mellitus, autoimmune disease, end-stage renal disease, severe alcoholic cirrhosis, neutropenia); and patients who were receiving immunosuppressive drugs that interfere with host defences (e.g. cyclosporine, steroids, cancer chemotherapeutic agents)
Interventions	**Arm 1:** oral amoxicillin 500 mg 3 times daily and intravenous placebo (normal saline) injection 4 times daily in the first 2 days after OS. Intravenous ampicillin 1 g during anaesthetic induction and 500 mg every 6 hours during the operation.Oral amoxicillin 500 mg 3 times daily for 3 days. (21 participants) **Arm 2:** intravenous ampicillin 1 g 4 times daily and oral lactose (placebo) 3 times daily for the first 2 days after OS. Intravenous ampicillin 1 g during anaesthetic induction and 500 mg every 6 hours during the operation.Oral amoxicillin 500 mg 3 times daily for 3 days (21 participants)
Outcomes	**SSI:** Participants were evaluated daily during their hospital stay. Subsequently, they were assessed at 1, 2, 4 and 6 weeks after the operation in the outpatient clinic Blinded clinical assessors evaluated all participants for infection based on the presence of the following clinical criteria, similar to previous studies: • Drainage or purulent exudates from the surgical site • Elevated body temperature (>37.5°C) for longer than 72 hours or sudden increase in body temperature after a normal temperature postoperatively • Increase in oedema, induration and erythema of wound edges and surrounding tissues • Unusual pain associated with the surgical site • Increased leucocyte count (> 10.10× 10^9/L) with an associated increase in immature forms of polymorphonuclear neutrophils • Elevated C-reactive protein level (> 0.76 mg/dL); localised, red, tender, overheated swelling, fluctuating or indurated
Notes	No adverse drug events were observed in this trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	All participants were randomly assigned in blocks of 4 to 2 groups, corresponding to a list of computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and surgeons were blinded to the postoperative prophylactic antibiotic regimen
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assesors were blinded to the postoperative prophylactic antibiotic regimen

Tan 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods were reported with sufficient details
Other bias	Low risk	No other biases were detected

Zijderveld 1999

Methods	Randomised controlled trial
Participants	**Number of participants enrolled:** 54 **Setting:** University Hospital Vrije Universiteit, Amsterdam, The Netherlands **Sex:** mean 25.5 years (18-40 years) **Age:** 24.07% male **Inclusion criteria:** not reported **Exclusion criteria:** history of allergy to penicillin or other beta-lactam antibiotics, any long-term medication use, use of antibiotics in the 4 weeks preceding admission and serum creatinine exceeding 110 mmol/L as an indication of renal dysfunction
Interventions	**Arm 1:** placebo (19 participants) 30 minutes before surgery **Arm 2:** 2200 mg amoxicillin-clavulanic acid 30 minutes before surgery (18 participants) **Arm 3:** 1500 mg cefuroxime 30 minutes before surgery (17 participants)
Outcomes	**SSI:** postoperatively and after 1 month The following criteria for infection were used. • Appearance of the wound on the third and seventh days postoperatively and after 1 month (subdivided into 4 categories: normal, oedematous, exudate with drainage of nonpurulent material or an abscess with drainage of purulent material with or without incision) • Presence of wound dehiscence was scored separately • In cases of drainage of purulent material, the pus was cultured and aerobic and anaerobic strains were identified • Body temperature and pulse rate were measured preoperatively, on the third and seventh days postoperatively and after 1 month • Furthermore, erythrocyte sedimentation rate (ESR) and the total white blood cell count were determined preoperatively, on the seventh day and after 1 month • For the purpose of this study, a wound infection was defined as any inflammatory condition previously described that prompted the surgeon to give additional treatment that was not part of the routine postoperative protocol
Notes	No adverse drug events were reported in this trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Zijderveld 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 3 groups, with no explanation how
Allocation concealment (selection bias)	Low risk	Code was maintained by the pharmacist during the entire period of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding is suggested
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific information about blinding of outcome assessors was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data were missing
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported with sufficient details
Other bias	Low risk	No other biases were detected

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

Study	Reason for exclusion
Bystedt 1987	No evidence suggested random allocation of participants
Danda 2011	Systematic review
Dumbach 1987	Participants underwent many types of maxillofacial surgery, and results for participants who underwent OS are not provided separately
Fenner 1950	Narrative review
Fridrich 1999	Discussion of a randomised controlled trial
Martis 1984	Retrospective study
Paterson 1970	Narrative review
Peterson 1976	Retrospective study
Schubert 1990	No evidence of random allocation of participants

(*Continued*)

Sixou 2006	Participants underwent any type of oral surgery
Spaey 2005	Case series
Tan 2011	Systematic review
Xiaoyi 1996	No clear description of the control arm. Study authors claim that participants received the standard of care; however, no standard of care is known, and additional details are not available
Yrastorza 1976	No evidence of random allocation of participants

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

NCT01823523

Trial name or title	Orthognathic Surgery and Postoperative Antibiotic Use
Methods	Double-blind randomised controlled trial
Participants	**Estimated enrolment:** 300 **Setting:** QEII VG hospital (Queen Elizabeth II Victoria General Hospital) **Inclusion criteria:** over 16 years old undergoing OS **Exclusion criteria:** use of antibiotics in past 2 weeks, active oral or odontogenic infection, significant medical condition, immunocompromised
Interventions	**Arm 1:** Group will be receiving 1 day of IV cefazolin or clindamycin followed by 2 days of oral cephalexin or clindamycin. Clindamycin will be used in participants with allergy **Arm 2:** Group will receive 1 day IV cefazolin or clindamycin followed by 2 days of oral placebo. Clindamycin will be used if participant has allergy
Outcomes	**Primary outcome measures:** rate of infection (time frame: 4 weeks following surgery), investigation of the incidence of postoperative infection following surgery in each of the 2 groups **Secondary outcome measures:** side effect from antibiotic use (time frame: 4 weeks), investigation of the incidence of side effects from an extended antibiotic regimen
Starting date	June 2013
Contact information	Clayton Davis, DDS 902-473-2070 cmd@dal.ca Victoria General Hospital Halifax, Nova Scotia, Canada, B3H 1W2 Canada
Notes	

DATA AND ANALYSES

Comparison 1. Short-term versus long-term antibiotic prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Surgical site infection	7	472	Risk Ratio (IV, Random, 95% CI)	0.42 [0.24, 0.74]

Comparison 2. Sensitivity analysis: short-term versus long-term antibiotic prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Surgical site infection	6	438	Risk Ratio (IV, Random, 95% CI)	0.41 [0.22, 0.75]

Comparison 3. Preoperative versus short-term antibiotic prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Surgical site infection	2	220	Risk Ratio (IV, Fixed, 95% CI)	0.34 [0.09, 1.22]
2 Adverse events	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Amoxicillin versus ampicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Surgical site infection	1		Risk Difference (IV, Random, 95% CI)	Totals not selected
2 Adverse events	1	42	Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Amoxicillin and clavulanic acid versus cefuroxime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Surgical site infection	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Short-term versus long-term antibiotic prophylaxis, Outcome 1 Surgical site infection.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 1 Short-term versus long-term antibiotic prophylaxis

Outcome: 1 Surgical site infection

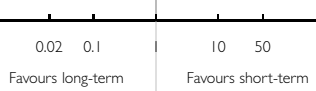
Study or subgroup	Long-term prophylaxis n/N	Short-term prophylaxis n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Ruggles 1984	0/20	3/20		3.8 %	0.14 [0.01, 2.60]
Jansisyanont 2008	1/60	1/62		4.2 %	1.03 [0.07, 16.15]
Fridrich 1994	1/14	1/16		4.5 %	1.14 [0.08, 16.63]
Bentley 1999	1/15	9/15		8.5 %	0.11 [0.02, 0.77]
Kang 2009	2/28	3/28		11.0 %	0.67 [0.12, 3.69]
Baqain 2004	2/17	4/17		13.2 %	0.50 [0.11, 2.38]
Samman 2010	8/80	19/80		54.7 %	0.42 [0.20, 0.91]
Total (95% CI)	**234**	**238**		**100.0 %**	**0.42 [0.24, 0.74]**

Total events: 15 (Long-term prophylaxis), 40 (Short-term prophylaxis)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.62$, df = 6 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 2.99 (P = 0.0028)

Test for subgroup differences: Not applicable

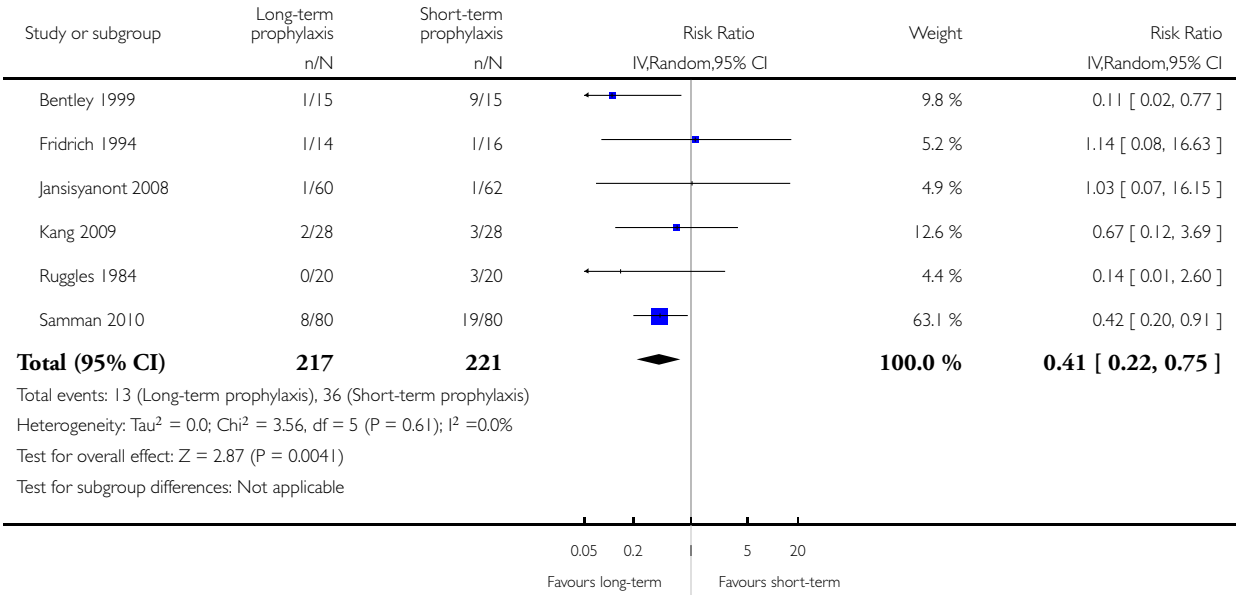


Analysis 2.1. Comparison 2 Sensitivity analysis: short-term versus long-term antibiotic prophylaxis, Outcome 1 Surgical site infection.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 2 Sensitivity analysis: short-term versus long-term antibiotic prophylaxis

Outcome: 1 Surgical site infection



Analysis 3.1. Comparison 3 Preoperative versus short-term antibiotic prophylaxis, Outcome 1 Surgical site infection.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 3 Preoperative versus short-term antibiotic prophylaxis

Outcome: 1 Surgical site infection

Study or subgroup	Short-term n/N	Preoperative n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Danda 2010	2/75	7/75		70.1 %	0.29 [0.06, 1.33]
Lindeboom 2003	1/35	2/35		29.9 %	0.50 [0.05, 5.27]
Total (95% CI)	**110**	**110**		**100.0 %**	**0.34 [0.09, 1.22]**

Total events: 3 (Short-term), 9 (Preoperative)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 1.65 (P = 0.099)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Preoperative versus short-term antibiotic prophylaxis, Outcome 2 Adverse events.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 3 Preoperative versus short-term antibiotic prophylaxis

Outcome: 2 Adverse events

Study or subgroup	Pre-operative n/N	Short-term n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lindeboom 2003	0/35	0/35			Not estimable
Total (95% CI)	**35**	**35**			**Not estimable**

Total events: 0 (Pre-operative), 0 (Short-term)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Amoxicillin versus ampicillin, Outcome 1 Surgical site infection.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 4 Amoxicillin versus ampicillin

Outcome: 1 Surgical site infection

Study or subgroup	Amoxicillin n/N	Ampicillin n/N	Risk Difference IV,Random,95% CI	Risk Difference IV,Random,95% CI
Tan 2011	3/21	6/21		-0.14 [-0.39, 0.10]

Analysis 4.2. Comparison 4 Amoxicillin versus ampicillin, Outcome 2 Adverse events.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 4 Amoxicillin versus ampicillin

Outcome: 2 Adverse events

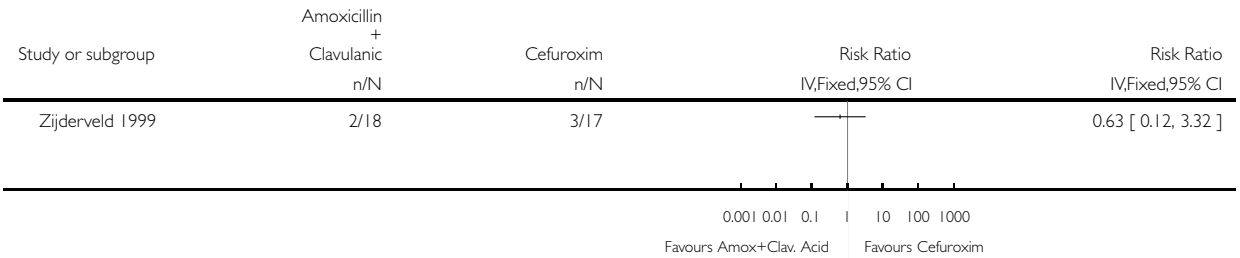
Study or subgroup	Amoxicillin n/N	Ampicillin n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Tan 2011	0/21	0/21			Not estimable
Total (95% CI)	**21**	**21**			**Not estimable**
Total events: 0 (Amoxicillin), 0 (Ampicillin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 5.1. Comparison 5 Amoxicillin and clavulanic acid versus cefuroxime, Outcome 1 Surgical site infection.

Review: Antibiotic prophylaxis for preventing infectious complications in orthognathic surgery

Comparison: 5 Amoxicillin and clavulanic acid versus cefuroxime

Outcome: 1 Surgical site infection



APPENDICES

Appendix 1. Ovid MEDLINE Search Strategy

1 exp Orthognathic Surgery/ (87)
2 exp Orthognathic Surgical Procedures/ (1052)
3 exp Osteotomy, Le Fort/ (1454)
4 (orthognathic adj5 surg*).tw. (2516)
5 (maxillary osteotom* or Le Fort osteotom* or (mandibular adj5 osteotom*) or vertical ramus osteotom* or genioplast*).tw. (2160)
6 or/1-5 (5695)
7 exp Antibiotic Prophylaxis/ (8683)
8 exp Anti-Bacterial Agents/ (527266)
9 (antibiotic* or cephalosporin* or cefazolin or cefuroxime or amox?cillin* or clindam?cin or penicillin* or levofloxacin).tw. (260904)
10 or/7-9 (629847)
11 6 and 10 (65)
12 randomized controlled trial.pt. (374960)
13 controlled clinical trial.pt. (88427)
14 randomi?ed.ab. (327203)
15 placebo.ab. (146420)
16 clinical trials as topic.sh. (170264)
17 randomly.ab. (193925)
18 trial.ti. (117951)
19 or/12-18 (878362)
20 exp animals/ not humans.sh. (3947165)
21 19 not 20 (807587)
22 11 and 21 (13)

Appendix 2. Ovid EMBASE search strategy

1 exp orthognathic surgery/ (1497)
2 exp maxilla osteotomy/ (2054)
3 (orthognathic adj5 surg*).tw. (2946)
4 (maxillary osteotom* or Le Fort osteotom* or (mandibular adj5 osteotom*) or vertical ramus osteotom* or genioplast*).tw. (2495)
5 or/1-4 (6681)
6 exp antibiotic prophylaxis/ (20802)
7 exp antibiotic agent/ (983143)
8 (antibiotic* or cephalosporin* or cefazolin or cefuroxime or amox?cillin* or clindam?cin or penicillin* or levofloxacin).tw. (345777)
9 or/6-8 (1089776)
10 5 and 9 (142)
11 Randomized controlled trials/ (52460)
12 Single-Blind Method/ (18336)
13 Double-Blind Method/ (115948)
14 Crossover Procedure/ (39087)
15 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab. (1331662)
16 (doubl$ adj blind$).ti,ab. (146816)
17 (singl$ adj blind$).ti,ab. (14503)
18 or/11-17 (1399256)
19 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (20296020)
20 human/ or human cell/ (14775294)
21 and/19-20 (14728616)
22 19 not 21 (5567404)
23 18 not 22 (1207860)
24 10 and 23 (20)

Appendix 3. EBSCO CINAHL search strategy

S23 S10 AND S22
S22 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21
S21 MH "Quantitative Studies"
S20 TI placebo* or AB placebo*
S19 MH "Placebos"
S18 TI random* allocat* or AB random* allocat*
S17 MH "Random Assignment"
S16 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S15 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S14 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S13 TI clinic* N1 trial* or AB clinic* N1 trial*
S12 PT Clinical trial
S11 MH "Clinical Trials+"
S10 S5 and S9
S9 S6 or S7 or S8
S8 TI ((antibiotic* or cephalosporin* or cefazolin or cefuroxime or amox?cillin* or clindam?cin or penicillin* or levofloxacin)) OR AB ((antibiotic* or cephalosporin* or cefazolin or cefuroxime or amox?cillin* or clindam?cin or penicillin* or levofloxacin))
S7 (MH "Antibiotics+")
S6 (MH "Antibiotic Prophylaxis")
S5 S1 or S2 or S3 or S4
S4 TI (mandibular N5 osteotom*) OR AB (mandibular N5 osteotom*)
S3 TI ((maxillary osteotom* or Le Fort osteotom* or vertical ramus osteotom* or genioplast*)) OR AB ((maxillary osteotom* or Le Fort osteotom* or vertical ramus osteotom* or genioplast*))
S2 TI (orthognathic N5 surg*) OR AB (orthognathic N5 surg*)

S1 (MH "Orthognathic Surgery")

CONTRIBUTIONS OF AUTHORS

Romina Brignardello-Petersen drafted the methods, results and discussion sections of the review, performed meta-analysis and assessed the quality of the evidence. She also edited complete the final version of the review and directed the screening process, data abstraction and risk of bias assessment.

Alonso Carrasco-Labra conceived of the review question and assisted with preparation of the methods section of the review. He assisted in statistical analysis, quality of evidence assessment and drafting of the final manuscript and was one of the full-text screening review authors.

Ignacio Araya and Nicolas Yanine drafted the background section. They also performed the title and abstract screening process and data abstraction.

Luis Cordova is a context expert. All aspects of the background and methodology related to the clinical application of the results are supported by his expertise. He also acted as a review author in the full-text screening process.

Julio Villanueva is a content expert. All aspects of the background and methodology related to clinical application of the results are supported by his expertise. He performed data abstraction and risk of bias assessments.

All authors approved the final version of the protocol and the final manuscript.

Contributions of editorial base

Nicky Cullum: edited the protocol; advised on methodology, interpretation and review content. Approved the final review before submission.
Liz McInnes, Editor: approved the final protocol before submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited and copy edited the protocol and edited the review.
Ruth Foxlee: designed the search strategy and ran the searches for the review.

DECLARATIONS OF INTEREST

Romina Brignardello-Petersen: non declared.

Alonso Carrasco-Labra: non declared.

Ignacio Araya: non declared.

Nicolas Yanine: non declared.

Luis Cordova: non declared.

Julio Villanueva: non declared.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes were made to the protocol.

- We had planned to perform a fixed-effect meta-analysis if heterogeneity was lower than 40%. However, because of variability in interventions and in some of the population characteristics, we decided that it was more appropriate to perform a random-effects meta-analysis, which allowed us to account for this variability.