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SYSTEMATIC REVIEW

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Is routine antibiotic prophylaxis warranted in dental implant surgery to prevent early implant failure? – a systematic review

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Abstract

Background The question of whether antibiotic prophylaxis should be administered routinely for dental implant surgery is unresolved. Despite the lack of conclusive supportive evidence, antibiotics are often administered to reduce the risk of infection, which could lead to early implant failure. Increasing antibiotic resistance is a major concern and it is therefore important to reduce the overall use of antibiotics, including in dentistry. The aim of the present systematic review and meta-analysis was to evaluate the efficacy of preoperative antibiotics in preventing early implant failure, in overall healthy patients undergoing dental implant surgery.

Methods An electronic search was undertaken of PubMed (Medline), Web of Science and the Cochrane Library up to October 1st, 2023, to identify randomized clinical trials (RCTs). All RCTs comparing antibiotic prophylaxis with no antibiotics/placebo in overall healthy patients receiving dental implants were included. The primary outcome was patients with early implant failure. Risk of bias was assessed, data were extracted, a meta-analysis was done, and GRADE certainty-of-evidence ratings were determined. The risk ratio (RR), the risk difference (RD) and 95% confidence intervals (CI) were estimated.

Results After removal of duplicates, 1086 abstracts were screened, and 17 articles were reviewed in full text. Seven RCTs with moderate or low risk of bias and with a total of 1859 patients and 3014 implants were included in the meta-analysis. With reference to early implant failure at patient level, the meta-analysis failed to disclose any statistically significant difference (RR: 0.66, 95% CI: 0.30-1.47) between antibiotic prophylaxis and a placebo. The risk difference was -0.007 (95% CI: -0.035-0.020) leading to a number needed to treat (NNT) of 143.

Conclusion Antibiotic prophylaxis for dental implant surgery does not seem to have any substantial effect on early implant failure (⨁⨁⨁◯). The results do not support routine antibiotic prophylaxis for dental implant surgery.

Keywords Dental implants, Antibiotic prophylaxis, Implant failure

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Background

Dental implants are commonly used to replace missing teeth in patients who have lost a tooth, or teeth, primarily due to dental caries, periodontal disease, or trauma [1]. While the procedure generally has a high success rate, complications can occur. The biological complications may be early or late. Early failure can be defined as loss of the implant within the first months after insertion and is usually due to lack of osseointegration [2]. Early implant failures have been attributed to bacterial contamination during implant surgery [3]. However, other factors have also been implicated, such as surgical technique, implant characteristics (size, length and surface characteristics of the dental implant), the surgeon's experience, a history of periodontitis and smoking habits [4–6].

To reduce the risk of infection, leading to failure of osseointegration, antibiotics can be administered in conjunction with implant surgery. Initially, the recommended routine was to administer antibiotics, both pre- and postoperatively, to all patients [7]. This routine was questioned as early as 25 years ago [8] and the issue of whether antibiotic prophylaxis is of benefit to implant placement remains unresolved. To date, no placebo-controlled, randomized clinical trial (RCT) has been able to show any statistically significant association between antibiotic prophylaxis and a reduction in the rate of early implant failure [9–19]. While one explanation might be that the RCTs were underpowered, two of the RCTs included quite large sample sizes, 506 [11] and 473 patients [12] respectively: conducting even larger RCTs would probably prove impractical.

Nevertheless, in reviews and meta-analyses it has been possible to compile studies with non-significant results and to show statistically that antibiotic prophylaxis significantly reduces early implant failures in healthy patients [20–24]. However, showing that antibiotic prophylaxis leads to a statistically significant reduction in the rate of early implant failure does not necessarily mean that routine antibiotic prophylaxis is clinically relevant. There is a need to determine the risk difference of implant failure when antibiotic prophylaxis is compared with a placebo. If this is very low, then perhaps antibiotic prophylaxis should be avoided. It is well known that all use of antibiotics contributes to the development of antibiotic resistance, which is a major global concern [25, 26]. Thus each dose of antibiotics, whether in healthcare or dentistry, should be carefully considered and prescribed only if it is truly necessary.

The consequences of early implant loss must be weighed against the risks associated with unnecessary administration of antibiotics to multiple patients. In this assessment, opinions differ. Some systemic reviews [20–23, 27–30] conclude that antibiotic prophylaxis is indicated to prevent early implant failure in healthy patients, whereas others conclude that routine use of antibiotics may not be warranted in such patients [31–35]. Inconsistent conclusions and opinions about the benefit of antibiotic prophylaxis for implant surgery have contributed to difficulties in formulating clear and generally acceptable guidelines.

Because of the limited number of RCTs in the field, previous systematic reviews and meta-analyses [20–24, 27–30, 33–35] have included studies which were not placebo-controlled, or not blinded, or which for other reasons were judged to have a high risk of bias. However, new RCTs have been published [12–14] in the last two years, one of which have not been included in any systematic review to date [14]. New, well-conducted RCTs should make it possible to conduct a meta-analysis without having to include RCTs with a high risk of bias. We therefore considered that a new systematic review was warranted, which included the most recent RCT and included the aspect of certainty of evidence, which has not been included in any published systematic review to date. The present study comprises a systematic review and meta-analysis. The aim was twofold: to evaluate the efficacy of preoperative antibiotics in prevention of early dental implant failure in healthy patients and secondly, to determine the certainty of the evidence.

Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [36]. The protocol for the current study was registered at: https://www.crd.york.ac.uk/prospero (ID code: CRD42021292610).

Focused question

The focused question was: "What is the effect of antibiotic prophylaxis compared to placebo/no antibiotics in overall healthy patients undergoing dental implant surgery regarding implant failure?"

The predefined study population, intervention, comparing therapies and outcome parameters (PICO) were:

- P (population): Patients without serious health issues undergoing dental implant surgery
- I (intervention): Administration of systemic prophylactic antibiotics in conjunction with dental implant surgery
- C (comparison): Administration of a placebo, or no antibiotic therapy in conjunction with dental implant surgery
- O (outcome): Early implant failure (implants which had to be removed before prosthetic loading, due to lack of osseointegration)

Eligibility criteria

Studies which met the following criteria were included:

Inclusion criteria

- Study population of at least 20 patients
- Randomized controlled trials (RCTs)
- At least 2 months' follow-up

Exclusion criteria

- Studies on mini-implants or orthodontic mini-screws
- Studies on immediate implant placement at a site with apical pathology
- Studies which included patients whose medical history indicated the need for antibiotic prophylaxis prior to dental implant surgery

Information sources and search strategies

Three electronic databases were searched: PubMed (Medline), the Cochrane Library and Web of Science, Table 1. The authors designed and undertook the searches in collaboration with information specialists at Malmö University. The searches included articles published up to October 1st, 2023. The review authors PM and BG carried out duplicate hand searches of the reference lists of relevant literature. Further searches were undertaken of the online databases providing information about ongoing clinical trials (clinicaltrials.gov; www.centerwatch.com/clinical-trials). An article identified by at least one of the two review authors was included for further scrutiny.

Data collection process

Initially, duplicates were removed from the database searches and the hand searches: thereafter, two of the authors (PM and BG) independently reviewed titles and abstracts of the retrieved studies for possible inclusion, according to the inclusion/exclusion criteria. In case of any ambiguity, the study was included. Selected studies were read in full text, also independently, by at least two of the five review authors. The studies were read to verify that they met the inclusion and exclusion criteria. During this process, any lack of consensus arising among the review authors was resolved by discussion. Reasons

Table 1 Search strategies used in the databases

Database	Search terms	References found
PubMed (Medline)	(("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ((("dental*"[Title/Abstract] AND "implant*"[Title/Abstract]) OR ("dental*"[Title/Abstract] AND "prosthes*"[Title/Abstract]) OR ("osseointegrat*"[Title/Abstract] AND "implant*"[Title/Abstract] AND ("oral"[Title/Abstract] OR "dental"[Title/Abstract])) OR (("overdentur*"[Title/Abstract] OR "crown*"[Title/Abstract] OR "bridge*"[Title/Abstract] OR "restoration*"[Title/Abstract]) AND ("dental"[Title/Abstract] OR "oral"[Title/Abstract]) AND "implant*"[Title/Abstract]) OR "implant supported dental prosthesis"[Title/Abstract] OR ("blade"[Title/Abstract] AND "implant*"[Title/Abstract] AND ("dental"[Title/Abstract] OR "oral"[Title/Abstract])) OR ("endosseous"[Title/Abstract] AND "implant*"[Title/Abstract] AND ("dental"[Title/Abstract] OR "oral"[Title/Abstract])) OR (("dental"[Title/Abstract] OR "oral"[Title/Abstract]) AND "implant*"[Title/Abstract]) OR "Dental Implants"[MeSH Terms] OR "Dental Implantation"[MeSH Terms] OR "dental prosthesis, implant supported"[MeSH Terms] OR "Bone-Anchored Prosthesis"[MeSH Terms]) AND ("antibiotic*"[Title/Abstract] OR ("Anti-Bacterial"[Title/Abstract] AND "agent*"[Title/Abstract]) OR "penicillin*"[Title/Abstract] OR "lincosamid*"[Title/Abstract] OR "Anti-Bacterial Agents"[MeSH Terms] OR "Penicillins"[MeSH Terms] OR "Antibiotic Prophylaxis"[MeSH Terms] OR "Chemoprevention"[MeSH Terms] OR "Lincosamides"[MeSH Terms]))	635
Cochrane Library	#1: antibiotic* OR (Anti-Bacterial AND Agent*) OR penicillin* OR lincosamid* #2: (Dental* AND implant*) OR (Dental* prosthes* OR osseointegrat* AND implant*) AND (oral OR dental) OR (overdentur* OR crown* OR bridge* OR restoration*) AND (dental OR oral) AND implant* OR "implant supported dental prosthesis" OR (blade AND implant*) AND (dental OR oral) OR (endosseous AND implant*) and (dental OR oral) OR ((dental OR oral) AND implant*) Searched: #1 AND #2	332
Web of Science	#1: antibiotic* OR (Anti-Bacterial AND Agent*) OR penicillin* OR lincosamid* (All Fields) #2: (Dental* AND implant*) OR (Dental* prosthes* OR osseointegrat* AND implant*) AND (oral OR dental) OR (overdentur* OR crown* OR bridge* OR restoration*) AND (dental OR oral) AND implant* OR "implant supported dental prosthesis" OR (blade AND implant*) AND (dental OR oral) OR (endosseous AND implant*) AND (dental OR oral) OR ((dental OR oral) AND implant*) (All Fields) **#**3: ((randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))) (All Fields) Searched: #1 AND #2 AND #3	300

MeSH Medical Subject Headings, used to index articles in the National Library of Medicine

for exclusion were recorded. A data extraction form was prepared, and the review authors PM and BG were calibrated. These two review authors extracted data independently and the remaining review authors checked that the data had been extracted correctly. Only information of relevance to the present systematic review was registered. All original clinical trials had implant failure as either a primary or a secondary outcome. Other relevant data such as age, gender, number of included patients, operation technique, number of implants, type of implants, follow-up time, and type of drugs administered were also extracted from the included original clinical trials. In cases of inadequate data, trial authors were contacted to provide additional information to complete the data collection process.

Study risk of bias assessment

After calibration, each of the five review authors independently assessed the risk of bias of each of the included studies. This was followed by a discussion among all the review authors, to reach consensus on points of difference. The risk of bias in randomized clinical trials of intervention tool (RoB-2) [37] was used to assess the studies as having low, moderate, or high risk of bias. The overall bias assessment for each study was determined by taking into consideration the results from each domain in the risk of bias tool that was used.

Synthesis methods

Studies assessed as having low or moderate risk of bias were included in the meta-analysis. A random effects model (Hedges) was used to calculate risk ratios (RR) and risk differences (RD). Statistical heterogeneity was assessed and presented with I^2 and Q statistics. Additional meta-analyses were made by creating two subgroups: one comprising only the studies using amoxicillin and the other comprising all studies except for the two which included patients who underwent immediate implant placement into extraction sockets.

Amoxicillin is the most common type of prophylactic antibiotic used in dental implant surgery and amoxicillin was used in all included studies except for one study where clindamycin was used. As clindamycin is an antibiotic with completely different properties than amoxicillin, it was decided to create a subgroup that excluded the study that used clindamycin to report only the effect of amoxicillin. The decision to create a subgroup that excluded the two studies that included immediate implant placement in extraction sockets was because these studies included a method reported to have a higher risk of failure.

Stata 16 SE was used for statistical calculations.

Certainty assessment

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [38] approach was used to determine the certainty of evidence related to the outcome "implant failure" in the RCTs, as high, moderate, low, or very low.

Results

Study selection

The search yielded a total of 1267 records. After removing 182 duplicates, 1085 titles and titles and abstracts were read and analyzed for relevancy. Of these, 1069 records were excluded, and the remaining 16 articles were read in full text. Hand-searches yielded yet another study that was read in full-text and included for further assessment. Five of these articles [39–43] were excluded because they were either not randomized, or they lacked a control group given no antibiotics or a placebo, Table 2. Hence, twelve studies were eligible for risk of bias assessment and seven were ultimately included in the meta-analysis. The flow charts presented in Fig. 1 illustrate the screening process.

Risk of bias in studies

Table 3 presents the risk of bias in the 12 studies included in the qualitative analysis. Five were judged to have an overall high risk of bias and were therefore excluded [16–19, 44]. Comments on these studies are presented in Table 4. Four studies were considered to have a low overall risk of bias [12–15]. Three studies were considered to have a moderate overall risk of bias, due to moderate risk of bias in the domain "Conflict of Interest" [9–11]. The existence of a number of RCTs within the scope of this review enabled the exclusion of studies with a high risk of bias. Exclusion of such RCTs increases the credibility of the results of the meta-analysis.

Table 2 Comments regarding reason for exclusion of studies read in full text

Author	Reason for exclusion
Binahmed et al. (2005) [39] Canada	Not randomized
Laskin et al. (2000) [41] USA	Not randomized
Karaky et al. (2011) [40] Jordan	Not randomized
Arduino et al. (2015) [42] Italy	Lacked control group given no antibiotics/ placebo
El-Kholey et al. (2014) [43] Saudi Arabia	Lacked control group given no antibiotics/ placebo

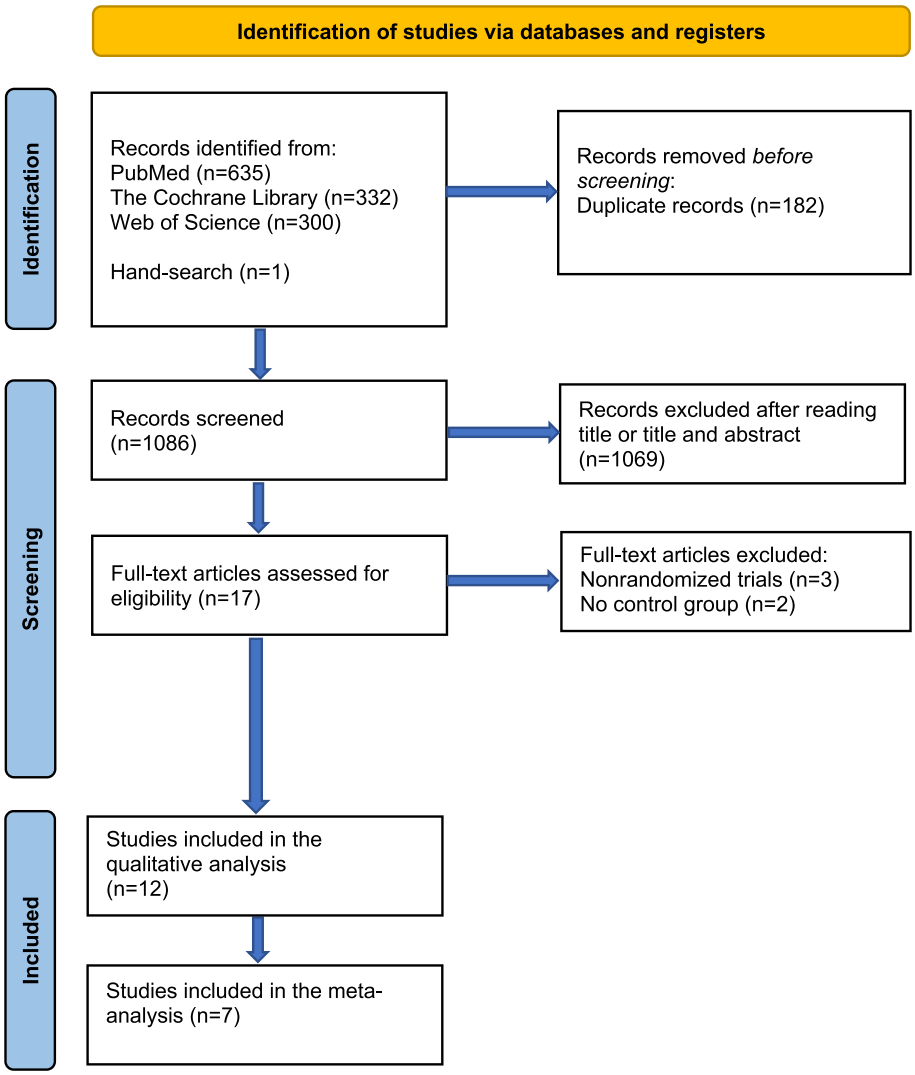

Fig. 1 Flow chart illustrating the screening process for eligible primary studies

Characteristics of studies included in the meta-analysis

Six of the seven studies included in the meta-analysis were multicenter RCTs [9–13, 15]. Six were conducted in Europe [9–14] and one in Asia [15]. Three studies were undertaken in private dental clinics [9–11], three mainly in university clinics [13–15], and one mainly in specialist public dental clinics [12]. Patients were recruited and treated from January 2006 to June 2021. All RCTs were double-blinded. In five RCTs, administration of 2 g of amoxicillin 1 hour prior to surgery was compared with a placebo [9–12, 15], one RCT compared 2 g of amoxicillin 1 hour prior to surgery + 500 mg thrice daily on days 1-3 after surgery, with a placebo [13] and one RCT compared 600 mg of clindamycin 1 hour prior to surgery with a placebo [14]. Three RCTs included patients who received conventional single implant placement without any bone-augmentation [9, 14, 15]. Two RCTs included a smaller number of implants inserted into fresh extraction sockets: 136 implants (19.5%) [10] and 136 implants (14.0%) [11], respectively. One RCT also included patients who underwent implant placement with simultaneous minor bone augmentation, a sinus lift, or guided bone regeneration (GBR), a total of 127 patients (29.9%) [12]. Finally, one RCT included only cases requiring implant placement with simultaneous GBR [13]. In this RCT, one study implant per patient was randomly selected. The main characteristics of the seven RCTs included in the meta-analysis are presented in Table 5.

The outcome variable "early implant failure" refers to the loss of an implant within the first few months after placement and before loading with the supraconstruction. [45] Most studies refer to an initial healning period of three to six months for evaluation of early implant failure, however is has been shown that the initial process of

Table 3 Methodological assessment of the remaining RCTs after full text assessment (*n*=12) with the Risk of Bias in RCTs of interventions (RoB-2) tool Abu-Ta'a et al. (2008) [18], Anitua et al. (2009) [9], Caiazzo et al. (2021) [49], Esposito et al. (2008) [10], Esposito et al. (2010) [11], Kashani et al. (2019) [44], Momand et al. (2022) [12], Moslemi et al. (2015) [19], Nolan et al. (2014) [17], Payer et al. (2020) [13], Santamaría Arrieta et al. (2022) [14], Tan et al. (2016) [15]

RCT	**Overall risk of bias**	Risk of bias arising from randomization process	Risk of bias due to deviations from intended interventions	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported results	Conflicts of interest
Abu-Ta'a et al (2007)	🔴	🟢	🟢	🟢	🔴	🟢	🟢
Anitua et al (2009)	🟡	🟢	🟢	🟢	🟢	🟢	🟡
Caiazzo et al (2021)	🔴	🟡	🔴	🟢	🟡	🟡	🟡
Esposito et al (2008)	🟡	🟢	🟢	🟢	🟢	🟢	🟡
Esposito et al (2010)	🟡	🟢	🟢	🟢	🟢	🟢	🟡
Kashani et al (2019)	🔴	🔴	🔴	🟢	🟡	🔴	🟢
Momand et al (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Moslemi et al (2015)	🔴	🟢	🟢	🟢	🟢	🔴	🟢
Nolan et al (2013)	🔴	🟢	🟢	🔴	🟢	🔴	🟢
Payer et al (2020)	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Santamaría Arrieta et al (2022)	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Tan et al (2013)	🟢	🟢	🟢	🟢	🟢	🟢	🟢

Risk of bias: 🟢 = low
🟡 = moderate
🔴 = high

soft and hard tissue integration following implant installation typically requires 6-12 weeks. [6, 46, 47]. The timing of early implant failure was not clearly reported in any of the included RCTs. Implant stability was tested at the final follow-up which took place 3-6 months [12], 4 months [10, 11] 3 months [9, 13], 2 months [14, 15] after placement.

With respect to the outcome measurement, there was some degree of heterogeneity among the included RCTs. The following definitions were used to consider early implant failure: Implant survival measured by testing the stability [9], implant mobility measured manually and/or any infection dictating implant removal [10, 11], implants lost or low implant stability [12], implant stability (Yes/No) [13], loss or removal of an implant (peri-implant radiolucency, manual mobility, or low implant stability) [14], implant stability [15]. In all, 1859 patients and 3014 implants were analyzed. Implant failure was observed in a total of 51 patients (2.7%).

Results of included studies

In the seven included studies, 929 patients received antibiotics and 930 were given placebos. Early implant failures occurred in 20 (2.2%) patients in the antibiotic group and 31 (3.3%) in the placebo group. The implant failure outcomes in the individual RCTs are presented in Table 6. In four of the RCTs the implant failure rate was lower in the groups given antibiotic prophylaxis [10–12, 15]. In two of the RCTs the implant failure rate was lower in the group receiving placebos [13, 14] and in one of the RCTs, the rate of implant failure was the same in both groups [9]. Overall, implant failure rates were very low and did not exceed 6.5% in any group, antibiotic or placebo. Two of the RCTs measured PROMs (Patient Reported Outcome Measures): pain and/or quality of life [13, 15]. Individually, none of the seven RCTs reported any statistical difference in the outcomes "early implant failure" or "postoperative infection".

Results of synthesis

As shown in Fig. 2, meta-analysis of the outcome measure of the seven included studies showed no significant difference between the groups (RR: 0.66, 95% CI: 0.30-1.47, P= 0.21). The risk difference (RD) was -0.007 (95% CI: -0.035-0.020), Fig. 3. A risk difference of -0.007 yielded an NNT of 143 (95% CI: 29-∞) to prevent implant failure in one patient. Meta-analysis of the subgroup of the six studies using amoxicillin [9–13, 15] resulted in RR: 0.60

Table 4 Comments regarding RCTs with high risk of bias

RCT	Comments
Abu-Ta'a et al. (2008) [18] Belgium	No placebo Treatment subjects not blinded Unclear outcome measurements Unclear randomization protocol No published study protocol
Caiazzo et al. (2011) [16] Italy	No placebo Treatment subjects not blinded Unclear outcome measurements Unclear presentation of baseline data Unclear randomization process and allocation concealment
Kashani et al. (2019) [44] Sweden	No placebo Treatment subjects not blinded Unclear randomization process Unclear outcome measurements
Moslemi et al. (2015) Iran	Unclear randomization protocol Unclear definition of outcome measure No published study protocol
Nolan et al. (2013) Ireland	Methods used to produce allocation sequence not presented No presentation of number of implants placed in treatment groups Unclear definition of outcome measure Very high loss to follow-up (28 patients, 35%) No published study protocol

(95% CI: 0.27-1.31) and RD: -0.011 (95% CI -0.029-0.006), Figs. 4 and 5. Meta-analysis of the subgroup comprising five studies (excluding the two [10, 11] which included patients undergoing immediate implant placement into extraction sockets) resulted in RR: 1.10 (95% CI: 0.35-3.45) and RD: 0.002 (95% CI: -0.027-0.030), Figs. 6 and 7. None of the subgroup meta-analyses showed a significant difference between the antibiotic group and the placebo group, Figs. 4, 5, 6 and 7. The results from all the meta-analyses are summarized in Table 7.

Certainty of evidence

The certainty of the scientific evidence in support of the hypothesis that "the effect of antibiotic prophylaxis in preventing implant failure is small" was moderate (⨁⨁⨁◯). Table 8 presents a summary of findings.

Discussion

This systematic review and meta-analysis included seven placebo-controlled, double-blinded RCTs assessed as having a low or moderate risk of bias. With reference to early implant failure, none of these RCTs could report any statistically significant difference between the antibiotic group and the placebo group. In two of the included RCTs, the trial authors conclude that routine administration of antibiotic prophylaxis might be advisable [10, 11]. However, in the other five studies, the trial authors conclude that antibiotic prophylaxis may not be needed [9, 12–15]. The present meta-analysis found evidence to suggest that routine use of antibiotic prophylaxis in conjunction with implant surgery to prevent early implant failures is not needed. The NNT to prevent early implant failure in one patient was 143 (95% CI: 29-∞). That the CI goes into infinity implies that antibiotic prophylaxis has no effect. In other words, routine use of antibiotic prophylaxis would likely mean that a very large number of patients would receive antibiotics unnecessarily. Most previous reviews have included RCTs with high risk of bias, likely due to the previously limited number of well-conducted RCTs in this field. Additional strengths of this review are that the meta-analysis included only placebo controlled RCTs with moderate or low risk of bias and that the certainty of evidence related to the outcome "implant failure" in the included RCTs was determined.

The results of the present review differ from those previously published in that no statistically significant difference was disclosed in early implant failure rates between patients who received antibiotic prophylaxis and patients who received a placebo. Several systematic reviews and meta-analyses reporting the effect of antibiotic prophylaxis do not discuss effectiveness and do not provide a recommendation [30, 33, 35]. However, there are exceptions: Lund et al. (2015) [31] reported an NNT of 50 to prevent a patient from losing an implant and concluded that in uncomplicated implant surgery, antibiotic prophylaxis was of no benefit [31]. Rodríguez Sánchez et al. (2018) [23], reporting an NNT of 67, concluded that antibiotic prophylaxis is effective and efficacious in preventing implant failures [23]. In 2015 the EAO consensus conference stated that antibiotic prophylaxis is not recommended for uncomplicated implant surgery [48]. A few years later, a consensus report published by the Italian Academy of Osseointegration recommended a single dose of antibiotics in uncomplicated cases [49]. These contradictory conclusions and recommendations have meant that the issue of antibiotic prophylaxis in dental implant surgery remains controversial.

The most recent review in this area [24], which included six RCTs with a total of 1504 patients, reported antibiotic prophylaxis to be statistically significant in preventing implant failure. However, three of the six included RCTs were not placebo-controlled and not blinded and another of the RCTs had a very high loss of patients to follow-up (28 patients, 35%). None of these four RCTs were included in our review, which was limited to placebo-controlled RCTs. Our review included seven RCTs with a total of 1859 patients and the meta-analysis of

Table 5 Characteristics of included RCTs with low or moderate risk of bias

RCT	Population	Study period	Antibiotics	Placebo	No. of centers	Surgical characteristics	Additional information
Anitua et al. (2009) [9]	n: 105 Age: 18-75 years Gender (m/f): 35/70 Implants inserted: 105	3 months	Amoxicillin 2 g 1 h preop	Placebo 1 h preop	8	Conventional single implant insertion: 105 (100%)	Smokers: 18 (17.1%) CHX rinse preop
Esposito et al. (2008) [10]	n: 316 Age: 18-78 years Gender (m/f): 142/174 Implants inserted: 696	4 months	Amoxicillin 2 g 1 h preop	Placebo 1 h preop	11	Immediate insertion in extraction sockets: 136 (43.0%)	Smokers: 109 (34.5%) CHX rinse preop and postop twice/day for 2 weeks
Esposito et al. (2010) [11]	n: 506 Age: 18-86 years Gender (m/f): 236/270 Implants inserted: 997	4 months	Amoxicillin 2 g 1 h preop	Placebo 1 h preop	10	Immediate insertion in extraction sockets: 136 (26.9%)	Smokers: 169 (33.4%) CHX rinse preop and postop twice/day for 2 weeks
Momand et al. (2022) [12]	n: 473 Age: 18-72 years (mean 57.4 years) Gender (m/f): 239/235 Implants inserted: 757	3-6 months	Amoxicillin 2 g 1 h preop	Placebo 1 h preop	7	Insertion with GBR: 29 (6.1%) Insertion with sinus lift: 21 (4.4%) Insertion with minor bone augmentations: 78 (16.5%)	Smokers: 86 (18.1%) CHX rinse was recommended in accordance with each operator
Payer et al. (2020) [13]	n: 236 Age: mean 46 years Gender (m/f): 125/111 Implants inserted: 236	3 months	Amoxicillin 2 g 1 h preop + 500 mg x 3 for 3 days	Placebo 1 h preop + x 3 for 3 days	7	Insertion with GBR: 236 (100%)	Smokers: 22 (9.3%) CHX rinse preop and postop 2 times/day for 2 weeks
Santamaría Arrieta et al. (2022) [14]	n: 62 Age: mean 48.6 years Gender (m/f): 22/40 Implants inserted: 62	2 months	Clindamycin 600 mg 1 h preop	Placebo 1 h preop	1	Conventional single implant insertion: 62 (100%)	Smokers: 13 (21.0%) CHX rinse: unknown
Tan et al. (2013)	n: 161 Age: mean 47.1 years Gender (m/f): 88/73 Implants inserted: 161	2 months	Amoxicillin 2 g 1 h preop	Placebo 1 h preop	7	Conventional single implant insertion: 161 (100%)	Smokers: 9.3% CHX rinse preop

the outcome measure showed no significant difference between the antibiotic group and the placebo group.

In six of the RCTs included in this systematic review [9–13, 15], the antibiotic prophylaxis comprised amoxicillin 2 g, 1 hour preoperatively: this is in accordance with the routine suggested in a Cochrane systematic review by Esposito et al. (2010) [50]. In one of the included RCTs, 2 g of preoperative amoxicillin was supplemented with postoperative amoxicillin, 500 mg x 3, on days 1-3 [13]. Finally, in the last of the included RCTs, clindamycin, 600 mg was administered 1 hour preoperatively [14]. The use of amoxicillin or clindamycin 1 hour preoperatively is in accordance with European and American guidelines for the prevention of infective endocarditis associated with invasive dental procedures in high-risk individuals [51, 52]. These guidelines recommend amoxicillin 2 g 1 hour before the procedure and in patients allergic to penicillin, clindamycin 600 mg. In a recent meta-analysis of cross-sectional studies representing five different countries, it was concluded that amoxicillin was the most frequently

Table 6 Outcome (patients with implant failure) of included RCTs with low or moderate risk of bias

RCT	Antibiotics	Placebo	Summary of conclusions according to the authors
Anitua et al. (2009) [9] Spain	2 of 52 patients (3.8%)lost implants	2 of 53 patients (3.8%) lost implants	Antibiotic prophylaxis may not be needed. No statistically significant difference between groups ($p > 0.05$).
Esposito et al. (2008) [10] Italy	2 of 158 patients (1.3%) lost implants	8 of 158 patients (5.1%) lost implants	It might be advisable to routinely administer antibiotic prophylaxis. No statistically significant difference between groups ($p > 0.05$).
Esposito et al. (2010) [11] Italy	5 of 252 patients (2.0%) lost implants	12 of 254 patients (4.7%) lost implants	It might be advisable to routinely administer antibiotic prophylaxis. No statistically significant difference between groups ($p > 0.05$).
Momand et al. (2022) [12] Sweden	6 of 238 patients (2.5%) lost implants	7 of 235 patients (3.0%) lost implants	The effect of antibiotic prophylaxis in conjunction with dental implant surgery in preventing implant loss is small and may not be clinically relevant. No statistically significant difference between groups ($p > 0.05$).
Payer et al. (2020) [13] Austria	3 of 117 patients (2.6%) lost implants	1 of 119 patient (0.8%) lost implant	Antibiotic prophylaxis did not provide additional benefits to prevention of postsurgical complications. No statistically significant difference between groups ($p > 0.05$).
Santamaría Arrieta et al. (2022) [14] Spain	2 of 31 patients (6.5%)lost implants	0 of 31 patients (0%) lost implants	Preoperative clindamycin administration in healthy adults may not reduce implant failure. No statistically significant difference between groups ($p > 0.05$).
Tan et al. (2013) Singapore	0 of 81 patients (0%) lost implants	1 of 80 patient (1.3%) lost implant	Antibiotic prophylaxis does not improve postsurgical complications. No statistically significant difference between groups ($p > 0.05$).

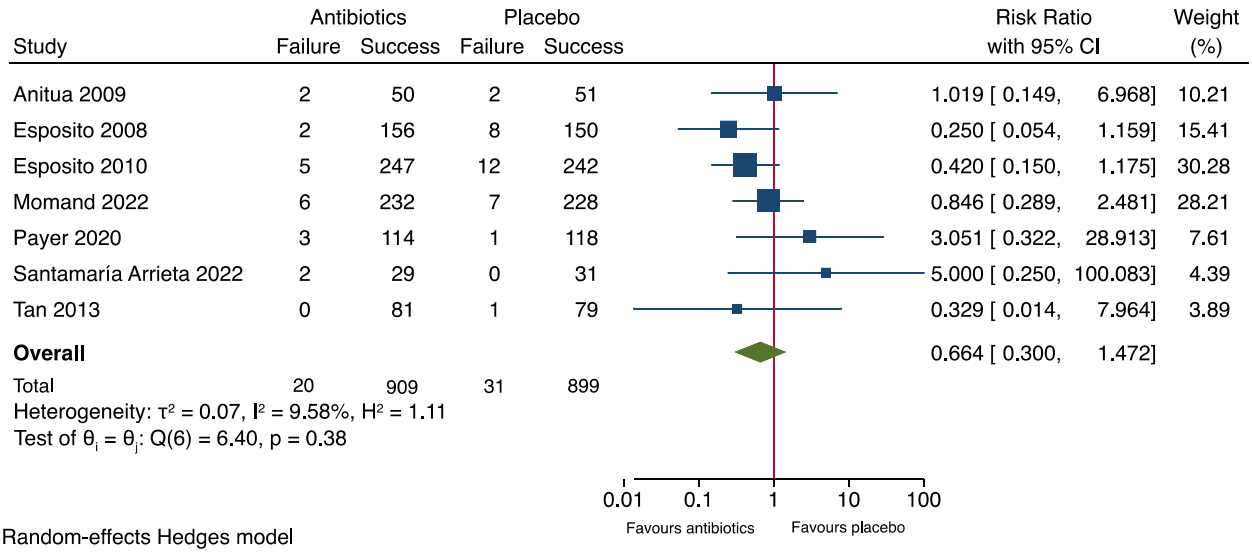

Fig. 2 Forrest plot (risk ratio) of comparison between treatment with antibiotic prophylaxis and placebo in all RCTs using the outcome patients with implant failure

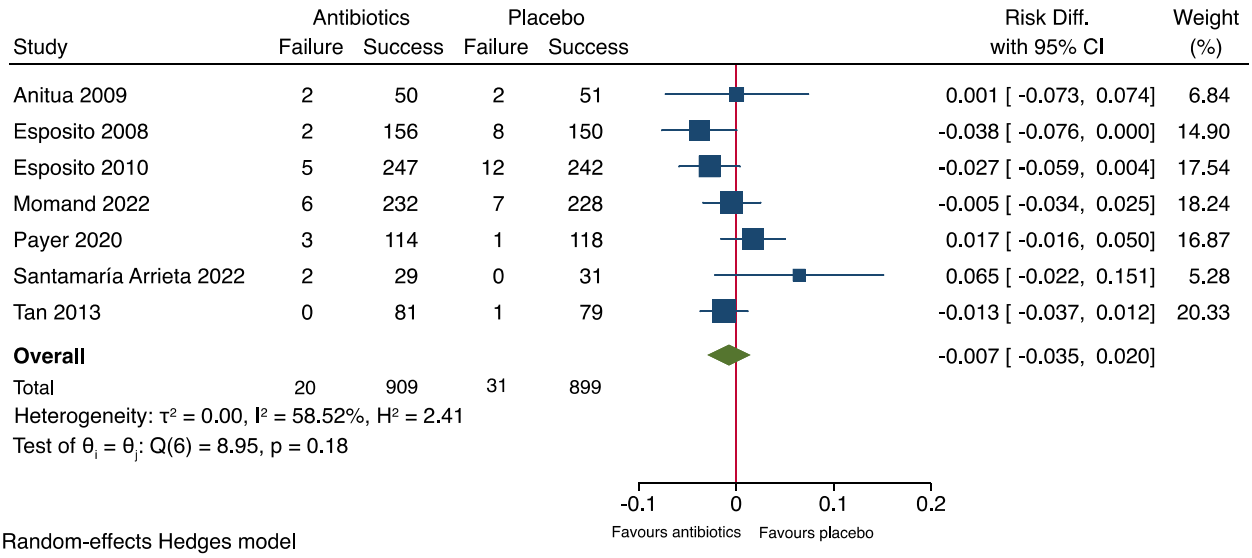

Fig. 3 Forrest plot (risk difference) of comparison between treatment with antibiotic prophylaxis and placebo in all RCTs using the outcome patients with implant failure

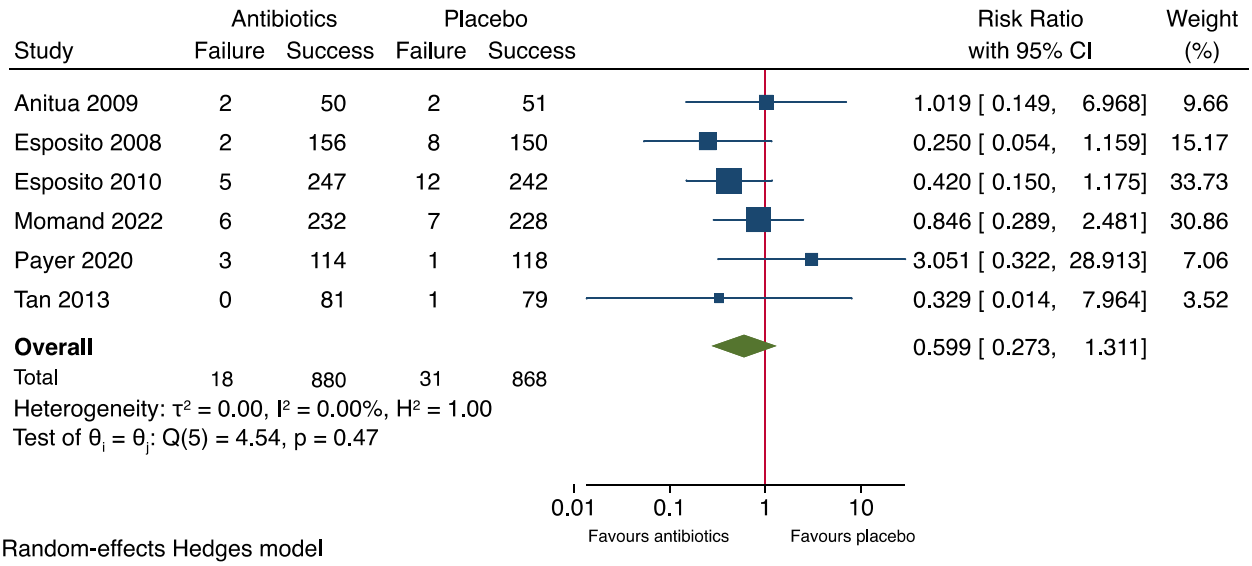

Fig. 4 Forrest plot (risk ratio) of comparison between treatment with antibiotic prophylaxis and placebo in a subgroup (only RCTs using amoxicillin) with the outcome patients with implant failure

prescribed prophylactic antibiotic for implant surgery [53]. Clindamycin is reported to be a common alternative to amoxicillin in implant surgery on patients allergic to penicillin [54, 55].

The main limitations of this review are firstly that only seven studies with a low or moderate risk of bias were identified and secondly that two RCTs with a low number of patients were included. Differences in study design are a further limitation. The timing of final follow-up, when implant stability was tested, varied among the included studies, but it is doubtful whether this would have affected the outcome. The use of chlorhexidine rinses also varied. Two of the included RCTs [9, 15] used preoperative chlorhexidine rinses, four RCTs [10–13] used chlorhexidine rinses both pre- and postoperatively, and one RCT [14] provided no information on general administration of chlorhexidine. As chlorhexidine is a bacteriostatic and bactericidal agent, this could have

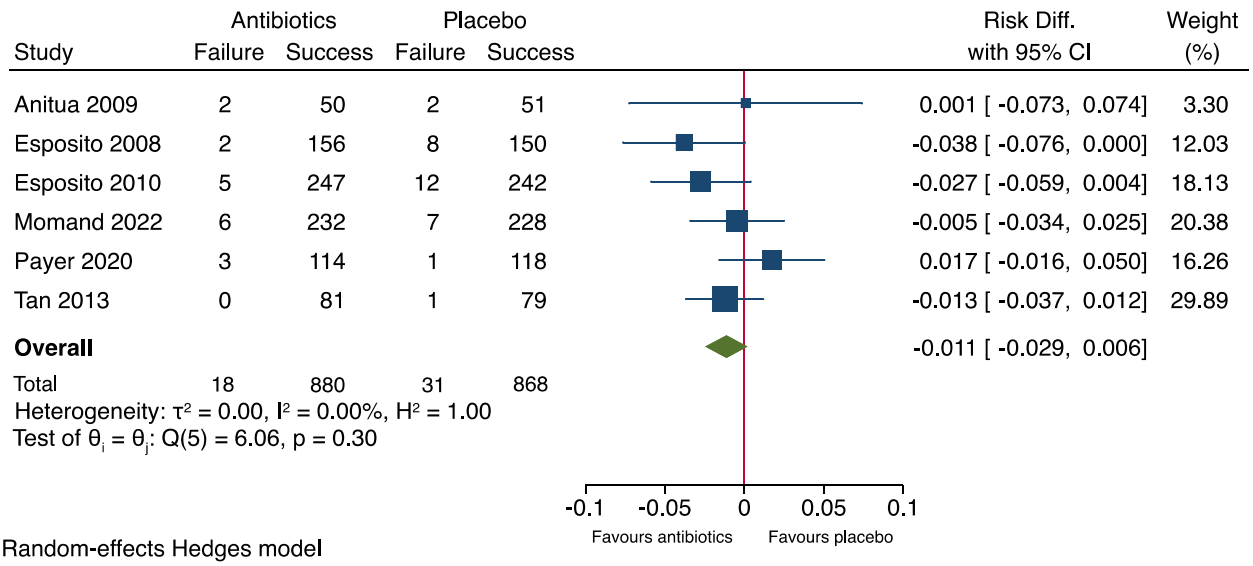

Fig. 5 Forrest plot (risk difference) of comparison between treatment with antibiotic prophylaxis and placebo in a subgroup (only RCTs using amoxicillin) with the outcome patients with implant failure

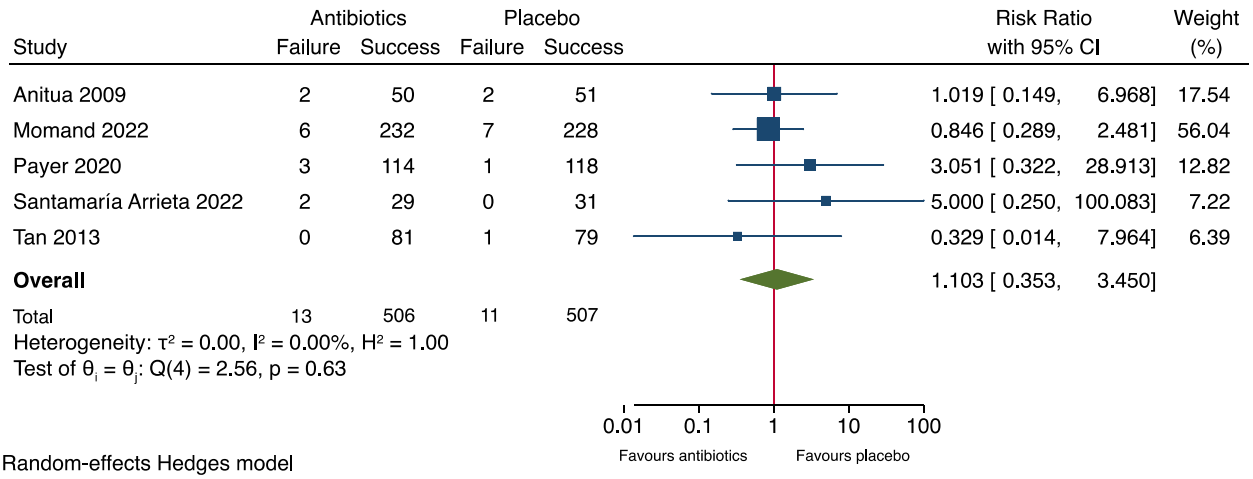

Fig. 6 Forrest plot (risk ratio) of comparison between treatment with antibiotic prophylaxis and placebo in a subgroup (two RCTs excluded due to inclusion of patients treated with immediate insertion of implants into extraction sockets) with the outcome patients with implant failure

been a confounding factor in this review [12]. A further limitation is the inadequate reporting of the patients' periodontal condition.

Another limitation is the variation in implant placement procedures. Three RCTs included only patients treated with single implants [9, 14, 15], one RCT included only those receiving implants with simultaneous GBR [13], and one included a number of procedures (straightforward, simultaneous minor bone augmentation, simultaneous GBR, simultaneous sinus lift) [12]. However, the diversity of surgical methods is not only a limitation. It also means that the basis for the meta-analysis more closely reflects the mix of surgical methods used by dentists who undertake different types of non-complex implant surgery. Finally, another limitation is that the proportion of smokers differed between the RCTs: from 9.3% to 34%. Smoking is a risk factor for early implant failure [56] but it is unclear whether antibiotic prophylaxis can reduce this risk. In two of the included RCTs [10, 11], some patients received immediate post-extraction implants and the incidence of implant failure was greater in these patients. This observation may have led to the conclusion from the EAO Consensus Conference in 2015 that there may be a beneficial effect of antibiotic

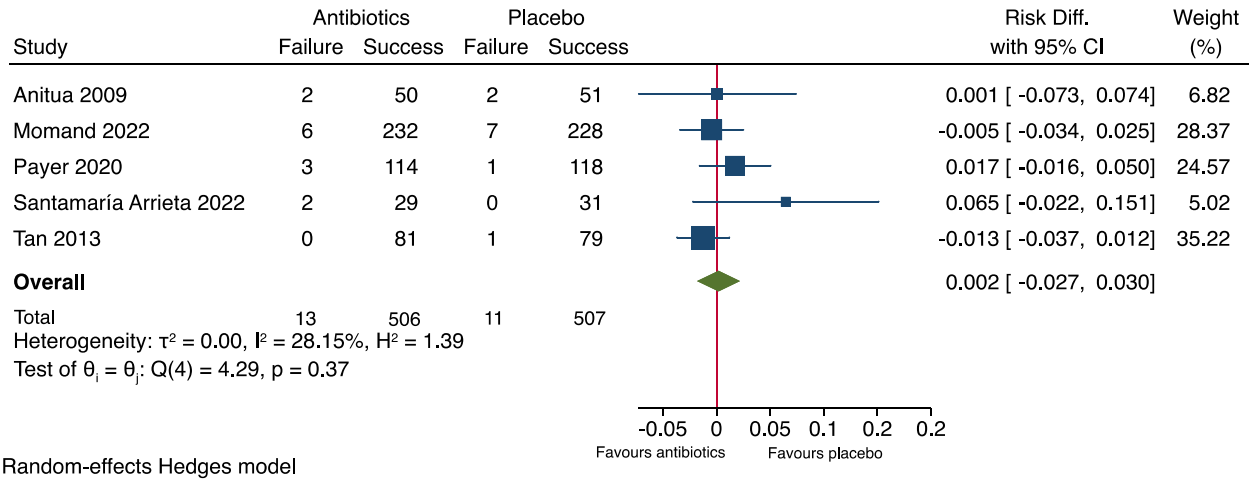

Fig. 7 Forrest plot (risk difference) of comparison between treatment with antibiotic prophylaxis and placebo in a subgroup (two RCTs excluded due to inclusion of patients treated with immediate insertion of implants into extraction sockets) with the outcome patients with implant failure

Table 7 Summary of the meta-analyses

Meta-analyses	Number of studies	Number of participants	Number of implants	Risk ratio (95% CI)	Risk difference (95% CI)
All studies	7	1859	3014	0.664 (0.300-1.472)	-0.007 (-0.035-0.020)
Subgroup I	6	1797	2952	0.599 (0.273-1.311)	-0.011 (-0.029-0.006)
Subgroup II	5	1037	1321	1.103 (0.353-3.450)	0.002 (-0.027-0.030)

Subgroup I: Consisting of RCTs using only amoxicillin

Subgroup II: Excluding two RCTs due to inclusion of patients treated with immediate insertion of implant into extraction sockets

Table 8 Summary of findings. Effects and certainty of evidence regarding antibiotic prophylaxis for prevention of early implant failure in health patients

Outcome measure	No. of participants	No. of RCTs	Risk Ratio (95% CI)	Risk Difference (95% CI)	Certainty of evidence (GRADE)	Comments
Patients with implant failure (loss of implant)	1859	7	RR: 0.66 (95% CI: 0.30-1.47)	RD: -0.007 (95% CI: -0.035-0.020)	⨁⨁⨁◯ Moderate certainty of evidence for a very small effect[1] of antibiotic prophylaxis regarding implant failure	Transferability[2]: -1

[1] : The effect difference between the two groups was evaluated as being very small

[2] : Lack of transferability in the included RCTs as the study period varied in each study

prophylaxis to cover immediate implant placement into fresh extraction sockets [48]. It is of interest to note that the two RCTs mentioned above reported a higher proportion of patients with implant failure in the placebo group (5.1% and 4.7%) than any of the other RCTs included in this meta-analysis. Moreover, in a recent systematic review by Salgado-Peralvo et al. (2021) of antibiotic therapy in conjunction with immediate implant surgery, preoperative administration of 2-3 g amoxicillin 1 hour before surgery followed by 500 mg/8 hour for five to seven days was recommended [57]. The rationale for the recommendation for extended antibiotic prophylaxis was that a tooth extracted for implant insertion should be treated as potentially infected. Under such circumstances, this is probably better described as antibiotic treatment, rather than antibiotic prophylaxis.

The overall non-significant difference between antibiotic and placebo groups with respect to the number of patients with implant failure and the high number of patients who need to be treated with antibiotic prophylaxis to prevent implant failure in one patient, mean that it seems inappropriate to recommend routine use of antibiotic prophylaxis in conjunction with implant surgery. All use of antibiotics entails a cost, a risk of side effects

and a risk of increased antibiotic resistance [58]. Antibiotics should, as far as possible, be used only to treat infections and in healthy patients it should be used for prophylaxis only in exceptional cases.

Conclusion

Based on this review and meta-analysis of results from high-quality RCTs, the benefit of antibiotic prophylaxis for implant surgery is likely to be very limited. In the context of increasing antibiotic resistance, antibiotic prophylaxis should be avoided in most cases of implant surgery. The results of this systematic review and meta-analysis could form the foundation of new and clearer clinical guidelines for antibiotic prophylaxis in implant surgery.

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Authors' contributions
PM: study planning, drafting article, data collection, data analysis/interpretation, statistical analysis. ANA: study planning, data analysis/interpretation, statistical analysis, critical revision of article, scientific advisor. MH: data analysis/interpretation, critical revision of article, scientific advisor. BL: data analysis/interpretation, critical revision of article, scientific advisor. BG: study planning, drafting article, data collection, data analysis/interpretation, critical revision of article, scientific advisor. All authors have read and approved the manuscript.

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Availability of data and materials
All datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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