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Original article

Antibiotics for preventing infection at the surgical site: Single dose vs. multiple doses

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ABSTRACT

Background: Surgical site infections are common and expensive infections that can cause fatalities or poor patient outcomes. To prevent these infections, antibiotic prophylaxis is used. However, excessive antibiotic use is related to higher costs and the emergence of antimicrobial resistance.
Objectives: The present *meta*-analysis aimed to compare the effectiveness of a single dosage versus several doses of antibiotics in preventing the development of surgical site infections.
Methods: PubMed was used to find clinical trials evaluating the effectiveness of a single dosage versus several doses of antibiotics in avoiding the development of surgical site infections. The study included trials that were published between 1984 and 2022. Seventy-four clinical trials were included in the analysis. Odds ratios were used to compare groups with 95% confidence intervals. The data were displayed using OR to generate a forest plot. Review Manager (RevMan version 5.4) was used to do the *meta*-analysis.
Results: Regarding clean operations, there were 389 surgical site infections out of 5,634 patients in a single dose group (6.90%) and 349 surgical site infections out of 5,621 patients in multiple doses group (6.21%) (OR = 1.11, lower CI = 0.95, upper CI = 1.30). Regarding clean-contaminated operations, there were 137 surgical site infections out of 2,715 patients in a single dose group (5.05%) and 137 surgical site infections out of 2,355 patients in multiple doses group (5.82%) (OR = 0.87, lower CI = 0.68, upper CI = 1.11). Regarding contaminated operations, there were 302 surgical site infections out of 3,262 patients in a single dose group (9.26%) and 276 surgical site infections out of 3,212 patients in multiple doses group (8.59%) (OR = 1.11, lower CI = 0.84, upper CI = 1.47). In general, there were 828 surgical site infections out of 11,611 patients in a single dose group (7.13%) and 762 surgical site infections out of 11,188 patients in multiple doses group (6.81%) (OR = 1.05, lower CI = 0.93, upper CI = 1.20). The difference between groups was not significant.
Conclusion: The present study showed that using a single-dose antimicrobial prophylaxis was equally effective as using multiple doses of antibiotics in decreasing surgical site infections.

1. Introduction

Healthcare-associated infections are infections that happen while getting medical care, develop in hospitals or other health centers, and appear forty-eight hours or more after admission to the hospital or within thirty days of receiving medical care (Haque et al., 2018). The US Centers for Disease Control and Prevention says that about 1,700,000 hospitalized patients get healthcare-associated infections every year

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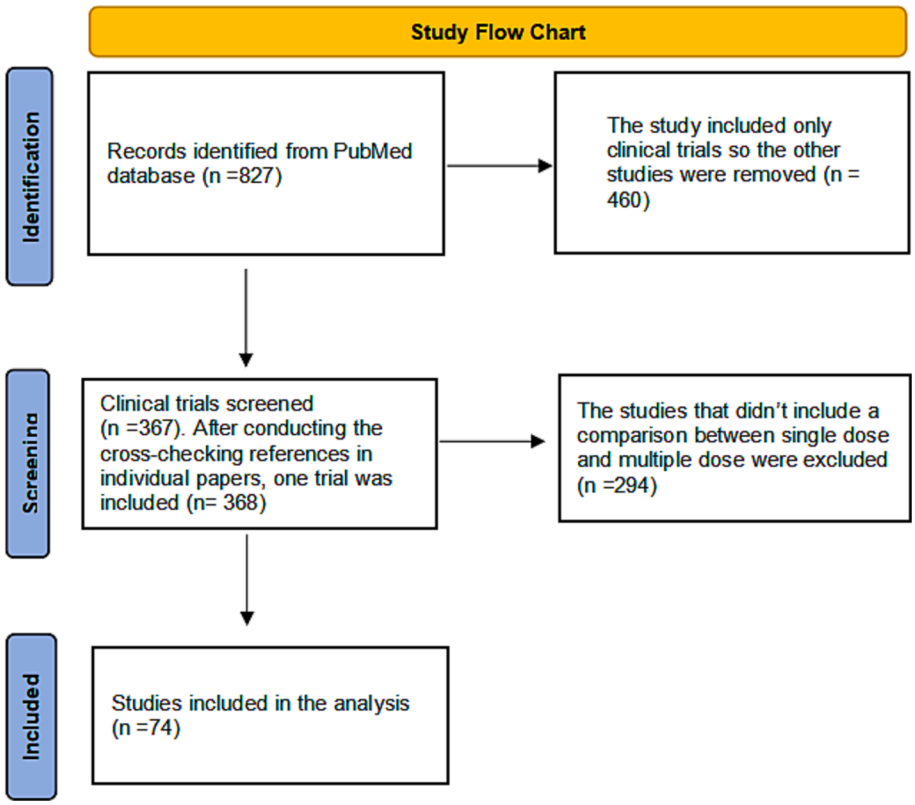

Fig. 1. PRISMA flow diagram.

while being managed for other health problems (Klevens et al., 2007). Patients who have surgery often get infections at the site of the surgery. This is the most prevalent infection caused by medical care (Borchardt and Tzizik, 2018).

Infection at the surgical site can affect any cavity, joint, bone, tissue, or prosthetic that was incised during or after surgery (Hall et al., 2015; Idris et al., 2020). Infections at surgical sites can be stratified into three categories based on the depth of the incision: deep incisional, superficial incisional, and infections in organs and spaces (Borchardt and Tzizik, 2018). Surgical procedures and their incisions are classified as dirty/infected, contaminated, clean-contaminated, or clean. A clean wound is "*an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered*". Clean-contaminated is "*an operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination*". A contaminated wound is " an *open, fresh, accidental wound. In addition, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract and incisions in which acute, nonpurulent inflammation is encountered are included in this category*". A dirty wound is "*an old traumatic wound with retained devitalized tissue and those that involve an existing clinical infection or perforated viscera*". (CDC, 1999).

If an infection develops within thirty days of surgery, or ninety days if a prosthesis was implanted, it is considered a surgical site infection (SSI) (Seidelman and Anderson, 2021). These infections are some of the most common and expensive ones that are connected to healthcare, and they can cause fatalities or poor patient outcomes (Zabaglo and Sharman, 2023). Local effects of SSI include delayed and ineffective wound healing, osteomyelitis, cellulitis, abscess formation, and the wound becoming worse over time. Systemic effects include bacteremia, which has a chance of distant hematogenous spread, and sepsis (Berríos-Torres et al., 2017).

Since SSIs are a major source of mortality and morbidity, many guidelines and standards have been established to reduce their prevalence (Edwards et al., 2006). To prevent SSIs, antibiotic prophylaxis is used (Engelman et al., 2007; Gordon et al., 1998). Nonetheless, the inappropriate use of antibiotics is one of the most serious global public health threats (Kabrah et al., 2022; Alhomoud et al., 2017; Hussein et al., 2022; Alsugoor et al., 2022; Shaheen et al., 2018, Ahmed et al., 2022). Using antibiotics to excess is linked to a greater risk of unpleasant effects, more frequent return visits, and increased use of medical therapy for illnesses that, if left untreated, would generally recover on their own. Furthermore, it is linked to the development of antimicrobial resistance and elevated mortality rates (Harbarth et al., 2000; Llor and Bjerrum, 2014; Kreter and Woods, 1992).

To avoid SSIs and improve postoperative recovery, a single dose of prophylactic antibiotic is recognized as a component of surgical practice in several procedures. The possible clinical advantages of giving the antibiotic in a single dose have drawn more attention in recent years (Bratzler and Houck, 2004; Gilbert et al., 2007; ASHP, 2023; Ahmed et al., 2022). Using a single dose of prophylaxis reduces antimicrobial resistance, diminishes superinfections and drug toxicity, and decreases care costs (Edwards et al., 2006).

New guidelines recommended the use of a reduced postoperative course of antibiotics that involves a single dosage or continuance for less than 24 h. According to a study conducted by McDonald et al., there was no discernible superiority between single- or multiple-dose regimens in terms of preventing SSIs. Consequently, they proposed the ongoing utilization of a single-dose antimicrobial prophylaxis for major surgical procedures (McDonald et al., 1998). Igwemadu et al. and Das et al. reported that antibiotic prophylaxis with one dose is just as effective as prophylaxis with several doses while being less expensive and less likely to lead to antibiotic resistance (Igwemadu et al., 2022; Das et al., 2021). Jogdand et al. stated that prophylactic use of combination chemotherapy, which is continued for 5 to 7 days, is the norm in India to prevent SSI. These prolonged treatment periods place a financial burden on the patient or the government without providing the patient with any further benefits, which ultimately results in resource waste (Jogdand

Table 1
The clinical trials that were included in the analysis.

Incision	Study	Type of surgery
Clean	Gahm et al., 2022	Breast reconstruction
	Igwemadu et al., 2022	Caesarean section
	Sheth et al., 2019	Dacryocystorhinostomy
	Wahab et al., 2013	Bilateral sagittal split osteotomies
	Danda et al., 2010	Orthognathic surgery
	Tamayo et al., 2008	Cardiac surgery
	Hellbusch et al., 2008	Instrumented lumbar fusion
	Lindeboom et al., 2005	Intraoral bone grafting procedures
	Su et al., 2005	Gynecologic surgery
	Lindeboom et al., 2003	Bilateral sagittal ramus osteotomies
	Salminen et al., 1999	Cardiovascular surgery
	Gagey et al., 1999	Open tibial fracture
	Kester et al., 1999	Vascular surgery
	Morimoto and Kinoshita, 1998	Breast cancer surgery
	Hall et al., 1998	Vascular surgery
	Kriaras et al., 1997	Cardiac surgery
	Nooyen et al., 1994	Coronary artery bypass grafting
	Morris, 1994	Upper abdominal operations
	Hall et al., 1993	Cardiac operations
	Galbraith et al., 1993	Cardiac operations
	Wertzel et al., 1992	Thoracic surgery
	Maier and Strutz, 1992	Head and neck surgery
	Nachtkamp et al., 1991	Abdominal surgery
	Olak et al., 1991	Thoracic surgery
	Buckley et al., 1990	Hip fracture surgery
	Karachalios et al., 1990	Peritrochanteric fractures
	Hall et al., 1989	Abdominal surgery
	Periti et al., 1988	Gynaecological and obstetric surgery
	Oostvogel et al., 1987	General operations
	Periti et al., 1984	Gynecologic and obstetrical surgery
Clean-Contaminated	Loozen et al., 2017	Cholecystitis
	Westen et al., 2015	Cesarean section
	Lyimo et al., 2013	Caesarean section
	Alekwe et al., 2008	Cesarean section
	Sakura et al., 2008	Prostatectomy
	Mohri et al., 2007	Gastric cancer surgery
	Kayihura et al., 2003	Biliary surgery
	Hotz et al., 1994	Maxillofacial surgery
	Meijer and Schmitz, 1993	Biliary surgery
	Hjortrup et al., 1991	Biliary surgery
	Galask et al., 1988	Cesarean section
	Roy et al., 1988	Hysterectomy
	McGregor et al., 1988	Cesarean section
	Fabian et al., 1988	Biliary surgery
	Berkeley et al., 1988	Hysterectomy
	El Mufti and Glessa, 1988	Cholecystectomy
	Gall & Hill, 1987	Cesarean operation
	Roy et al., 1984	Hysterectomy
	Maki et al., 1984	Biliary tract operations or hysterectomy
	Kellum et al., 1984	biliary operations
Contaminated	Espin Basany et al., 2020	Colon surgery
	Rafiq et al., 2013	Appendectomy
	Ishibashi et al., 2014	Rectal cancer surgery
	Ahn et al., 2013	Colorectal surgery
	Oshima et al., 2013	Proctocolectomy
	Fujita et al., 2007	Colorectal surgery
	Mui et al., 2005	Appendicitis
	Li et al., 2003	Colorectal resection
	Zelenitsky et al., 2000	Colorectal surgical
	Håkansson et al., 1993	Colorectal surgery
	Elusoji, 1992	Appendectomy
	Tsang et al., 1992	Appendectomy
	Cuthbertson et al., 1991	Colorectal surgery
	Rowe-Jones et al., 1990	Colorectal surgery
	Hershman et al., 1990	Colorectal surgery
	Periti et al., 1989	Colorectal surgery
	Bittner et al., 1989	Colorectal surgery
	Jagelman et al., 1988	Colorectal surgery
	Juul et al., 1987	Colorectal surgery
	Stubbs et al., 1987	large bowel surgery
	Fabian et al., 1984	Colorectal surgery or small bowel obstruction
	Göransson et al., 1984	Colorectal surgery
	Lohr et al., 1984	Colorectal surgery
	Viitanen et al., 1984	Appendectomy

et al., 2017). The aim of this *meta*-analysis was to examine the hypothesis that the efficacy of a single-dose antibiotic regimen is comparable to that of multiple doses of antibiotics in decreasing the incidence of SSIs.

2. Materials and Methods

PubMed was used to find studies evaluating the effectiveness of a single dosage versus several doses of antibiotics in avoiding the occurrence of SSIs. In the advanced search, the terms "surgical site infections," single dosage," and "antimicrobial" were used.

The analysis was limited to published clinical research involving human beings. Other studies are not included in the present analysis. The study included clinical trials that compared single doses with multiple doses that were received by patients who had different types of operations. Furthermore, cross-checking of references in individual papers was conducted.

The study included trials that were published between 1984 and 2022. Most of the included trials were published in English, but there were several papers that were written in other languages, but their abstracts in English included the required data. In addition to the overall number of patients who received a single prophylactic antibiotic dose, the number of SSIs among these patients was also gathered. The study also examined the overall number of patients who received multiple prophylactic antibiotic doses and the incidence of SSIs among these patients.

The rate of SSIs in the single-dose and multiple-doses groups was the endpoint of the present study. The numbers and odds ratios of SSIs were compared between these groups. The included studies were categorized according to the types of operations that the patients had into three categories: clean operations, clean-contaminated operations, and contaminated operations.

Odds ratios were used to compare groups with 95% confidence intervals. The data were displayed using OR to generate a forest plot. The heterogeneity of the studies was analyzed using the I^2 statistic. A score of 50% or higher for I^2 indicated significant heterogeneity among trials. A p value of 0.05 was used as the threshold for statistical significance. Review Manager version 5.4 was used to do the *meta*-analysis (The Cochrane Collaboration, 2020 Copenhagen, Denmark).

3. Results

Seventy-four clinical trials were included in the analysis. The included trials were published between 1984 and 2022. The study flow chart is shown in Fig. 1.

Among the clinical trials that were included in the present study, thirty trials included clean incisions, twenty trials included clean-contaminated incisions, and twenty-four trials included contaminated incisions. Twenty-six studies were published after 2000. Table 1 shows the clinical trials that were included in the study.

Regarding clean operations, there were 389 SSIs out of 5,634 patients in a single dose group (6.90%) and 349 SSIs out of 5,621 patients in multiple doses group (6.21%) (OR = 1.11, lower CI = 0.95, upper CI

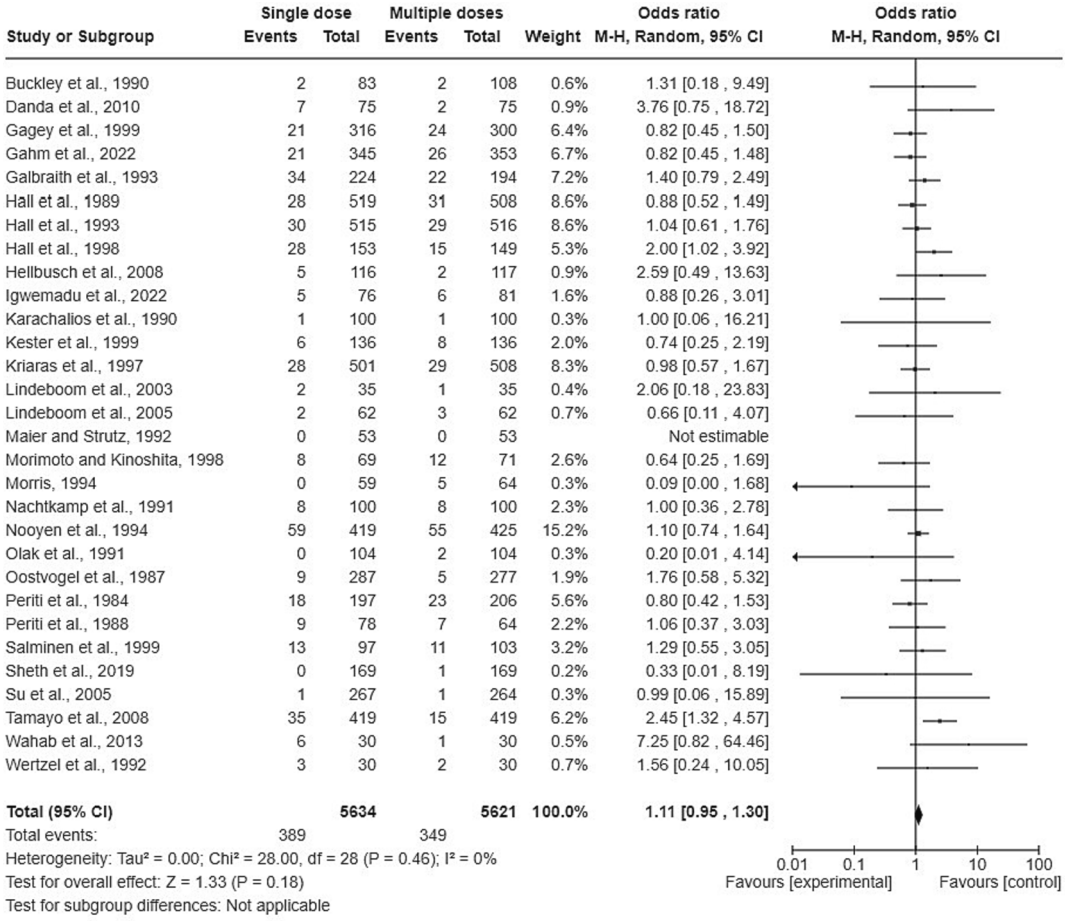

Fig. 2. The forest plot of the clinical trials that included clean operations.

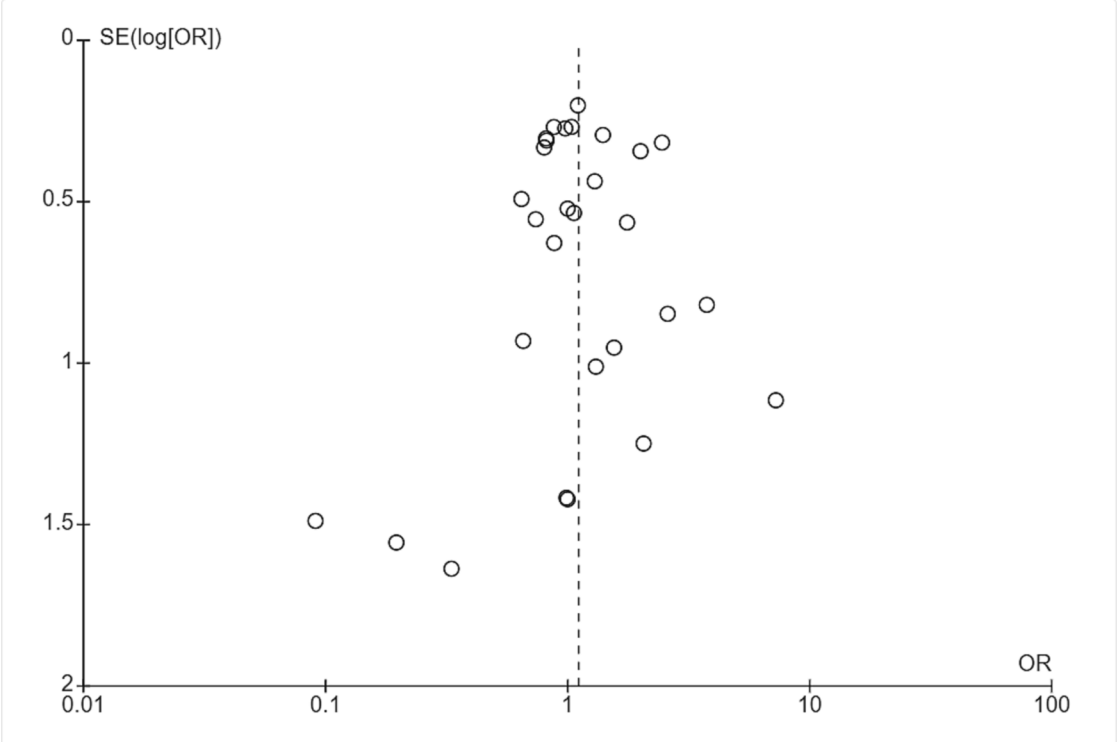

Fig. 3. Funnel plot of the trials that included clean operations.

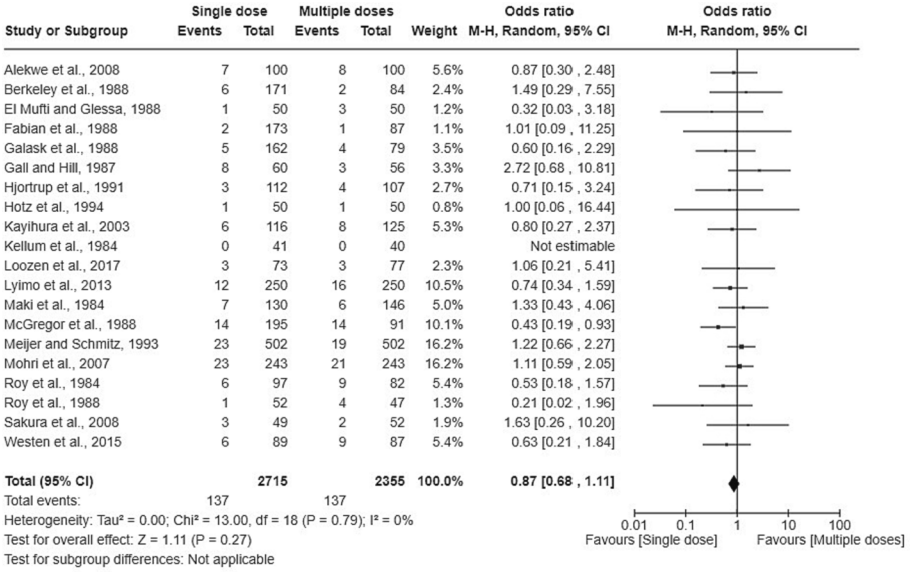

Fig. 4. The forest plot of the clinical trials that included clean-contaminated operations.

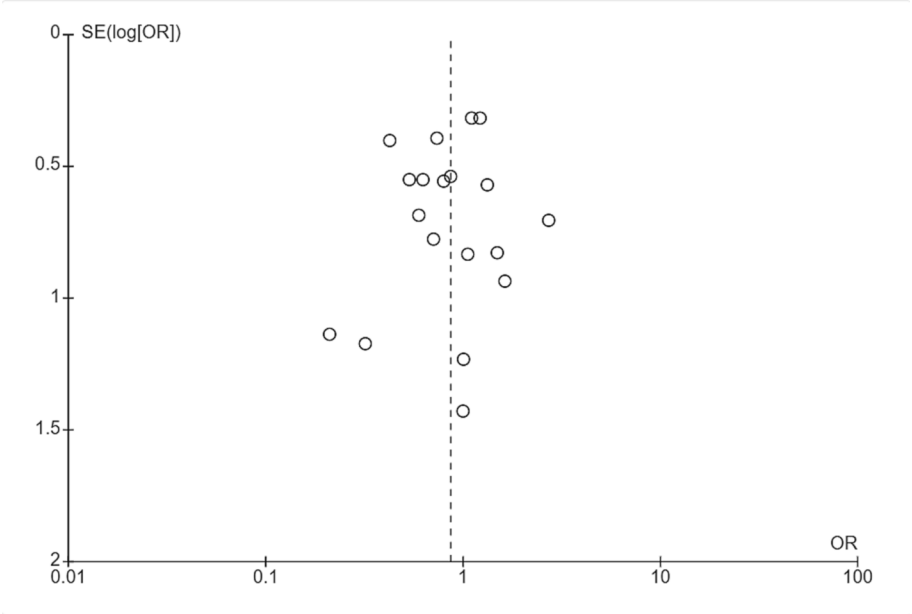

Fig. 5. Funnel plot of the trials that included clean-contaminated operations.

= 1.30). Fig. 2 shows the forest plot of the clinical trials that included clean operations. There was no significant difference observed in the incidence of SSIs between individuals who received a single dosage and those who received repeated doses of antibiotics (P = 0.18).

The heterogeneity of the trials that included clean operations was low, as shown in Fig. 3. Furthermore, the heterogeneity I^2 was 0, and the p value of the heterogeneity was not significant (p = 0.46).

Regarding clean-contaminated operations, there were 137 SSIs out of 2,715 patients in a single dose group (5.05%) and 137 SSIs out of 2,355 patients in multiple doses group (5.82%) (OR = 0.87, lower CI = 0.68, upper CI = 1.11). Fig. 4 shows the forest plot of the clinical trials that included clean-contaminated operations. As shown in the figure, the difference between the efficacy of a single-dose group and a multiple-doses group was not statistically significant (P = 0.27).

The heterogeneity of the trials that included clean-contaminated operations was low, as shown in Fig. 5. Furthermore, the heterogeneity I^2 was 0, and the p value of the heterogeneity was not significant (p = 0.79).

Regarding contaminated operations, there were 302 SSIs out of 3,262 patients in a single dose group (9.26%) and 276 SSIs out of 3,212 patients in multiple doses group (8.59%) (OR = 1.11, lower CI = 0.84, upper CI = 1.47). Fig. 6 shows the forest plot of the clinical trials that included clean-contaminated operations. As shown in the figure, the difference between the efficacy of a single-dose group and a multiple-doses group was not statistically significant (P = 0.44).

Fig. 7 shows the funnel plot of the trials that included contaminated operations. The heterogeneity of the trials was high, as shown in the funnel plot, and the heterogeneity of I^2 was more than 50% and p = 0.002.

A sensitivity analysis was conducted to decrease the heterogeneity. After that, the Håkansson et al. study was removed from the analysis. The I^2 decreased to 34% after deleting the study (Fig. 8). Regarding

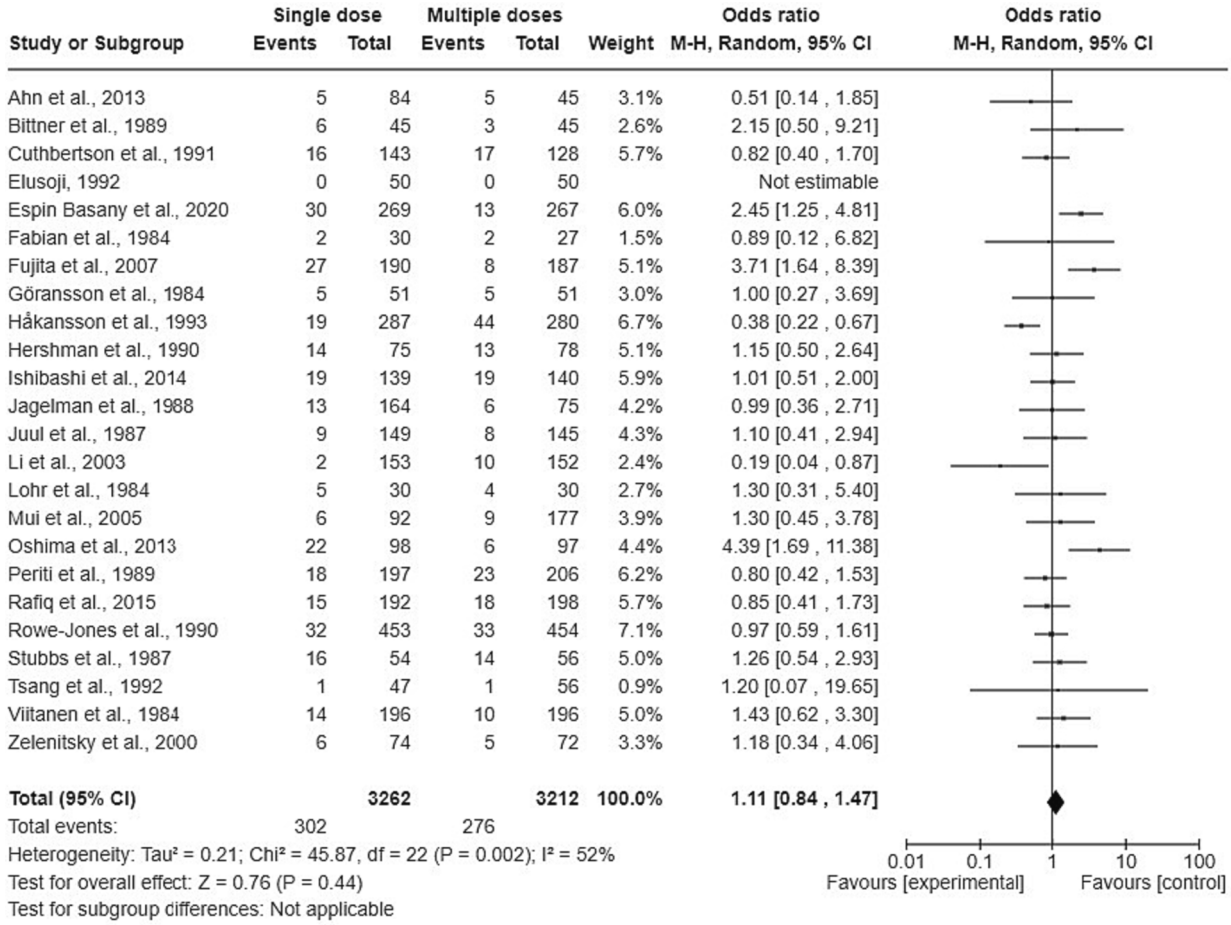

Fig. 6. The forest plot of the clinical trials that included contaminated operations.

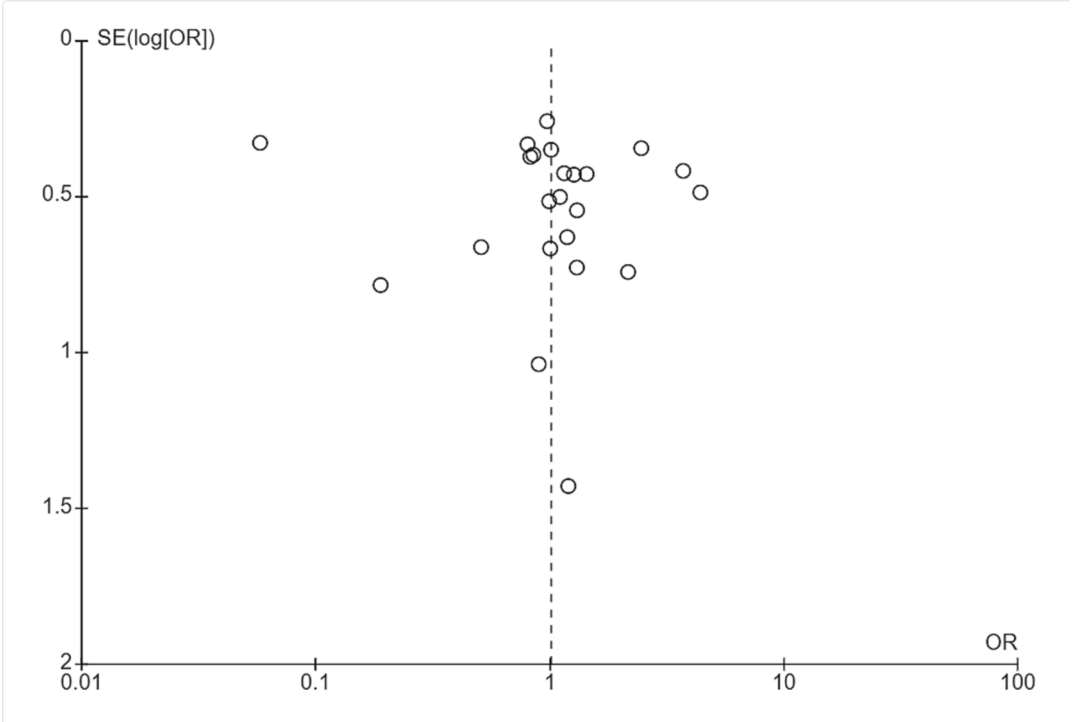

Fig. 7. Funnel plot of the trials that included contaminated operations.

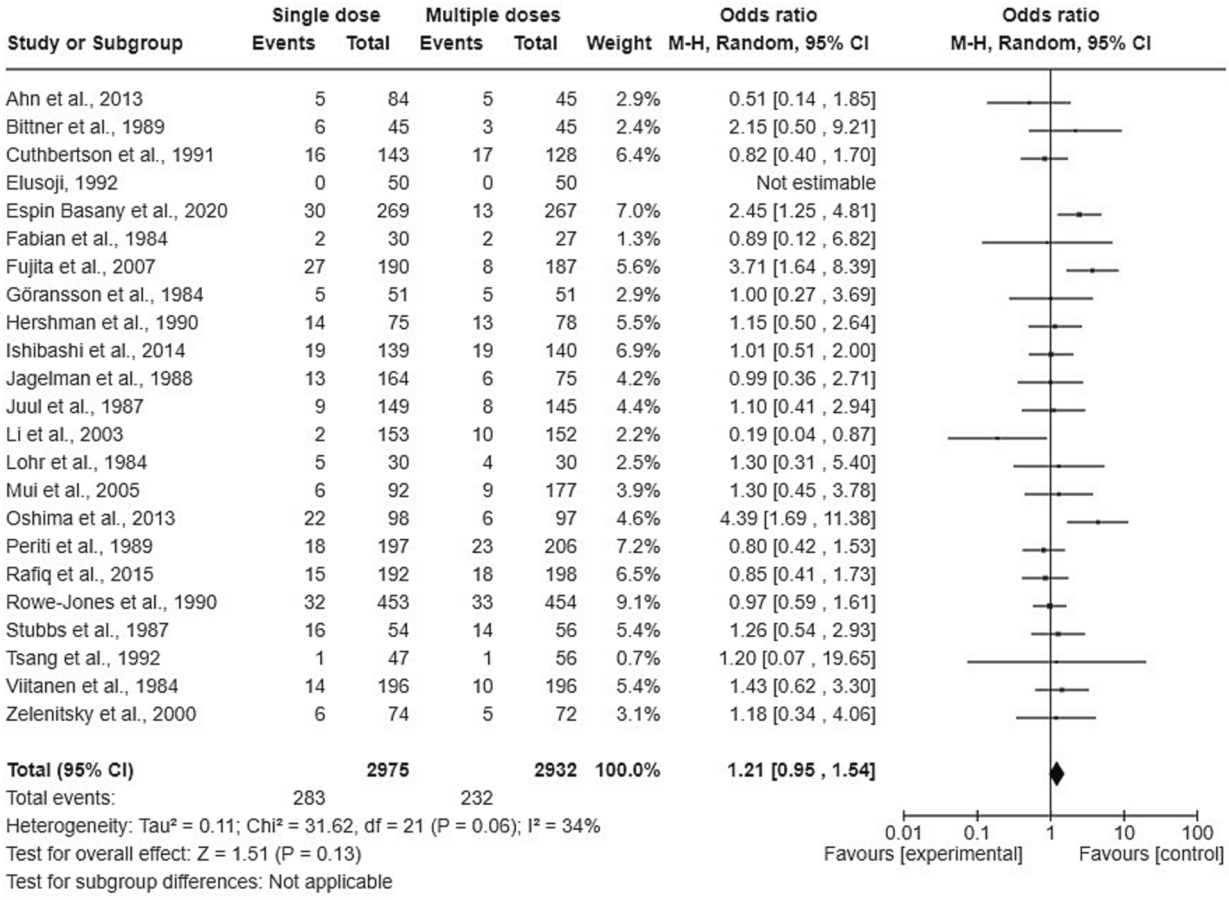

Fig. 8. The forest plot of the clinical trials that included contaminated operations after conducting sensitivity analysis.

contaminated operations, there were 283 SSIs out of 2,975 patients in a single dose group (9.51%) and 232 SSIs out of 2,932 patients in a multiple doses group (7.91%) (OR = 1.21, lower CI = 0.95, upper CI = 1.54). The difference between the efficacy of a single-dose group and a multiple-doses group was not statistically significant (P = 0.13).

Fig. 9 shows the forest plot of the clinical trials that included all of the operations (clean, clean-contaminated, and contaminated operations). There were 828 SSIs out of 11,611 patients in a single dose group (7.13%) and 762 SSIs out of 11,188 patients in multiple doses group (6.81%) (OR = 1.05, lower CI = 0.93, upper CI = 1.20). As shown in the figure, the difference between the efficacy of a single-dose group and a multiple-doses group was not statistically significant (P = 0.44).

Fig. 10 shows the funnel plot of the seventy-four clinical trials that were included in the analysis. In general, the included studies were sufficiently homogeneous (I^2 less than 50%, p = 0.06).

4. Discussion

Surgical antimicrobial prophylaxis is a recognized component of surgical practice in specific operations to reduce SSIs and improve postoperative recovery. When people take too many antibiotics before surgery, they are more likely to have side effects, have to come back more often and get treatment for infections that would go away on their own. It is also linked to the development of bacteria that are resistant to antibiotics. For operations where there is evidence of benefit, using a single dose of antibiotic before the surgical incision is usually sufficient. Calderwood et al. (2023) reported that antimicrobial prophylaxis should be discontinued at the time of surgical closure in the operating room. Nonetheless, repeat intraoperative doses are indicated for lengthy procedures where a short-acting medication is used or if remarkable blood loss occurs.

Our study showed that the difference in the rate of SSIs between the single-dose group and the multiple-doses group was insignificant. Similar to the result of the present study, previous studies found that a single-dose prophylaxis is as effective as multiple-dosage antibiotic prophylaxis in reducing the occurrence of SSIs (Akkour et al., 2020; McDonald et al., 1998; Gahm et al., 2022; Vathana and Muhunthan, 2018; Mugisa et al., 2018; Slobogean et al., 2010; Igwemadu et al., 2022; Kannan et al., 2021; Koirala et al., 2019; Bhatnagar et al., 2017; Salkind and Rao, 2011; Basany et al., 2020; Ahn and Lee, 2013; Ishibashi et al., 2014). Furthermore, Das et al. reported that there are no notable differences between single-dose and multiple-doses antibiotic prophylaxis to prevent SSIs in patients undergoing elective clean-contaminated and clean operations and that a single dosage is more cost-effective (Das et al., 2021). Pooja et al. reported that the use of a single-dose antibiotic regimen should be advocated to reduce antibiotic resistance while also being cost-efficient (Pooja et al., 2021). Moreover, Kannan et al. reported that using extra doses of cefazolin after surgery provides no benefit over the use of a single dose and that a single-dose regimen has the advantages of reduced resistance emergence, fewer allergies or toxicity, and lower cost (Kannan et al., 2021).

Previous *meta*-analyses compared the use of single-dose vs. multiple-dose regimens. Similar to our results, they found no significant differences between single-dose and multiple-dose regimens in reducing SSIs. Several *meta*-analyses included clean incisions. They failed to show that multiple-dose prophylaxis was superior to a single-dose method in terms of lowering the SSI rate (Slobogean et al., 2008; Morrison et al., 2012; Ryan et al., 2019; Gillespie et al., 2010; Costa and Krauss, 2004; Barker, 1994; Barker et al., 2002). Meijer et al. and Zhang et al. included clean-contaminated incisions in their *meta*-analyses. They evaluated wound

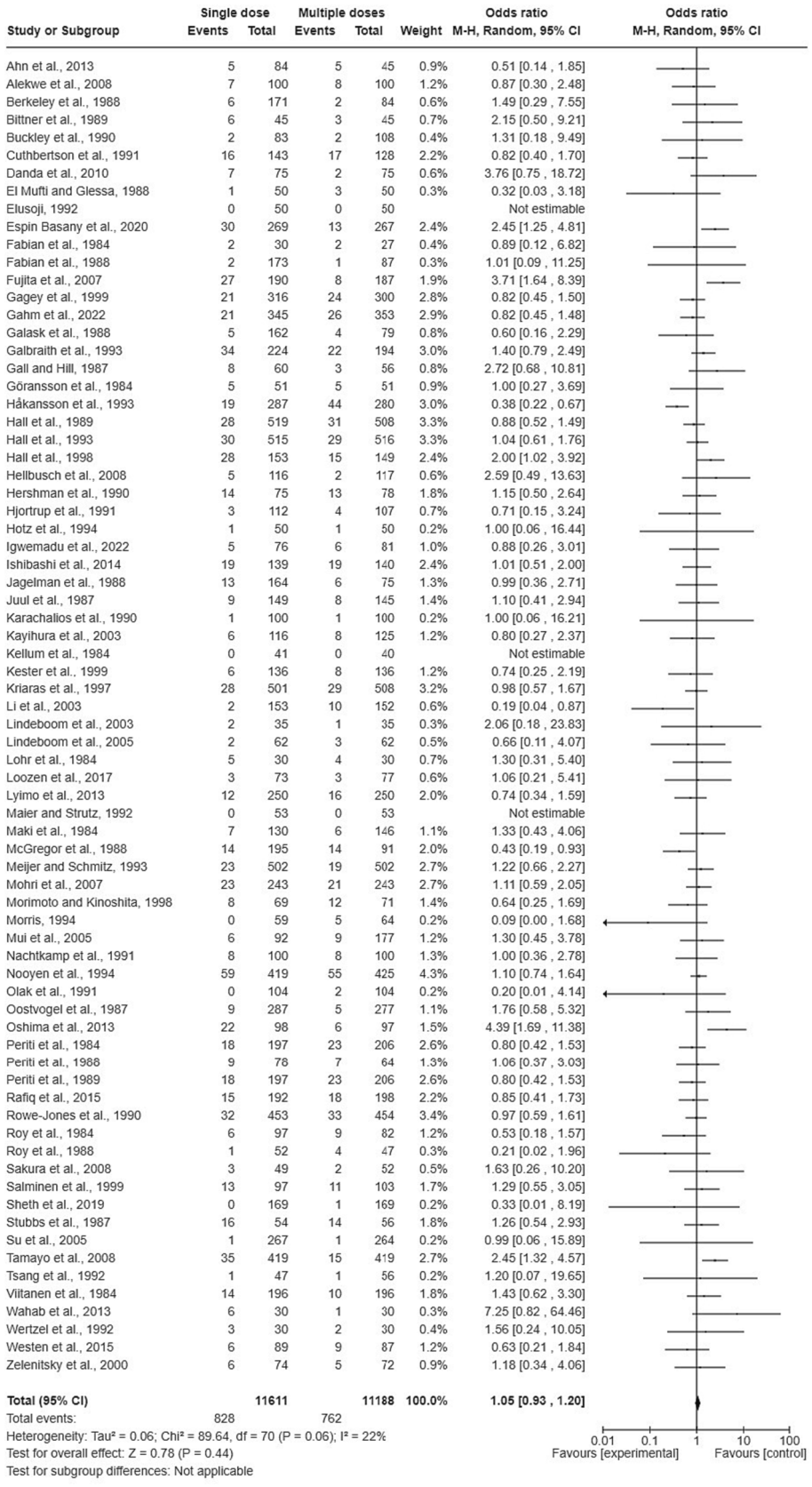

Fig. 9. The forest plot of the clinical trials that included all of the operations.

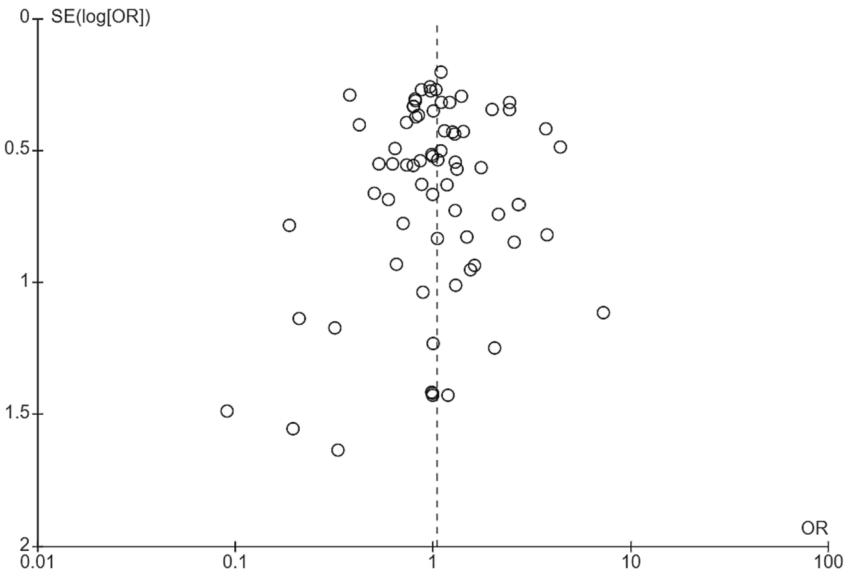

Fig. 10. Funnel plot of the seventy-four clinical trials.

infection rates between single-dose and multiple-dose regimens and found no significant difference (Meijer et al., 1990; Zhang et al., 2013). Furthermore, two *meta*-analyses included contaminated incisions. When comparing single-dose to multiple-dosage antibiotics, they found no statistically significant differences (Nelson et al., 2009; Nelson et al., 2014).

The present study showed that there was no remarkable difference between multiple doses and a single dose of antibiotic prophylaxis in preventing SSIs. Nonetheless, the patients should receive more than one dose for prolonged operative duration or in the case of severe blood loss. According to the Scottish Intercollegiate Guideline Network, there is consistent evidence that prophylaxis for the duration of the surgery alone is sufficient. Prophylaxis for longer periods had no remarkable benefit (SIGN, 2014). According to Munckhof et al., a single dosage of antibiotic is normally sufficient if the surgery lasts 4 h or less (Munckhof et al., 2005). Dehne et al. reported that surgery duration of more than 4 h or predicted blood losses of more than 1.5 L necessitate repeat intra-operative dosing of antibiotics (Dehne et al., 2001). Prophylactic antibiotics should be stopped within twenty-four hours, according to Crader and Varacallo (Crader and Varacallo, 2023). The Saudi Ministry of Health informed that the length of antimicrobial prophylaxis after surgery should be limited to less than twenty-four hours, regardless of the existence of indwelling catheters, drains, or prostheses (MOH, 2021). Ongom et al. (2013) reported that for prophylaxis duration, a shorter course of antibiotics after surgery is recommended. Even if there are indwelling drains and intravascular devices, the duration of prophylaxis should be less than 24 h (Ongom et al., 2013).

Our findings indicated that the administration of a single dose of prophylactic antibiotics significantly reduces the risk of infection, without the need for additional doses. This approach is not only more convenient for patients, but it also reduces the risk of antibiotic resistance and associated side effects. Therefore, we highly recommend the use of single-dose prophylaxis for all patients undergoing surgical procedures, regardless of the classification of their wounds.

The main strength of the present study was that it included seventy-four clinical trials. There were several previous *meta*-analyses that compared the use of single doses vs. multiple doses, but they focused on specific operations and included only a few trials. Nonetheless, there are several limitations to the current study. The first limitation of the study was that the antibiotics employed in the various studies were not standardized for all of the clinical trials that were included in the analysis. The remarkable discrepancy between the number of cases in the control and intervention groups in several trials was the second limitation. This would have an impact on the odd ratio comparisons. Furthermore, the quality of the studies included in the *meta*-analysis can vary, leading to potential bias and affecting the overall results. The fourth limitation was that several trials were available as abstracts only and didn't contain the required information in the abstract, so they were excluded from the study. Limited data availability or incomplete reporting can limit the ability to conduct a comprehensive *meta*-analysis. Moreover, SSI trials that do not include prospective, direct observation can be biased because relying on patient self-reporting or retrospective chart review may lead to underreporting of infections.

5. Conclusion

The present study showed that single-dose antimicrobial prophylaxis was equally effective as multiple-dose antimicrobial prophylaxis in decreasing the occurrence of SSIs. So, a single-dose antibiotic regimen can be safely practiced before clean, clean-contaminated, and contaminated incisions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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