Systematic Review and/or Meta-analysis

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# Antibiotic prophylaxis for surgical wound infections in clean and clean-contaminated surgery: an updated systematic review and meta-analysis

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**Background:** The efficacy and necessity of prophylactic antibiotics in clean and clean-contaminated surgery remains controversial.
**Methods:** The studies were screened and extracted using databases including PubMed, Embase, Cochrane Library, Web of Science, and Clinical Trials.gov according to predefined eligibility criteria. Randomized controlled trials (RCTs) comparing the effect of preoperative and postoperative prophylactic antibiotic use on the incidence of surgical site infections (SSIs) in patients undergoing any clean or clean-contaminated surgery.
**Results:** A total of 16 189 participants in 48 RCTs were included in the primary meta-analysis following the eligibility criteria. The pooled odds ratio (OR) for SSI with antibiotic prophylaxis versus placebo was 0.60 (95% CI: 0.53–0.68). The pooled OR among gastrointestinal, oncology, orthopedics, neurosurgery, oral, and urology surgery was 3.06 (95% CI: 1.05–8.91), 1.16 (95% CI: 0.89–1.50), 2.04 (95% CI: 1.09–3.81), 3.05 (95% CI: 1.25–7.47), 3.55 (95% CI: 1.78–7.06), and 2.26 (95% CI: 1.12–4.55), respectively. Furthermore, the summary mean difference (MD) for patients' length of hospitalization was – 0.91 (95% CI: – 1.61, – 0.16). The results of sensitivity analyses for all combined effect sizes showed good stability.
**Conclusion:** Antibiotics are both effective, safe, and necessary in preventing surgical wound infections in clean and clean-contaminated procedures, attributed to their reduction in the incidence of surgical site infections as well as the length of patient hospitalization.

**Keywords:** clean-contaminated surgery, length of hospitalization, prophylactic antibiotic, safety, surgical site infection

## Introduction

Any intervention carries the risk of infection. In surgical procedures, more than 90% of surgical wounds develop pathogenic bacteria that are present in small numbers but are able to proliferate during the suturing process[1]. Surgical site infections (SSIs) are infections of the incision, organ, or space that occur after surgery and are a common cause of post-surgical morbidity[2]. Studies have reported that SSIs occur in up to 5% of patients after surgery, with an average increase in mean hospitalization time of 9.7 days on average[3]. Therefore, the Centers for Disease Control and Prevention Guidelines for the Prevention of Surgical Site Infections (2017 edition) emphasize the importance of emerging evidence for the prevention of SSIs, and antibiotic prophylaxis for SSIs is a key topic therein[2]. There remains widespread controversy regarding the impact of prophylactic antibiotics on SSIs in clean and clean-contaminated procedures, but the majority of clinicians around the world continue to

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acquiesce to or amplify their efficacy, contributing to the global pandemic of antibiotic resistance[4–6]. However, the original intent of antibiotic prophylaxis has often been used to bridge the gap between the lack of routine best practices and other infection prevention measures, which conflicts with the basic principles of antibiotic stewardship[7]. This controversial topic has become increasingly popular in recent years as new evidence from randomized controlled trial studies continues to emerge[8,9].

Prophylactic antibiotics are an option with several advantages, including a high drug concentration at the application site, a low incidence of systemic side effects, and good patient compliance. Nevertheless, there is still controversy over their use owing to possible detrimental effects, such as allergic reactions, gastrointestinal discomfort, and the emergence of resistant organisms with antibiotic exposure[10]. Although the effectiveness of appropriate antibiotic prophylaxis to prevent SSIs in indicated procedures is well established for a long time[11], the efficacy and necessity of prophylactic antibiotic use have been widely questioned as antibiotic resistance soars globally, and a growing number of studies suggest that prophylactic antibiotics are unnecessary in certain clean and clean-contaminated surgeries[12–15]. In its 2016 Global Guidelines for the Prevention of Surgical Site Infections, WHO strongly recommends against the continued use of antibiotic prophylaxis after surgery[16]. Similar recommendations have been made by the US Centers for Disease Control and Prevention (CDC) and the National Institute for Health and Care Excellence (NICE)[11].

Despite this recommendation, post-surgical antibiotic prophylaxis remains a common practice worldwide. According to incomplete statistics, globally, approximately one-sixth of hospital antibiotic prescriptions are for surgical antibiotic prophylaxis, which usually lasts for several days before and after surgery[17]. Simultaneously, due to the increased number of cases of postoperative wound infections in recent years, questions about intraoperative antibiotic use remain unanswered[18]. As new evidence has continued to emerge with the publication of new randomized controlled trials (RCTs), some of the data used in the initial evaluation might no longer be representative of best practice standards for surgical antibiotic prophylaxis.

A previous meta-analysis involving 13 RCTs only assessed the efficacy of topical antibiotics in preventing surgical wound infections in clean and clean-contaminated procedures, while the efficacy of antibiotics resulting from other types of routes of administration, such as intravenous drips or oral administration, remains unknown[19]. Therefore, a systematic literature review and meta-analysis was conducted to update the original guidelines as well as the evidence suggested by previous studies[1,19,20]. Specifically, our meta-analysis expanded the inclusion criteria of the studies without setting a limit on the route of administration of antibiotics and included a large number of recent RCTs to adequately assess the efficacy of antibiotics in the prevention of surgical wound infections in clean and clean-contaminated surgeries. To fill the research gap in recent years on the efficacy and safety of prophylactic antibiotics for the prevention of SSI in surgery and to compare the effect of prophylactic antibiotics on the length of hospitalization of patients with a view to reaching a broader consensus.

### HIGHLIGHTS

- Antibiotics are effective and safe in preventing wound infections in clean and clean-contaminated surgery.
- Prophylactic antibiotic use in clean and clean-contaminated surgeries reduces patient hospital stays.
- Prophylactic antibiotics do not reduce tumor resection wound infections.
- Prophylactic antibiotic use reduces oral surgery wound infections.

## Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/JS9/C933, Supplemental Digital Content 2, http://links.lww.com/JS9/C934) guidelines[21]. The protocol for this review was registered and published in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID). The methodological quality was assessed by a Measurement Tool to Assess Systematic Reviews (AMSTAR, Supplemental Digital Content 3, http://links.lww.com/JS9/C935) 2[22].

### *Search strategy*

Articles were retrieved through a systematic search of PubMed, Embase, Cochrane Library, Web of Science, and Clinical Trials.gov databases up to 15 March 2023. To broaden the search scope and improve accuracy, a selected search strategy combining keywords and subject terms was used to optimize the results. Briefly, the initial search strategy mainly included keywords such as antibiotic, prophylaxis, clean surgery, cleaning-contamination surgery, surgical wound, and SSIs, and the detailed search strategies were presented in Supplementary Material 1, Supplemental Digital Content 4, http://links.lww.com/JS9/C936. These terms were used following Cochrane's highly sensitive search strategy for identifying RCTs. The association of similarly defined search terms was first restricted by the logical character word "OR", and then the final retrieval of differently defined 6-digit similarly defined search terms was associated with the character logical word "AND". In addition, any non-English databases or non-English articles were not included in the search scope, and studies for which full text was not available were not considered. The searches were conducted simultaneously by three participants, and the corresponding disagreements were resolved through consultation with a fourth senior analyst.

### *Eligibility criteria*

Surgical wounds were grouped into four classes, according to the National Academy of Sciences and the National Research Council: clean (I); clean-contaminated (II); contaminated (III); and infected/dirty (IV)[23]. The prophylaxis strategy was defined as the administration of antibiotics to wounds before the development of infection. The initial filtering method was as follows: initially, titles were filtered for potentially relevant articles followed by an elaborate screening of abstracts to confine the search. Full texts of the article were filtered and shortlisted based on eligibility and relevance to the topic. The inclusion criteria were as follows: (a) Only clean (I) or clean-contaminated (II) surgical procedures were considered. (b) Studies in which SSIs were assessed as the primary outcome and were only expressed as a percentage or frequency; (c) Only RCTs studies were included; (d) Studies in which antibiotic use is clearly defined as prophylactic; (e) Explicit antibiotics are used for pre or postoperative surgical procedures; however, studies that meet any of the following criteria were excluded: (a) Data in any language other than English; (b) Studies in which placebo was not explicitly used as a control group; (c) Full-text research is not available.

### *Data extraction*

Two reviewers independently screened the titles and abstracts according to the same selection criteria, and three reviewers extracted the data of potentially relevant studies based on a predefined qualification criteria form (MS Excel). Resolution of disagreements between the three reviewers was done based on the review of eligibility and discussion with a senior independent reviewer until a consensus was reached. After eliminating duplicate articles and data, we formulated a data extraction strategy flow chart following the PRISMA guidelines. Briefly, the following information was extracted from studies included in the systematic review: First author & year of publication, country, number of participants, antibiotics, surgery type, gender ratio, age (denoted as "MD" or "MD ± SD"), and SSI positive outcome (denoted as "N" and' '%"). "NR" is denoted as the presence of unclear data in the extracted articles.

### *Risk-of-bias assessments*

Two authors independently assessed the risk of bias in included studies using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs, and where disagreement arose, the senior author was involved in consultation to reach a consensus. The specific deviation assessment items include random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Results were displayed in summary figures generated by Review Manager 5.3 (RevMan 5.3). The possibility of publication bias was visually assessed with a contour-enhanced funnel plot[24] and an Egger's test[25]. Specifically, a funnel plot was generated based on the sample size as well as the OR of each included study, with large-sample studies clustered in the middle and top of the graph and small-sample studies at the bottom. Egger's test was performed using Stata 15.1 software. In addition, the Jadad scale was used to supplement the assessment of the risk of bias in randomized controlled studies, with a scale score of less than 3 being considered a low-quality study, = 3 being a moderate-quality study, and greater than 3 being considered a high-quality study[26].

### *Statistical analysis*

Meta-analyses of available comparisons for the included studies were performed using RevMan 5.3. The primary analysis included RCTs of any clean and clean-contaminated surgeries comparing preoperative or postoperative antibiotic prophylaxis of any duration with a placebo. The primary outcome was the effect of preoperative or postoperative antibiotic prophylaxis on the occurrence of SSIs. Subgroup analyses compared the effectiveness of prophylactic antibiotic use for different surgical procedures. We calculated the combined odds ratio (OR) for the corresponding 95% C) using a random effects model (DerSimonian and Laird) and assessed heterogeneity and dispersion of effect sizes using $I^2$ and L'Abbe plots. The heterogeneity was considered low, moderate, and high if the cut-off points for $I^2$ values of 25%, 50%, and 75% or more were found, respectively[27]. Moreover, sensitivity analyses analyzed using Stata 15.1 software were used to assess the stability of the combined effect size. Specifically, it was performed by removing individual studies one by one and conducting a meta-analysis after removing each study. This cumulative analysis was widely used to estimate the effect of the largest study on the pooled effect size.

## Results

### *Studies selection*

The initial search yielded 2190 articles published between 3 August 1984 and 1 March 2022, from which 2051 duplicates were removed, following which 131 full-text articles were assessed for eligibility. After screening the titles and abstracts, 65 articles qualified for full-text assessment and were included in the further assessment. After an in-depth screening of articles for the presence of placebo with outcome indicator SSIs, the final 48 eligible articles were finalized and included. The PRISMA flow diagram detailing the study extraction process is presented in Fig. 1.

### *Characteristics of the included articles*

A total of 16 189 participants in 48 RCTs were included in the primary meta-analysis following the eligibility criteria, of which 55.3% of men and 44.7% of women in studies with relevant information and a median age of 49.9 years. The source countries

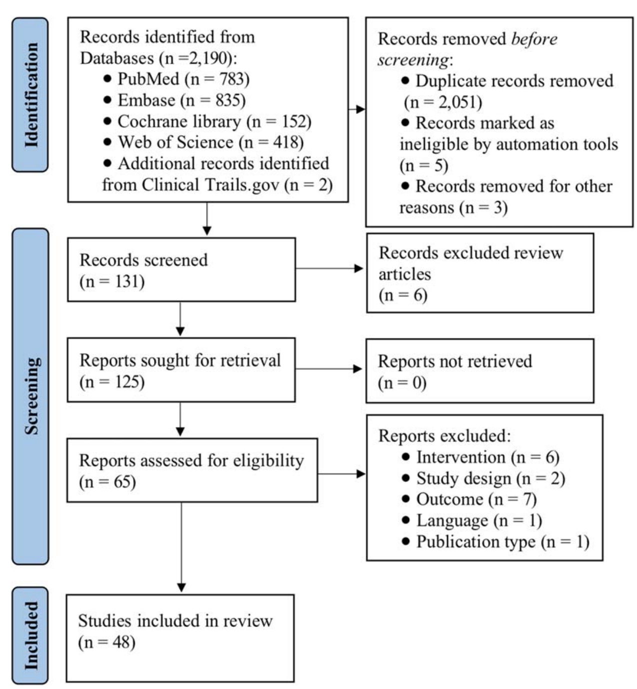


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the systematic review and meta-analyses selection process.

**Table 1**

**Baseline characteristics of the included studies.**

| Study | Country | Surgery type | Antibiotics | Sample size | Age (years) | Female/male | Positive SSIs (ANT vs. PLA) |
|---|---|---|---|---|---|---|---|
| Barbara *et al.*, 2022[28] | Austria | Oral cavity | Amoxicillin | 50 | 21.2 ± 3.3 | 29/21 | 3/47; 8/42 |
| Yotam *et al.*, 2017[29] | Israel | Head-neck | Cefazolin | 53 | 54.5 ± 15.7 | 39/14 | 12/31 ; 9/22 |
| Francesco *et al.*, 2021[30] | Italy | Gastrectomy | Amoxiclav | 47 | NR | 24/23 | 2/22; 6/25 |
| Zaid *et al.*, 2004[31] | Jordan | Oral cavity | Amoxicillin | 34 | Mean 27 | 21/13 | 2/17 ; 4/17 |
| Ronald *et al.*, 1987[32] | USA | Neurosurgery | Cefazolin | 830 | 42.7 ± 1.1 | 389/441 | 4/418;15/412 |
| Leila *et al.*, 2017[33] | Iran | Anorectal | Ciprofloxacin | 307 | 41.6 ± 14.5 | 83/224 | 22/156; 45/150 |
| Richard *et al.*, 1987[34] | USA | Fracture | Cefazolin | 101 | Mean 29 | 11/90 | 5/56; 19/45 |
| Edgard *et al.*, 2020[35] | Brazil | Mammaplasty | Cephalothin | 124 | Mean 34 | 124/0 | 3/62; 6/62 |
| Pichit *et al.*, 2018[36] | Thailand | Tracheostomy | Clindamycin | 60 | 49.9 ± 11.9 | 12/48 | 2/30; 7/30 |
| J. C *et al.*, 2006[37] | Australia | Breast | Flucloxacillin | 618 | Mean 55 | 2/616 | 10/311; 14/307 |
| Claire *et al.*, 2022[38] | Australia | Laparoscopic | Cefazolin | 107 | Mean 33 | 107/0 | 3/53; 5/54 |
| Fumitoshi *et al.*, 2013[39] | Japan | Liver resection | Flomoxef | 188 | Mean 68 | 121/67 | 20/94; 24/94 |
| Yoichi *et al.*, 2014[40] | Japan | Cholecystectomy | Cephalothin | 1037 | NR | 547/490 | 4/518; 19/519 |
| Takero *et al.*, 2014[41] | Japan | Hernia | Cefazolin | 200 | Mean 69 | 183/17 | 2/100; 13/100 |
| Emily *et al.*, 2020[42] | USA | Gynecologic | Polymyxin | 216 | 51.2 ± 1.1 | 216/0 | 12/105;11/114 |
| Mervyn *et al.*, 1986[43] | Israel | Neurosurgery | Gentamicin | 148 | 31.7 ± 25.2 | 97/51 | 2/71; 9/77 |
| TahaŞükrü *et al.*, 2022[44] | Turkey | Craniotomy | Cefazolin | 80 | 39.4 ± 15.2 | 39/41 | 1/40; 2/40 |
| Helena *et al.*, 2018[45] | Australia | Dermatological | Cefalexin | 142 | 66.3 ± 11.1 | 79/63 | 8/69; 1/73 |
| Saadeddin *et al.*, 2005[46] | UK | Gastrostomy | Amoxiclav | 99 | Mean 71 | 45/54 | 5/45; 18/38 |
| Issam *et al.*, 1997[47] | USA | Tumor | Novobiocin | 26 | Mean 43 | 11/15 | 3/12; 4/14 |
| Sung *et al.*, 2022[48] | Korea | Cholecystectomy | Cefazolin | 234 | 51.6 ± 15.5 | 97/137 | 10/116; 9/118 |
| Pinar *et al.*, 2017[49] | Turkey | Cholecystectomy | Cephalosporin | 162 | Mean 53 | 40/122 | 2/68; 1/56 |
| Metin *et al.*, 2006[50] | Turkey | Urology | Cefazolin | 118 | Mean 63 | 41/77 | 10/29; 12/30 |
| James *et al.*, 1984[51] | Ireland | Neurosurgery | Vancomycin | 402 | Mean 44 | NR | 1/203; 7/199 |
| Irfan *et al.*, 2015[52] | Indonesia | Urology | Cefazolin | 42 | 42.4 ± 2.4 | 0/42 | 0/21; 0/21 |
| Willemiek *et al.*, 2022[53] | Netherlands | Cholecystectomy | Cefazolin | 457 | 58.0 ± 13.9 | 233/224 | 16/226; 29/231 |
| Michelle *et al.*, 2022[54] | Canada | Oncology | Cephalosporins | 604 | 41.2 ± 21.9 | 243/361 | 44/293; 52/311 |
| Nicolás *et al.*, 2021[55] | Chile | Molar | Amoxicillin | 154 | 21.1 ± 4.3 | 107/47 | 2/77; 5/77 |
| Sheila *et al.*, 2022[56] | UK | Cancer | Amoxiclav | 871 | 59.1 ± 10.5 | 866/5 | 71/438; 83/433 |
| Robert *et al.*, 2021[57] | USA | Orthopedics | Vancomycin | 980 | 45.7 ± 13.7 | 343/637 | 29/481; 46/499 |
| Claudia *et al.*, 2018[58] | USA | Prostatectomy | Ciprofloxacin | 167 | 63.0 ± 6.8 | NR | 3/83; 5/84 |
| Thomas *et al.*, 2019[59] | USA | Gastroenterology | Polymyxin B | 190 | 63.7 ± 1.3 | NR | 10/95; 14/95 |
| Rubens *et al.*, 2020[60] | Brazil | Cancer surgery | Cefazolin | 124 | Mean 62 | NR | 1/62; 0/62 |
| Lissauer *et al.*, 2019[61] | UK | Miscarriage | Doxycycline | 3412 | 26.2 ± 6.6 | NR | 68/1676; 90/1684 |
| Davin *et al.*, 2020[62] | USA | Oculofacial | Erythromycin | 401 | Mean 44 | 239/162 | 0/201; 5/187 |
| Erin *et al.*, 2019[63] | USA | Pelvic | Nitrofurantoin | 151 | 61.7 ± 11.9 | NR | 13/75; 13/76 |
| Abiodun *et al.*, 2020[64] | Nigeria | Neurosurgery | Ceftriaxone | 132 | Mean 48 | 50/82 | 2/66; 1/66 |
| Maria *et al.*, 2020[65] | USA | Sternal surgery | Vancomycin | 1037 | 62.7 ± 13.5 | 225/812 | 14/517; 21/520 |
| Rodrigo *et al.*, 2019[66] | Me´xico | Urology | Fosfomycin | 82 | 41.9 ± 16 | 30/52 | 3/41; 15/41 |
| Gabrielle *et al.*, 2021[67] | Canada | Lumpectomy | Cefazolin | 312 | 60.7 ± 10.5 | NR | 5/60; 9/152 |
| Maria *et al.*, 2020[68] | Spain | Oral cavity | Amoxicillin | 92 | 27.5 ± 10.71 | 55/37 | 3/30; 6/30 |
| PU *et al.*, 2012[69] | India | Osteotomies | Amoxicillin | 60 | Mean 26 | 29/31 | 1/30; 6/30 |
| David *et al.*, 2013[70] | USA | Thoracic surgery | Cefazolin | 251 | Mean 63 | 139/112 | 6/125; 5/126 |
| JP *et al.*, 2004[71] | UK | General surgery | Fluoxacillin | 157 | Mean 31 | 28/129 | 2/46; 8/55 |
| Samuel *et al.*, 2014[72] | Australia | Skin excisions | Cefalexin | 52 | Mean 69 | 24/28 | 3/24; 10/28 |
| Palwasha *et al.*, 2021[73] | Sweden | Oral cavity | Amoxicillin | 474 | 57.1 ± 13.7 | 235/239 | 2/238; 5/235 |
| Steven *et al.*, 1999[74] | Holland | Orthognathic | Amoxiclav | 54 | Mean 25 | 41/13 | 5/35; 10/19 |
| Zhi *et al.*, 2019[75] | China | Intrarenal | Ciprofloxacin | 426 | 45.3 ± 13.3 | 140/286 | 7/142; 14/142 |

Sample size, sex, and positive SSIs expressed in specific numbers.
ANT, antibiotic; NR, unclear or unavailable; PLA, placebo; SSI, surgical site infection.

for these RCTs were 17 countries including Australia, China, Brazil, France, India, Iran, Israel, the Netherlands, the UK, and the USA. All RCTs had at least 2 study groups including placebo, of which only a small number provided data for multiple comparisons, and the primary outcome was SSIs (expressed as "%"). 27 studies presented age as "Mean ± SD", followed by 21 studies that explicitly used age expressed as "Mean". The 48 studies included types of surgery for gastrointestinal surgery[3], tumor resection[4], orthopedics[5], oral surgery[5], neurosurgery[4], urology[5], and others[22]. The baseline characteristics of the studies are shown in Table 1, and all unclear or unavailable data are indicated by 'NR'. The risk of bias for the included studies was stable overall (Fig. 2), and the funnel plot for evaluating publication bias was symmetrically distributed with no indication of publication bias (Fig. 3). As shown in Fig. 4 and Supplementary Material 2, Supplemental Digital Content 5, http://links.lww.com/JS9/C937, the results of the Egger test similarly showed no significant publication bias. In addition, as shown in Table 2, the

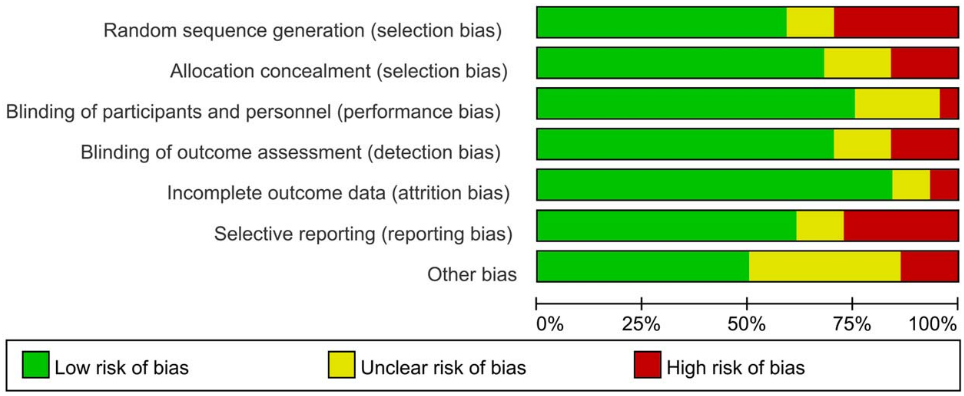


**Figure 2.** A summary of the authors' judgments of risk of bias for each included randomized controlled trial.

Jadad scale scores indicated that 37 out of 48 studies were of high quality (scores > 3), 8 were of moderate quality (scores = 3), and 3 were of low quality (scores < 3).

### *Antibiotic prophylaxis significantly reduces SSIs overall*

A total of 16 189 participants in 48 RCTs[28–75] were included in the primary meta-analysis following the eligibility criteria. These studies involved a total of 18 clean and clean-contaminated procedures as well as 12 antibiotics. The pooled odds ratio (OR) for SSIs with antibiotic prophylaxis versus placebo was 0.60 (95% CI: 0.53–0.68), with low heterogeneity in effect size between studies ($\chi^2 = 76.57$, df = 46, $P = 0.003$, $I^2 = 37\%$) and an overall effect test value of Z = 8.08 ($P < 0.00001$) as presented in Fig. 5. The results showed that the overall efficacy of prophylactic antibiotics in reducing SSIs in clean and clean-contaminated surgeries was significant up to now ($P = 0.00001$). The results of the sensitivity analysis showed no significant change in the combined effect values after excluding any of the literature, thus indicating good stability of the meta-analysis results (Supplementary Material 3, Supplemental Digital Content 6, http://links.lww.com/JS9/C938).

### *Subgroup analysis*

As shown in Fig. 6, to further validate our conclusions, we selected a selection of controversial types of clean and clean-contaminated surgeries, and these controversial findings were encapsulated in the 26 included studies that evaluated the outcomes of surgical site infections associated with antibiotic prophylaxis compared to placebo, respectively. All surgical types analyzed in the subgroups were classified and judged according to the International Classification of Diseases, Ninth Revision, Clinically Modified Version, Volume 3 (ICD-9-CM-3) promulgated by the National Center for Health Statistics and the WHO[76]. The funnel plot used to evaluate publication

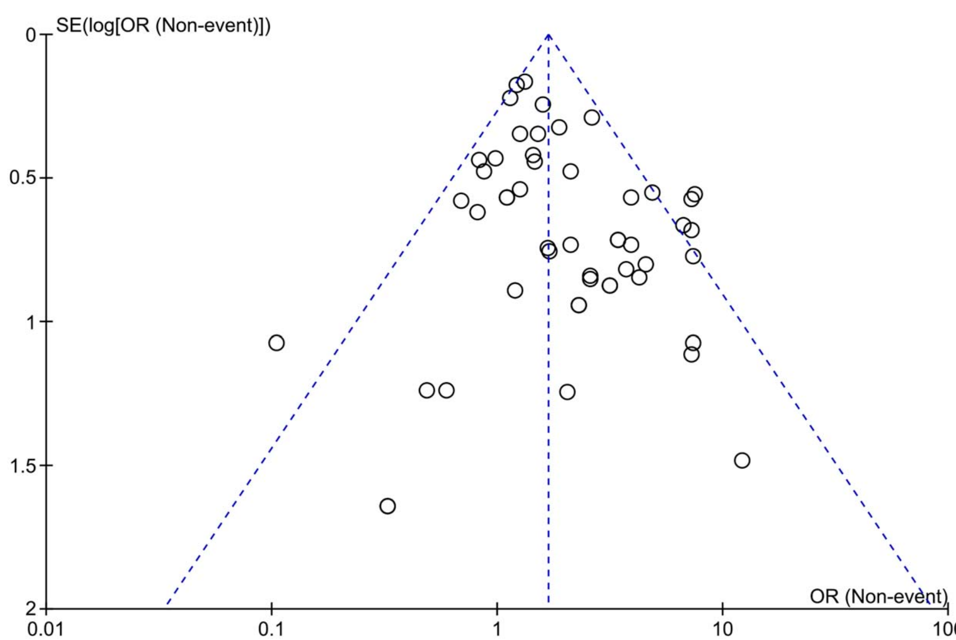


**Figure 3.** Funnel plot for evaluating overall publication bias. The horizontal line represents the summary effect estimates, and the dotted lines are pseudo-95% CIs. OR, odds ratio.

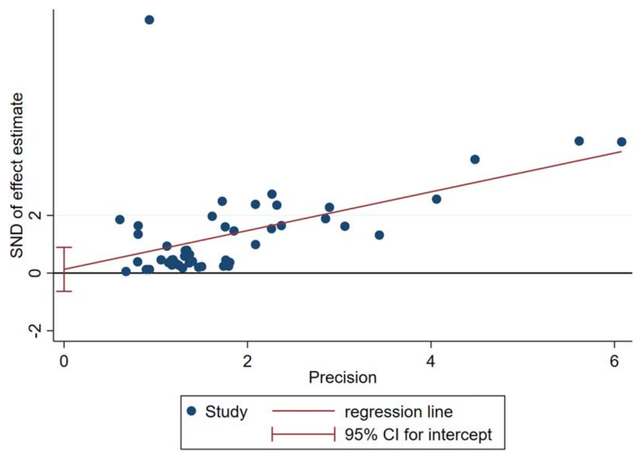


**Figure 4.** Meta-regression analysis of prophylactic antibiotics and surgical site infections. The horizontal line represents the summary effect estimates, and the diagonal lines represent pseudo-95% CI limits. SND, small-N designs.

bias in the subgroup-analyzed articles was symmetrically distributed with no signs of publication bias (Fig. 7). As shown in Fig. 8 and Supplementary Material 2, Supplemental Digital Content 5, http://links.lww.com/JS9/C937, the results of the Egger test for subgroup analysis also showed no significant publication bias. In addition, we analyzed the effect of prophylactic antibiotics on patient length of stay in the included studies (Fig. 9).

### Gastrointestinal surgery

Three of the 48 studies[30,46,59] (320 participants) were included in this subgroup analysis of patients whose type of surgery included gastrointestinal polypectomy and partial gastrectomy. Cefazolin, cefadroxil, novobiocin, and ciprofloxacin were selected as prophylactic agents for surgical site infection, with a pooled OR of 3.06 (95% CI: 1.05–8.91) for SSI prophylaxis with antibiotics compared to placebo. The overall effect test was $Z=2.05$ ($P<0.04$), accompanied by moderate heterogeneity ($\chi^2=4.84$, df = 2, $P=0.11$, $I^2=59\%$).

### Oncology surgery

Four of the 48 studies[47,54,56,67] (1,713 participants) were included in this subgroup analysis of patients with cancer whose type of surgery was accurately defined as tumor removal. Cephalosporins, as well as amoxiclav, were selected for prophylaxis of surgical site infectivity after tumor resection, with a pooled OR of 1.16 (95% CI: 0.89–1.50) for SSI of antibiotic prophylaxis compared to placebo. The overall effect test value of $Z=1.09$ ($P=0.28$) was accompanied by low heterogeneity ($\chi^2=0.90$, df = 3, $P=0.83$, $I^2=0\%$).

### Orthopedics surgery

Five studies[34,57,63,65,69] (1803 participants) were included in this subgroup analysis of patients whose type of surgery included joint replacement and fracture reduction. Ciprofloxacin, erythromycin, ceftriaxone, and amoxicillin were selected as prophylactic agents for surgical site infections, with a pooled OR of 2.04 (95% CI: 1.09–3.81) for SSI prophylaxis with antibiotics compared to placebo. The overall effect test was $Z=2.23$ ($P=0.03$), accompanied by moderate heterogeneity ($\chi^2=10.55$, df = 4, $P=0.03$, $I^2=62\%$).

### Neurosurgery

Four studies[32,44,51,64] (1444 participants) were included in this subgroup analysis of patients whose type of surgery consisted primarily of traumatic brain injury debridement. Amoxicillin, polymyxin, gentamicin, cefazolin, and furantoin were selected as prophylactic agents for surgical site infection, with a pooled OR of 3.05 (95% CI: 1.25–7.47) for SSI prophylaxis with antibiotics compared to placebo. The overall effect test was $Z=2.45$ ($P=0.01$), accompanied by low heterogeneity ($\chi^2=3.15$, df = 3, $P=0.37$, $I^2=5\%$).

### Oral surgery

Five studies[28,31,55,73,74] (1227 participants) were included in this subgroup analysis of patients whose type of surgery consisted primarily of oral implants versus orthodontics. Amoxicillin, a cephalosporin class, was selected as prophylaxis for surgical site infections, with a pooled OR of 3.55 (95% CI: 1.78–7.06) for SSI prophylaxis with antibiotics compared to placebo. The overall effect test was $Z=3.61$ ($P=0.0003$), accompanied by low heterogeneity ($\chi^2=1.39$, df = 4, $P=0.85$, $I^2=0\%$).

### Urology

Five studies[50,52,58,66,75] (1,527 participants) were included in this subgroup analysis of patients whose type of surgery consisted mainly of urethral stone removal with prostatectomy. Cefazolin, ceftriaxone, and amoxicillin were selected as prophylactic agents for surgical site infections, with a pooled OR of 2.26 (95% CI: 1.12–4.55) for SSI prophylaxis with antibiotics compared to placebo. The overall effect test was $Z=2.29$ ($P=0.02$), accompanied by low heterogeneity ($\chi^2=4.31$, df = 3, $P=0.23$, $I^2=30\%$).

### Length of hospitalization

Nine studies[29,30,40,41,43,44,51,58,59] with no limiting considerations for type of surgery were included in this subgroup analysis. As shown in Fig. 9, antibiotic prophylaxis significantly reduced the length of hospitalization for patients compared with placebo (summary MD = − 0.91, 95% CI: − 1.61, − 0.16, $P=0.02$).

### Safety assessment

As shown in Table 3, a total of 16 antibiotic-induced adverse events including flushing ($n=1$), rash (n = 4), secondary infection ($n=5$), and diarrhea ($n=6$) were reported in 5 of the 48 RCTs[24,33,48,49,61], and those studies with insufficient evidence of antibiotic-associated adverse events were not considered. As shown in Fig. 10, the mean incidence of adverse reactions in the antibiotic group was 5.18% with a summarized Risk Difference (RD) of 0.02 (95% CI: − 0.00, 0.04). All reported symptoms of rash, flushing, and diarrhea were mild and resolved spontaneously, and secondary infections recovered after supplemental antibiotic therapy.

## Discussion

This meta-analysis found that prophylactic antibiotics continue to significantly reduce SSIs in clean and clean-contaminated surgeries

**Table 2**

**Study design and Jadad scale rating.**

| No. | First author and year published | Randomization | Blinding | Design | Jadad Score 1) | 2) | 3) | 4) | 5) | Total | Qualitative rating [I] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Barbara *et al.*, 2022[28] | Yes | Yes | Parallel group | 1 | 1 | 1 | 0 | 1 | 4 | High |
| 2 | Yotam *et al.*, 2017[29] | Yes | Yes | Parallel group | 1 | 1 | 0 | 1 | 1 | 4 | High |
| 3 | Francesco *et al.*, 2021[30] | Yes | Yes | Parallel group | 0 | 1 | 1 | 1 | 1 | 5 | High |
| 4 | Zaid *et al.*, 2004[31] | Yes | No | Parallel group | 1 | 0 | 1 | 0 | 1 | 3 | Medium |
| 5 | Ronald *et al.*, 1987[32] | No | No | Parallel group | 0 | 0 | 0 | 1 | 1 | 2 | Low |
| 6 | Leila *et al.*, 2017[33] | Yes | Yes | Before-after | 0 | 1 | 1 | 1 | 1 | 4 | High |
| 7 | Richard *et al.*, 1987[34] | Yes | Yes | Before-after | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 8 | Edgard *et al.*, 2020[35] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 9 | Pichit *et al.*, 2018[36] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 10 | JC *et al.*, 2006[37] | No | Yes | Parallel group | 0 | 0 | 1 | 1 | 1 | 3 | Medium |
| 11 | Claire *et al.*, 2022[38] | Yes | Yes | Parallel group | 0 | 1 | 1 | 1 | 1 | 4 | High |
| 12 | Fumitoshi *et al.*, 2013[39] | No | No | Before-after | 0 | 0 | 0 | 0 | 1 | 1 | Low |
| 13 | Yoichi *et al.*, 2014[40] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 14 | Takero *et al.*, 2014[41] | Yes | Yes | Parallel group | 1 | 1 | 0 | 1 | 1 | 4 | High |
| 15 | Emily *et al.*, 2020[42] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 16 | Mervyn *et al.*, 1986[43] | Yes | Yes | Crossover | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 17 | TahaŞükrü *et al.*, 2022[44] | Yes | Yes | Parallel group | 1 | 1 | 0 | 1 | 1 | 4 | High |
| 18 | Helena *et al.*, 2018[45] | Yes | Yes | Parallel group | 1 | 0 | 1 | 1 | 1 | 4 | High |
| 19 | Saadeddin *et al.*, 2005[46] | NR | Yes | Parallel group | 1 | 0 | 0 | 1 | 1 | 3 | Medium |
| 20 | Issam *et al.*, 1997[47] | No | No | Parallel group | 0 | 0 | 0 | 1 | 1 | 2 | Low |
| 21 | Sung *et al.*, 2022[48] | Yes | Yes | Parallel group | 1 | 1 | 0 | 0 | 1 | 3 | Medium |
| 22 | Pinar *et al.*, 2017[49] | Yes | Yes | Crossover | 1 | 1 | 1 | 0 | 1 | 4 | High |
| 23 | Metin *et al.*, 2006[50] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 24 | James *et al.*, 1984[51] | Yes | No | Parallel group | 0 | 1 | 1 | 1 | 0 | 3 | Medium |
| 25 | Irfan *et al.*, 2015[52] | Yes | Yes | Parallel group | 1 | 1 | 0 | 1 | 1 | 4 | High |
| 26 | Willemiek *et al.*, 2022[53] | Yes | Yes | Before-after | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 27 | Michelle *et al.*, 2022[54] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 28 | Nicolás *et al.*, 2021[55] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 29 | Sheila *et al.*, 2022[56] | Yes | Yes | Before-after | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 30 | Robert *et al.*, 2021[57] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 31 | Claudia *et al.*, 2018[58] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 32 | Thomas *et al.*, 2019[59] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 33 | Rubens *et al.*, 2020[60] | Yes | Yes | Parallel group | 1 | 1 | 1 | 0 | 1 | 4 | High |
| 34 | Lissauer *et al.*, 2019[61] | Yes | Yes | Parallel group | 0 | 0 | 1 | 1 | 1 | 3 | Medium |
| 35 | Davin *et al.*, 2020[62] | Yes | Yes | Parallel group | 1 | 1 | 1 | 0 | 1 | 4 | High |
| 36 | Erin *et al.*, 2019[63] | Yes | No | Parallel group | 1 | 0 | 0 | 1 | 1 | 3 | Medium |
| 37 | Abiodun *et al.*, 2020[64] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 38 | Maria *et al.*, 2020[65] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 39 | Rodrigo *et al.*, 2019[66] | Yes | Yes | Parallel group | 1 | 1 | 1 | 0 | 1 | 4 | High |
| 40 | Gabrielle *et al.*, 2021[67] | Yes | Yes | Parallel group | 1 | 0 | 1 | 1 | 1 | 4 | High |
| 41 | Maria *et al.*, 2020[68] | Yes | Yes | Before-after | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 42 | PU *et al.*, 2012[69] | Yes | Yes | Parallel group | 1 | 1 | 1 | 0 | 1 | 4 | High |
| 43 | David *et al.*, 2013[70] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 44 | JP *et al.*, 2004[71] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 45 | Samuel *et al.*, 2014[72] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 0 | 4 | High |
| 46 | Palwasha *et al.*, 2021[73] | No | Yes | Parallel group | 1 | 0 | 1 | 1 | 0 | 3 | Medium |
| 47 | Steven *et al.*, 1999[74] | Yes | Yes | Parallel group | 1 | 1 | 1 | 1 | 1 | 5 | High |
| 48 | Zhi *et al.*, 2019[75] | Yes | Yes | Before-after | 0 | 1 | 1 | 1 | 1 | 4 | High |

[I] Total Jadad scores were classified into three categories: high- (4,5), medium- (3), and low-quality- (0,1,2).

and can significantly shorten the length of hospital stay for surgical patients, but particular caution is needed in cancer surgery. The use of prophylactic antibiotics remains safe and effective overall, and surgeons can still confidently prescribe antibiotics for the prophylaxis of wound infections after surgical procedures. This will help to alleviate disagreements about the efficacy of prophylactic antibiotics and prescribing concerns among clinical surgeons.

Our meta-analysis expanded the inclusion criteria of the studies without setting a limit on the route of administration of antibiotics and included a large number of recent RCTs to adequately assess the efficacy of antibiotics in the prevention of surgical wound infections in clean and clean-contaminated surgeries. Twenty-eight of the 48 studies were new RCTs published so far in 2018. All studies involved 17 countries, 18 surgical procedures, and 12 prophylactic antibiotics for preoperative or postoperative surgical site infections such as cephalosporins, amoxicillin, quinolones, etc. Strikingly, only 20 RCTs out of 48 studies recommended preoperative and postoperative antibiotic

| Study or Subgroup | Antibiotic Prophylaxis Events | Antibiotic Prophylaxis Total | Placebo Events | Placebo Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Abiodun et al. 2020 | 2 | 66 | 1 | 66 | 0.1% | 2.03 [0.18, 22.96] |
| Barbara et al. 2022 | 3 | 47 | 8 | 42 | 1.2% | 0.29 [0.07, 1.18] |
| Claire et al. 2022 | 3 | 53 | 5 | 54 | 0.7% | 0.59 [0.13, 2.59] |
| Claudia et al. 2018 | 3 | 83 | 5 | 84 | 0.7% | 0.59 [0.14, 2.56] |
| David et al. 2013 | 6 | 125 | 5 | 126 | 0.7% | 1.22 [0.36, 4.11] |
| Davin et al. 2020 | 0 | 201 | 5 | 187 | 0.9% | 0.08 [0.00, 1.50] |
| Edgard et al. 2020 | 3 | 62 | 6 | 62 | 0.9% | 0.47 [0.11, 1.99] |
| Emily et al. 2020 | 12 | 105 | 11 | 114 | 1.4% | 1.21 [0.51, 2.87] |
| Erin et al. 2019 | 13 | 75 | 13 | 76 | 1.6% | 1.02 [0.44, 2.37] |
| Francesco et al. 2021 | 2 | 22 | 6 | 25 | 0.8% | 0.32 [0.06, 1.77] |
| Fumitoshi et al. 2013 | 20 | 94 | 24 | 94 | 2.9% | 0.79 [0.40, 1.55] |
| Gabrielle et al. 2021 | 5 | 60 | 9 | 152 | 0.7% | 1.44 [0.46, 4.50] |
| Helena et al. 2018 | 8 | 69 | 1 | 73 | 0.1% | 9.44 [1.15, 77.62] |
| Irfan et al. 2015 | 0 | 21 | 0 | 21 | | Not estimable |
| Issam et al. 1997 | 3 | 12 | 4 | 14 | 0.4% | 0.83 [0.15, 4.78] |
| J. C et al. 2006 | 10 | 311 | 14 | 307 | 2.1% | 0.70 [0.30, 1.59] |
| J.P et al. 2004 | 2 | 46 | 8 | 55 | 1.1% | 0.27 [0.05, 1.33] |
| JAMES et al. 1984 | 1 | 203 | 7 | 199 | 1.1% | 0.14 [0.02, 1.11] |
| Leila et al. 2017 | 22 | 156 | 45 | 150 | 6.1% | 0.38 [0.22, 0.68] |
| Lissauer et al. 2019 | 68 | 1676 | 90 | 1684 | 13.3% | 0.75 [0.54, 1.03] |
| Maria et al. 2020 | 3 | 30 | 6 | 30 | 0.8% | 0.44 [0.10, 1.97] |
| Maria et al. 2020 | 14 | 517 | 21 | 520 | 3.1% | 0.66 [0.33, 1.32] |
| Mervyn et al. 1986 | 2 | 71 | 9 | 77 | 1.3% | 0.22 [0.05, 1.05] |
| Metin et al. 2006 | 10 | 29 | 12 | 30 | 1.2% | 0.79 [0.27, 2.27] |
| Michelle et al. 2022 | 44 | 293 | 52 | 311 | 6.6% | 0.88 [0.57, 1.36] |
| Nicolás et al. 2021 | 2 | 77 | 5 | 77 | 0.7% | 0.38 [0.07, 2.04] |
| P. U et al. 2012 | 1 | 30 | 6 | 30 | 0.9% | 0.14 [0.02, 1.23] |
| Palwasha et al. 2021 | 2 | 238 | 5 | 235 | 0.8% | 0.39 [0.07, 2.03] |
| Pichit et al. 2018 | 2 | 30 | 7 | 30 | 1.0% | 0.23 [0.04, 1.24] |
| Pinar et al. 2017 | 2 | 68 | 1 | 56 | 0.2% | 1.67 [0.15, 18.87] |
| Richard et al. 1987 | 5 | 56 | 19 | 45 | 3.0% | 0.13 [0.04, 0.40] |
| Robert et al. 2021 | 29 | 481 | 46 | 499 | 6.5% | 0.63 [0.39, 1.02] |
| Rodrigo et al. 2019 | 3 | 41 | 15 | 41 | 2.1% | 0.14 [0.04, 0.52] |
| Ronald et al. 1987 | 4 | 418 | 15 | 412 | 2.3% | 0.26 [0.08, 0.78] |
| Rubens et al. 2020 | 1 | 62 | 0 | 62 | 0.1% | 3.05 [0.12, 76.30] |
| SAADEDDIN et al. 2005 | 5 | 45 | 18 | 38 | 2.7% | 0.14 [0.05, 0.43] |
| Samuel et al. 2014 | 3 | 24 | 10 | 28 | 1.2% | 0.26 [0.06, 1.08] |
| Sheila et al. 2022 | 71 | 438 | 83 | 433 | 10.8% | 0.82 [0.58, 1.16] |
| Steven et al. 1999 | 5 | 35 | 10 | 19 | 1.7% | 0.15 [0.04, 0.55] |
| Sung et al. 2022 | 10 | 116 | 9 | 118 | 1.3% | 1.14 [0.45, 2.92] |
| TahaŞükrü et al. 2022 | 1 | 40 | 2 | 40 | 0.3% | 0.49 [0.04, 5.60] |
| Takero et al. 2014 | 2 | 100 | 13 | 100 | 2.0% | 0.14 [0.03, 0.62] |
| Thomas et al. 2019 | 10 | 95 | 14 | 95 | 1.9% | 0.68 [0.29, 1.62] |
| Willemieke et al. 2022 | 16 | 226 | 29 | 231 | 4.1% | 0.53 [0.28, 1.01] |
| Yoichi et al. 2014 | 4 | 518 | 19 | 519 | 2.9% | 0.20 [0.07, 0.61] |
| Yotam et al. 2017 | 12 | 31 | 9 | 22 | 1.0% | 0.91 [0.30, 2.78] |
| Zaid et al. 2004 | 2 | 17 | 4 | 17 | 0.5% | 0.43 [0.07, 2.76] |
| Zhijian et al. 2019 | 7 | 142 | 14 | 142 | 2.0% | 0.47 [0.19, 1.21] |
| **Total (95% CI)** | | **7755** | | **7842** | **100.0%** | **0.60 [0.53, 0.68]** |
| Total events | 458 | | 720 | | | |

Heterogeneity: Chi² = 76.57, df = 46 (P = 0.003); I² = 40%
Test for overall effect: Z = 8.08 (P < 0.00001)

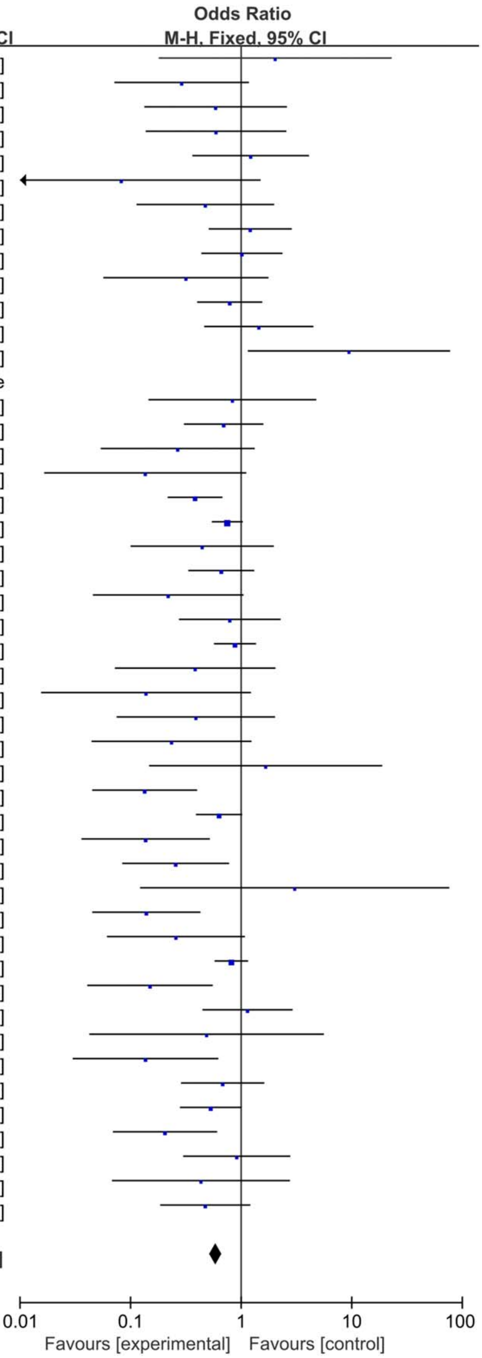


**Figure 5.** Forest plot of overall effect comparing antibiotics with placebo. df, degrees of freedom; M-H, Mantel-Haenszel; OR, odds ratio.

prophylaxis for surgical site infections, while 28 randomized controlled studies showed the opposite result, showing great controversy. These controversial procedures focused on oral, head and neck, fracture, breast plasticity, tumor resection, pelvic, craniotomy, cholecystectomy, urology, duodenectomy, abortion, cardiac, thoracic, and limb resections, with the most controversial procedures being oral surgery versus urology surgery. All RCTs had at least 2 study groups including placebo, of which only a small number provided data for multiple comparisons. To further mitigate this great divergence and discrepancy, we evaluated the actual effectiveness of prophylactic antibiotics in preventing SSIs preoperatively or postoperatively in six clean and clean-contaminated procedures in a subgroup analysis. The detailed discussion is as follows.

### *Antibiotic prophylaxis in neurosurgery*

In craniotomy, the risk of infection can be as high as 5% without antibiotic prophylaxis. This risk averages 10% if a cerebrospinal fluid shunt is present[1]. A previous meta-analysis involving 272 patients showed a significant difference between the incidence of SSI of gram-positive bacterial infections in the group of patients

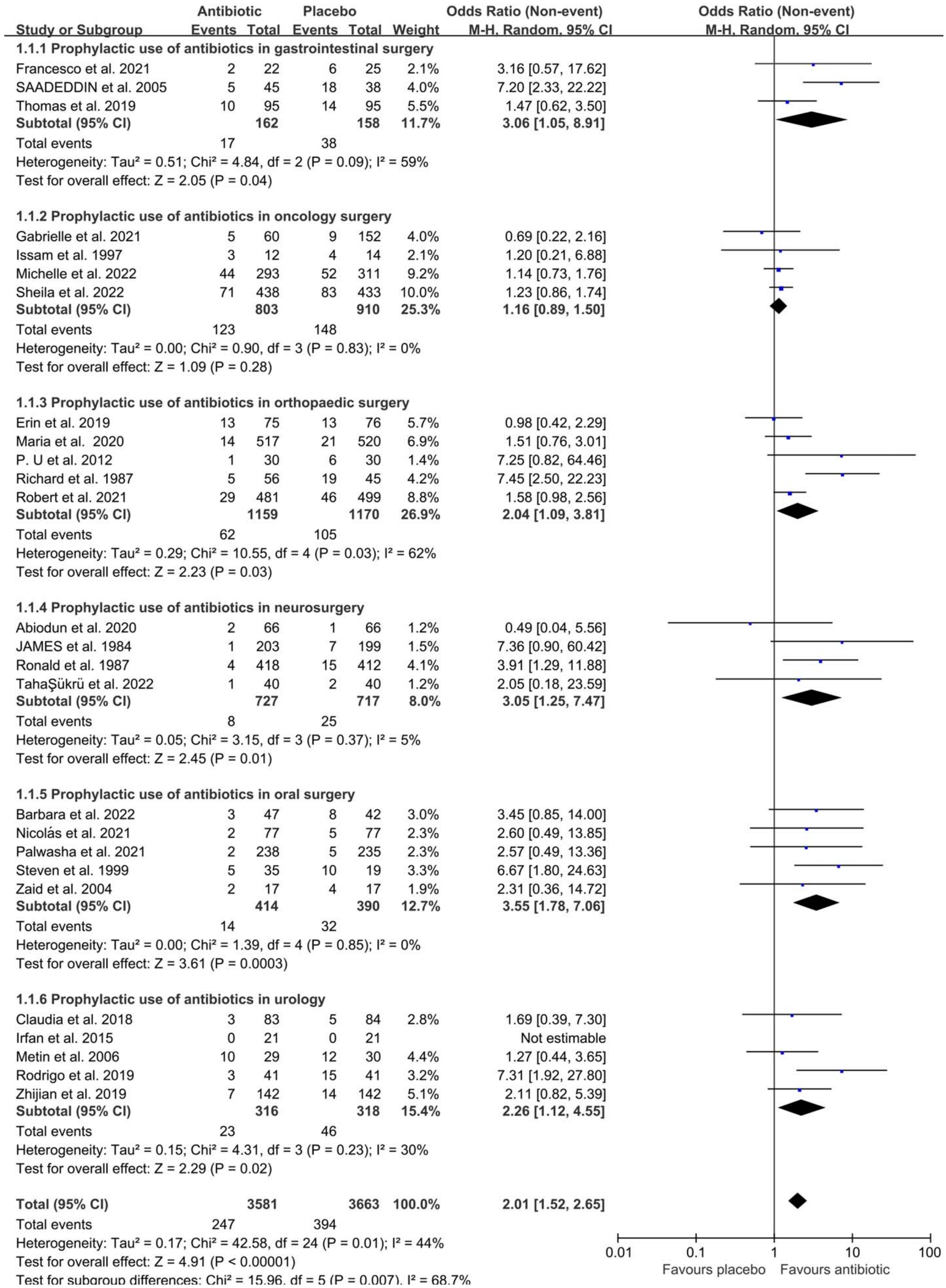


**Figure 6.** Forest plot of subgroup analyses comparing antibiotic versus placebo effects. df, degrees of freedom; M-H, Mantel-Haenszel; OR, odds ratio.

without cephalosporin intervention after craniotomy, which was 1.00%, and in the group of cephalosporin interventions, which was 8.70%[77], which is in general agreement with the results of our study. Furthermore, an interesting meta-analysis also showed that prophylactic antibiotics also reduced the incidence of meningitis after cranial surgery[78]. Therefore, we continue to recommend prophylactic antibiotics in neurosurgery to reduce the incidence of SSIs, from which patients are likely to benefit.

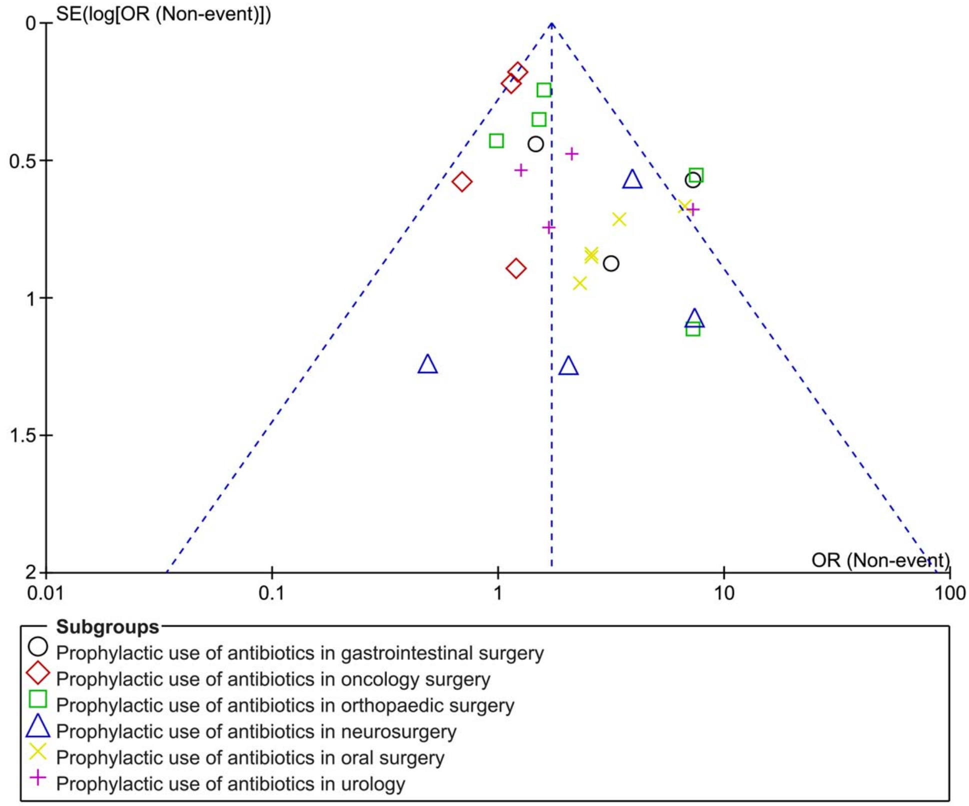


**Figure 7.** Funnel plots for evaluating subgroup publication bias. OR, odds ratio.

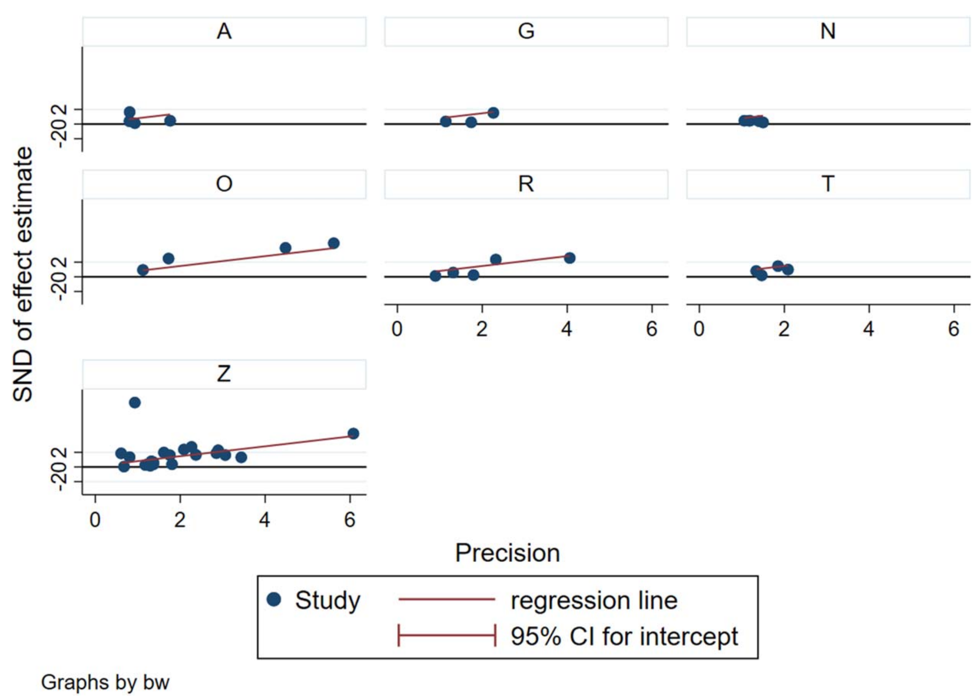


**Figure 8.** Meta-regression analysis of prophylactic antibiotics and surgical site infections in subgroup analysis. G = gastrointestinal surgery, O = oncology surgery, R = orthopedic surgery, A = neurosurgery, N = oral surgery, T = urology, Z = Total value of subgroup analysis. SND, small-N designs.

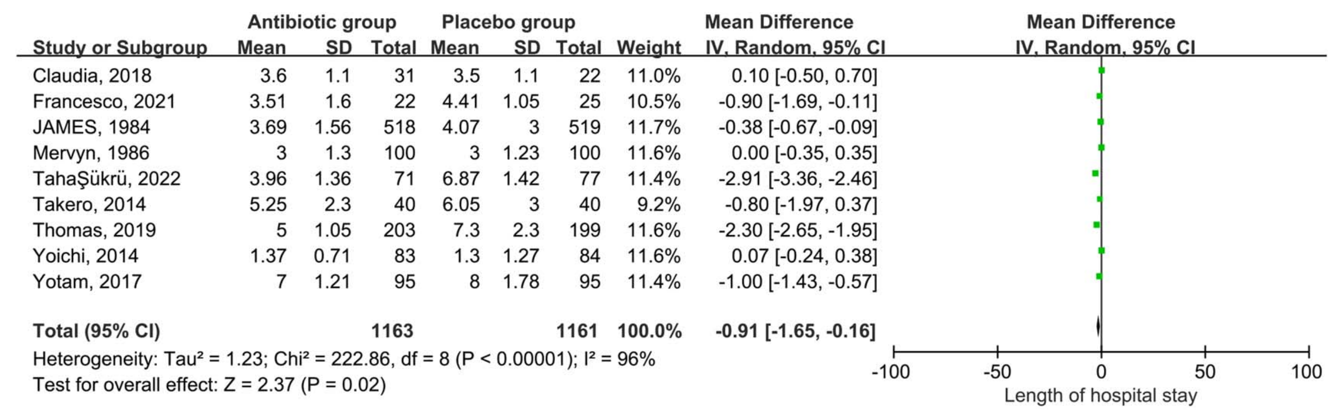


**Figure 9.** Forest plot of the overall length-of-hospitalization effect of antibiotics versus placebo. df, degrees of freedom; MD, mean difference.

### *Antibiotic prophylaxis in gastrointestinal surgery*

Most gastrointestinal surgeries are clean or clean-contamination surgeries, and laparoscopic surgery follows the same principles as conventional surgery. In colorectal surgery, oral antibiotics given the day before surgery are associated with intravenous antibiotics given before surgery, but evidence is still lacking[1]. A previous Meta-analysis demonstrated a significant increase in the rate of SSIs after colorectal surgery and a decrease in the effectiveness of antibiotics in preventing SSIs after colorectal surgery, and new studies are needed to determine how to modify antibiotic prophylaxis recommendations in the context of decreasing efficacy of colorectal surgery[79]. The results of our updated meta-analysis similarly suggest that the use of prophylactic antibiotics in gastrointestinal surgery is beneficial, and we did not find 1 case reporting an adverse reaction to the use of prophylactic antibiotics in gastrointestinal surgery. However, there is still an overall lack of such studies, and clinicians still need to contextualize their clinical decisions.

### *Antibiotic prophylaxis in orthopedics surgery*

Studies have shown that the incidence of postoperative prosthetic joint infections without antibiotic prophylaxis is 3–5%, and prophylactic antibiotics can reduce this rate to less than 1%[1]. A systematic evaluation by Lin *et al.*[80] demonstrated that prophylactic antibiotics significantly reduced the incidence of SSIs in orthopedic surgery by 31%, and another meta-analysis similarly recommended that orthopedic surgery patients undergo early systemic antibiotic prophylaxis, but the researchers also noted that consensus on best practices may require additional randomized controlled trials[81]. In conclusion, the results of the two previous meta-analyses are generally consistent with our findings that prophylactic antibiotic use in orthopedic surgery remains beneficial.

### *Antibiotic prophylaxis in oral surgery*

The risk of infection in open oropharyngeal surgery in oral and maxillofacial surgery is ~30%, indicating that prophylactic measures are clearly necessary[1]. Nevertheless, the controversy over antibiotic prophylaxis in oral surgery is still very serious. In the subgroup analysis of this study alone, three of the included studies with RCT findings were dissenting, and our conclusions were contrary to the findings of a previous meta-analysis, which concluded that there is still a lack of evidence that the use of prophylactic antibiotics in oral and maxillofacial surgery is necessary[82]. However, our final meta-analysis suggests that the use of prophylactic antibiotics in oral and maxillofacial surgery is beneficial because it significantly reduces the incidence of SSIs, which may be helpful for clinical decision-making by oral surgeons.

### *Antibiotic prophylaxis in urology surgery*

Prophylactic antibiotics also remain very controversial in urology, and the efficacy and timing of the use of fluoroquinolones in urologic surgery, in particular, is widely debated, with the prophylactic use of antibiotics in renal and urethral surgery requiring particular caution[1]. In addition, Ivan *et al.*[83] noted numerous controversies and conflicts between antimicrobial prophylaxis guidelines for urologic surgery and called for further randomized controlled studies to provide stronger and consistent guidelines for antimicrobial prophylaxis and management of SSIs in the field

**Table 3**

**Baseline characteristics of adverse reactions occurring with antibiotics vs. placebo.**

| First author and year published | Surgery type | Antibiotics | No. patients (*M*) | Age (years) | No. ADR reaction, *n* (%) | Types of ADR |
|---|---|---|---|---|---|---|
| Yotam *et al.*, 2017[29] | Head-neck surgery | Cefazolin | 53 | 54.5 ± 15.7 | 1/31 (3.23) | Flush (1) |
| Claire *et al.*, 2022[38] | Laparoscopic surgery | Cefazolin | 107 | Mean 33.0 | 2/53 (3.78) | Rash (2) |
| Michelle *et al.*, 2022[54] | Oncology surgery | Cephalosporins | 604 | 41.2 ± 21.9 | 4/293 (1.37) | Superinfection (4) |
| Sheila *et al.*, 2022[56] | Cancer surgery | Amoxiclav | 871 | 59.1 ± 10.5 | 2/438 (0.46) | Rash (2) |
| Rodrigo *et al.*, 2019[66] | Kidney transplantation | Fosfomycin | 82 | 41.9 ± 16.0 | 7/41 (17.07) | Superinfection (1), diarrhea (6) |

ADR, adverse drug reaction.

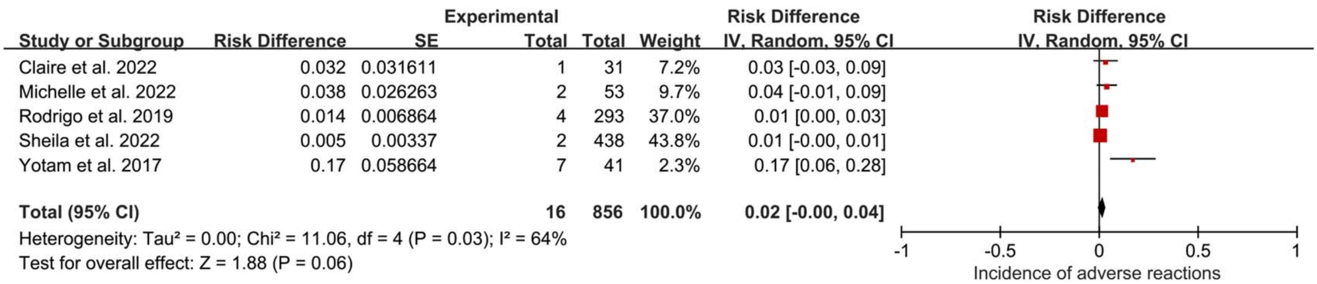


**Figure 10.** Forest plot of an overall adverse effect of antibiotics versus placebo. df, degrees of freedom; RD, risk difference.

of urology. The results of this updated meta-analysis suggest that prophylactic antibiotics in urologic surgery likewise significantly reduce the incidence of SSIs, which is consistent with the findings of the meta-analysis by Yu *et al.*[84].

### *Antibiotic prophylaxis in oncology surgery*

Oncology surgery in clean and clean-contaminated surgery types is equally controversial; nevertheless, many clinicians around the world continue to supplement prophylactic antibiotics in their clinical decision-making. A large cohort study spanning 5 years demonstrated that prophylactic antibiotic use in oncology surgery significantly reduced the odds of C. difficile infection[85]. Another large retrospective prospective (two-way) study spanning 3 years showed that perioperative antibiotic prophylaxis in breast cancer did not reduce surgical site infections, that there was no value in using antibiotics in breast cancer surgery, and revealed that Staphylococcus aureus may be the main microorganism causing SSIs in oncology surgery[86]. However, this study also pointed out the large sample size difference between its test and control groups, and more studies are needed to continue to update this conclusion. In addition, a meta-analysis of retrospective and prospective studies demonstrated the importance of antibiotic prophylaxis in preventing SSIs in patients with head and neck tumors and exposed penicillin and cephalosporins as the best choices[87]. Whereas, two other meta-analyses showed that prophylactic antibiotic use in cancer surgery is unnecessary as it does not reduce the risk of postoperative complications as well as wound infection[88,89]. Our updated meta-analysis similarly suggests that the use of prophylactic antibiotics in cancer surgery may be unnecessary and did not find a significant effect on SSI rates. Given the magnitude of the hierarchical validity of the evidence-based evidence, we believe that the results of the meta-analysis are likely to be higher than that of individual clinical studies, and therefore oncologic surgeons should not make antibiotic prescribing decisions without sufficient evidence. Given the current lack of studies, we call for more high-quality randomized controlled trials in oncology to address differences in the efficacy of prophylactic antibiotics in oncologic surgery.

Furthermore, antibiotic prophylaxis significantly reduced the length of hospitalization for patients compared with placebo. Our conclusions therefore eliminate the disagreement of the 3 RCTs[29,38,53] that concluded that prophylactic antibiotics did not have a significant benefit in terms of shorter length of stay compared with placebo. The high heterogeneity ($I^2 = 96\%$) accompanying the meta-analysis on length of stay may be due to significant differences in the allocation of patients' length of stay due to different types of clean or clean-contaminated surgery. Pooled analyses of 48 studies showed low heterogeneity of effects ($I^2 = 35\%$), and the results of subgroup analyses showed similarly low heterogeneity, except for orthopedic surgery ($I^2 = 62\%$). Finally, we similarly performed an enrichment analysis of the safety of prophylactic antibiotics. Those studies with insufficient evidence of antibiotic-associated adverse events were not considered. A previous systematic evaluation involving 14 studies (including 6 high risk-of-bias studies) showed that prophylactic antibiotics appeared to be effective in reducing the incidence of SSIs, but the authors also pointed out the need for more high-quality studies, especially randomized clinical trials, to increase the level of evidence of the available information for decision-making[20]. Although our study reached similar conclusions to theirs, it also contradicts the findings of Chen *et al.*[19], which may be attributed to the fact that Chen and colleagues. Only discussed the effect of topical antibiotics on SSIs and their inclusion in the literature was further limited. In conclusion, there remains widespread controversy regarding the effect of prophylactic antibiotics on SSIs in clean and clean-contaminated procedures. This meta-analysis, which included 48 RCTs, is an update and addition to the existing clinical evidence in an effort to mitigate the disagreement and provide theoretical support to clinical surgeons when making appropriate antibiotic prescribing decisions, but these conclusions may also still need to be updated as new RCT evidence becomes available.

We also recognize several limitations in our meta-analysis. Firstly, all included studies were RCTs, which may be unrepresentative in specific areas. Secondly, we included only RCTs that had to contain a placebo group and ignored some of the positive control results. Thirdly, we did not analyze the effectiveness of prophylactic antibiotics for a wider range of surgical procedures due to a lack of data. Fourthly, given the continued lack of research at this stage on situations where oncologic surgery is accompanied by other types of surgery (e.g. surgery for gastrointestinal cancer), conclusions on the effects of prophylactic antibiotics in cancer surgery remain limited. Fifthly, we did not explore in depth which antibiotic would be more appropriate for surgical prophylaxis.

## Conclusion

In conclusion, prophylactic antibiotics still significantly reduce SSI in clean and clean-contaminated surgeries and have a good safety profile, as well as shortening the patient's hospital stay.

Antibiotic prophylaxis remains effective in neurosurgery, oral surgery, gastrointestinal surgery, urology, and orthopedic surgery. Surgeons should make antibiotic prescription decisions without obvious unnecessary use of antibiotics.

## Ethical approval

This systematic evaluation itself does not involve ethical issues, and all included literature has ethical review approval. These ethical documents can be accurately found in the content of each included article.

## Consent

This systematic evaluation is not a single clinical study, therefore it does not involve informed consent of patients. All included articles are known and open access, and all patient information in this manuscript is anonymized.

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## Author contribution

X.B., Q.K.Y., and L.H.K. searched the articles and extracted the core data whereas L.H.J. was involved in resolving disagreements and analyzing the extracted data. T.X.F., B.Y.P., and D.L.H. performed risk-of-bias assessment. Z.J.Q. completed the initial editing of the manuscript (including figure design), and T.X.F., L. W.F., Z.M., Z.M., and Y.S.Y. assisted in completing the initial revisions of the manuscript and conducting a secondary evaluation of its scientific validity. T.B. conducted the final proofreading of the manuscript and conducted a comprehensive review of the manuscript.

## Conflicts of interest disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Research registration unique identifying number (UIN)

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The protocol for this review was registered and published in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023445822).

## Guarantor

The guarantor (Jia-Quan Zhu) is the corresponding author of this article and assumes full responsibility for the research work.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

## Provenance and peer review

Not commissioned, externally peer-reviewed.



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