

# Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications (Review)

Esposito M, Worthington HV, Loli V, Coulthard P, Grusovin MG



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[Intervention Review]

# Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

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## ABSTRACT

### Background

Some dental implant failures may be due to bacterial contamination at implant insertion. Infections around biomaterials are difficult to treat and almost all infected implants have to be removed. In general, antibiotic prophylaxis in surgery is only indicated for patients at risk of infectious endocarditis, for patients with reduced host-response, when surgery is performed in infected sites, in cases of extensive and prolonged surgical interventions and when large foreign materials are implanted. To minimise infections after dental implant placement various prophylactic systemic antibiotic regimens have been suggested. More recent protocols recommended short term prophylaxis, if antibiotics have to be used. With the administration of antibiotics adverse events may occur, ranging from diarrhoea to life-threatening allergic reactions. Another major concern associated with the widespread use of antibiotics is the selection of antibiotic-resistant bacteria. The use of prophylactic antibiotics in implant dentistry is controversial.

### Objectives

To assess the beneficial or harmful effects of systemic prophylactic antibiotics at dental implant placement versus no antibiotic/placebo administration and, if antibiotics are of benefit, to find which type, dosage and duration is the most effective.

### Search methods

The Cochrane Oral Health Group's Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched up to 2nd June 2010. Several dental journals were handsearched. There were no language restrictions.

### Selection criteria

Randomised controlled clinical trials (RCTs) with a follow up of at least 3 months comparing the administration of various prophylactic antibiotic regimens versus no antibiotics to patients undergoing dental implant placement. Outcome measures were prosthesis failures, implant failures, postoperative infections and adverse events (gastrointestinal, hypersensitivity, etc).

### Data collection and analysis

Screening of eligible studies, assessment of the methodological quality of the trials and data extraction were conducted in duplicate and independently by two review authors. Results were expressed as random-effects models using risk ratios (RRs) for dichotomous outcomes with 95% confidence intervals (CIs). Heterogeneity was to be investigated including both clinical and methodological factors.

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### **Main results**

Four RCTs were identified: three comparing 2 g of preoperative amoxicillin versus placebo (927 patients) and the other comparing 1 g of preoperative amoxicillin plus 500 mg 4 times a day for 2 days versus no antibiotics (80 patients). The meta-analyses of the four trials showed a statistically significant higher number of patients experiencing implant failures in the group not receiving antibiotics: RR = 0.40 (95% CI 0.19 to 0.84). The number needed to treat (NNT) to prevent one patient having an implant failure is 33 (95% CI 17 to 100), based on a patient implant failure rate of 5% in patients not receiving antibiotics. The other outcomes were not statistically significant, and only two minor adverse events were recorded, one in the placebo group.

### **Authors' conclusions**

There is some evidence suggesting that 2 g of amoxicillin given orally 1 hour preoperatively significantly reduce failures of dental implants placed in ordinary conditions. No significant adverse events were reported. It might be sensible to suggest the use of a single dose of 2 g prophylactic amoxicillin prior to dental implant placement. It is still unknown whether postoperative antibiotics are beneficial, and which is the most effective antibiotic.

## **PLAIN LANGUAGE SUMMARY**

### **Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications**

Missing teeth can sometimes be replaced with dental implants to which a crown, bridge or denture can be attached. Bacteria introduced during placement of implants can lead to infection and sometimes implant failure. It appears that the oral administration of 2 grams of amoxicillin 1 hour before placement of dental implants is effective in reducing implant failures. More specifically, giving antibiotics to 33 patients will avoid one patient experiencing early implant losses. It is still unclear whether postoperative antibiotics are of any additional benefits.

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

| Antibiotics compared with no antibiotics at placement of dental implants  |  |                        |                          |                              |                                 |          |
|---|--|------------------------|--------------------------|------------------------------|---------------------------------|----------|
| <b>Patient or population:</b> patients requiring dental implants<br><b>Settings:</b> dental practice<br><b>Intervention:</b> prophylactic antibiotics<br><b>Comparison:</b> no antibiotics or placebo   |  |                        |                          |                              |                                 |          |
| Outcomes  | Illustrative comparative risks* (95% CI) |                        | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|   | Assumed risk                             | Corresponding risk     |                          |                              |                                 |          |
|   | Without antibiotic                       | Antibiotic             |                          |                              |                                 |          |
| Implant failure at 4 months   | <b>Low risk population</b>               |                        | RR 0.40 (0.19 to 0.84)   | 1007 (4)                     | +++0 moderate quality           |          |
|   | 10 per 1000                              | 4 per 1000 (2 to 8)    |                          |                              |                                 |          |
|   | <b>High risk population</b>              |                        |                          |                              |                                 |          |
|   | 100 per 1000                             | 40 per 1000 (19 to 84) |                          |                              |                                 |          |
| *The basis for the <b>assumed risk</b> (e.g. the median control group risk across studies) is provided in footnotes. The <b>corresponding risk</b> (and its 95% CI) is based on the assumed risk in the comparison group and the <b>relative effect</b> 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 (+++0):** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality (++00):** 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 (+000):** We are very uncertain about the estimate.

## BACKGROUND

Dental implants are widely used for replacing missing teeth. Despite the high success rates published in the literature, implant failures do occur (Esposito 1998a). It is believed that a certain number of early dental implant losses are due to bacterial contamination at implant insertion (Esposito 1998b). It is known that infections around biomaterials are very difficult to treat and almost all infected implants have to be removed sooner or later (Esposito 1998b). The likelihood of an infection around dental implants is influenced by the surgical skill (traumatic and prolonged surgery is more likely to favour infections) and by the degree of asepsis. In general, antibiotic prophylaxis in surgery is only indicated in the following situations: patients at risk of infectious endocarditis, patients with reduced host-response, when surgery is performed in infected sites, in cases of extensive and prolonged surgical interventions and when large foreign materials are implanted.

In order to minimise infections after dental implant placement various prophylactic systemic antibiotic regimens have been suggested. Initially, antibiotics were recommended preoperatively and up to 10 days postoperatively, one of the most commonly followed protocols being the administration of 2 g of phenoxymethylpenicillin (penicillin-V), orally, about 1 hour preoperatively and then 2 g twice a day for 10 days (Adell 1985). More recent protocols (Flemmig 1990) recommended short term prophylaxis: 2 g of penicillin-V (or amoxicillin or amoxicillin/clavulanate) administered orally, 1 hour prior to surgery and 500 mg of penicillin-V 4 times a day for 1 day. The prolongation of the prophylaxis should not be extended beyond the first 3 postoperative days since it may not provide additional protection.

While on one hand it is important to minimise risk of implant failures, on the other it is sensible to minimise the use of antibiotics since adverse events may occur. Complications most commonly associated with the use of antibiotics range from diarrhoea to life-threatening allergic reactions. Another major concern associated with the widespread use of antibiotics is the selection of antibiotic-resistant bacteria.

The use of antibiotics in implant dentistry is controversial and some controlled clinical trials (CCTs) yielded contradictory results (Dent 1997; Gynther 1998; Laskin 2000; Binahmed 2005). The first study on this subject (Dent 1997) evaluated implant success at abutment connection (4 to 6 months after implant placement) comparing various dosages and various antibiotics given preoperatively and postoperatively, in most of the cases, versus no antibiotics or antibiotics given with an insufficient dosage in an unknown number of patients (2641 implants). Significantly fewer failures occurred in the antibiotic group (1.5% versus 4%). The study was updated by a second publication (Laskin 2000) that presented data with a follow up of 3 years after loading. There were 387 patients (1743 implants) in the antibiotic groups and 315 patients (1247 implants) in the control group. The results suggested fewer failures when antibiotics were used (4.6% versus 10%). This

multicentre trial was initially described as a randomised controlled trial (RCT), but in reality dentists were free to choose when to give antibiotics, which antibiotics to give, and which dosage to use. In addition, there was no blind assessment and patients were not considered the statistical unit of the analysis, so the possible clustering of failures was not taken into account. In a retrospective controlled clinical study (Gynther 1998), 147 patients (790 implants) who received 1 g of phenoxymethylpenicillin 1 hour preoperatively and 1 g every 8 hours postoperatively for 10 days were compared with 132 patients (664 implants) who did not receive any antibiotics. Both groups were treated at the same centre but at different time points (antibiotic group between 1980 and 1985; no antibiotic group between 1991 and 1995). No differences in survival rates were reported. In another prospective multicentre controlled clinical study (Binahmed 2005), the comparison was of a single preoperative dose of penicillin G or V (1,000,000 units) or 600 mg of clindamycin versus an identical preoperative dose plus 300 mg penicillin V orally 4 times a day, or in case of penicillin allergy, 150 mg clindamycin orally 3 times a day for 7 days. A single dose was given to 125 patients (445 implants) whereas long term prophylactic antibiotics were given to 90 patients (302 implants). Only biological complications were evaluated at 1, 2 weeks and just before abutment connection. There were no differences regarding biological complications: three wound dehiscences in each group, one developing an infection in the long term antibiotic group. The authors concluded that long term prophylactic antibiotic use was of no advantage or benefit over a single dose, however implant success, which should have been the primary outcome measure, was not evaluated. Unfortunately, all these studies were highly biased in their methodology, so the validity of their conclusions can be questioned. A recent systematic review on this topic concluded that there is little evidence for the use of antibiotic prophylaxis in general dentistry and recommended to monitor antibiotic use among dental practitioners (Schwartz 2007). It would be useful to know whether prophylactic antibiotics are effective in reducing postoperative infections and failures of dental implants and which is the most effective antibiotic, at what dose and duration.

## OBJECTIVES

### Primary objective

To test the null hypothesis of no difference in the proportion of prosthesis failures, implant failures, postoperative infections and adverse events between patients receiving antibiotic prophylaxis, and those receiving a placebo or no antibiotic, at placement of dental implants, against the alternative hypothesis of a difference.

### Secondary objective

To test the null hypothesis of no difference in the proportion of prosthesis failures, implant failures, postoperative infections and adverse events between groups of patients receiving different prophylactic antibiotics, or different doses/duration of the same antibiotic, against the alternative hypothesis of a difference.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled clinical trials (RCTs) with a follow-up of at least 3 months.

#### Types of participants

Any group of patients undergoing dental implant placement.

#### Types of interventions

- Administration of prophylactic antibiotics versus no antibiotics/placebo.
- Administration of different antibiotics.
- Administration of different doses or different duration of the same antibiotic.

#### Types of outcome measures

##### Primary outcomes

- Implant failure: implant mobility and removal of stable implants dictated by progressive marginal bone loss or infection.
- Prosthesis that could not be placed or prosthesis failure if secondary to implant failures.

##### Secondary outcomes

- Postoperative infections.
- Adverse events (gastrointestinal, hypersensitivity, etc).

### Search methods for identification of studies

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database. The search strategy used a combination of controlled vocabulary

and free text terms and was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009] (Higgins 2009). Details of the MEDLINE search are provided in [Appendix 1](#).

#### Searched databases

The Cochrane Oral Health Group's Trials Register (2nd June 2010) (see [Appendix 2](#)).

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 5) (see [Appendix 3](#)).

MEDLINE via OVID (1950 to 2nd June 2010) (see [Appendix 1](#)).

EMBASE via OVID (1980 to 2nd June 2010) (see [Appendix 4](#)).

The most recent electronic search was undertaken on 2nd June 2010.

#### Language

There were no language restrictions.

#### Unpublished studies

We wrote to all the authors of the identified RCTs, we checked the bibliographies of all identified RCTs and relevant review articles, and we used personal contacts in an attempt to identify unpublished or ongoing RCTs. In the first version of this review we also wrote to more than 55 oral implant manufacturers and we requested information on trials through an Internet discussion group (implantology@yahoo.com), however we discontinued this due to poor yield.

#### Handsearching

Details of the journals being handsearched by the Cochrane Oral Health Group's ongoing programme are given on the website: <http://www.ohg.cochrane.org/>.

The following journals have been identified as being potentially important to be handsearched for this review: *British Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *European Journal of Oral Implantology*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *International Journal of Prosthodontics*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral Implantology*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontology*, and *Journal of Prosthetic Dentistry*. Where these have not already been searched as part of the Cochrane Journal Handsearching Programme, the journals were handsearched by

one review author up to the month in which the last electronic search was undertaken.

## Data collection and analysis

### Study selection

The titles and abstracts (when available) of all reports identified through the electronic searches were scanned independently by two review authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. The full reports obtained from all the electronic and other methods of searching were assessed independently by two review authors to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted. All studies meeting the inclusion criteria then underwent validity assessment and data extraction. Studies rejected at this or subsequent stages were recorded in the table of excluded studies, and reasons for exclusion recorded.

### Data extraction

Data were extracted by two review authors independently using specially designed data extraction forms. The data extraction forms were piloted on several papers and modified as required before use. Any disagreement was discussed and a third review author consulted where necessary. All authors were contacted for clarification or missing information.

For each trial the following data were recorded.

- Year of publication, country of origin and source of study funding.
- Details of the participants including demographic characteristics, source of recruitment and criteria for inclusion.
- Details of the type of intervention.
- Details of the outcomes reported, including method of assessment, and time intervals.

### Measure of treatment effect

For each outcome, all of which were binary, the estimate of effect of an intervention was expressed as risk ratios together with 95% confidence intervals.

### Unit of analysis issues

The statistical unit was the patient and not the prosthesis or implant.

### Dealing with missing data

Trial authors were contacted to retrieve missing data where necessary. Data were excluded until further clarification was available if agreement could not be reached. Methods for estimating missing standard deviations in section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009) will be used. An ITT analysis was undertaken if data available and appropriate.

### Assessment of heterogeneity

The significance of any discrepancies in the estimates of the treatment effects from the different trials was to be assessed by means of Cochran's test for heterogeneity and heterogeneity would have been considered significant if  $P < 0.1$ . The  $I^2$  statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance, was used to quantify heterogeneity with  $I^2$  over 50% being considered moderate to high heterogeneity.

### Assessment of reporting biases

If there had been sufficient numbers of trials (more than 10) in any meta-analysis publication bias would have been assessed according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). If asymmetry was identified we would have examined possible causes.

### Data synthesis

Only if there were studies of similar comparisons reporting the same outcome measures a meta-analysis was done. Risk ratios were combined for dichotomous data, using random-effects models provided there were more than 3 studies in the meta-analysis. Numbers needed to treat (NNT) were calculated for patients affected by implant failures. The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009) recommendations were followed for studies with zero-cell counts. The fixed value of 0.5 was added to all cells with zero-cell counts and risk ratios calculated with the RevMan software. If there were no events in both arms, no calculations were undertaken because in this situation the study does not provide any indication of the direction or magnitude of the relative treatment effect.

### Subgroup analysis and investigation of heterogeneity

Clinical heterogeneity was to be assessed by examining the types of participants and interventions for all outcomes in each study. It was decided to formulate the following hypotheses to be investigated for subgroup analyses. However since the number of trials included in the meta-analysis was small (less than 10) this was not undertaken. This may be done in future updates of this review for the following subgroups:

- Single vs multiple implants.
- Postextractive implants vs implants in completely or partially healed sites.
  - Long vs short procedures.
  - Complicated versus simple procedures.

### Sensitivity analyses

It was planned to undertake sensitivity analyses to examine the effect of the study quality assessment on the overall estimates of effect. In addition, the effect of including unpublished literature on the review's findings was also to be examined. There were too few trials to undertake these analyses.

### Assessment of risk of bias in included studies

This was conducted using the recommended approach for assessing risk of bias in studies included in Cochrane reviews (Higgins 2009). It is a two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other

issues'). Each domain includes one specific entry in a 'Risk of bias' table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

The risk of bias assessment of the included trials was undertaken independently and in duplicate by two review authors as part of the data extraction process. In the case that the paper to be assessed had one or more review authors in the authors list, it was independently evaluated only by those review authors not involved in the trials.

### Summarising risk of bias for a study:

After taking into account the additional information provided by the authors of the trials, studies were grouped into the following categories. We assumed that the risk of bias was the same for all outcomes and each study was assessed as follows:

| Risk of bias          | Interpretation  | Within a study                                    | Across studies  |
|-----------------------|---|---|---|
| Low risk of bias.     | Plausible bias unlikely to seriously alter the results.         | Low risk of bias for all key domains.             | Most information is from studies at low risk of bias.   |
| Unclear risk of bias. | Plausible bias that raises some doubt about the results.        | Unclear risk of bias for one or more key domains. | Most information is from studies at low or unclear risk of bias   |
| High risk of bias.    | Plausible bias that seriously weakens confidence in the results | High risk of bias for one or more key domains.    | The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results |

## RESULTS

### Description of studies

See: [Characteristics of included studies](#).

See 'Characteristics of included studies' table.

### Included studies

Four randomised controlled trials (RCTs) were identified and included (Abu-Ta'a 2008; Esposito 2008a; Anitua 2009; Esposito 2010).

Two multicentre trials were conducted in Italy (Esposito 2008a; Esposito 2010), one multicentre trial in Spain (Anitua 2009), and one single-centre trial in Belgium (Abu-Ta'a 2008).

Two trials (Esposito 2008a; Esposito 2010) received free placebo and antibiotics from a patient working in a pharmaceutical company producing generic drugs. One trial was supported by the implant manufacturer (Anitua 2009). No external funding was received in the other trial (Abu-Ta'a 2008).

The multicentre trials were conducted in private practices (Esposito 2008a; Anitua 2009; Esposito 2010) and the single-centre trial (Abu-Ta'a 2008) in a university hospital.

### Interventions

The following hypotheses were tested.

**(1) Whether prophylactic antibiotics are effective in reducing failures and complications (four trials with 1007 patients).**

- One trial ([Abu-Ta'a 2008](#)) compared 1 g of amoxicillin given 1 hour preoperatively plus 500 mg of amoxicillin 4 times a day for 2 days versus no antibiotics. All patients rinsed with chlorhexidine digluconate for 1 minute just prior to surgery and postoperatively twice a day for 7 to 10 days. The perioral skin was disinfected for 30 seconds with cetrimonium bromide 0.5 and chlorhexidine 0.05 in water. Measures of asepsis included use of sterile drapes around the patient's mouth, head, and over the supine body of the patient, a meshed nose guard, and two suction tips (one only for the mouth and one only for the wound). Postoperative complications were assessed at 7 to 10 days and implant success at 5 months. An unknown type of dental implant was used.

- Two placebo-controlled trials ([Esposito 2008a](#); [Esposito 2010](#)) compared 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. One week prior to implant placement, all patients underwent at least one session of oral hygiene instruction and professionally delivered debridement when required. All patients rinsed with chlorhexidine digluconate for 1 minute just prior to surgery and postoperatively twice a day for at least 1 week. Operators were allowed to place and restore the implants according to their routine procedures. Postoperative complications were assessed at 1 and 2 weeks, and implant success at 4 months. Various implant systems brands were used (Zimmer Dental, Dentsply Friadent, Nobel Biocare, Intra-Lock, Camlog, Dyna, Biomet 3i, Endopore, Z-system, PF Tecom, Ghimas, Silpo, MegaGen and Geass).

- One placebo-controlled trial ([Anitua 2009](#)) compared 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. Patients received, during the days prior to the intervention, appropriate prophylaxis and adequate oral hygiene instructions. Antibiotics and other medications were not allowed 15 days before the surgery. All patients rinsed with 2% chlorhexidine digluconate for 1 minute just prior to surgery. Only single implants in medium bone quality were included and all implants were inserted after flap elevation. Before installation, implants were carefully humidified with liquid plasma rich in growth factors (PRGF). Peripheral blood (20 to 30 ml) from each patient was taken by venipuncture before surgery and placed directly into 9 ml tubes containing 3.8% (wt/vol) sodium citrate as anticoagulant. Liquid PRGF was prepared by centrifugation (PRGF System®, BTI) at 460 × g for 8 minutes at room temperature. 1 ml plasma fraction was collected and deposited in a glass dish. In order to initiate clotting, PRGF activator (calcium chloride) was added to the liquid PRGF preparation (50 µl PRGF activator per ml of preparation).

Postoperative infections were assessed at days 3, 10, 30 and 60. Implant stability was also evaluated at month 3 using Osstell. BTI dental implants were used.

**(2) Which is the most effective antibiotic, dose and duration (no trials).**

**Outcomes**

All trials reported all the outcome measures under investigation in the present review:

- Prosthesis failure: [Abu-Ta'a 2008](#); [Esposito 2008a](#); [Anitua 2009](#); [Esposito 2010](#).
- Implant failure: [Abu-Ta'a 2008](#); [Esposito 2008a](#); [Anitua 2009](#); [Esposito 2010](#).
- Postoperative infections: [Abu-Ta'a 2008](#); [Esposito 2008a](#); [Anitua 2009](#); [Esposito 2010](#).
- Adverse events: [Abu-Ta'a 2008](#); [Esposito 2008a](#); [Anitua 2009](#); [Esposito 2010](#).

**Duration of follow up**

- Three months after implant placement ([Anitua 2009](#)).
- Four months after implant placement ([Esposito 2008a](#); [Esposito 2010](#)).
- Five months after implant placement ([Abu-Ta'a 2008](#)).

**Main inclusion criteria**

- Any patient older than 18 years old, able to sign an informed consent, undergoing dental implant placement ([Esposito 2008a](#); [Esposito 2010](#)).
- Patients requiring single implants in bone of medium density. Bone density was measured in Hounsfield's (HU) on high resolution scans with the BTI Scan® program (BTI, Vitoria, Spain). Medium bone density was defined as from 400 to 1100 HU ([Anitua 2009](#)).
- Fully or partially edentulous patients ([Abu-Ta'a 2008](#)).

**Main exclusion criteria**

- At risk of bacterial endocarditis ([Abu-Ta'a 2008](#); [Esposito 2008a](#); [Esposito 2010](#)).
- Having implanted biomaterials in the body (hip or knee prostheses, etc) ([Esposito 2008a](#); [Esposito 2010](#)).
- Immunosuppressed or immunocompromised ([Abu-Ta'a 2008](#); [Esposito 2008a](#); [Esposito 2010](#)).
- Affected by diabetes (controlled or uncontrolled) ([Esposito 2008a](#); [Esposito 2010](#)).
- Uncontrolled diabetes mellitus ([Abu-Ta'a 2008](#)).

- Received radiotherapy in the head and neck area (Abu-Ta'a 2008; Esposito 2008a; Esposito 2010); only if > 5000 rads (Anitua 2009).
- Need of augmentation procedure concomitant with implant placement (Esposito 2008a; Esposito 2010).
- Allergic to penicillin (Abu-Ta'a 2008; Esposito 2008a; Anitua 2009; Esposito 2010).
- Presence of chronic/acute infections in the vicinity of the planned implant site (Esposito 2008a; Esposito 2010).
- Already under antibiotic treatment for any other reasons (Esposito 2008a; Anitua 2009; Esposito 2010).
- Treated or under treatment with intravenous amino-bisphosphonates (Esposito 2008a; Esposito 2010).
- Pregnant and lactating (Esposito 2008a; Esposito 2010).

**Sample size**

A priori calculation for the sample size was undertaken in 3 trials (Esposito 2008a; Anitua 2009; Esposito 2010).

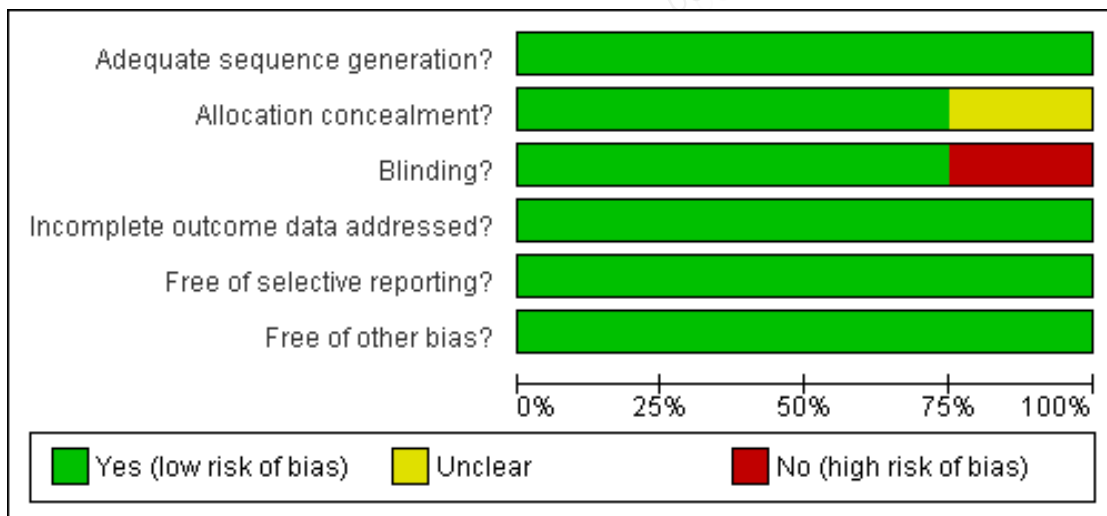
**Baseline comparability between treatment groups**

No apparent major baseline differences were observed in any of the trials (Abu-Ta'a 2008; Esposito 2008a; Anitua 2009; Esposito 2010).

**Risk of bias in included studies**

The final risk of bias assessment after having incorporated the additional information kindly provided by the author of one trial (Abu-Ta'a 2008) is summarised in Figure 1 and Figure 2. For each trial we assessed whether it was at low, unclear or high risk of bias. Three trials were judged to be at low risk of bias (Esposito 2008a, Anitua 2009, Esposito 2010) and one (Abu-Ta'a 2008) at high risk of bias.

**Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**



**Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

|                | Adequate sequence generation? | Allocation concealment? | Blinding? | Incomplete outcome data addressed? | Free of selective reporting? | Free of other bias? |
|----------------|-------------------------------|-------------------------|-----------|------------------------------------|------------------------------|---------------------|
| Abu-Ta'a 2008  | +                             | ?                       | -         | +                                  | +                            | +                   |
| Anitua 2009    | +                             | +                       | +         | +                                  | +                            | +                   |
| Esposito 2008a | +                             | +                       | +         | +                                  | +                            | +                   |
| Esposito 2010  | +                             | +                       | +         | +                                  | +                            | +                   |

### Effects of interventions

See: [Summary of findings for the main comparison](#)

The following hypotheses were tested.

#### (I) Whether prophylactic antibiotics are effective in reducing failures and complications (four trials with 1007 patients).

- One trial ([Abu-Ta'a 2008](#)) compared 1 g of amoxicillin given 1 hour preoperatively plus 500 mg of amoxicillin 4 times a day for 2 days versus no antibiotics. Forty patients were included in each group and none dropped out after 5 months. No prosthesis failed. Five implants failed in three patients who did not receive antibiotics. One patient in the antibiotic group and four patients in the control group experienced a postoperative infection. No adverse events were reported. No statistically

significant differences were observed for any of the outcome measures.

- One placebo-controlled trial ([Esposito 2008a](#)) compared 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. One hundred and sixty-five patients were included in each group, but seven patients from each group had to be excluded from the analyses for various reasons. Two patients in the antibiotic group experienced a prosthesis failure versus four patients in the placebo group. Two patients (two implants) in the antibiotic group experienced implant losses versus eight patients (nine implants) in the placebo group. Three patients in the antibiotic group presented sign of infection versus two patients in the placebo group. One minor adverse event was recorded in each group. No statistically significant differences were observed for any of the outcome measures.

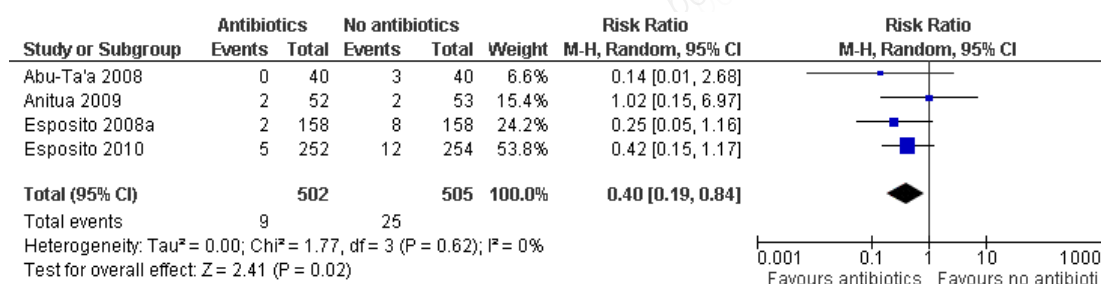
- One placebo-controlled trial (Anitua 2009) compared 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. Fifty-two patients were included in the antibiotic group and 53 in the placebo group. Two patients in each group experienced an implant/crown failure and six patients in each group experienced a postoperative infection. No adverse events were reported. No statistically significant differences were observed for any of the outcome measures.

- One placebo-controlled trial (Esposito 2010) compared 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. Two hundred and fifty-four patients were included in the antibiotic group and 255 in the placebo group, but two patients from the antibiotic group and one from the placebo group had to be excluded from the analyses for various reasons. Four patients in the antibiotic group experienced a prosthesis failure versus 10 patients in the placebo group. Five patients in the antibiotic group experienced seven implant losses versus 12 patients that lost 13 implants in the placebo group. Four patients

in the antibiotic group presented clear signs of infection versus eight patients in the placebo group. No adverse events were reported. No statistically significant differences were observed for any of the outcome measures.

In total 1007 patients were included in the four trials. More patients experienced implant losses in the group that did not receive antibiotics and this was statistically significant (Figure 3) risk ratio (RR) 0.40, 95% confidence interval (CI) 0.19 to 0.84. In order to illustrate the magnitude of the effect of implant failures, the number of patients needed to treat (NNT), i.e. given antibiotics, to prevent one patient having an implant failure is 33 (95% CI 17 to 100). This is based on a patient implant failure of 5% in patients not receiving antibiotics, as seen in the meta-analysis. No heterogeneity was observed in the meta-analysis ( $P = 0.62$ ;  $I^2 = 0\%$ ). The meta-analyses of the four trials for the other outcomes showed no statistically significant differences for prosthesis failures (Analysis 1.2), postoperative infections (Analysis 1.3), and adverse events (Analysis 1.4).

**Figure 3. Forest plot of comparison: 1 Antibiotics versus placebo/no antibiotics, outcome: 1.1 Implant failures.**



**(2) Which is the most effective antibiotic, dose and duration (no trials).**

**DISCUSSION**

The meta-analysis of four randomised controlled trials (RCTs) suggests that short term antibiotics (2 g of amoxicillin administered 1 hour prior to implant placement (Esposito 2008a; Anitua 2009; Esposito 2010) or 1 g of amoxicillin administered 1 hour prior to implant placement and 500 mg 4 times a day for 2 days postoperatively (Abu-Ta'a 2008)) significantly decrease early implant failures. This observation has important clinical implications, mean-

ing that antibiotics would prevent one patient experiencing an early implant loss every 33 patients receiving antibiotics. Only two minor adverse events were reported, one in the antibiotic group (diarrhoea and somnolence) and one in the placebo group (itching for 1 day), which suggest that the antibiotic regimens used may not have a tremendous negative impact on the patients' well-being. In other words the benefit of using short term antibiotics may outweigh the risks in the short term for individual patients.

All included trials appeared to be underpowered to detect a clinically significant difference, even though they showed clear trends favouring antibiotics. A statistically and clinically significant difference in implant failures was found after the meta-analyses. This underscores the importance of meta-analyses to increase sample size of individual trials to reach more precise estimates of the ef-

fects of interventions.

The studies were conducted in different environments: one trial was conducted in a hospital where very stringent asepsis procedures were implemented (Abu-Ta'a 2008), whereas three trials (Esposito 2008a; Anitua 2009; Esposito 2010) were conducted in various Italian and Spanish private practices where more 'relaxed' aseptic procedures might have been used. However, three trials (Abu-Ta'a 2008; Esposito 2008a; Esposito 2010) provided similar results, i.e. clear trends favouring the use of antibiotics, which strengthens the results of the meta-analyses. Conversely one trial (Anitua 2009) did not show any trends with both procedures achieving exactly the same results. It is difficult to explain this, however the sample size was small and the results could have been simply affected by the play of chance or by the different types of patients included. In fact, only patients receiving single implants in medium bone quality were included. It is possible that there is no benefit of using antibiotic prophylaxis when performing simple implant placement procedures in patients having ideal bone conditions. Therefore, dentists have to decide whether to provide or not prophylactic antibiotic cover according to the complexity of the placement procedure. On the other hand, it may not always be possible to predict with certainty how simple a surgical procedure could be.

While the efficacy of antibiotics in reducing early implant losses was evident, no apparent significant effects of antibiotics on the occurrence of postoperative infections were observed. A possible explanation is that asymptomatic infections could have determined the loss of some implants. The histocompatibility of the peri-implant tissues without apparent clinical sign of infection observed in a consecutive series of early failed implants was compatible with an asymptomatic infection failure modality (Esposito 1999).

In two trials (Esposito 2008a; Esposito 2010) it was decided not to include patients undergoing bone augmentation procedures concurrent to implant placement because it was known that patients could have undergone unnecessary risks of infections. This was based on the findings of a pilot placebo-controlled RCT (Lindeboom 2003) comparing a preoperative single dose of 2 g penicillin phenethicillin with a placebo in 20 patients undergoing intraoral buccal onlay grafting with resorbable barriers to allow implant placement (the implants were not placed in the study). Two patients developed an infection at both the receptor and donor sites; two patients developed a wound infection at the receptor site; and one patient developed an infection at the donor site only. All of these patients (50%) were in the placebo group. No infections were observed in the antibiotic group. It could be concluded that there was a statistically significant increased risk of having an infectious complication after bone augmentation with resorbable barriers without antibiotic prophylaxis.

Additional information can be obtained from two double-blinded RCTs evaluating the efficacy of prophylactic antibiotics used for bone augmentation procedures prior to implant placement

(Lindeboom 2005; Lindeboom 2006). One RCT (Lindeboom 2006) compared 2 g penicillin phenethicillin versus 600 mg of clindamycin as single dose in patients treated with block-shaped bone graft harvested from the mandibular ramus and covered by resorbable barriers (the implants were not placed in the study). Seventy-five patients were included in each group and the presence of infection was assessed weekly for 8 weeks. No statistically significant differences were observed for postoperative infections (four infections at the augmented sites of the penicillin phenethicillin versus two in the clindamycin group, and three infections at the donor site of each group). The findings of this trial suggest that both penicillins and clindamycin are effective in reducing infection at augmented sites. No side effects related to the single-administration of antibiotics were reported. The same group in another similar RCT (Lindeboom 2005) evaluated whether it was more effective to use a single dose of 600 mg clindamycin 1 hour prior to onlay bone grafting procedures followed by either placebo or 300 mg clindamycin every 6 hours for 1 day. Sixty-two patients were included in each group. No statistically significant differences were observed for postoperative infections (two infections at the augmented sites of the single dose group versus three infections in the 1 day group, and four infections at the donor sites of the single dose group versus two infections in the 1 day group). Again no side effects related to the administration of antibiotics were reported.

There are public health concerns regarding prolonged antibiotics usage, however we were unable to find any evidence suggesting that a single dose of 2 g of amoxicillin was associated with a significant selection of antibiotic-resistant bacteria, nor did the included trials suggest a significant occurrence of adverse events. In addition no statistically significant alterations in microflora composition were observed in one trial (Anitua 2009) where a preoperative and a 3-day postoperative microbiological evaluation was performed.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

There is evidence from a meta-analysis including four trials with 1007 patients suggesting that 2 g of amoxicillin given orally 1 hour preoperatively significantly reduce early failures of dental implants placed in ordinary conditions. More specifically, giving antibiotics to 33 patients will avoid one patient experiencing early implant losses. No statistically significant differences in postoperative infections and adverse events were observed. No major adverse events were reported. It might be sensible to suggest a routine use of a single dose of 2 g of prophylactic amoxicillin just before placing dental implants. It remains unclear whether an adjunctive use of postoperative antibiotics is beneficial, and which is the most effective antibiotic.

## Implications for research

Priority should be given to large pragmatic double-blinded RCTs evaluating the efficacy of prolonged antibiotic prophylaxis when compared to a single preoperative dose into those subgroups of patients where implant failures are more likely to occur, particularly in those patients receiving immediate post-extractive implants and augmentation procedures in conjunction with implant placement. It could be also useful to evaluate which could be the most effective antibiotic type.

## ACKNOWLEDGEMENTS

We wish to thank Anne Littlewood (Cochrane Oral Health Group) and Sylvia Bickley for their assistance with literature searching; Luisa Fernandez Mauleffinch and Phil Riley (Cochrane Oral Health Group) for their help with the preparation of this review; Richard Oliver, Minesh Talati and Peter Thomsen for their contributions in previous versions of the present review; Mahmoud Abu-Ta'a and Gorka Orive for providing us with information on their trials. We would also like to thank the following referees: Ian M Brook, Matteo Chiapasco, Anne-Marie Glenny, Lee Hooper, Jerome Lindeboom, David R Moles, Ian Needleman, Michele Nieri, and Gorka Orive.

## REFERENCES

### References to studies included in this review

#### Abu-Ta'a 2008 *{published data only}*

Abu-Ta'a M, Quirynen M, Teughels W, van Steenberghe D. Asepsis during periodontal surgery involving oral implants and the usefulness of peri-operative antibiotics: a prospective, randomized, controlled clinical trial. *Journal of Clinical Periodontology* 2008;**35**(1):58–63.

#### Anitua 2009 *{published data only}*

Anitua E, Aguirre JJ, Gorosabel A, Barrio P, Errazquin JM, Román P, et al. A multicentre placebo-controlled randomised clinical trial of antibiotic prophylaxis for placement of single dental implants. *European Journal of Oral Implantology* 2009;**2**(4):283–92.

#### Esposito 2008a *{published data only}*

Esposito M, Cannizzaro G, Bozzoli P, Consolo U, Felice P, Ferri V, et al. Efficacy of prophylactic antibiotics for dental implants: a multicentre placebo-controlled randomised clinical trial. *European Journal of Oral Implantology* 2008;**1**(1):23–31.

#### Esposito 2010 *{published data only}*

Esposito M, Cannizzaro G, Bozzoli P, Checchi L, Ferri V, Landriani S, et al. Effectiveness of prophylactic antibiotics at placement of dental implants: a pragmatic multicenter placebo-controlled randomized clinical trial. *European Journal of Oral Implantology* in press.

### Additional references

#### Adell 1985

Adell R, Lekholm U, Branemark PI. Surgical procedures. In: Branemark PI, Zarb GA, Albrektsson T editor(s). *Tissue-integrated prostheses*. Chicago: Quintessence Publishing Co, Inc, 1985:211–32.

#### Binahmed 2005

Binahmed A, Stoykewych A, Peterson L. Single preoperative dose versus long-term prophylactic antibiotic regimens in dental implant surgery. *The International Journal of Oral and Maxillofacial Implants* 2005;**20**(1):115–7.

#### Dent 1997

Dent CD, Olson JW, Farish SE, Bellome J, Casino AJ, Morris HF, et al. The influence of preoperative antibiotics on success of endosseous implants up to and including stage II surgery: a study of 2,641 implants. *Journal of Oral and Maxillofacial Surgery* 1997;**55**(12 Suppl 5):19–24.

#### Egger 1997

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 1997;**315**(7109):629–34.

#### Esposito 1998a

Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (I) Success criteria and epidemiology. *European Journal of Oral Sciences* 1998;**106**(1):527–51.

#### Esposito 1998b

Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (II) Etiopathogenesis. *European Journal of Oral Sciences* 1998;**106**(3):721–64.

#### Esposito 1999

Esposito M, Thomsen P, Ericson LE, Lekholm U. Histopathologic observations on early oral implant failures. *The International Journal of Oral and Maxillofacial Implants* 1999;**14**(6):798–810.

#### Flemmig 1990

Flemmig TF, Newman MG. Antimicrobials in implant dentistry. In: Newman MG, Kornman K editor(s). *Antibiotics/antimicrobial use in dental practice*. Chicago: Quintessence Publishing Co, Inc, 1990:187–200.

#### Gynther 1998

Gynther GW, Kondell PA, Moberg LE, Heimdahl A. Dental implant installation without antibiotic prophylaxis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* 1998;**85**(5):509–11.

#### Higgins 2009

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated

September 2009]. The Cochrane Collaboration, 2009. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

**Laskin 2000**

Laskin DM, Dent CD, Morris HF, Ochi S, Olson JW. The influence of preoperative antibiotics on success of endosseous implants at 36 months. *Annals of Periodontology* 2000;**5**(1):166–74.

**Lindeboom 2003**

Lindeboom JA, van den Akker HP. A prospective placebo-controlled double-blind trial of antibiotic prophylaxis in intraoral bone grafting procedures: a pilot study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* 2003;**96**(6):669–72.

**Lindeboom 2005**

Lindeboom JA, Tuk JG, Kroon FH, van den Akker HP. A randomized prospective controlled trial of antibiotic prophylaxis in intraoral bone grafting procedures: single-dose clindamycin versus 24-hour clindamycin prophylaxis. *Mund-, Kiefer- und Gesichtschirurgie* 2005;**9**(6):384–8.

**Lindeboom 2006**

Lindeboom JA, Frenken JW, Tuk JG, Kroon FH. A randomized prospective controlled trial of antibiotic prophylaxis in intraoral bone-grafting procedures: preoperative single-dose penicillin versus preoperative single-dose clindamycin. *International Journal of Oral and Maxillofacial Surgery* 2006;**35**(5):433–6.

**Schwartz 2007**

Schwartz AB, Larson EL. Antibiotic prophylaxis and postoperative complications after tooth extraction and

implant placement: a review of the literature. *Journal of Dentistry* 2007;**35**(12):881–8.

**References to other published versions of this review**

**Esposito 2003**

Esposito M, Coulthard P, Oliver R, Thomsen P, Worthington HV. Antibiotics to prevent complications following dental implant treatment. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [Art. No.: CD004152. DOI: 10.1002/14651858.CD004152]

**Esposito 2008**

Esposito M, Grusovin MG, Talati M, Coulthard P, Oliver R, Worthington HV. Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [Art. No.: CD004152. DOI: 10.1002/14651858.CD004152.pub2]

**Esposito 2008b**

Esposito M, Grusovin MG, Coulthard P, Oliver R, Worthington HV. The efficacy of antibiotic prophylaxis at placement of dental implants: a Cochrane systematic review of randomized controlled clinical trials. *European Journal of Oral Implantology* 2008;**1**(2):95–103.

**Esposito 2010b**

Esposito M, Grusovin MG, Loli V, Coulthard P, Worthington HV. Effectiveness of prophylactic antibiotics at placement of dental implants: a Cochrane systematic review. *European Journal of Oral Implantology* in press.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Abu-Ta'a 2008

|               |  |
|---------------|--|
| Methods       | Parallel RCT of 5 months duration. No drop outs.   |
| Participants  | Partially and fully edentulous patients. Adults treated at the Department of Periodontology of the University Hospital of the Catholic University Leuven. Patients were excluded if they were allergic to penicillins, needing endocarditis prophylaxis, immunodeficient, with uncontrolled diabetes mellitus, irradiated in the head and neck area. 40 patients included in each group and results given for 40 |
| Interventions | 1 g of amoxicillin given 1 hour preoperatively plus 500 mg of amoxicillin 4 times a day for 2 days versus no antibiotics. Unknown type of dental implants  |
| Outcomes      | Implant failures, postoperative infections, adverse events, microbiological evaluation. Postoperative infections were assessed 7 to 10 days after placement, and implant success at 5 months   |
| Notes         |  |

#### *Risk of bias*

| Item                          | Authors' judgement | Description  |
|-------------------------------|--------------------|--|
| Adequate sequence generation? | Yes                | Quoted from the article: "These patients were randomly assigned into one of two groups (with and without antibiotics = AB) of 40 patients each using random sampling with masking of the person performing the randomization."<br>Author's replay: "After verification of the inclusion criteria, 80 patients were enrolled into the study. All patients were assigned a patient number, and were randomly assigned to one of the two treatment regimens. Assignment was performed by one of our department's nurses using a randomization table and by applying the simple randomization method." |
| Allocation concealment?       | Unclear            | No information provided in the article.<br>Author's reply: "Masking: It was maintained up to the day of implant installation. Afterwards, of course, it was difficult to maintain the masking since patients were asked about their postoperative experiences and any side effect of the antibiotic when   |

**Abu-Ta'a 2008** (Continued)

|  |     |  |
|--|-----|--|
|  |     | removing the stitches.”  |
| Blinding?<br>All outcomes                          | No  | Quoted from the article: “Both the surgical team and the patients were blinded to the groups.”<br>Author’s reply: “No, see above.” |
| Incomplete outcome data addressed?<br>All outcomes | Yes | No missing data or excluded patients.  |
| Free of selective reporting?                       | Yes | All outcome measures reported.   |
| Free of other bias?                                | Yes | No other bias identified.  |

**Anitua 2009**

|               |   |
|---------------|---|
| Methods       | Parallel RCT of 3 months duration. No drop outs.  |
| Participants  | Only patients needing single implants in medium bone quality were included and all implants were inserted after flap elevation. Adults treated in 8 private Spanish dental practices. Patients were excluded if they were allergic to beta-lactam antibiotics, had concurrent local or systemic infections requiring antibiotic treatment, had systemic diseases that contraindicate the surgery including cardiovascular diseases, respiratory diseases, haematological and metabolic disorders, bone diseases, collagenosis, immunodeficiencies and renal insufficiency, received irradiation to the head and neck (> 5000 rads). 52 patients included in the antibiotic group and 53 in the placebo group and results given for 52 and 53 patients, respectively |
| Interventions | 2 g of amoxicillin given 1 hour preoperatively compared with identical placebo tablets. Before installation, implants were carefully humidified with liquid plasma rich in growth factors (PRGF). Postoperative infections were assessed at days 3, 10, 30 and 60. At month 3 also implant stability was evaluated using Osstell. BTI dental implants were used   |
| Outcomes      | Implant failures (assessed with Ostell at 3 months), postoperative infections, adverse events, microbiological evaluation. Postoperative infections were assessed 3 days, 10 days, 1 month and 3 months after placement   |
| Notes         |   |

**Risk of bias**

| Item                          | Authors’ judgement | Description  |
|-------------------------------|--------------------|--|
| Adequate sequence generation? | Yes                | Quoted from the article: “The randomisation was performed using a random numbers table, assigning each patient to one of two treatment groups (active or placebo). Each of the enrolled patients had a patient |

**Anitua 2009** (Continued)

|  |     |   |
|--|-----|---|
|  |     | number and, according to the randomisation table, was assigned to each treatment group.”  |
| Allocation concealment?                            | Yes | Quoted from the article: “Both researchers and patients remained blinded to the received treatment group. For this purpose, the tablets corresponding to each patient were included in a package identified only by the study number and the patient code. Researchers had a sealed envelope for each patient to establish the randomly assigned treatment if necessary. The envelope was opened at the end of the study. Only in those situations in which the clinician observed any side-effect was the envelope opened before.” |
| Blinding?<br>All outcomes                          | Yes | See above.  |
| Incomplete outcome data addressed?<br>All outcomes | Yes | No missing data or excluded patients.   |
| Free of selective reporting?                       | Yes | All outcome measures reported.  |
| Free of other bias?                                | Yes | No other bias identified.   |

**Esposito 2008a**

|               |  |
|---------------|--|
| Methods       | Multicentre placebo-controlled parallel RCT of 4 months duration. 7 exclusions from each group for various explained reasons   |
| Participants  | Partially and fully edentulous patients. Adults treated in 11 private Italian dental practices. Patients were excluded if they were allergic to penicillins, needing endocarditis prophylaxis, had implanted prostheses, immunodeficient, diabetic, required bone augmentation at implant placement, with infections in the vicinity of the implant site(s), irradiated in the head and neck area, already under antibiotic treatment, treated or under treatment with intravenous amino-bisphosphonates, pregnant or lactating. 165 patients included in each group and results given for 158 |
| Interventions | 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. Operators were allowed to place and restore the implants according to their routine procedures. Various implant systems brands were used (Zimmer Dental, Dentsply Friadent, Nobel Biocare, Intra-Lock, Camlog, Dyna, Biomet 3i, and Endopore)   |
| Outcomes      | Prosthesis and implant failures, postoperative complications, adverse events. Postoperative complications were assessed 1 and 2 weeks after placement, and implant stability at  |

**Esposito 2008a** (Continued)

|  |                           |   |
|--|---------------------------|---|
|  | 4 months                  |   |
| Notes  |                           |   |
| <b>Risk of bias</b>                                |                           |   |
| <b>Item</b>  | <b>Authors' judgement</b> | <b>Description</b>  |
| Adequate sequence generation?                      | Yes                       | Quoted from the article: "Twelve computer generated restricted randomization lists with equal groups of participants were made."  |
| Allocation concealment?                            | Yes                       | Quoted from the article: "Only one of the investigators (Dr Marco Esposito), not involved in the selection and treatment of the patients, was aware of the randomization sequence and could have access to the randomization lists stored in his password protected portable computer. The randomized codes (1 or 2) were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially 1 hour prior to implant placement and patients assumed 2 tablets taken from identical white plastic containers labelled with the same code of the envelopes (1 or 2), containing the antibiotic or identical placebo tablets. Therefore treatment allocation was concealed to the investigators in charge of enrolling and treating the patients..." |
| Blinding?<br>All outcomes                          | Yes                       | Quoted from the article: "...and both patients and operators/outcome assessors were blinded to the tested intervention. Also the statistician was kept blind and performed all analyses without knowing to which group the patients were allocated."  |
| Incomplete outcome data addressed?<br>All outcomes | Yes                       | All exclusions and missing data reported and explained.   |
| Free of selective reporting?                       | Yes                       | All outcome measures reported.  |
| Free of other bias?                                | Yes                       | No other bias identified.   |

**Esposito 2010**

|               |  |
|---------------|--|
| Methods       | Multicentre placebo-controlled parallel RCT of 4 months duration. Two exclusions from the antibiotic group and one from the placebo group for various explained reasons  |
| Participants  | Partially and fully edentulous patients. Adults treated in 10 private Italian dental practices. Patients were excluded if they were allergic to penicillins, needing endocarditis prophylaxis, had implanted prostheses, immunodeficient, diabetic, required bone augmentation at implant placement, with infections in the vicinity of the implant site(s), irradiated in the head and neck area, already under antibiotic treatment, treated or under treatment with intravenous amino-bisphosphonates, pregnant or lactating. 254 patients included in the antibiotic group and 255 in the placebo group and results given for 242 and 254 patients, respectively |
| Interventions | 2 g of amoxicillin given 1 hour preoperatively with identical placebo tablets. Operators were allowed to place and restore the implants according to their routine procedures. Various implant systems brands were used (Zimmer Dental, Dentsply Friadent, Nobel Biocare, Intra-Lock, Camlog, Dyna, Biomet 3i, Endopore, Z-system, PF Tecom, Ghimas, Silpo, MegaGen and Geass)   |
| Outcomes      | Prosthesis and implant failures, postoperative complications, adverse events. Postoperative complications were assessed 1 and 2 weeks after placement, and implant stability at 4 months   |
| Notes         |  |

***Risk of bias***

| Item                          | Authors' judgement | Description  |
|-------------------------------|--------------------|--|
| Adequate sequence generation? | Yes                | Quoted from the article: "Thirteen computer generated restricted randomization lists with equal groups of participants were made."   |
| Allocation concealment?       | Yes                | Quoted from the article: "Only one of the investigators (Dr Marco Esposito), not involved in the selection and treatment of the patients, was aware of the randomization sequence and could have access to the randomization lists stored in his password protected portable computer. The randomized codes (1 or 2) were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes were opened sequentially 1 hour prior to implant placement and patients assumed 2 tablets taken from identical white plastic containers labelled with the same code of the envelopes (1 or 2), containing the antibiotic or identical placebo tablets. Therefore treatment allo- |

**Esposito 2010** (Continued)

|  |     |  |
|--|-----|--|
|  |     | cation was concealed to the investigators in charge of enrolling and treating the patients..."   |
| Blinding?<br>All outcomes                          | Yes | Quoted from the article: "...and both patients and operators/outcome assessors were blinded to the tested intervention. Also the statistician was kept blind and performed all analyses without knowing to which group the patients were allocated." |
| Incomplete outcome data addressed?<br>All outcomes | Yes | All exclusions and missing data reported and explained.  |
| Free of selective reporting?                       | Yes | All outcome measures reported.   |
| Free of other bias?                                | Yes | No other bias identified.  |

RCT = randomised controlled trial

## DATA AND ANALYSES

### Comparison 1. Antibiotics versus placebo/no antibiotics

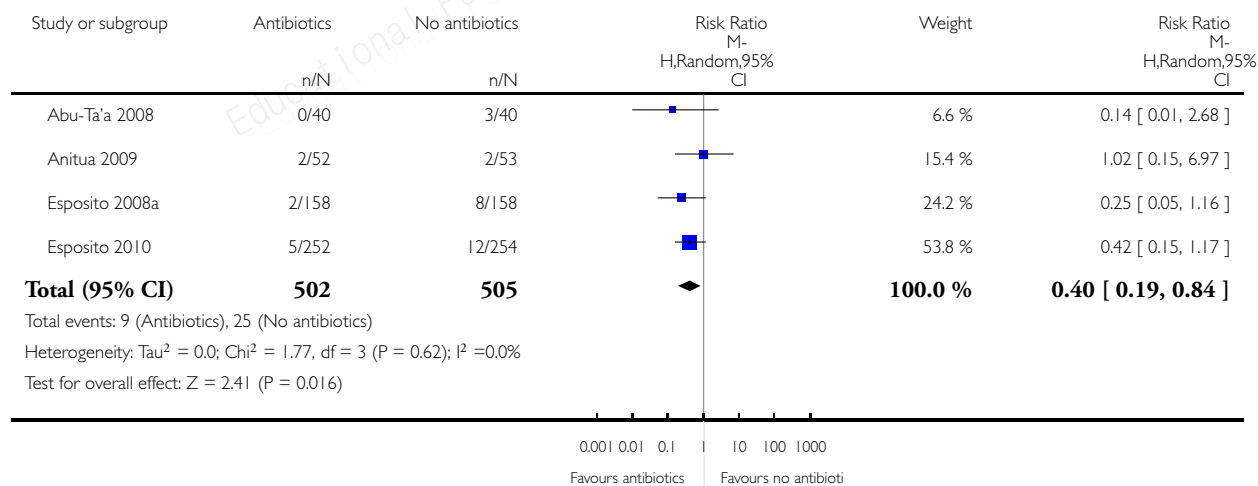
| Outcome or subgroup title  | No. of studies | No. of participants | Statistical method               | Effect size       |
|----------------------------|----------------|---------------------|----------------------------------|-------------------|
| 1 Implant failures         | 4              | 1007                | Risk Ratio (M-H, Random, 95% CI) | 0.40 [0.19, 0.84] |
| 2 Prosthesis failures      | 4              | 1007                | Risk Ratio (M-H, Fixed, 95% CI)  | 0.50 [0.22, 1.17] |
| 3 Postoperative infections | 4              | 1007                | Risk Ratio (M-H, Random, 95% CI) | 0.74 [0.37, 1.47] |
| 4 Adverse events           | 4              | 1007                | Risk Ratio (M-H, Fixed, 95% CI)  | 1.0 [0.06, 15.85] |

#### Analysis 1.1. Comparison 1 Antibiotics versus placebo/no antibiotics, Outcome 1 Implant failures.

Review: Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

Comparison: 1 Antibiotics versus placebo/no antibiotics

Outcome: 1 Implant failures

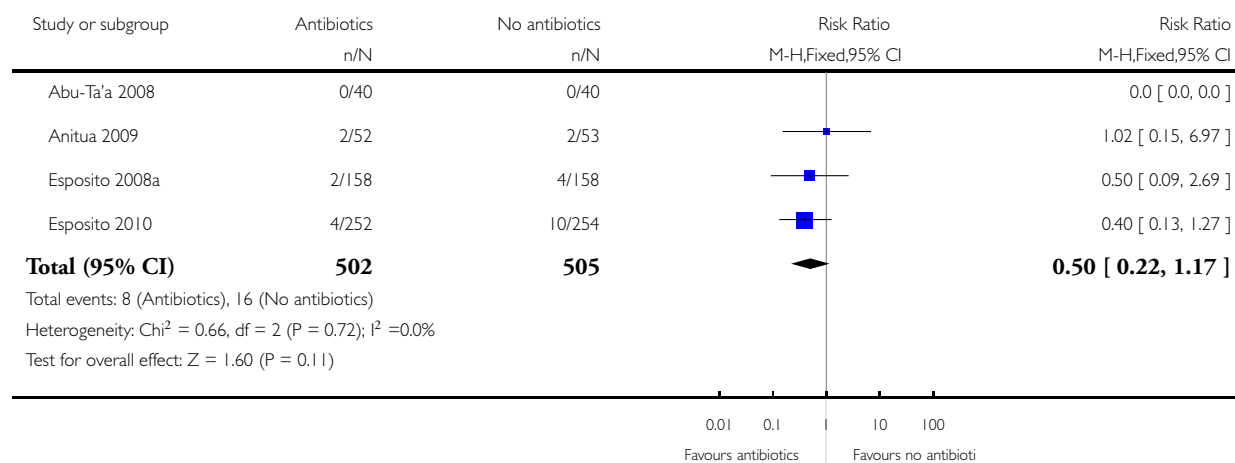


### Analysis 1.2. Comparison 1 Antibiotics versus placebo/no antibiotics, Outcome 2 Prosthesis failures.

Review: Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

Comparison: 1 Antibiotics versus placebo/no antibiotics

Outcome: 2 Prosthesis failures

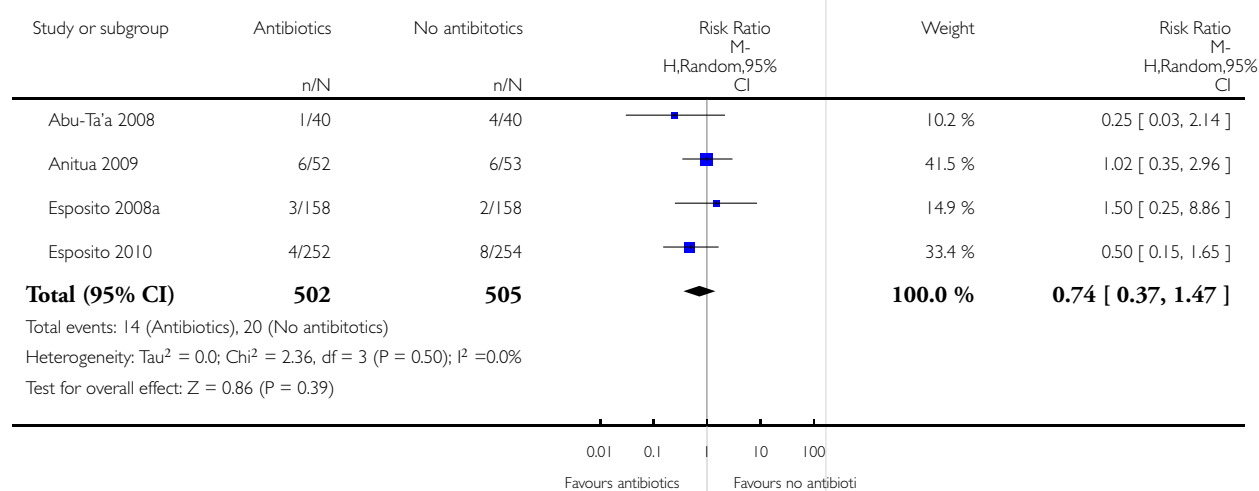


### Analysis 1.3. Comparison 1 Antibiotics versus placebo/no antibiotics, Outcome 3 Postoperative infections.

Review: Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

Comparison: 1 Antibiotics versus placebo/no antibiotics

Outcome: 3 Postoperative infections

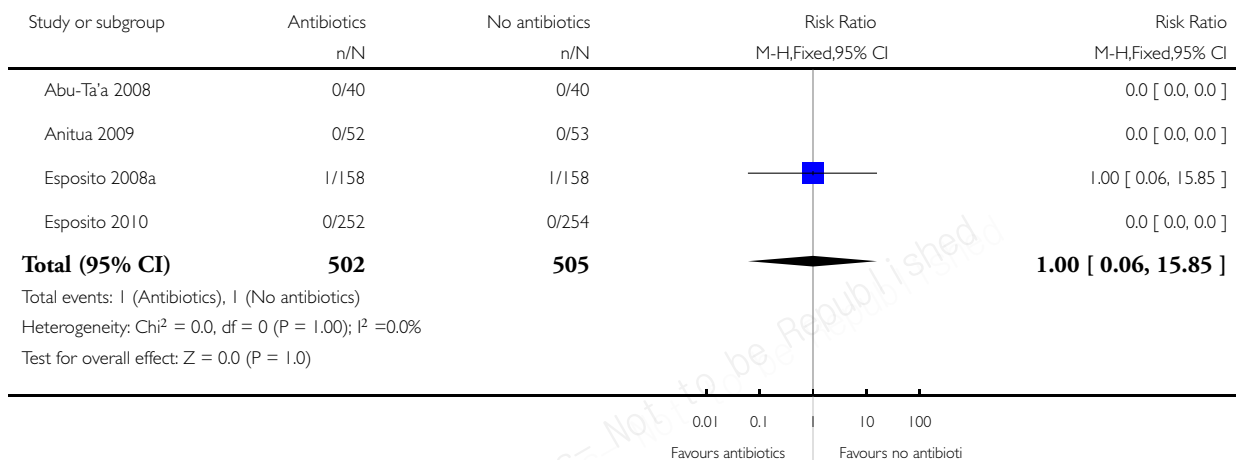


#### Analysis 1.4. Comparison 1 Antibiotics versus placebo/no antibiotics, Outcome 4 Adverse events.

Review: Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications

Comparison: 1 Antibiotics versus placebo/no antibiotics

Outcome: 4 Adverse events



## APPENDICES

### Appendix I. Search strategy for MEDLINE (OVID)

1. exp Dental Implants/
2. exp Dental Implantation/ or dental implantation
3. exp Dental Prosthesis, Implant-Supported/
4. ((osseointegrated adj implant\$) and (dental or oral))
5. dental implant\$
6. (implant\$ adj5 dent\$)
7. (((overdenture\$ or crown\$ or bridge\$ or prosthesis or restoration\$) adj5 (Dental or oral)) and implant\$)
8. "implant supported dental prosthesis"
9. ("blade implant\$" and (dental or oral))
10. ((endosseous adj5 implant\$) and (dental or oral))
11. ((dental or oral) adj5 implant\$)
12. OR/1-11

This search was run with the Cochrane Highly Sensitive Search Strategy (CHSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of The Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009].

1. randomized controlled trial.pt.

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

## Appendix 2. The Cochrane Oral Health Group Trials Register Search Strategy

(dental-implants OR "dental implant\*" OR "oral implant\*" OR dental-implantation OR dental-prosthesis-implant-supported OR "implant supported" OR "implant supported prosthesis" OR dental-implantation-endosseous-endodontic OR "endosseous implant\*" OR blade-implantation OR "blade implant\*" OR (implant\* AND (oral OR dental)) or dental-implantation-subperiosteal OR "subperiosteal implant" OR (implant\* AND overdenture\*) OR ((overdenture\* OR crown\* OR bridge\* OR prosthesis OR prostheses OR restoration\*) AND ("dental implant\*" OR "Oral implant" OR (zygoma\* AND implant\*))))

## Appendix 3. The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) Search Strategy

- #1 DENTAL IMPLANTS explode all trees (MeSH)
- #2 DENTAL IMPLANTATION explode all trees (MeSH)
- #3 DENTAL PROSTHESIS IMPLANT-SUPPORTED single term (MeSH)
- #4 ((osseointegrat\* near implant\*) and (dental\* or oral\*))
- #5 (dental next implant\*)
- #6 (implant\* near dent\*)
- #7 dental-implant\*
- #8 ((overdenture\* near dental\*) and implant\*)
- #9 ((overdenture\* near oral\*) and implant\*)
- #10 ((crown\* near dental\*) and implant\*)
- #11 ((crown\* near oral\*) and implant\*)
- #12 ((bridge\* near dental\*) and implant\*)
- #13 ((bridge\* near oral\*) and implant\*)
- #14 ((prosthesis near dental\*) and implant\*)
- #15 ((prosthesis near oral\*) and implant\*)
- #16 ((prostheses near dental\*) and implant\*)
- #17 ((prostheses near oral\*) and implant\*)
- #18 ((restoration\* near dental\*) and implant\*)
- #19 ((restoration\* near oral\*) and implant\*)
- #20 (implant next supported next dental next prosthesis)
- #21 (blade next implant\*)
- #22 ((endosseous near implant\*) and dental)
- #23 ((endosseous near implant\*) and oral\*)
- #24 ((dental\* near implant\*) or (oral\* near implant\*))
- #25 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)

## Appendix 4. EMBASE Search Strategy

1. tooth implantation/
2. ((implant-supported or implant\$) adj support\$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
3. ((osseointegrated adj implant\$) and (dental or oral)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
4. ((dental implant\$ or dental-implant or implant\$) adj (dent\$ or oral or tooth)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
5. (((overdenture\$ or crown\$ or bridge\$ or prosthesis or prostheses or restoration\$) adj5 (dental or oral)) and implant\$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6. "implant supported dental prosthesis".mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. ("blade implant\$" and (dental or oral or tooth or teeth)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8. ((endosseous adj5 implant\$) and (dental or oral or tooth or teeth)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
9. ((dental or oral or tooth or teeth) and implant\$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
10. or/1-9

The above search was run with the Cochrane Oral Health Group's search strategy for isolating RCTs in EMBASE:

1. random\$.ti,ab.
2. factorial\$.ti,ab.
3. (crossover\$ or cross over\$ or cross-over\$).ti,ab.
4. placebo\$.ti,ab.
5. (doubl\$ adj blind\$).ti,ab.
6. (singl\$ adj blind\$).ti,ab.
7. assign\$.ti,ab.
8. allocat\$.ti,ab.
9. volunteer\$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

## WHAT'S NEW

Last assessed as up-to-date: 1 June 2010.

| Date         | Event  | Description   |
|--------------|--|---|
| 15 June 2010 | New citation required but conclusions have not changed | New authorship.   |
| 15 June 2010 | New search has been performed                          | Substantive amendment. New search. New methods. 2 new included studies. Conclusions not changed |

## HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 3, 2003

| Date       | Event  | Description  |
|------------|--|--|
| 2 May 2008 | Amended  | Converted to new review format.  |
| 2 May 2008 | New citation required and conclusions have changed | Substantive amendment. Title was modified. 2 randomised controlled trials were included. The conclusions changed |
| 2 May 2008 | New search has been performed                      | Search updated to January 2008.  |

## CONTRIBUTIONS OF AUTHORS

Conceiving, designing and co-ordinating the review: Marco Esposito (ME).

Developing search strategy and undertaking searches: ME, Paul Coulthard (PC).

Screening search results and retrieved papers against inclusion criteria: ME, PC, Vassiliki Loli (VL).

Writing to authors for additional information: ME.

Appraising quality: Maria Gabriella Grusovin (GG), VL, ME.

Data extraction: ME, GG, VL.

Analysis and interpretation of the data: ME, Helen Worthington (HW).

Writing the review: ME.

Providing general advice on the review: PC, GG.

Performing previous work that was the foundation of current study: ME, PC.

## DECLARATIONS OF INTEREST

Marco Esposito is the first author of two of the included studies, however, he was not involved in the quality assessment of these trials.

## SOURCES OF SUPPORT

### Internal sources

- School of Dentistry, The University of Manchester, UK.

### External sources

- Swedish Medical Research Council (9495), Sweden.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Antibiotic Prophylaxis [adverse effects]; Amoxicillin [administration & dosage]; Anti-Bacterial Agents [administration & dosage]; Bacterial Infections [\*prevention & control]; Dental Implants [\*adverse effects]; Dental Restoration Failure; Drug Administration Schedule; Jaw, Edentulous, Partially [\*surgery]; Randomized Controlled Trials as Topic

### MeSH check words

Humans