

Journal section: Oral Surgery  
Publication Types: Review

doi:10.4317/medoral.25999

## Prophylactic therapy for prevention of surgical site infection after extraction of third molar: An overview of reviews

Yiting Cao <sup>1</sup>, Qian Jiang <sup>2</sup>, Jingzhou Hu <sup>3</sup>

<sup>1</sup> Department of Pediatric Dentistry, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology; Shanghai Research Institute of Stomatology. Shanghai, China

<sup>2</sup> Department of Oral Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology; Shanghai Research Institute of Stomatology. Shanghai, China

<sup>3</sup> Department of Oral and Maxillofacial-Head and Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology; Shanghai Research Institute of Stomatology. Shanghai, China

### Correspondence:

Department of Oral and Maxillofacial-Head and Neck Oncology  
Shanghai Ninth People's Hospital  
Shanghai Jiao Tong University School of Medicine  
Shanghai, 200011, China  
huyayi@shsmu.edu.cn

Received: 03/03/2023  
Accepted: 26/06/2023

Cao Y, Jiang Q, Hu J. Prophylactic therapy for prevention of surgical site infection after extraction of third molar: An overview of reviews. Med Oral Patol Oral Cir Bucal. 2023 Nov 1;28 (6):e581-7.

Article Number: 25999 <http://www.medicinaoral.com/>  
© Medicina Oral S. L. C.I.F. B 96689336 - pISSN 1698-4447 - eISSN: 1698-6946  
eMail: [medicina@medicinaoral.com](mailto:medicina@medicinaoral.com)  
**Indexed in:**  
Science Citation Index Expanded  
Journal Citation Reports  
Index Medicus, MEDLINE, PubMed  
Scopus, Embase and Emcare  
Indice Médico Español

### Abstract

**Background:** To compare the effect of different prophylactic therapies on prevention of surgical site infection after extraction of third molars with different degree of impaction.

**Material and Methods:** Systematic reviews and meta-analyses evaluating the effect of different prophylactic therapies on prevention of surgical site infection after extraction of third molars were included. An electronic search was performed in PubMed, EMBASE, and the Cochrane Database of Systematic reviews. AMSTAR 2 tool was used to evaluate the confidence in results from the included reviews. Descriptive analyses were performed.

**Results:** Six reviews were included. A significant benefit of different antibiotics to the prevention of site infection after extraction of third molars was reported. Amoxicillin/amoxicillin clavulanic acid could significantly reduce the rate of surgical site infection versus placebo. Chlorhexidine gel could significantly reduce the frequency of alveolar osteitis versus placebo.

**Conclusions:** Based on the limited evidence, there is a significant benefit of prophylactic therapy while the comparative effect of different types of prophylactic regimes are controversial.

**Key words:** Third molar extraction, antibiotics, chlorhexidine, overview.

## Introduction

Extraction of third molars with different impaction degree has been a common practice in dental clinics. Although third molar extraction is commonly considered as a safe procedure, complications might occur during or after surgery. A previous cross-sectional study reported a post-surgery complication rate of 6.9%, including alveolitis, infection, and paresthesia of the inferior alveolar nerve (1). A recent review summarizes the frequency of post-surgery complications, including alveolitis (0.5 to 32.5%), infection (0.9 to 4.2%), postoperative bleeding (0.2 to 1.5%), as well as transient and permanent dysfunction of the inferior alveolar nerve (0.6 to 5.5%, 0.1 to 0.9%, respectively) (2). The complications during or after surgery might lead to patient discomfort, impaired oral and systematic health, and reduced quality of life (3). Thus, more attention should be paid to the prevention and management of complications following third molar extraction.

Third molars usually not fully erupt and the complexity of surgery procedure might increase the risks of surgery site infection (1). Use of prophylactic therapy has been reported to prevent surgery site infection after third molar extraction. Prescription of systematic antibiotics is a wide spread practice among dentists. A previous systematic review reports that 19 people need to be treated with antibiotics to prevent one infection following extraction of impacted third molars (4). However, inappropriate use of antibiotics has the risks of adverse reactions and antibiotic resistance (5). Thus, prophylactic antibiotic therapy is usually not indicated in healthy patients. Some authors explored to use chlorhexidine as prophylactic therapy due to broad spectrum activity, covering anaerobes, and no registered resistance. However, the benefit of chlorhexidine on prevention of infection following third molar extraction is also unclear (6,7).

Currently, several systematic reviews have addressed the effect of different prophylactic therapies on prevention of infection following third molar extraction. However, an overall critical appraisal and synthesis has not been performed. Thus, the objective of the present review is to systematically identify and critically appraise current systematic reviews on the application of prophylactic medication for the prevention of surgical site infection after extraction of third molars with different degree of impaction.

## Material and Methods

The protocol of the present review was elaborated prospectively (Supplement 1). The present overview is reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (8). No ethics approval is required for this overview.

### - Eligible criteria

The PICOS format research question is as follows. Patients were those who need extraction of third molars with different degree of impaction. Interventions were different types of prophylactic medication. Comparisons were types of prophylactic medication other than interventions, or placebo. Primary outcome measure was frequency of surgical site infection, including infection, dry socket, fever, lymphadenopathy, or alveolar osteitis. The study design was systematic review with or without meta-analysis.

### - Search strategy

Electronic search was performed in PubMed, Embase, and the Cochrane database of systematic review. No limitation was set on language and publication time. The search was performed in January, 2023. The search strategy was (review[Title]) AND (third molar\*[Title/Abstract]) AND (remov\*[Title/Abstract] OR extract\*[Title/Abstract] OR infect\*[Title/Abstract]). Hand search was performed by screening reference lists and citing articles of key studies.

### - Study selection

Two review authors performed study selection independently and in duplicate. Firstly, title/abstract of records were screened. Secondly, full articles were screened. A data mining tool Rayan (<https://www.rayan.ai>) was used as a third screener to assist in study selection. Any disagreement was solved by discussion with experts. The inter-reviewer reliability (kappa correlation coefficient) of the title/abstract screening and full-text screening was 0.86 and 0.81, respectively.

### - Data extraction

Data extraction was performed by two review authors independently and in duplicate. The following information was extracted: bibliometrics information (author, publication year), study methods (patient characteristics, interventions, comparison, outcome measures), information for risks of bias assessment (risk of bias tool, funding, conflict of interest), main results (type of data synthesis, effect size, 95% confidence interval, p-value, and heterogeneity), and main conclusions.

### - Risks of bias assessment

Risks of bias of included systematic reviews was assessed by a MeaSurement Tool to Assess systematic Reviews (AMSTAR)-2 tool (9). Two review authors performed risk of bias assessment independently and in duplicate. Briefly, seven domains with 16 items were assessed, including protocol registration, adequacy of literature search, justification for excluding individual studies, risks of bias of individual studies, appropriateness of meta-analysis methods, consideration of risks of bias in result interpretation, and assessment of publication bias. The overall confidence of each systematic review was assessed as high, moderate, low,

and very low with the presence of no or one non-critical weakness, more than one non-critical weakness, one critical weakness with or without one non-critical weakness, and more than one critical weakness, respectively.

- Data synthesis

Qualitative analysis was performed summarizing the frequency of surgical site infection, reported in relative or absolute frequencies as main summary measure.

**Results**

- Study selection

Electronic search identified 87, 68, and 18 records in PubMed, Embase, and Cochrane Database of System-

atic reviews, respectively. After removal of duplicates, 112 records were screened for titles/abstracts. Fifteen studies were screened for full publication and ten were excluded. Hand search identified one study. Procedures for study selection is showed in Fig. 1. Finally, six studies were included (10-15).

- Characteristics of included studies

Characteristics of included studies are listed in Table 1. All the reviews included only randomized controlled trials (RCTs). The interventions include amoxicillin/amoxicillin clavulanic acid only (10), chlorhexidine only (15), or combination of different therapies. The comparisons include placebo alone or different therapies other than intervention. The outcome measure was incidence of infection.

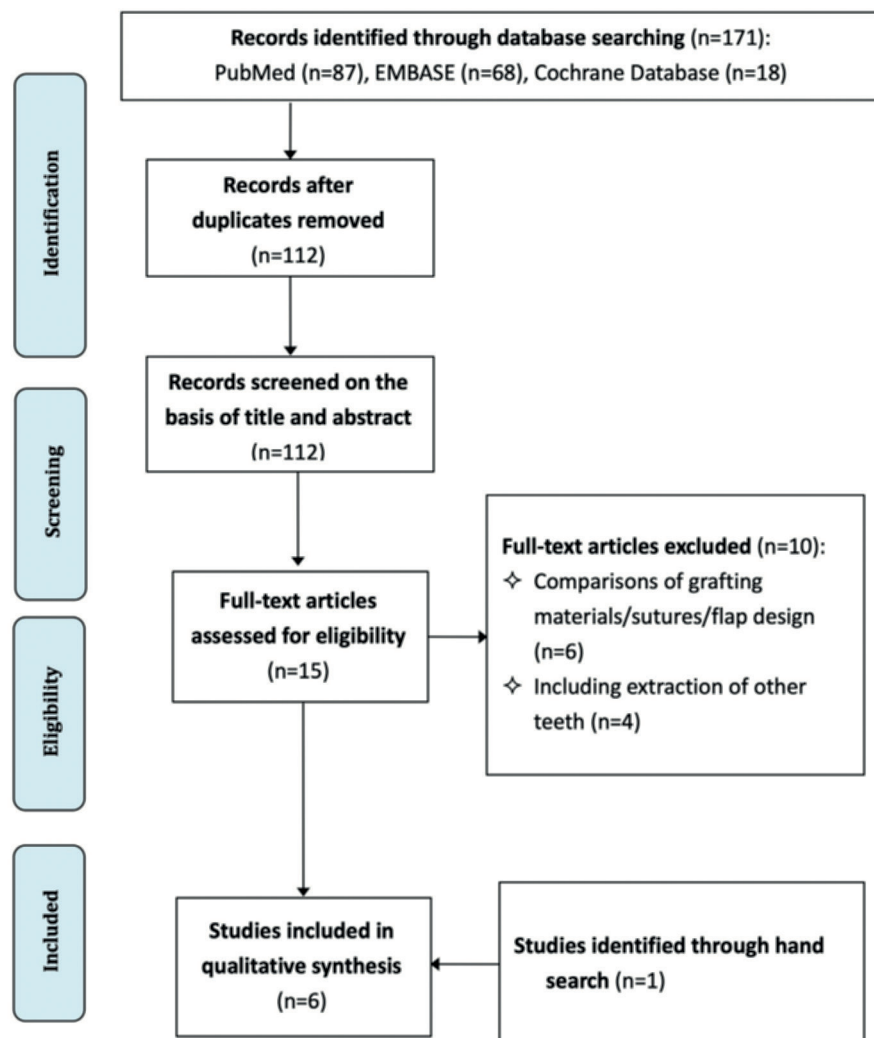


Fig. 1: Flow diagram.

**Table 1:** Characteristics of included reviews.

Study	Participant	Intervention	Control	No. of studies	Outcome measure	Meta-analysis	Main conclusions
Arteagoitia 2016	Extraction of third molars with any degree of impaction	Amoxicillin/Amoxicillin clavulanic acid	Placebo	10	The incidence of dry socket, infection, or both	Amoxicillin alone or with clavulanic acid vs placebo 10 studies, 1997 extractions: 1072 in experimental groups and 925 in control (placebo) groups, random effect model RR 0.35, 95% CI 0.21 to 0.57, $p < 0.001$ , $I^2 = 0$ Subgroup analysis, Amoxicillin alone vs placebo 7 studies, 1167 extractions: 606 in experimental groups and 561 in controls with 14 and 27 events of dry socket and/or infection, random effect model RR 0.56, 95% CI 0.30 to 1.08, $p = 0.082$ , $I^2 = 0$ Subgroup analysis, Amoxicillin and clavulanic acid vs placebo 3 studies, 830 extractions: 466 in experimental groups and 364 in controls with 13 and 47 events of dry socket and/or infection, random effect model RR 0.22 95% CI 0.12 to 0.40, $p < 0.001$ , $I^2 = 0$	Prophylactic use of amoxicillin does not significantly reduce the risk of infection and/or dry socket after third molar extraction. With amoxicillin/clavulanic acid, the risk decreases significantly.
Cervino 2019	Extraction of third molars, not specified	Amoxicillin/Amoxicillin clavulanate/chlorhexidine 0.12% rinse	Different antibiotic therapy or placebo	12	Postoperative surgical site infection	No meta-analysis was performed	The most commonly used protocol involves the use of penicillin and clavulanate, obtaining safe clinical and prophylactic results in the management of infections. Postoperative surgical site infection does not show significant differences between study groups.
Marcussen 2016	Extraction of partially or totally impacted lower third molars	Amoxicillin/Amoxicillin clavulanate/ Penicillin/ Metronidazole	Placebo	10	Incidence of surgical site infection	All types of prophylactic antibiotics vs, placebo 10 RCTs, 1390 patients, fixed effect model OR 0.30, 95% CI 0.19 to 0.47, $p < 0.001$ , $I^2 = 26\%$ Subgroup analysis, Amoxicillin vs. placebo 5 RCTs, 287 patients, fixed effect model OR 0.19, 95% CI 0.08 to 0.45, $p < 0.001$ , $I^2 = 0$	Use of antibiotics significantly reduces the incidence of surgical site infection. Amoxicillin reduces the incidence of surgical site infection and penicillin reduces the incidence of alveolar osteitis.
Ramos 2016	Extraction of third molars with any degree of impaction	Amoxicillin/Amoxicillin clavulanate/ Penicillin/ Metronidazole/other antibiotics regime	Placebo	22	Incidence of infection	All antibiotics vs. placebo 21 RCT, 3304 patients, fixed effect model RR 0.43, 95% CI 0.33 to 0.56, $p < 0.001$ , $I^2 = 19.3\%$ Subgroup analysis, penicillins (amoxicillin, amoxicillin/clavulanic acid, azidocillin) vs. placebo 13 RCTs, 2264 patients, fixed effect model RR 0.40, 95% CI 0.27 to 0.59, $p < 0.001$ , $I^2 = 24.2\%$ Subgroup analysis, nitroimidazoles (metronidazole, tinidazole) vs. placebo 8 RCTs, 888 patients, fixed effect model RR 0.56, 95% CI 0.38 to 0.82, $p < 0.001$ , $I^2 = 23.7\%$	Antibiotics, administered to prevent dry socket and/or infection after third molar extraction, reduces the risk of infection by 57%. The efficacy of penicillins is slightly higher than that of nitroimidazoles.
Sologova 2022	Extraction of third molars	Amoxicillin/Amoxicillin clavulanic acid /Ceftazidime levofloxacin	Placebo	10	Incidence of dry socket and infection	No meta-analysis was performed	Amoxicillin/amoxicillin clavulanic is currently the most widely prescribed group of antibiotics. The widespread use of this antibiotic group can lead to antimicrobial resistance.
Teshome 2017	Extraction of mandibular third molars	Chlorhexidine gel	Placebo	10	Incidence of alveolar osteitis	Chlorhexidine gel vs. placebo 10 RCTs, 842 patients, fixed effect model RR 0.43, 95% CI 0.32 to 0.58, $p < 0.001$ , $I^2 = 40\%$	Chlorhexidine gel is superior to a placebo in reducing the incidence of alveolar osteitis after mandibular third molar extraction.

- Risks of bias of included studies

Risk of bias of included studies assessed by the AMSTAR-2 tool is listed in Table 2. Three studies were assessed as low confidence and three as very low.

-Descriptive data analysis

1 Any type of antibiotics

Two studies reported significant benefit of different antibiotics to the prevention of site infection after extraction of third molars. Marcussen *et al* (2016) included 10 RCTs with 1390 participants and reported significant benefit of different regime of antibiotics compared with placebo (OR=0.30, 95% CI 0.19 to 0.47,  $p<0.001$ , I2=26%). Similarly, Ramos *et al* (2016) included 21 RCTs with 3304 participants and reported significant benefit of different regime of antibiotics compared with placebo (RR=0.43, 95% CI 0.33 to 0.56,  $p<0.001$ , I2=19.3%). These two studies concluded that use of antibiotics significantly reduced the frequency of surgical site infection.

2 Amoxicillin/amoxicillin clavulanic acid

One study, including 10 studies and 1997 participants, focused on the effect of amoxicillin/amoxicillin clavulanic acid (10). This study reported that amoxicillin alone did not significantly reduce the rate of surgical site infection (RR=0.56, 95% CI 0.30 to 1.08,  $p=0.082$ , I2=0) while amoxicillin with clavulanic acid significantly reduced the rate of surgical site infection (RR=0.22, 95% CI 0.12 to 0.40,  $p<0.001$ , I2=0). The study also reported that 1 out of 26 patients treated with amoxicillin with or without clavulanic acid had some types of adverse events. Marcussen *et al* (2016) included different types of antibiotics and performed subgroup analysis on the effect of amoxicillin versus placebo. The result showed that amoxicillin clavulanic acid could significantly reduce the incidence of surgical site infection (5 RCTs, 287 patients, OR=0.19, 95% CI 0.08 to 0.45,  $p<0.001$ , I2=0).

3 Penicillin

One study performed subgroup analysis on penicillin versus placebo and reported that penicillin could significantly reduce the incidence of alveolar osteitis (2 RCTs, 188 patients, OR=0.10, 95% CI 0.03 to 0.30,  $p<0.001$ , I2=0).

4 Chlorhexidine

One study including 10 RCTs and 842 patients compared the prevention effect of chlorhexidine gel versus placebo regarding the frequency of alveolar osteitis (15). The meta-analysis showed benefit of using chlorhexidine gel (RR=0.43, 95% CI 0.32 to 0.58,  $p<0.001$ , I2=40%).

**Discussion**

This is the first overview to systematically summarize and critically appraise the available high-level evidence on the benefit of prophylactic therapy on prevention of incidence of surgery site infection after extraction of third molar with different degree of impaction. The current evidence suggests that there is a significant benefit of prophylactic therapy while the comparative effect of different types of prophylactic regimes are controversial. It is difficult to determine which one is the best prophylactic therapy following third molar extraction. Overall, two studies reported significant benefit of different antibiotics to the prevention of site infection after extraction of third molars (12,13). This is in accordance to a previous Cochrane systematic review, which reported that following extraction of third molars, antibiotic prophylaxis might reduce the rate of postsurgical infectious complications by 66% and reduce the risks of dry socket by 34%, respectively (4).The results indicated that 19 and 46 patients need to be treated with antibiotics to prevent one infection and dry socket, respectively. Based on the current evidence, there is significant benefit of antibiotics on the prevention of infection after third molar extraction. However, the adverse events of antibiotics should be remembered. The risk of post-surgery infection is associated with several factors, including the impaction degree and anatomical position of third molar, patient oral and systematic health, surgeon's experience, and management of hemostasis during surgery (1,16-18). Clinicians should carefully study the patient conditions and evaluate risks of infection, before prescription of antibiotics.

Amoxicillin, alone or combined with clavulanic acid, is reported to be the most widely used prophylactic antibiotics (14). Two studies reported significant benefit of

**Table 2:** AMSTAR 2 assessment of confidence in results of systematic reviews included.

Study	AMSTAR 2 items																Confidence in results
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Arteagoitia 2016	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	N	Low
Cervino 2019	Y	N	Y	N	N	N	N	N	N	N	NA	NA	N	NA	NA	N	Very low
Marcussen 2016	Y	N	N	Y	N	N	N	Y	N	N	Y	N	N	N	Y	N	Very low
Ramos 2016	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	N	Very low
Sologova 2022	Y	N	N	Y	Y	Y	N	Y	Y	Y	NA	NA	NA	Y	NA	Y	Low
Teshome 2017	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	N	Low



amoxicillin clavulanic acid (10,12) while the effect of amoxicillin alone was not significant (10). The results should be interpreted with cautious because of the limited sample size and very low confidence in results. In addition, the adverse events of amoxicillin/amoxicillin clavulanic acid should be addressed. Another study reported that a single preoperative oral dose of 2 g of amoxicillin significantly reduce the risks of surgical site infection (12). This study discussed that there was no evidence of development of resistance after application of a single prophylactic dosage of an antibiotic. The different results derived from different studies might be attributed to the different third molar impaction degree, surgical techniques, dose of antibiotics, and control groups (placebo or other types of antibiotics).

A significant beneficial effect of chlorhexidine gel on the prevention of alveolar osteitis was reported in one study (15). Chlorhexidine has been used in dentistry for over 40 years as an antiplaque agent, due to its high substantivity and broad antimicrobial spectrum (19). It was reported that chlorhexidine mouth rinse could prevent dry socket and bacteremia after tooth extraction (20,21). However, disadvantages of chlorhexidine mouth rinse have been reported, including impaired taste sensation, increased supragingival calculus formation, oral mucosal lesion, as well as tooth restoration and tongue staining (22-24). In addition, mouth rinse should be avoided within 24 hours after tooth extraction. Thus, application of chlorhexidine gel might be a better choice. It has been reported that chlorhexidine gel could promote wound healing after tooth extraction (19), which was in accordance with the present review.

There are some limitations of the present overview. Firstly, the overall confidence in results was low to very low, due to the inferior methodology of included systematic reviews. Secondly, there was large heterogeneity among studies, due to different jaw locations, impaction degree, surgical interventions, dosage of prophylactic therapies, and patient conditions. Thirdly, we failed to perform a quantitative analysis due to the different choice of prophylactic therapies among studies and large heterogeneity. Thus, in the present review, we failed to draw a conclusion on which therapy was better to prevent infection after third molar extraction. In the future, trials comparing different types of prophylactic therapies are recommended. Trials should apply strictly eligible criteria, high-quality methodology, validated outcome measures, and well-formatted reporting structures.

## Conclusions

The current evidence suggests that, regarding prevention of infection of third molar extraction, there is a significant benefit of prophylactic therapy while the comparative effect of different types of prophylactic regimens are controversial. Based on the limited evidence,

it is difficult to determine which one is the best prophylactic therapy following third molar extraction.

## References

- Blondeau F, Daniel NG. Extraction of impacted mandibular third molars: postoperative complications and their risk factors. *J Can Dent Assoc.* 2007;73:325.
- Candotto V, Oberti L, Gabrione F, Scarano A, Rossi D, Romano M. Complication in third molar extractions. *J Biol Regul Homeost Agents.* 2019;33:169-72.
- Lee CT, Zhang S, Leung YY, Li SK, Tsang CC, Chu CH. Patients' satisfaction and prevalence of complications on surgical extraction of third molar. *Patient Prefer Adherence.* 2015;9:257-63.
- Lodi G, Azzi L, Varoni EM, Pentenero M, Del Fabbro M, Carrassi A, Manfredi M. Antibiotics to prevent complications following tooth extractions. *Cochrane Database Syst Rev.* 2021;2:Cd003811.
- Milic T, Raidoo P, Gebauer D. Antibiotic prophylaxis in oral and maxillofacial surgery: a systematic review. *Br J Oral Maxillofac Surg.* 2021;59:633-42.
- Caso A, Hung LK, Beirne OR. Prevention of alveolar osteitis with chlorhexidine: a meta-analytic review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;99:155-59.
- Yengopal V, Mickenautsch S. Chlorhexidine for the prevention of alveolar osteitis. *Int J Oral Maxillofac Surg.* 2012;41:1253-64.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
- Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj.* 2017;358:j4008.
- Arteagoitia MI, Barbier L, Santamaria J, Santamaria G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis. *Med Oral Patol Oral Cir Bucal.* 2016;21:e494-504.
- Cervino G, Cicciù M, Biondi A, Bocchieri S, Herford AS, Laino L, *et al.* Antibiotic Prophylaxis on Third Molar Extraction: Systematic Review of Recent Data. *Antibiotics (Basel).* 2019;8:53.
- Marcussen KB, Laulund AS, Jørgensen HL, Pinholt EM. A Systematic Review on Effect of Single-Dose Preoperative Antibiotics at Surgical Osteotomy Extraction of Lower Third Molars. *J Oral Maxillofac Surg.* 2016;74:693-703.
- Ramos E, Santamaria J, Santamaria G, Barbier L, Arteagoitia I. Do systemic antibiotics prevent dry socket and infection after third molar extraction? A systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016;122:403-25.
- Sologova D, Diachkova E, Gor I, Sologova S, Grigorevskikh E, Arazashvili L, Tarasenko S. Antibiotics Efficiency in the Infection Complications Prevention after Third Molar Extraction: A Systematic Review. *Dent J (Basel).* 2022;10:72.
- Teshome A. The efficacy of chlorhexidine gel in the prevention of alveolar osteitis after mandibular third molar extraction: a systematic review and meta-analysis. *BMC Oral Health.* 2017;17:82.
- Cullifer RM, Makai G, Pacis M, Huynh T. Topical hemostatic and tissue-sealing agents in gynecologic surgery. *Curr Opin Obstet Gynecol.* 2020;32:285-91.
- Nguyen E, Grubor D, Chandu A. Risk factors for permanent injury of inferior alveolar and lingual nerves during third molar surgery. *J Oral Maxillofac Surg.* 2014;72:2394-401.
- Sukegawa S, Yokota K, Kanno T, Manabe Y, Sukegawa-Takahashi Y, Masui M, *et al.* What are the risk factors for postoperative infections of third molar extraction surgery: A retrospective clinical study?. *Med Oral Patol Oral Cir Bucal.* 2019;24:e123-9.
- Amaliya A, Ramadhanti R, Hadikrishna I, Maulina T. The Effectiveness of 0.2% Chlorhexidine Gel on Early Wound Healing after Tooth Extraction: A Randomized Controlled Trial. *Eur J Dent.* 2022;16:688-94.

20. Arteagoitia I, Rodriguez Andrés C, Ramos E. Does chlorhexidine reduce bacteremia following tooth extraction? A systematic review and meta-analysis. *PLoS One*. 2018;13:e0195592.
21. Halabi D, Escobar J, Alvarado C, Martinez N, Muñoz C. Chlorhexidine for prevention of alveolar osteitis: a randomised clinical trial. *J Appl Oral Sci*. 2018;26:e20170245.
22. McCoy LC, Wehler CJ, Rich SE, Garcia RI, Miller DR, Jones JA. Adverse events associated with chlorhexidine use: results from the Department of Veterans Affairs Dental Diabetes Study. *J Am Dent Assoc*. 2008;139:178-83.
23. Supranoto SC, Slot DE, Addy M, Van der Weijden GA. The effect of chlorhexidine dentifrice or gel versus chlorhexidine mouthwash on plaque, gingivitis, bleeding and tooth discoloration: a systematic review. *Int J Dent Hyg*. 2015;13:83-92.
24. Van Strydonck DA, Slot DE, Van der Velden U, Van der Weijden F. Effect of a chlorhexidine mouthrinse on plaque, gingival inflammation and staining in gingivitis patients: a systematic review. *J Clin Periodontol*. 2012;39:1042-55.

### **Funding**

Supported by Shanghai Key Laboratory of Stomatology & State Key Laboratory of Translational Research on Oral Ecosystem and Major Chronic Diseases (Planned) (Grant No. 2022SKLS-KFKT003).

### **Conflict of interest**

The authors declare no conflict of interest.

### **Ethics**

Udam sae coneculpa eariost, accae. Nam sunt, sent, num ut mo luplatem resecta sunt.

### **Authors contributions**

Yiting Cao and Qian Jiang are co-first authors and both have contributed equally to this work. Conceptualization: YT-C and JZ-H; Investigation: YT-C and Q-J; Methodology:YT-C and Q-J; Data curation: JZ-H; Validation: YT-C, JZ-H and Q-J; Writingoriginal draft preparation: YT-C; Writing-review and editing: YT-C, JZ-H and Q-J; Supervision: JZ-H; All authors have read and agreed to the final draft.