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Meta-Analysis
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Does the use of amoxicillin/amoxicillin–clavulanic acid in third molar surgery reduce the risk of postoperative infection? A systematic review with meta-analysis

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R. K. Menon, D. Gopinath, K. Y. Li, Y. Y. Leung, M. G. Botelho: Does the use of amoxicillin/amoxicillin–clavulanic acid in third molar surgery reduce the risk of postoperative infection? A systematic review with meta-analysis. Int. J. Oral Maxillofac. Surg. 2019; 48: 263–273.

Abstract. The objectives of this systematic review were to investigate the efficacy of amoxicillin/amoxicillin–clavulanic acid for reducing the risk of postoperative infection after third molar surgery and to evaluate the adverse outcomes in these patients, as well as in healthy volunteers. A systematic search of four databases was performed on May 26, 2017. Eleven studies qualified for the qualitative analysis and eight were found suitable for meta-analysis. The results suggest that both amoxicillin–clavulanic acid and amoxicillin significantly reduce the risk of infection after third molar extraction (overall relative risk (RR) 0.25, $P < 0.001$). However, with the exclusion of randomized controlled trials with a split-mouth design (due to an inadequate crossover period after antibiotic treatment), only amoxicillin–clavulanic acid was found to be effective (RR 0.21, $P < 0.001$). The risk of adverse effects was significantly higher in the amoxicillin–clavulanic acid group (RR = 4.12, $P = 0.023$) than in the amoxicillin group (RR 1.57, $P = 0.405$). In conclusion, amoxicillin–clavulanic acid and amoxicillin may significantly reduce the risk of infection after third molar extraction. However, their use in third molar surgery should be viewed with caution, as recent clinical trials on healthy volunteers have shown evidence of the negative impact of amoxicillin use on bacterial diversity and antibiotic resistance.

Key words: molar; third; meta-analysis; adverse effects; long term; review; amoxicillin; amoxicillin–potassium clavulanate combination.

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The rate of postoperative infection reported after third molar surgery is in the range of 0.8% to 4.2%[1–9]. Numerous randomized controlled trials (RCTs) have evaluated the efficacy of different antibiotics in preventing postoperative infections but have failed to lead to a consensus among practitioners regarding the type of antibiotic to be used and the appropriateness of antibiotic prescription for third molar surgery[10]. Third molar surgeries are frequently performed in healthy young adults with minimal or no infection of the associated teeth, based on the clinical impression that future complications may arise from these teeth. This approach has been rigorously criticized[11].

Amoxicillin along with amoxicillin–clavulanic acid combination are amongst the antibiotics most preferred by dentists globally for the prevention of postoperative infection after third molar surgery[12–23]. Unfortunately, antibiotic prescribing preference does not seem to follow an evidence-based approach, but shows regional variation. Two studies surveying third molar prescription practices in Switzerland reported that 18–25% of dentists would prescribe antibiotics for third molar surgery[24,25] when compared to 60–90% of dentists in other countries[26,27].

Systematic reviews are widely used to assist in formulating clinical decisions. A recent systematic review investigating the effectiveness of antibiotic use in preventing dry socket and infections after third molar surgery concluded that antibiotic use significantly reduces the risk of dry socket and infection[28]. Another systematic review that focused on amoxicillin concluded that there is no justification for the routine prescription of amoxicillin with or without clavulanic acid in third molar surgery[29]. Nonetheless, previous systematic reviews on antibiotic use in third molar extractions have not addressed the question of antibiotic resistance. It has been suggested previously that RCTs and clinical studies should sample and follow up bacterial communities in various sites of the human body to assess the impact of antibiotic use and that such data should be an integral part of systematic reviews assessing antibiotic use[30].

Short-term antibiotic use has been associated with the persistence of antibiotic-resistant bacteria in the intestine for a number of years[31–33]. The impact of antibiotic treatment is not limited to its influence on the development of antibiotic resistance in bacteria, as it can also disrupt the healthy microbiome[34,35], facilitate the overgrowth of yeast[36] and *Clostridium difficile*[37], interfere with the absorption and metabolism of vitamins and other nutrients, and increase susceptibility to future infections[38].

Antibiotic use in third molar surgery should be evidence-based and the evidence should include an evaluation of the effectiveness of a particular antibiotic and reflect all of the possible adverse outcomes of that antibiotic. Such evidence could contribute to a reduction in inappropriate prescription by providing appropriate evidence of the harms of antibiotic treatment, including the possibility of antibiotic resistance[39].

The aim of this systematic review and meta-analysis was to provide critical information to dental practitioners and to inform current prescription practices based on clinical and microbiological evidence, using the following key clinical questions: Does the use of amoxicillin and amoxicillin–clavulanic acid or not in patients undergoing third molar surgery or in healthy volunteers result in a reduced risk of postoperative complications after extractions? Does the use of amoxicillin cause significant antibiotic-related side effects or long-term adverse effects including a shift in bacterial diversity or antibiotic resistance?

Materials and methods

The four databases PubMed, Web of Science, Medline-Ovid, and Cochrane Central Register of Controlled Trials were searched using selected key words based on the patient, intervention, comparison, and outcome (PICO) format, combining the key words with Boolean operators 'AND' and 'OR': [Patient (P): Surgery; Oral OR Molar; Third OR Healthy Volunteers] AND [Intervention (I): Amoxicillin OR Amoxicillin–Potassium Clavulanate Combination] AND [Comparison (C): Placebo OR Control OR No Antibiotic] AND [Outcome (O): Surgical Wound Infection OR Long Term Adverse Effects OR Drug-Related Side Effects and Adverse Reactions OR Postoperative Complications OR Drug Resistance; Microbial OR Drug Resistance; Bacterial OR Diversity; Microbial OR Shift; Microbial OR Bacteria OR Bacteremia]. The detailed search strategy for the PubMed database and the Cochrane Central Register of Controlled Trials; with the search date; is provided in the Supplementary Material (File S1).

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The database searches were conducted and further screening was performed by two independent researchers (RKM, DG) in two stages. The study selection criteria for the stage I (based on title) and stage II (full text) screening are given in Table 1. The studies that were excluded at stage II, with the reasons for their exclusion, are given in the Supplementary Material (File S2). Studies involving third molar extraction alone were considered for estimation of the relative risk and number needed to treat to prevent one case of postoperative infection. The quality and bias of the selected trials were assessed based on the *Cochrane Handbook for Systematic Reviews of Interventions*[40] (Supplementary Material, File S3). All selected studies were assessed for reported and measured adverse outcomes, including bacterial diversity and antibiotic resistance related to amoxicillin use. Further, the relative risk of infection and adverse effects of pre-surgical or post-surgical antibiotic prescription were assessed.

Statistical analysis

Data were combined for meta-analysis using Stata version 13.1[41]. Heterogeneity was assessed using the χ^2-based Q-statistics method and measurement of I^2. Because of the expected inter-study heterogeneity, the random-effects model was used. Publication bias was investigated by visual detection of the funnel plot and regression asymmetry tests – Egger and Begg tests. Adverse outcomes were also investigated by meta-analysis.

Subgroup analyses for the intervention group (amoxicillin–clavulanic acid and amoxicillin alone groups) and time of administration (pre-surgery, post-surgery, and mixed groups) were performed. For split-mouth studies, the corresponding estimates were calculated from the matched nature of data[42,43]. Also, the subgroup analysis or sensitivity analysis was performed based on the study design (parallel and split-mouth design) if available. The relative risks (RR) are reported at the 0.05 significance level, along with the 95% confidence intervals (CI).

Results

A flow diagram of the search and results is presented in Fig. 1.

Eleven studies qualified for the qualitative analysis[44–54], and eight randomized controlled trials were included in the quantitative analysis (Table 2)[44–51]. The meta-analysis with random-effects model for relative risk was performed to evaluate whether amoxicillin and amoxicillin–clavulanic

Table 1. Stage I and stage II screening—study selection criteria.

Stage	Inclusion criteria	Exclusion criteria
Stage I (Title)	• All studies generated from the database search	• Studies that did not involve third molar surgery or healthy volunteers • Combination of amoxicillin with other drugs or antibiotics • Animal studies and in vitro studies
Stage II (Full text)	• RCTs involving third molar surgery or healthy volunteers • Amoxicillin or amoxicillin–clavulanic acid was used	• Studies that did not have a control group not receiving antibiotics • Studies that were not double-blind for third molar surgery • Studies that did not classify infections as surgical site infections and clinically report them as frank purulence; studies that used CRP levels and other indicators of inflammation that have not been proven to be clinical indicators of infection • Studies that were not RCTs • Other antibiotics or combinations of antibiotics were used • Perspective articles • Questionnaires • Case reports • Preliminary reports • Reviews • Others

CRP, C-reactive protein; RCT, randomized controlled trial.

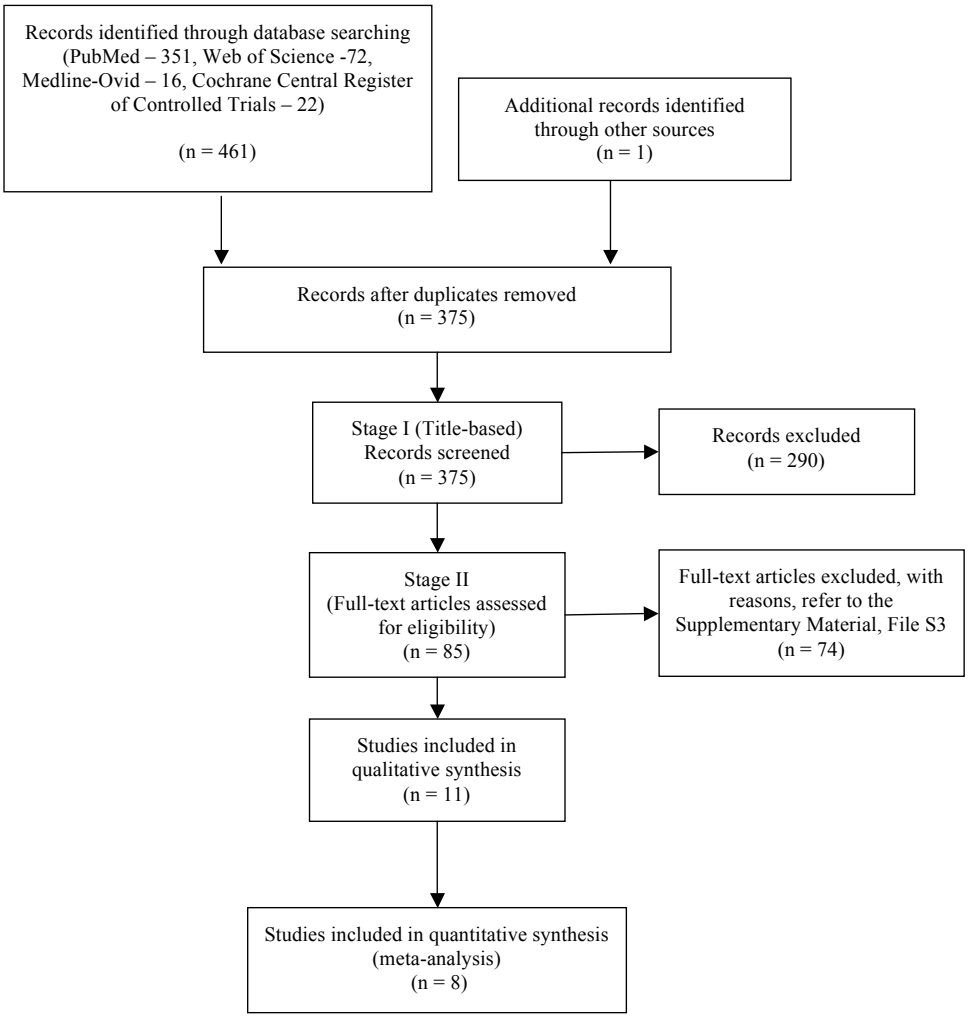


Fig. 1. PRISMA flowchart of the search results.

Table 2. Selected studies involving amoxicillin treatment for third molar surgery.

Author Year	Antibiotics: dose and duration	Sample size	Postoperative outcomes[a]	Follow-up appointments	Number of cases reporting with infection[b]	Adverse outcomes related to antibiotic use
Arteagoitia et al. 2005[45]	Ab group: AMX–CLA 500/125 mg three times daily, oral, for 4 days Control: placebo tablets same size and appearance	490	Inflammation Erythema Pain *Abscess	7 days, 8 weeks	Ab group: 5/259 Control: 30/231	Ab group: 14/259 Control: 2/231
Lacasa et al. 2007[47]	Group 1: placebo Group 2: single pre-surgical dose of two tablets AMX–CLA 1000/62.5 mg Group 3: post-surgery therapy of two tablets AMX–CLA 1000/62.5 mg twice daily for 5 days	222	*Infection Pain reduction	1, 3, 7, 15 days	Group 1: 12/75 Group 2: 4/75 Group 3: 2/72	Group 1: 3/75 Group 2: 1/75 Group 3: 8/72
Siddiqi et al.[c] 2010[50]	Group 1: 1st visit, oral AMX 1 g at 1 h preoperative; 2nd visit (3 weeks later), placebo (glucose) 1 g at 1 h before surgery, or vice versa Group 2: 1st visit, oral AMX 1 g at 1 h preoperative and AMX 500 mg 8-hourly for 2 days after surgery; 2nd visit (3 weeks later), placebo under the same regimen or vice versa	95	Pain Swelling *Infection Trismus Temperature	3 days, 1 week, 2 weeks	AMX and placebo: 1 AMX no placebo: 1 Placebo no AMX: 3 No infection: 90	No adverse reactions reported
Bezerra et al.[c] 2011[51]	Group E: AMX two 500 mg capsules 1 h before surgery Group C: placebo (starch) two 500 mg capsules before surgery	34	Soft tissue oedema Pain Limitation of mouth opening *Presence of purulent secretion Alveolitis	3 days, 1 week, 2 weeks	AMX and placebo: 0 AMX no placebo: 1 Placebo no AMX: 4 No infection: 29	No adverse reactions reported
López-Cedrún et al. 2011[48]	Group A: AMX 500 mg 4 tablets 2 h before surgery Group B: placebo Group C: AMX 500 mg three times a day for 5 days	123	Pain *Wound infection Trismus Temperature Intra- and extraoral swelling Dysphagia Side effects	4 weeks	Group A: 0/39 Group B: 5/40 Group C: 0/44	Group A: 7/39 Group B: 4/40 Group C: 6/44
Pasupathy and Alexander 2011[49]	E1: oral AMX 1 g at 1 h before surgery E2: oral metronidazole 800 mg at 1 h before surgery C: placebo	89	Increase in body temperature *Purulent discharge from the wound	7 days	E1: 2/31 E2: 0/29 C: 3/29	No adverse outcomes of antibiotics reported

Adde et al. 2012[44]	Group A: AMX 500 mg three times daily, oral, for 7 days Group B: clindamycin 300 mg four times daily, oral, for 7 days Group C: no antibiotic	71	Pain Oedema Inter-incisal distance *Infection	1 week	Group A: 0/24 Group B: 0/23 Group C: 0/24	No adverse outcomes of antibiotics reported
Arteagoitia et al. 2015[46]	Group EG: 2 g AMX/125 mg CLA at 2 h before surgery; postoperatively twice a day for 4 days Group CG: placebo	118	Pain Oedema Mouth opening *Abscess Alveolitis Dehiscence	1 week, up to 8 weeks	Group EG: 2/60 Group CG: 5/58	Group EG: 12/60 Group CG: 1/58

Ab, antibiotic; AMX, amoxicillin; CLA, clavulanic acid.

[a] Infection outcomes marked with an asterisk (*).

[b] For the split-mouth studies, since the same patient was administered both amoxicillin and placebo and vice versa at the different times, the number of infections was reported for each patient and the corresponding estimates were calculated from the matched nature of data[42,43]. 'AMX and placebo' represents the number of patients who reported an infection after amoxicillin treatment and also the placebo treatment; 'AMX no placebo' represents the number of patients who reported an infection after amoxicillin treatment but not after placebo treatment; 'Placebo no AMX' represents the number of patients who reported an infection after placebo treatment but not after antibiotic treatment.

[c] Studies employing a split-mouth protocol.

acid reduce the risk of infection after third molar surgery.

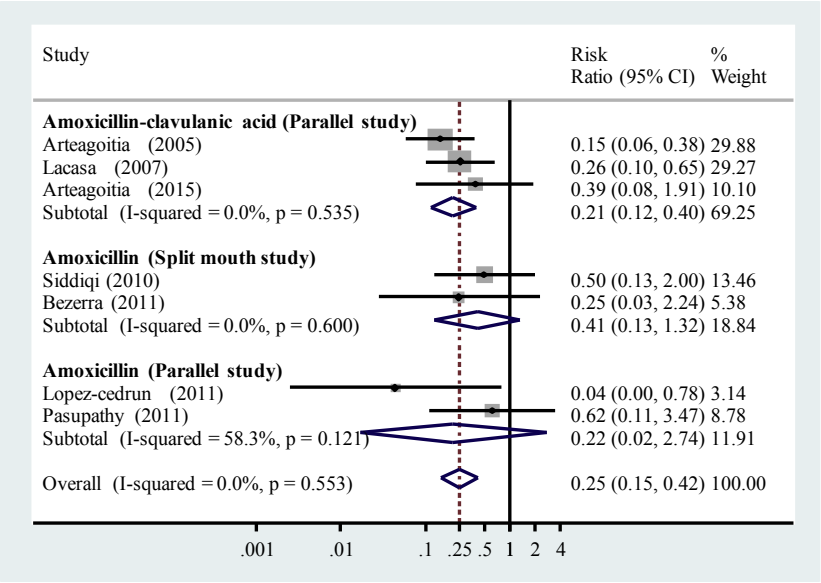
The meta-analysis results revealed that the pooled relative risk of infection in the treatment group overall was 0.25 (95% CI 0.15–0.42, $P < 0.001$). For amoxicillin–clavulanic acid, the relative risk was 0.21 (95% CI 0.12–0.40, $P < 0.001$). In the amoxicillin group, the relative risk was 0.37 (95% CI 0.15–0.92, $P = 0.033$), with RR 0.22 (95% CI 0.02–2.74, $P = 0.237$) for the parallel studies and RR 0.41 (95% CI 0.13–1.32, $P = 0.136$) for the split-mouth studies. The crossover time after one extraction and antibiotic treatment in the split-mouth study by Siddiqi et al.[50] was 3 weeks, while it was not specified in the study by Bezerra et al.[51]. With the exclusion of the split-mouth studies[50,51], the relative risk of infection in the amoxicillin group was no longer significant (RR 0.22, 95% CI 0.02–2.74, $P = 0.237$). Moderate heterogeneity was found in the amoxicillin parallel study group ($I^2 = 58.3\%$), which was not significant (heterogeneity test: $P = 0.121$), and heterogeneity was not significantly found in the amoxicillin split-mouth study group, amoxicillin–clavulanic acid group, or the overall treatment group ($I^2 = 0.0\%$, heterogeneity test: $P = 0.600$; $I^2 = 0.0\%$, heterogeneity test: $P = 0.535$; $I^2 = 0.0\%$, heterogeneity test: $P = 0.553$, respectively) (Fig. 2a).

When classifying the treatments by the time of administration of antibiotics (pre-surgery, post-surgery, and mixed), the pre-surgery group had a relative risk of infection of 0.32 (95% CI 0.12–0.85, $P = 0.023$), while the post-surgery group had a relative risk of 0.15 (95% CI 0.06–0.38, $p < 0.001$) (Fig. 2b). With the exclusion of the split-mouth studies, the relative risk of infection in the pre-surgery group was no longer significant (RR 0.33, 95% CI 0.10–1.11, $P = 0.073$).

The number needed to treat (NNT) to prevent one case of postoperative infection was next estimated from the meta-analysis with random-effects model for risk difference. The overall NNT for the treatment group was 14.9, while the NNT for the amoxicillin–clavulanic acid group was 9.9 and for the amoxicillin group was 26.3 (parallel study: 19.6; split-mouth study: 35.7). When classifying the treatments by time of administration, the pre-surgery group, post-surgery group, and mixed group had NNT values of 13.0, 16.7, and 16.1, respectively.

The funnel plot was slightly asymmetric, but there was no evidence of publication bias using the Egger test ($P = 0.842$) or Begg test ($P = 1.000$). This suggested

a.



b.

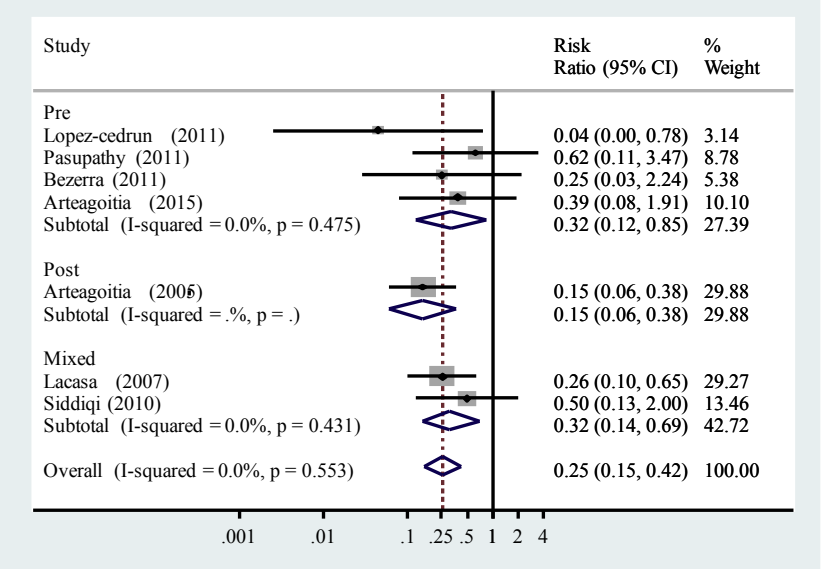


Fig. 2. (a) Meta-analysis with random-effects model for the relative risk of infection with the use of amoxicillin–clavulanic acid and amoxicillin overall and individually. (b) Meta-analysis with random-effects model for the relative risk of infection in groups classified according to the time of antibiotic administration: pre-surgery (pre), post-surgery (post), and mixed pre- and post-surgery.

no publication bias in the meta-analysis (Supplementary Material, File S4).

Overall, the risk of adverse effects was significantly greater with antibiotic use (RR 2.95, 95% CI 1.16–7.50, $P = 0.023$), particularly with the use of amoxicillin–clavulanic acid (RR 4.12, 95% CI 1.21–14.00, $P = 0.023$); however, there was no significant effect on adverse effects for the use of amoxicillin alone (RR 1.57, 95% CI 0.55–4.50, $P = 0.405$) (Fig. 3a). When classifying the treatments by time of administration, the pre-surgery group had a relative risk of adverse effects of 3.59 (95% CI 0.47–27.40, $P = 0.218$) and the post-surgery group had a relative risk of 6.24 (95% CI 1.43–27.18, $P = 0.015$) (Fig. 3b).

The number needed to harm (NNH; the number of patients needed to be treated for one additional patient to report an adverse effect) was next estimated from the meta-analysis of adverse effects with the random-effects model for risk difference. Overall for the treatment group, the NNH was 25.0, while the NNH for amoxicillin–clavulanic acid was 14.9 and for amoxicillin was 125. The NNH for the pre-surgery group was 13.2 and for the post-surgery group was 27.0.

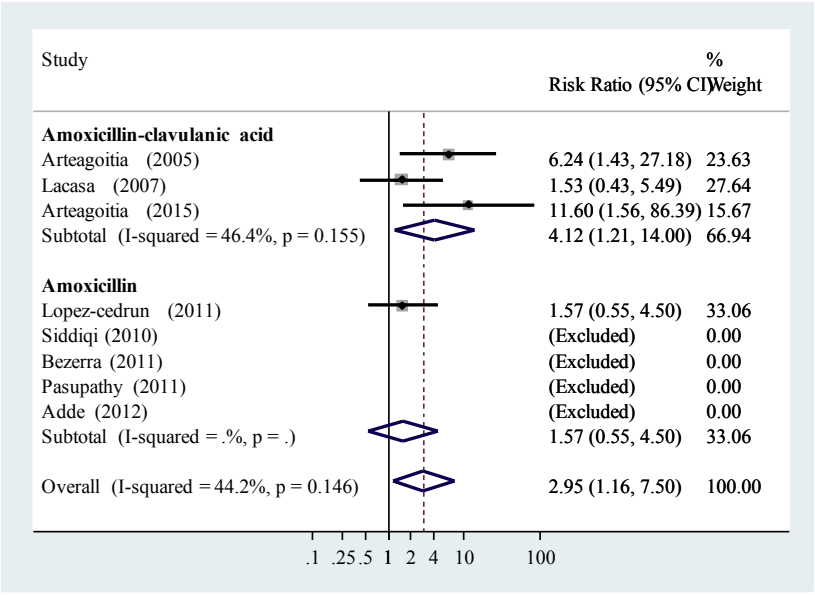
Three prospective studies were identified in which amoxicillin was administered to healthy volunteers and the adverse effects, including the impact on bacterial diversity and antibiotic resistance, were monitored prospectively[52–54]. The selected studies and the key findings are given in Table 3. The study by Abeles et al.[52] showed significant changes in the relative abundances of bacteria in the gut, saliva, and skin of healthy volunteers treated with amoxicillin compared to the controls. Bacterial diversity was reduced after amoxicillin treatment in the gut, saliva, and skin, and the decrease persisted for a period of up to 6 months. The reduction in diversity was more pronounced for the group in which amoxicillin treatment was continued for 7 days compared to the group that received amoxicillin only for 3 days. The study by Kirchner et al.[53] focused on Gram-negative faecal isolates after antibiotic treatment and found that blaTEM-positive *Escherichia coli* was the major contributor to the antibiotic resistance, with an increase from 13.9% to 48.3% for the amoxicillin group; this persisted up to 1 month and did not return to pre-administration levels. The proportion of isolates with a multidrug-resistant genotype increased from 22% to 49% for the group treated with amoxicillin, whereas it stayed at 38.5% for the placebo group. In the placebo group, blaTEM-positive *E. coli* isolates remained between 33% and 40% throughout the study. Further, the authors reported an increase in tetB-positive *E. coli* from 8.3% to 20% for the amoxicillin group. The study by Zaura et al.[54] did not find a significant effect on bacterial diversity in faeces and saliva after amoxicillin treatment. However, they found an increase in antibiotic resistance genes belonging to the blaTEM and multidrug resistance category post antibiotic treatment.

Discussion

The clinical implications of the study findings and suggested areas for future research are discussed below.

The same multi-field search was used for all of the databases by combining the key words in PICO format using Boolean

a.



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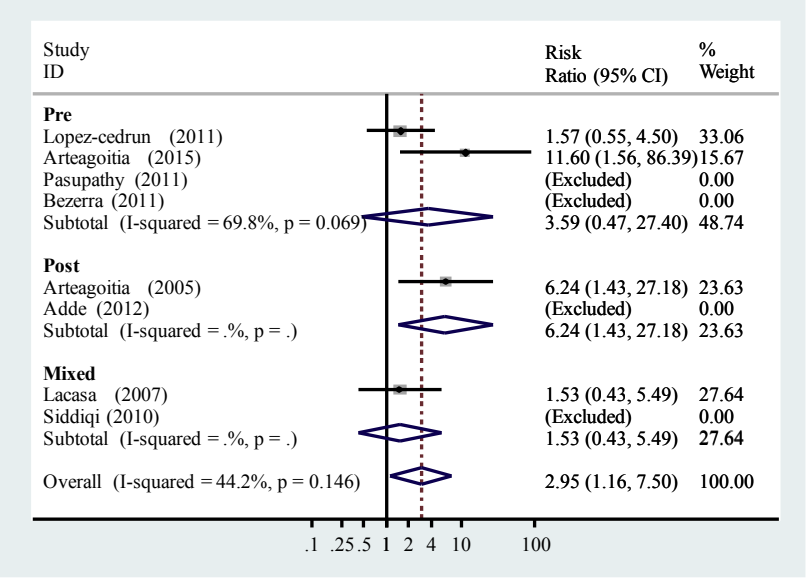

Fig. 3. (a) Meta-analysis with random-effects model for the relative risk of adverse effects with the use of amoxicillin–clavulanic acid and amoxicillin overall and individually. (b) Meta-analysis with random-effects model for the relative risk of adverse effects in groups classified according to the time of antibiotic administration: pre-surgery (pre), post-surgery (post), and mixed pre- and post-surgery.

operators 'AND' and 'OR'. The overall number of initial hits from the databases was lower than that reported in a previous review that investigated amoxicillin use in third molar surgery[29]. The results from the search strategy employed in the present study highlight the benefits of employing carefully selected consistent medical subject heading (MeSH) terms in a PICO format, combined by Boolean operators 'AND' and 'OR' in generating comprehensive yet accurate results based on the research question. However, the limited number of results for Medline-Ovid as compared to PubMed suggests that this strategy is not suited for searching the Medline-Ovid database.

The study by Adde et al.[44] was excluded from the meta-analysis of the relative risk of infection since no infections were reported in either treatment group, and any measure of effect summarized as a ratio such as the relative risk is undefined. Overall, the present study results showed that the use of amoxicillin–clavulanic acid combination and amoxicillin alone, irrespective of the time of administration, significantly reduced postoperative infection after third molar surgery. However, when split-mouth studies on amoxicillin were excluded, the use of amoxicillin alone and preoperative antibiotic use were found not to result in a reduction in the risk of infection after third molar extraction. The differences in results when studies with a split-mouth design were excluded might have been due to the lack of power as a result of the limited number of studies remaining after exclusion. However, in the split-mouth studies investigating antibiotic use in which patients received antibiotics after the extraction on the first side, the time allowed in the crossover design was not sufficient for the associated bacterial shift to re-establish the normal flora before the second extraction. This may have introduced bias with regard to the second extraction in the same patient. There have been numerous recent reports on the impact of antibiotic treatment on the oral microbiome suggesting that antibiotic use in an individual might alter the oral microbiome, which may take up to 3 months or longer to revert to its pre-treatment state[31,54]. Hence it is proposed that future RCTs investigating antibiotic use for third molar extraction should ideally schedule the second extraction in the same patient after an extended crossover period to eliminate bias.

The NNT values provide useful information to clinicians regarding the number of patients who need to be treated with an antibiotic to prevent one additional case of infection[55]. It was found that 10 patients needed to be treated with amoxicillin–clavulanic acid and 26 with amoxicillin alone to prevent one case of postoperative infection. When considered in light of the fact that most postoperative infections in a minor surgical procedure like third molar surgery usually resolve completely after rescue medication[56–59] and the paucity of longitudinal clinical trials evaluating the impact of antibiotic treatment on the development of antibiotic-resistant bacteria, this information suggests that the prophylactic use of amoxicillin for this procedure based on current evidence should be investigated further.

Arteagoitia et al.[29] have previously investigated the effectiveness of amoxicillin and amoxicillin–clavulanic acid for the prevention of dry socket and infections after third molar surgery. They found a significant difference in the reduction of infection when comparing the amoxicillin–clavulanic acid group to the

Table 3. Selected studies involving amoxicillin treatment for healthy volunteers.

Author Year	Antibiotics: dose and duration	Sample size	Sample collected	Time points of sample collection	Technique	Adverse outcomes	Key findings
Kirchner et al. 2014[53]	Group 1: AMX 250 mg three times daily for 7 days Group 2: placebo	29	Faeces	Baseline, day 11, 1 month, 2 months, 4 months, 1 year	DNA microarray of 75 resistance genes from purified faecal Gram-negative bacterial isolates	Group 1: 3/15 Group 2: 2/14	Increase in blaTEM-positive *E. coli*, tetB-positive *E. coli*, and MDR isolates after AMX treatment
Zaura et al. 2015[54]	Group 1: AMX Group 2: placebo	29	Faeces, saliva	Baseline, 1 week, 1 month, 2 months, 4 months, 1 year	DNA extraction, 16S rRNA gene sequencing, metagenomic shotgun sequencing of selected samples and resistome analysis with ARDB	Group 1: 2/14 Group 2: 0/13	Increase in beta-lactamase resistance and MDR after AMX treatment More profound effect on gut flora compared to saliva
Abeles et al. 2016[52]	Group 1: AMX 3-day therapy, 500 mg twice daily Group 2: AMX 7-day therapy, 500 mg twice daily Placebo: 500 mg vitamin C twice daily	24	Faeces, saliva, skin swab	Baseline, 3 days, 1 week, 2 months, 6 months	DNA extraction, 16S rRNA gene sequencing	No adverse outcomes reported	Decrease in bacterial diversity after antibiotic treatment in gut, saliva, and skin that persisted up to 6 months Greater reduction in diversity for a greater duration in antibiotic treatment

AMX, amoxicillin; ARDB, Antibiotic Resistance Genes Database; CLA, clavulanic acid; *E. coli*, *Escherichia coli*; MDR, multi-drug resistance.

amoxicillin group, with the latter shown to be ineffective. The present review indicates that both are effective and that the difference in results could be attributed to the additional studies that were excluded from the present review based on the predetermined exclusion criteria (Table 1; Supplementary Material, File S2). However, in this review, when the split-mouth studies were excluded from the analysis, the risk reduction was found not to be significant with amoxicillin. This result may be due to the limited number of remaining studies after exclusion based on the study design and hence the consequent lack of power. Further, a stratified analysis based on the time of administration of the antibiotic (pre-surgery, post-surgery, or mixed) was performed in this review. Moreover, the present authors propose the addition of outcomes related to antibiotic resistance in future trials investigating antibiotic use in third molar surgery following the evaluation of studies investigating related outcomes in healthy volunteers after amoxicillin use. Both reviews focused on the most common antibiotic used for third molar surgery and agree in the questionability of prophylactic amoxicillin use to prevent infections considering the number needed to treat and the potential harms of antibiotic use.

Apart from determining targeted antibiotic prescription, there is also the need to investigate the possible long-term sequelae of dental antibiotic prescriptions, which are rampant in certain countries. An understanding of these harmful effects will help develop guidelines to reduce the over-prescription and speculation in antibiotic treatment. Four papers – Adde et al.[44], Pasupathy and Alexander[49], Siddiqi et al.[50], and Bezerra et al.[51] – were excluded from the meta-analysis of the relative risk of adverse effects, since no adverse reactions were reported in these studies, therefore they contained no events in either group, and any measure of effect summarized as a ratio such as the relative risk is undefined. The results showed that amoxicillin–clavulanic acid was associated with a higher risk of adverse effects related to antibiotic use. Amoxicillin when used alone was associated with a relatively lower risk of adverse effects when compared to amoxicillin–clavulanic acid. Further, only the postoperative use of antibiotics was found to be significantly associated with an increased chance of adverse effects.

The NNH value indicates the number of patients who need to be treated before a harmful outcome is reported[55]. Compara-

tively, the use of amoxicillin alone was found to be less harmful, as 125 patients need to be treated with amoxicillin before an adverse effect is reported. However, for amoxicillin–clavulanic acid, an adverse effect is reported for every 15 additional patients. These results should be interpreted with caution, as four of the included studies on amoxicillin did not report on the adverse effects after amoxicillin use[44,49–51]. Incomplete reporting of outcomes of RCTs in this instance regarding the adverse effects of antibiotics will eventually encourage clinical prescription practices that are based on biased evidence.

Further, adverse outcomes of antibiotic use are not restricted to short-term side effects alone, as measured by these studies. Studies that have investigated the adverse outcomes related to antibiotic use in third molar surgery have previously restricted their outcome assessment to common immediate side effects like diarrhoea, nausea, and vomiting and those not related to antibiotic use, like headache[10]. The present review included prospective studies in which amoxicillin was administered to healthy volunteers in addition to studies assessing amoxicillin use for third molar surgery because of the absence of any study that has looked into the impact of antibiotic treatment on bacterial diversity and antibiotic resistance after third molar surgery.

There is increasing interest and evidence on the detrimental longer-term impact of antibiotic use with regard to antibiotic resistance. Evidence from the three studies included in this review clearly demonstrated a prolonged impact on bacterial diversity and antibiotic resistance in healthy volunteers after amoxicillin treatment. Amoxicillin use led to an increase in antibiotic resistance genes belonging to the blaTEM class, as well as multidrug resistance genes post exposure to the antibiotic[53,54]. The increase in blaTEM-positive *E. coli* in the gut following amoxicillin use is disturbing and may indicate the proliferation of a multi-resistant *E. coli* or spread of a multi-resistant plasmid. The potential of plasmids to spread between bacteria has been demonstrated previously in the gut[60]. blaTEM generate ampicillin and penicillin resistance in Gram-negative bacteria like *Haemophilus influenzae* and *Neisseria gonorrhoeae*. Further they can promote multidrug resistance in the form of extended-spectrum beta-lactamases after specific mutations[61,62]. Alterations in bacterial diversity have previously been associated with disease states at different sites[63,64], mainly caused by a dysbiosis of a 'healthy core microbiome'[34,35]. A persistent reduction in bacterial diversity in the gut, saliva, and skin after amoxicillin use up to 6 months is a significant finding that must be considered when evaluating the cost–benefit ratio of antibiotic use, in situations where it can be avoided.

It is aimed to present these critical findings regarding antibiotic use to clinical practitioners and decision-makers for consideration in the development of guidelines for antibiotic use in minor surgical procedures with minimal infection rates.

Amoxicillin and amoxicillin–clavulanic acid appear to be the most preferred antibiotics among dentists worldwide when attempting to prevent infection after third molar surgery[24–27,65–68]. Even though the data are based on questionnaire studies, which have inherent biases associated with them, the results of these studies clearly highlight the lack of guidelines for antibiotic prescriptions in third molar surgery. When compared to questionnaires, the use of audits[66] and evaluations[69] could represent a more effective way of analyzing prescription patterns, since questionnaires have potential bias and low response rates[24,25]. The efficiency of audits in modifying prescribing habits has been demonstrated previously by Steed and Gibson[70]. To facilitate accurate audits and evaluations, proper documentation of case variables, antibiotic prescriptions, and infections, including the microbiological data, is needed.

Evidence suggests that continuing education based on previous survey findings seems to have little impact on prescription practices and that no microbiological diagnosis is performed before antibiotic prescription[65], which is quite alarming. Further, when managing these postoperative infections, the appropriate prescription of antibiotics clinically should include a thorough understanding of the likely organisms involved in the infection, which in turn will avoid the prescription of unsuitable antibiotics. Therefore, knowledge of the evidence base for prescribing antibiotics should prevent unnecessary and detrimental contributions to the global threat posed by antibiotic resistance.

A detailed analysis of the microbiological outcomes of third molar infections is heavily constrained due to the limitations associated with culture-based methods. Also, culture methods selectively screen using particular media, which further limits a full profile examination of the pathogenic infection. Recent next-generation sequencing techniques like 16S rRNA gene sequencing allow more precise analysis of bacterial profiling and should be utilized in this regard; these could deliver a vast amount of information regarding the microorganisms. Further, shotgun metagenomic and transcriptomics techniques could be used to evaluate the functional potential of the microorganisms identified. This information could lead to the development of novel specific antibacterial strategies in place of widespread non-specific broad-spectrum antibiotic use.

The results of this systematic review and meta-analysis show that both amoxicillin–clavulanic acid and amoxicillin are effective in the prevention of postoperative infection and complications after third molar surgery. However, studies with a split-mouth protocol have been designed with inadequate crossover periods, further questioning the reliability of the data on the use of amoxicillin alone and its effectiveness. There is a significantly higher chance of adverse effects after amoxicillin–clavulanic acid use. Although amoxicillin is not associated with significant adverse effects, most of the selected studies on amoxicillin use have not reported adequately regarding short-term adverse effects. Further, there is evidence that the use of amoxicillin is associated with a sustained reduction in bacterial diversity and elevation in antibiotic resistance in healthy volunteers. However, no such data exist for amoxicillin–clavulanic acid use.

Clinical practitioners should be made aware of the adverse outcomes of amoxicillin use in healthy adults, including changes in bacterial diversity and resistance. Considering the limited information on the microbiology of post–treatment infections, biased information on prescription patterns, and the absence of long-term evaluation of patients who did not report with infections after antibiotic treatment with regard to the development of antibiotic resistance, three important areas for future research in third molar infections were identified: (1) The use of next-generation sequencing techniques to identify the microbiome of post-treatment infections after third molar surgery. (2) Improving documentation of clinical and microbiological variables, enabling accurate periodic audits and evaluations for antibiotic use and infection rates. (3) Long-term evaluation of clinical samples from patients undergoing third molar extraction and antibiotic treatment to assess the impact on antibiotic resistance. Studies in these three areas would bring us a step closer to developing guidelines for effective and ethical antibiotic prescription for dental surgical procedures including third molar extractions.

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Competing interests

None to declare.

Ethical approval

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Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.08.002.

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