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The effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis.

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Summary

Background: Surgical antibiotic prophylaxis (SAP) is frequently continued for one or more days after surgery to prevent surgical site infection (SSI). Continuing SAP after the operation may have no advantage compared to immediate discontinuation and unnecessarily expose patients to risks associated with antibiotic use. In 2016, the World Health Organization (WHO) recommended discontinuation of SAP. We aim to update the evidence that formed the basis for this recommendation.

Methods: For this systematic review and meta-analysis we searched MEDLINE, Embase, CINAHL, CENTRAL, and WHO regional medical databases from Jan 1990 to August 2018 for randomised controlled trials (RCT) comparing the effect of postoperative SAP continuation to its discontinuation. We excluded, amongst others, studies that did not administer the first dose preoperatively by intravenous infusion. A protocol for this review was registered with at PROSPERO: http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017060829.

Findings: We identified 83 relevant RCTs. The main meta-analysis included 52 RCTs with 19,273 participants. The combined relative risk of SSI comparing postoperative SAP continuation with discontinuation was 0·89 (95% confidence interval: 0·79-1·00; tau^2: 0·001. Pre-specified subgroup analyses and meta-regression showed a significant association between the effect estimate and best practice standards of SAP, defined by the American Society of Health-System Pharmacists guidelines, involving timing and intraoperative repetition (Subgroup: P = 0·048, variance explained: 100%). There was evidence of effect in trials that did not meet best practice standards of SAP regarding timing and intraoperative repetition (RR: 0·79; 95%CI: 0·67-0·94 RR, tau^2 = 0·019), but not in trials that did (RR: 1·04; 95%CI: 0·85-1·27, tau^2 = 0·00).

Interpretation: Overall there is no strong evidence for a benefit of postoperative continuation of SAP. When SAP best practice standards were followed, post-operative SAP continuation did not yield any additional benefit in reduction of SSI. These findings support WHO recommendations against this practice.

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Panel: Research in context

Evidence before this study

Antibiotics should be used judiciously and according to the evidence due to concerns about the emergence of antimicrobial resistance and other hazardous side effects. One in seven in-hospital prescriptions for antibiotics is for surgical antibiotic prophylaxis (SAP) and is frequently continued for several days after surgery. While the effectiveness of appropriate SAP to prevent surgical site infections (SSI) in indicated procedures is well established, an increasing body of evidence suggests that a single preoperative dose of SAP with intraoperative repeat of administration when indicated may be as effective as a prolonged postoperative regimen. Longer exposure to antibiotics has been associated with an increased risk of antimicrobial resistance, *Clostridium difficile* infection and acute kidney injury. Across surgical subspecialties, many randomised controlled trials (RCTs) and some systematic reviews exist. No systematic review considers all the available evidence. In 2015, the World Health Organization (WHO) conducted a systematic review and meta-analysis and based on the results strongly recommended against postoperative continuation of SAP, but only a summary of the review was published. A recent European multi-country study found that SAP is still routinely continued up to several days after surgery. Additional trials became available after publication of the guidelines, and some of the data included in the original WHO review may no longer be representative for current best practice standards of SAP.

Added value of this study

We searched MEDLINE, Embase, CINAHL, CENTRAL, and WHO regional medical databases from Jan 1990 to August 2018 for studies investigating the effect of postoperative continuation of preoperative SAP compared to postoperative discontinuation, in patients undergoing any surgical procedures with SAP indication, on the incidence of SSI. This systematic review of 83 RCTs, of which 52 RCTs were included in the main meta-analysis, provides a comprehensive overview of all the available evidence on the practice of postoperative continuation of SAP across surgical subspecialties. We found no conclusive evidence that patients benefit from continued SAP after surgery based on moderate quality of evidence. Pre-specified subgroup analysis indicated that postoperatively continued SAP is only effective when preoperative SAP is not timed adequately and not repeated according to the duration of the procedure. In contrast, when SAP best practices standards on timing and intra-operative repetition were applied, no effect of postoperative SAP continuation in reducing SSI risk was found.

Implications of all the available evidence

In this systematic review and meta-analysis, no conclusive evidence for a benefit of postoperative continuation of SAP as compared to postoperative discontinuation for the reduction of SSI was found. When SAP best practices were followed, post-operative SAP continuation did not yield any additional benefit in reduction of SSI. Considering the possible adverse effects, there is no basis for postoperative continuation of SAP. Increased awareness and education about best practices are warranted for both patients and practitioners and need to be the basis of stewardship efforts among surgeons. Future research to further clarify effectiveness of SAP continuation, if any, should include monitoring of pre-specified adverse events and standardize preoperative timing and intraoperative dose repetition according to evidence-based standardized criteria.

Introduction

Antibiotic use is under scrutiny due to concerns about the emergence of antimicrobial resistance and other hazardous side effects.[1,2] One in seven in-hospital prescriptions for antibiotics is for surgical antibiotic prophylaxis (SAP) and is frequently continued for several days after surgery.[3] While the effectiveness of appropriate SAP to prevent surgical site infections (SSI) in indicated procedures is well established,[4] an increasing body of evidence suggests that a single preoperative dose of SAP, with intraoperative repeat of administration when indicated, may be as effective as a prolonged postoperative regimen in a variety of procedures.[5,6] Longer exposure to antibiotics has been associated with an increased risk of antimicrobial resistance, *clostridium difficile* infection and acute kidney injury,[7-9] while avoiding postoperative continuation of antibiotic prophylaxis has been associated with reduced risk of *clostridium difficile* infection.[10] Based on a systematic review and meta-analyses that included a wide range of surgical subspecialties, the World Health Organization (WHO) strongly recommended against postoperative continuation of SAP in the 2016 global guidelines for SSI prevention.[11] The Centers for Disease Control and prevention (CDC), the National Institute for Health and Care excellence (NICE) and other organizations made similar recommendations.[4,12,13] Despite this, SAP continuation is still very common across the world.[14] A recent global point prevalence study revealed that the percentage of patients that receive SAP for more than one day ranged from 29,5% in Western Europe to 92,5% in Africa.[14] Lack of utilization monitoring and poor implementation of antimicrobial stewardship programmes may facilitate the continuation of this practice.[15,16] However, limited awareness of the existing evidence or new potentially contradicting evidence may also contribute. Only a summary of the systematic review conducted for the WHO recommendation was published.[13] Evidence continues to emerge through publication of new randomized controlled trials,[17,18] and some of the existing data used in the initial review may no longer be representative for current best practice standards of SAP.[4] We therefore conducted a systematic literature review and meta-analysis, updating the evidence on which the 2016 WHO recommendation was based, and re-assessed the effect of postoperative continuation of preoperative SAP on the incidence of SSI compared to postoperative discontinuation in patients undergoing surgical procedures.

Methods

Search strategy and selection criteria

The protocol for this systematic review and meta-analysis was registered in the PROSPERO register (see http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017060829[19] and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[20]

Randomised controlled trials (RCTs) investigating the effect on the incidence of SSI of postoperative continuation of preoperative SAP compared to postoperative discontinuation, in patients undergoing any surgical procedures with an indication for SAP[4] were eligible. We excluded studies that compared regimens that also differed with regard to dose and agent used, studies that did not administer the first dose preoperatively by intravenous infusion, studies on dirty procedures or established infections where antibiotic use was classified as treatment, and observational and pre-clinical studies. We limited eligibility to studies published from 1990 onwards because infection prevention practices before 1990 differed significantly from current practices. We applied no restrictions regarding the definition of outcomes, length of follow up or language.

We searched Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases from 1990 to August 2018. The search terms used were: surgical wound infection, surgical site infection, SSI, SSIs, surgical wound infection, surgical infection, post-operative wound infection, postoperative wound infection, antibiotic prophylaxis, antimicrobial, antibiotic, prolong, duration, short, long, single dose, multi dose. These terms were combined with the highly sensitive search strategy of Cochrane for identifying RCTs.[21] The full search strategy is available in the appendix, p 1.

Two authors (QB and SW) independently screened the titles and abstracts for eligibility. When title and abstract indicated potential eligibility, the full-text article was obtained. To avoid language bias, articles published in languages other than English were translated by authors proficient in the language or, when unavailable, by an online multilingual machine translation service (https://translate.google.com).[22] Any disagreements were resolved through discussion or, when necessary, after consultation with the senior author (MB).

Data analysis

Two authors independently reviewed each eligible article and extracted relevant data using a standardized data extraction form. Data collection covered design, publication date, scope, number of participants, type of surgery, contamination by CDC wound classification,[23] outcome definition, follow up, dosage and regimen of antibiotics in both intervention and control group including timing of the preoperative dose and intraoperative repeat of administration when indicated, results, resource use and adverse events. We contacted all authors by email, or surface mail when email was not available, for detailed information on timing of the first dose, procedure duration, intraoperative repeat of administration, adverse events and the antibiotics used. We collected drug characteristics from the American Society of Health-System Pharmacists (ASHP) clinical practice guidelines for antimicrobial prophylaxis in surgery and a comprehensive database for bioinformatics and cheminformatics (DrugBank Version 5·0 https://www.drugbank.ca).[4,24] When finally insufficient information could be retrieved on timing of the preoperative dose or intraoperative repeat of administration, we assumed this was not standardized during the study.

Two authors (QB and SW) independently assessed the risk of bias of included studies using the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[21] Criteria for risk of bias are listed in the appendix, p 2. Conflicts were resolved through discussion or after consultation with the senior author (MB). Results were displayed in summary figures generated by Review Manager Version 5·3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark; 2008). The possibility of publication bias was visually assessed using a contour enhanced funnel plot.[25]

Trials of any surgical procedure that compared postoperative continuation of SAP of any duration with immediate postoperative discontinuation were included in the main analysis. Further analyses were conducted comparing postoperative regimens of different duration. We calculated summary relative risks (RR) with the corresponding 95% confidence interval (CI) using a random effects model (DerSimonian and Laird), thus taking into account statistical heterogeneity.[26] The χ^2 test for heterogeneity was performed, and the ratio of true heterogeneity to total variation in observed effects was expressed using the I^2 statistic. The extent of heterogeneity was evaluated using tau^2.

Current best practice standards of SAP are described in the ASHP clinical practice guidelines for antimicrobial prophylaxis in surgery.[4] We accounted for these standards in pre-specified subgroup analyses for studies standardizing: 1) timing of the first preoperative dose within 60 minutes prior to incision, 2) redosing when procedure duration exceeded two times the half-life of the antibiotic agent, and 3) adherence to current best practice standards meeting both these conditions. To explore potential procedure specific effects, we performed sub-group analyses by procedure type. For each subgroup analysis, we used random-effects meta-regression to investigate the association of subgroup characteristics with the intervention effect.[27] The proportion of variance explained was calculated by examining the change in tau^2.[28]

Statistical analyses were done in Stata version 15·0 (Stata Corporation, College Station, TX, USA).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to judge the quality of the retrieved evidence (GRADE Pro software, http://gradepro.org/).[29] Predefined subgroups with a strong association with the intervention effect where graded individually. Optimal information size, defined as the number of participants needed for a single adequately powered trial, was calculated assuming a type-1 error (α) of 0·05, a type 2 error (β) of 0·2 and a relative risk reduction of 0·25.[29] If a confidence interval failed to exclude appreciable benefit of SAP continuation, defined as a relative risk reduction of 0·25, the quality of evidence was downgraded regardless of the optimal information size.[29]

Role of the funding source

There was no funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The search retrieved 3,238 potentially relevant records and 24 additional records were identified through other sources. We assessed 147 full-text publications for eligibility; 83 RCTs were critically appraised and included in meta-analyses. The selection procedure is summarised in Figure 1. Reasons for exclusion after full text assessment are described in the appendix, pp 3-4.

Study characteristics are listed in the appendix, pp 5-11. In total, 24,434 participants were included in 83 RCTs comparing different postoperative SAP regimens with SSI as an outcome. Source countries included Iran, Saudi Arabia, The United States of America, Hong Kong, Japan, Italy, India, Argentina, Korea, The Netherlands, France, Pakistan, Israel, Australia, The United Kingdom, Sweden, Tanzania, Taiwan, Spain, Canada, China, Germany, Brazil, Romania, Korea, Switzerland and Thailand. The average age of included patients was 47,8 years and ranged from 8 to 77 years. All but one study focused primarily on adult participants. Nineteen studies included children. The percentage of female patients included was on average 47,6% and ranged from 10% to 100%. Procedures were diverse and represented gastro-intestinal, cardiac, thoracic, head and neck, gynaecological, obstetrics, trauma/orthopaedics and maxillofacial surgery. All but 17 trials were single centre studies.

Fifty-two RCTs including 19,273 participants compared continued postoperative regimens, varying from one postoperative administration to five days of postoperative continuation, to postoperative discontinuation of SAP. Thirty-three RCTs including 5,516 participants compared postoperative SAP regimens of different duration. Of these 33 trials, one RCT with 227 participants compared postoperative continuation of SAP up to 24 hours with a single postoperative dose, 25 RCTs including 4,280 participants compared postoperative continuation of SAP for more than 24 hours to postoperative continuation for less than 24 hours six RCTs including 754 participants compared postoperative continuation for more than 48 hours to postoperative continuation for less than 48 hours, and one RCT including 255 participants compared postoperative continuation for more than 72 hours to postoperative continuation for less than 72 hours. Two RCTs had several study arms and provided data on multiple comparisons. Timing of the first preoperative dose of antibiotics was standardized as within 60 minutes of the first incision in 57 RCTs. Forty-six RCTs standardized intraoperative redosing or had procedure durations that did not exceed two halftimes of the antibiotic used. Adherence to current best practice standards, i.e. correct timing prior to incision and repeat of administration during surgery when indicated, was standardized in 34 RCTs. The outcome definition was described as the current CDC definition of SSI in 26 RCTs.[23] The other 57 studies used descriptions ranging from purulent discharge to extensive, field specific descriptions of the clinical manifestation of SSI. All the definitions used are listed in the appendix, p 12. Twenty-four studies reported adverse events and 6 studies described resource use.

The results of the analyses are presented in Table 1. Meta-analysis of 52 RCTs showed that there was an indication, but not conclusive evidence of a benefit of postoperative continuation of SAP in the prevention of SSI when compared to postoperative discontinuation (RR: 0·89; 95%CI: [0·79-1·00]). Heterogeneity was low ($tau^2 = 0·001$, chi-squared $P = 0·459$, $I^2 = 0·7$ %). Subgroup analyses and meta-regression indicated that compliance with current best practice standards for SAP modified the association between continuation of postoperative SAP and the incidence of SSI (Subgroup: $P = 0·048$, variance explained: 100%). Only in trials not compliant with current best practice standards (i.e. timing of the first preoperative dose within 60 minutes prior to incision and redosing when procedure duration exceeded two times the half-life of the antibiotic agent was not standardized), continuation of SAP prevented SSI compared with discontinuation (28 RCTs, RR: 0·79; 95%CI: [0·67-0·94], $tau^2 = 0·019$, Chi^2 $P = 0·312$, $I^2 = 10·3$ %). When the analysis was restricted to trials that met best practice standards of SAP regarding timing and redosing, this benefit of postoperative SAP continuation was no longer present (24 RCTs, RR: 1·04; 95%CI: [0·85-1·27], $tau^2 = 0·00$, Chi^2 $P = 0·784$, $I^2 = 0·0$ %). The forest plot is presented in figure 2; the P value for the subgroup difference was 0·048.

Adequate timing or redosing alone did not affect the effect estimate (P for subgroup differences = 0·127 and P = 0·882 respectively). Exploratory subgroup analysis identified some evidence that postoperative continuation of SAP may reduce the risk of SSI when compared to postoperative discontinuation in maxillofacial surgery and cardiac surgery (P for subgroup differences = 0·024 and P = 0·005 respectively). Only studies that did not adhere to best practice standards were available for both these subgroups. All exploratory subgroup analyses are presented in the appendix, pp 13-14. The remaining meta-analyses, comparing continued postoperative SAP regimens beyond the first preoperative dose of different durations, did not show conclusive evidence of benefit for longer continuation of postoperative antibiotic prophylaxis. Forest plots of the individual meta-analyses are presented in the appendix, pp 15-20.

Some 24 studies described possible harms or adverse events related to SAP. Of these, 18 studies reported no adverse events attributable to antibiotic use in both the intervention and control group. Six

studies reported more adverse events in the groups with prolonged regimens. One study reported more cases of *Clostridium difficile* infection in the postoperative continuation group. The other studies reported a higher frequency of rash pruritus, erythema, phlebitis, hypotension, gastrointestinal disturbance including nausea and diarrhoea, and unspecified local and systemic side-effects. No study reported on antimicrobial resistance. Due to heterogeneity in the comparisons made, and the outcomes measured, no meta-analysis could be done. Adverse events are listed in the appendix, p 21.

Five studies addressed cost effectiveness and reported a cost increase associated with longer antibiotic prophylaxis regimens, in some cases also depending on treatment of side effects and hospitalisation time, which varied from $36,90 to $78,95. None of these studies incorporated cost for the emergence of antimicrobial resistance. All five studies were conducted in high income countries. Costs are listed in the appendix, p 22.

A summary of the risk of bias evaluations is presented in figure 3 and the full evaluations in the appendix, pp 23-28. Overall the risk of bias was considered serious due to the many unclear assessments, and some assessments of high risk of bias. No funnel plot asymmetry was detected both for the comparisons of continued postoperative regimen with postoperative discontinuation, and postoperative continuation for more than 24 hours with less than 24 hours. There were too few data for the three other comparisons to allow adequate evaluation of the funnel plots. Funnel plots are presented in Figure 4 and the appendix, p 29.

An evidence table with full GRADE assessments is presented in table 2. All included studies were RCTs, thus the starting quality of the evidence for each comparison was high. For the main analysis, comparing any postoperative continuation to postoperative discontinuation, the quality of evidence was downgraded to moderate due to serious risk of bias. One subgroup analysis was graded individually because of a strong association with the intervention effect. For the subgroup of studies that reported adherence to current best practice standards the quality of evidence was downgraded to moderate due to serous risk of bias. For the subgroup of studies that did not report adherence to current best practice standards the quality of evidence was downgraded to moderate due to risk of bias. The quality of evidence for the remaining analyses, comparing postoperative regimens of different durations, was downgraded to low in each due to serious risk of bias and imprecision.

Discussion

Moderate quality evidence from meta-analysis of 52 RCTs and 19,273 participants showed no conclusive evidence for a benefit of postoperative continuation of SAP in reducing the SSI rate as compared to postoperative discontinuation. Similarly, low quality evidence from comparisons of postoperative regimens of different duration showed no conclusive evidence of a benefit of prolonged regimens. Subgroup analysis showed that the effectiveness of postoperatively discontinued SAP depends on appropriateness of SAP practices. When SAP best practices (i.e., timely administration of the first dose and redosing when indicated according to the procedure duration) were applied, moderate quality evidence showed there was no benefit of postoperative SAP continuation in reducing SSI compared to discontinuation of SAP. Moderate quality of evidence showed that postoperative SAP continuation was effective only when these standard conditions of SAP administration were not met. There was some evidence from exploratory analysis that postoperative continuation of SAP may reduce the risk of SSI in maxillofacial surgery and cardiac surgery. Only studies that did not adhere to best practice standards were available for these subgroups. When costs and adverse events were reported, postoperative continuation led to increased cost and more adverse events.

These findings are in line with the initial review that supported the strong WHO recommendation against postoperative continuation of SAP and found an odds ratio of 0·89; 95%CI: [0·77-1·03].[11] In comparison to this initial WHO meta-analysis, the confidence interval resulting from the present meta-analysis narrowed slightly as more data has accrued, but the point estimate remains unchanged. While there is some evidence of a small benefit in both estimates, the confidence intervals include unity, and do not indicate appreciable benefit with regard to SSI. In particular when SAP best practices were applied, there was no benefit of postoperative SAP continuation overall, or in any specific subspecialty. Antibiotic use itself is associated with important adverse effects in a treatment duration dependent fashion.[7,30,31] In turn, these adverse effects are associated with a substantial economic burden that adds on to additional acquisition- and administration costs related to postoperative SAP continuation.[32-34] Waste that is particularly dreadful in countries with limited resources where this practice is most prevalent.[14] Postoperative SAP continuation is often used to compensate for lack of routine SAP best practices and gaps in other infection prevention measures; this conflicts with the basic principles of antibiotic stewardship and should be changed.[35]

Most guidelines issued before the WHO SSI prevention guidelines recommended prolongation of SAP to a maximum of 24-48, but were not based on rigorous evaluation of the existing evidence by systematic review.[4,12] Other systematic reviews that addressed this question were limited to one specific procedure, limiting power and generalizability, and included studies that compare regimens that also differed in dosage or agent in addition to the duration of administration.[36,37] Indications that postoperative antibiotic prophylaxis may have no added value arose as early as the 1960s.[38] Since then, routine postoperative continuation has persisted,[39] while concerns on AMR and other adverse effects have risen.[1,2] Despite the recent guidelines, SAP is still routinely continued up to several days after surgery.[14] New trials emerged after publication of the guidelines, and some of the included data may not be representative for current best practice standards of SAP.[4] The current findings show that there is no conclusive evidence for a benefit of postoperative continuation of SAP overall. When SAP best practices was followed, post-operative SAP continuation did not yield any additional benefit in reduction of SSI.

An important limitation of the current review is that slightly less than half of the included studies standardized current SAP best practices. Any effect identified in the overall estimate could reflect compensation of poor preoperative timing or failure to repeat administration when indicated and overestimate the true effect of SAP continuation. To account for this well-known issue, we conducted pre-specified a subgroup analysis for standardization of current SAP best practices. However, we were limited to aggregate data extracted from publications and did not have individual patient data, thus limiting the granularity of the data and the possibilities for detailed subgroup analysis.[40] Exploratory subgroup analysis into the effect of postoperative SAP continuation in specific surgical subspecialties was limited by a large number of subgroups, and consequently small numbers per subgroup. These characteristics lead to a high risk of false positive results, and the analysis should be interpreted with caution. Strengths of this study include the broad inclusion, and relevant exclusion criteria. Data from 28 different countries, the adult and paediatric population, and a wide variety of different surgical procedures suggest broad generalizability. Whereas the exclusion of studies on regimens that also differed with regard to dose and agent used, or studies that concerned antibiotic treatment rather than prophylaxis ensured the elimination of important sources of bias. Poor reporting of surgical trials, as previously noted, was an issue in this review as well.[41] This is in part due to the only recent provision of reporting standards.[42] As a result, a considerable proportion of the risk of bias was unclear, and important information on either timing of the first dose of antibiotics, procedure duration,

intraoperative repeat of administration, adverse events or the antibiotic used was frequently missing. We contacted the authors of the concerning studies to request further information, but not all replied to our request. Consequently, we had to assume SAP best practices were not in place in some studies because the required information could not be attained. The subgroup analysis might therefore be contaminated by reporting standards and responsiveness of the corresponding author and should be interpreted with caution. Over half of the included studies used definitions of SSI other than, or not exactly matching, the widely accepted CDC criteria.[23] In most cases this is again attributable to the time of publication. In the 1990s, the CDC definitions were not as widely used as they are now and many alternatives, including preceding versions of the CDC definitions were in use. This challenges interpretation of the clinical importance of the outcomes reported, and comparison of these findings to results of potential future studies. However, an important part of the aim of the present study was to consider all available evidence, and there is evidence that alternative definitional systems provide information similar to that captured in the CDC system.[43] Lastly, costs and adverse events were poorly reported if at all, and no meaningful meta-analyses could be conducted to assess these outcomes. Future research to clarify the importance of SAP continuation, if any, should include monitoring of pre-specified adverse events, costs, and standardize preoperative timing and intraoperative repeat of administration.

We found no conclusive evidence for a benefit of postoperative continuation of surgical antibiotic prophylaxis as compared to postoperative discontinuation for the reduction of SSI. When SAP best practices are followed, moderate quality of evidence shows that post-operative SAP continuation does not yield any additional benefit in reduction of SSI. These findings support WHO recommendations against this practice. Considering the associated adverse effects, in particular in terms of antimicrobial resistance, there is no basis for this prevalent practice. Increased awareness and education are warranted for both health care professionals and patients, especially by prioritising stewardship efforts among surgeons and anaesthetists and insisting on other infection prevention measures in addition to SAP.

Contributors

SW and MA designed the study. SW and QJ screened records, extracted data and assessed risk of bias. SW conducted statistical analysis. SW, M, G, B, PE, JS, QJ, MA, analysed and interpreted the data. SW and QJ drafted the manuscript. All authors provided critical conceptual input, interpreted the data analysis, and critically revised the manuscript.

Declaration of interests

S.W. de Jonge, Q.J.J. Boldingh, J.S. Solomkin, B. Allegranzi and M. Egger declare no conflict of interest.
P.E. Dellinger reports personal fees from Destiny Pharma, outside the submitted work
M.A. Boermeester reports grants and other from KCI, grants and other from Johnson&Johnson/Ethicon, grants from New Compliance, grants from Mylan, other from Bard, other from Gore, other from Smith&Nephew, outside the submitted work.
G. Salanti reports other from Biogen, other from Merck, outside the submitted work.

Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. WHO takes no responsibility for the information provided or the views expressed in this paper.

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Tables

Table 1. Meta-analysis and subgroup analyses of incidence of SSI in Postoperative continuation of SAP vs. postoperative discontinuation of SAP

	No. of studies	SSI in longer regimen	SSI in shorter regimen	Relative risk (95%CI)	tau^2_{MA}	tau^2_{MR}	P-Value for subgroup differences	% of heterogeneity variance explained
Comparison 1: Postoperative continuation of SAP vs postoperative discontinuation of SAP								
Overall summary effect								
Overall	52	492 of 9,726	549 of 9,547	0·89 (0·79, 1·00)	0·001	NA	NA	NA
Timing of first dose specified and within 60 min prior to surgery								
Yes	33	303 of 6,249	314 of 6,151	0·96 (0·82, 1·12)	0·000	0	0·127	100%
No	19	189 of 3,477	236 of 3,396	0·77 (0·61, 0·96)	0·033			
Intraoperative repeat of administration specified when indicated								
Yes	34	265 of 6,126	288 of 5,944	0·89 (0·76, 1·05)	0·000	0·005	0·882	0
No	18	227 of 3,600	262 of 3,603	0·86 (0·70, 1·05)	0·021			
Adherence to current best practice standards of SAP: Timing of first dose specified and within 60 min prior to surgery and intraoperative repeat of administration specified when indicated								
Yes	24	196 of 4,648	186 of 4,552	1·04 (0·85, 1·27)	0·000	0	0·048	100%
No	28	296 of 5,078	364 of 4,995	0·79 (0·67, 0·94)	0·019			
Comparison 2: Postoperative continuation of SAP for multiple postoperative doses <24h vs. postoperative continuation of SAP for one postoperative dose								
Overall	1	44 of 113	39 of 113	0·82 (0·57-1·40)	NA	NA	NA	NA
Comparison 3: Postoperative continuation of SAP > 24h vs postoperative continuation of SAP <= 24h								
Overall	25	170 of 2,038	191 of 2,052	0·93 (0·76, 1·13)	0·000	NA	NA	NA
Comparison 4: Postoperative continuation of SAP > 48h vs postoperative continuation of SAP <= 48h								
Overall	6	42 of 372	31 of 382	1·35 (0·89, 2·03)	0·000	NA	NA	NA
Comparison 5: Postoperative continuation of SAP > 72h vs postoperative continuation of SAP <= 72h								
Overall	1	3 of 125	4 of 130	0·61	NA	NA	NA	NA

				(0·14, 2·63)				

SSI: Surgical site infection, CI: Confidence interval, tau^2: Tau-squared (moment estimator), MR: Meta-regression, MA: Meta-analysis, % of heterogeneity variance explained: $\left(\frac{\tau^2{}_{MA\,(overal)} - \tau^2{}_{MR.}}{\tau^2{}_{MA\,(overal)}}\right)$, <: less than; >: more than; <= less than or equal to; >=more than or equal to, SAP: Surgical antibiotic prophylaxis, NA: not available

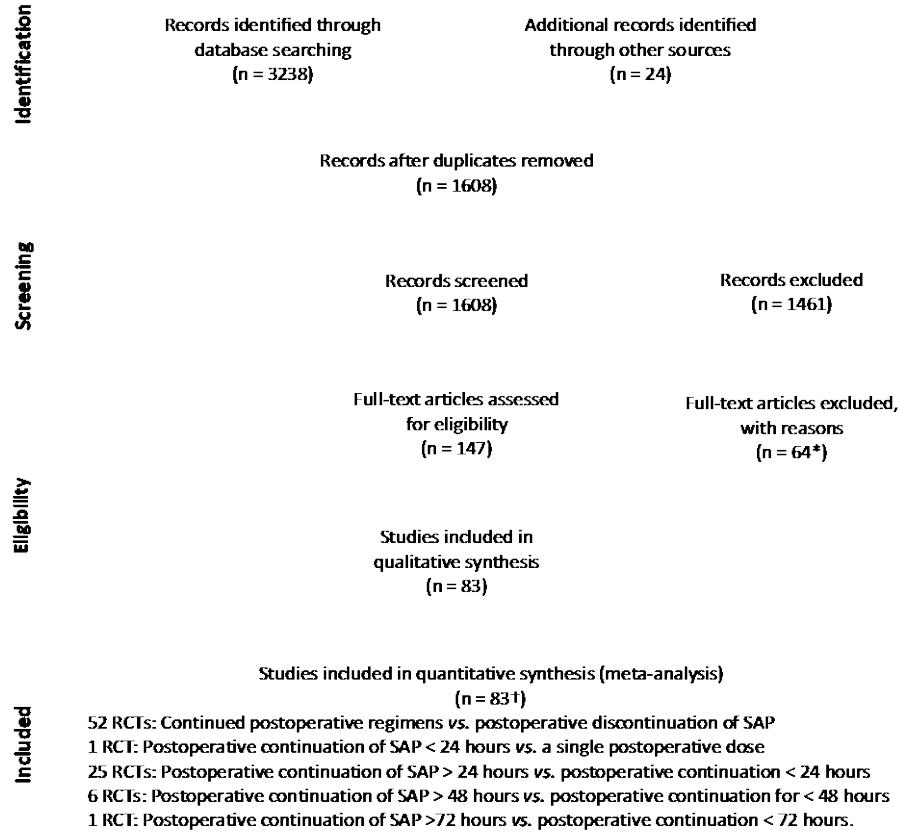
Table 2. GRADE assessment of the included evidence

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Postoperative continuation**	**Postoperative discontinuation**	**Relative (95% CI)**	**Absolute (95% CI)**	◯ - ⊕⊕⊕ ⊕
Comparison 1: Postoperative continuation of SAP vs postoperative discontinuation of SAP, Overall summary effect											
52	randomised trials	serious[a]	not serious	not serious	not serious (OIS: 3629 per arm)	none	492/9726 (5.1%)	549/9547 (5.8%)	**RR 0.89** (0.79 to 1.00)	**6 fewer per 1,000** (from 12 fewer to 0 fewer)	⊕⊕⊕ ◯ MODERATE
Comparison 1, subgroup: Postoperative continuation of SAP vs postoperative discontinuation of SAP, Adherence to current best practice standards of SAP											
24	randomised trials	serious[a]	not serious	not serious	not serious (OIS: 5185 per arm)	none	196/4648 (4.2%)	186/4552 (4.1%)	**RR 1.04** (0.85 to 1.27)	**2 more per 1,000** (from 6 fewer to 11 more)	⊕⊕⊕ ◯ MODERATE
Comparison 1, subgroup: Postoperative continuation of SAP vs postoperative discontinuation of SAP, No adherence to current best practice standards of SAP											
28	randomised trials	serious[a]	not serious	not serious	not serious (OIS: 2823 per arm)	none	296/5078 (5.8%)	364/4995 (7.3%)	**RR 0.79** (0.67 to 0.94)	**15 fewer per 1,000** (from 24 fewer to 4 fewer)	⊕⊕⊕ ◯ MODERATE
Comparison 2: Postoperative continuation of SAP for multiple postoperative doses <24h vs. postoperative continuation of SAP for one postoperative dose											
1	randomised trials	serious[a]	not serious	not serious	serious[b,c] (OIS: 444 per arm)	none	44/113 (38.9%)	39/113 (34.5%)	**RR 0.82** (0.57 to 1.40)	**62 fewer per 1,000** (from 148 fewer to 138 more)	⊕⊕◯ ◯ LOW
Comparison 3: Postoperative continuation of SAP > 24h vs postoperative continuation of SAP <= 24h											
25	randomised trials	serious[a]	not serious	not serious	serious[b] (OIS: 2168 per arm)	none	170/2038 (8.3%)	191/2052 (9.3%)	**RR 0.93** (0.76 to 1.13)	**7 fewer per 1,000** (from 22 fewer to 12	⊕⊕◯ ◯ LOW

										more)	
Comparison 4: Postoperative continuation of SAP > 48h vs postoperative continuation of SAP <= 48h											
6	randomised trials	serious [a]	not serious	not serious	serious [b] (OIS: 2515 per arm)	none	42/372 (11.3%)	31/382 (8.1%)	**RR 1.35** (0.89 to 2.03)	**28 more per 1,000** (from 9 fewer to 84 more)	⊕⊕◯◯ LOW
Comparison 5: Postoperative continuation of SAP > 72h vs postoperative continuation of SAP <= 72h											
1	randomised trials	serious [a]	not serious	not serious	serious [b,c] (OIS: 6950)	none	3/125 (2.4%)	4/130 (3.1%)	**RR 0.61** (0.14 to 2.63)	**12 fewer per 1,000** (from 26 fewer to 50 more)	⊕⊕◯◯ LOW

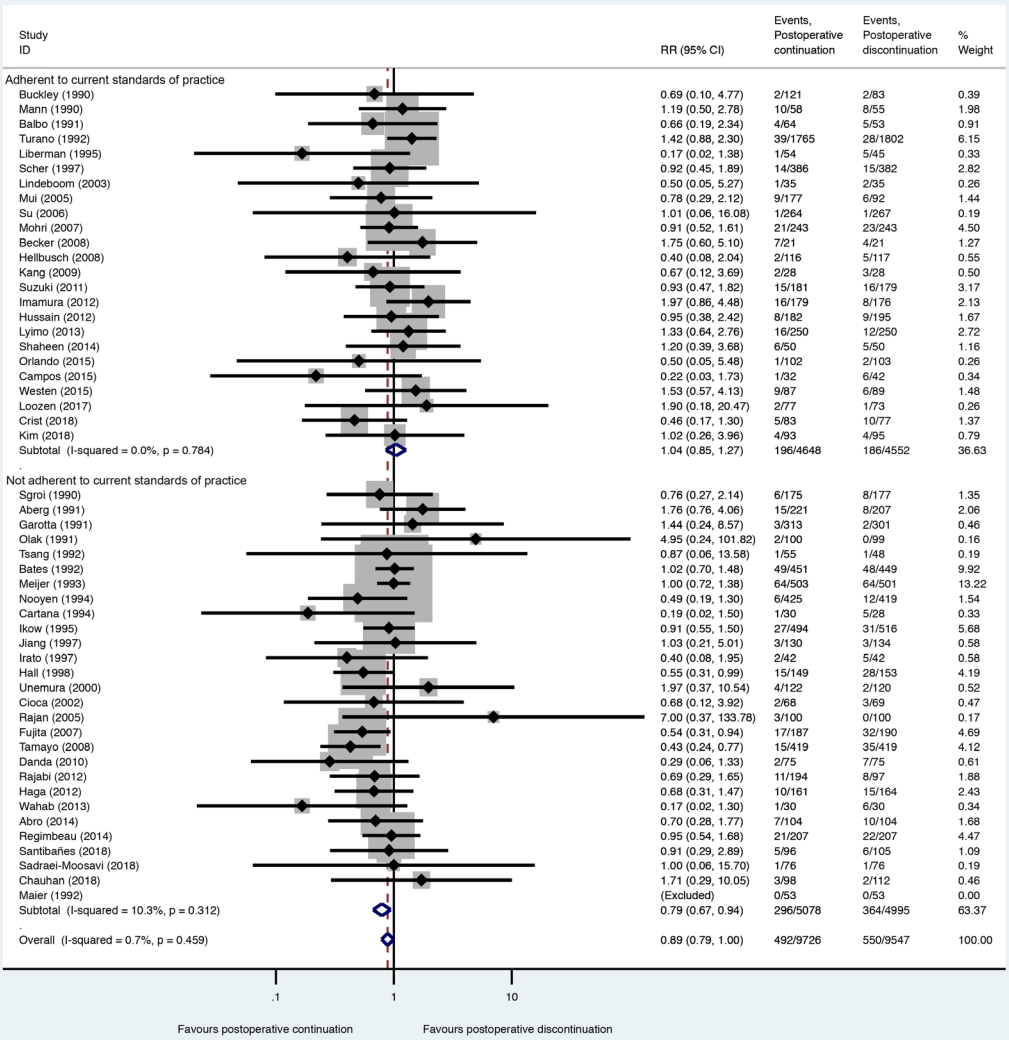
a: Risk of selection bias, performance bias, detection bias, attrition bias and reporting bias; **b:** Optimal information was not obtained; **c:** Optimal information was obtained, but confidence interval included considerable benefit of SAP continuation (> RRR 0.25); **CI:** Confidence interval; **RR:** Risk ratio; **SAP:** Surgical antibiotic prophylaxis; **OIS:** Optimal information size

Figure 1. PRISMA flowchart of the study selection process



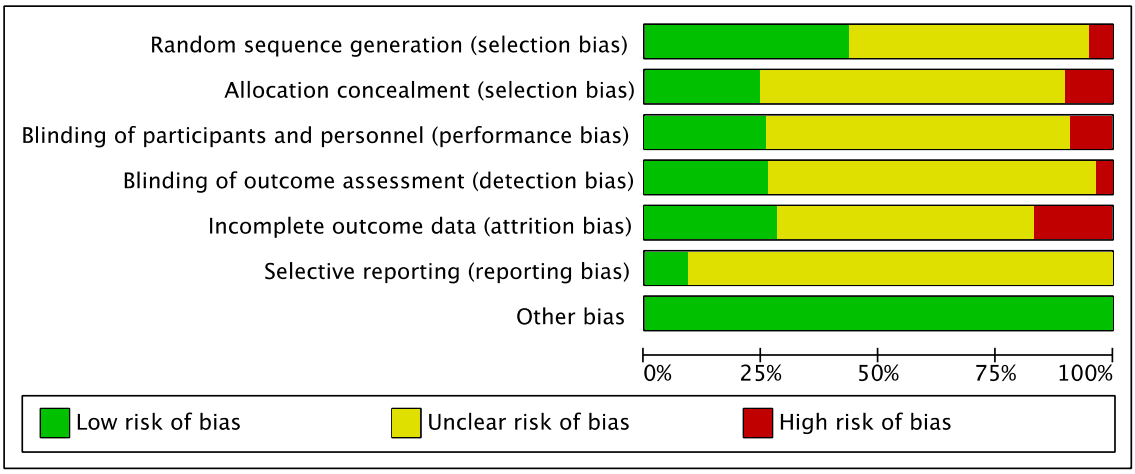
The figure provides a visualisation of the study selection. *: Reasons for exclusion after full-text assessment are shown in the appendix, pp3-4; †: Two RCTs had several study arms and provided data on multiple comparisons; RCT: Randomized controlled trial; >: More than; <: Less than.

Figure 2. Forest plot: Postoperative continuation vs. postoperative discontinuation of surgical antibiotic prophylaxis. Subgroup analysis: *Adherence to current best practice standards of SAP*



Forest plot of meta-analysis, comparing the effect of postoperatively continued surgical antibiotic prophylaxis with postoperative discontinuation - using the same agent and the same dose per administration - on the risk of surgical-site infection (SSI). The forest plot is sub grouped by adherence to current best practice standards of SAP for perioperative surgical antibiotic prophylaxis (1 meaning adherent, 0 meaning not adherent). A DerSimonian & Laird random-effects model was used. Relative risk is shown with 95% confidence intervals. Solid diamonds and horizontal lines represent point estimates and corresponding 95% confidence intervals of die individual studies respectively. The transparent diamond represents the overall estimate and 95% confidence interval.

Figure 3. Risk of bias graph of the included studies



The figure illustrates the proportion of studies with each of the judgments ('Low risk', 'High risk', 'Unclear risk' of bias) for each of the criteria for risk of bias assessment; random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Figure 4. Funnel plot: Postoperative continuation of surgical antibiotic prophylaxis vs. postoperative discontinuation of surgical antibiotic prophylaxis.

The figure illustrates the distribution of effect estimates of the different studies (x-axis) against their precision (y-axis). Asymmetry across the vertical midline, representing the overall effect estimate of the meta-analysis, indicates publication bias. Both funnel plots show a symmetrical distribution and no indication of publication bias.