Liberal versus restrictive antimicrobial prophylaxis for surgical site infection: Systematic review and meta-analysis of randomised trials.

Alexander J Fowler MBBS[1], Priyanthi Dias PhD[2], Sara Hui MSc[3], Richard Cashmore MBBS[4], Ryan Laloo MBChB[5], Adil N Ahmad MBBS[6], Michael A Gillies MD[7], Yize I Wan PhD[8], Rupert M Pearse MD[9*], Tom EF Abbott PhD[10*]

[*] Joint senior authors

1. NIHR Doctoral Research Fellow, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ
2. Senior Trials Coordinator, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ
3. Medical Student, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ
4. Clinical Research Fellow, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ
5. Surgical Registrar, Leeds Vascular Institute, The Leeds Teaching Hospitals NHS Trust, Leeds, UK, LS9 7TF
6. Surgical Registrar, Department of General Surgery, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK, B71 4HJ
7. Professor of Anaesthesia and Critical Care, Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK, EH16 4SA
8. Clinical Lecturer in Critical Care, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ
9. Professor of Perioperative Medicine, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ
10. Clinical Lecturer in Anaesthesia, Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Queen Mary University of London, UK EC1M 6BQ

Correspondence to:

Tom Abbott

Research Office

Adult Critical Care Unit

Royal London Hospital

London

E1 1FR

United Kingdom

e-mail: t.abbott@qmul.ac.uk

Tel: +44 20 3594 0346

ABSTRACT

Background: Antimicrobial prophylaxis is widely used to prevent surgical site infection (SSI). Amid growing concern about antimicrobial resistance, we determined the effectiveness of antimicrobial prophylaxis.

Methods: We searched MEDLINE, EMBASE, CENTRAL and WHO-ICTRP between 1st January 1990 and 1st January 2020 for trials randomising adults undergoing surgery to liberal (more doses) or restrictive (fewer or no doses) perioperative antimicrobial prophylaxis. Pairs of researchers reviewed articles and extracted data, a senior author resolved discrepancies. The primary outcome measure was SSI or bacteriuria for urological procedures. We calculated average risk difference (RD) with 95% confidence intervals and prediction intervals (PI) using random-effects models, and present risk ratios. We assessed evidence certainty using GRADE methodology, and risk of bias using the Cochrane Risk of bias tool. (PROSPERO:42018116946)

Results: From 6,593 records, we identified 294 trials including 86,146 patients. SSI occurred in 2,237/44,113 (5.1%) patients receiving liberal prophylaxis versus 2,889/42,033 (6.9%) receiving restrictive prophylaxis (RD-0.01[-0.02 to -0.01]; RR0.72 [0.67 to 0.77]; I^2=52%,PI: -0.05 to 0.02). There was a small benefit in 161 trials comparing no prophylaxis to ≥1 dose (RD-0.02 [-0.03 to -0.02]; RR0.58 [0.52 to 0.65]; I^2=62%, PI: -0.06 to 0.02). Treatment effect varied from a strong effect in urology to no benefit in 7/19 specialities. Tests for publication bias suggest 62 unreported trials and evidence certainty was very low. 43/294 trials reported treatment harms.

Conclusions: More liberal antimicrobial prophylaxis is associated with only a small reduction in the risk of SSI, while antimicrobial harms are poorly reported. Further evidence about the risks of antimicrobial prophylaxis to inform current widespread use is urgently needed.

Keywords: Antimicrobial resistance; Surgery; Perioperative medicine; Surgical site infection; Antimicrobial prophylaxis.

INTRODUCTION

Surgical site infection is an important postoperative complication which affects one in ~~ten~~ twenty patients after surgery and is associated with prolonged hospital stay, increased treatment costs and early postoperative death.[1–4] Historically, antimicrobial prophylaxis, often administered by anaesthetists, has been an important method of preventing surgical infection. ~~This is based on the theory that introducing~~ The presence of antimicrobial drugs in cutaneous tissues before surgical incision and before skin closure can eliminate bacteria and prevent infection. However, in recent years antimicrobial resistance has become a worldwide threat to healthcare practices.[5] The precise future burden of antimicrobial resistance is unclear, but it is feared that by 2050 it will result in as many as 10 million deaths each year.[6,7] The principal driver of antimicrobial resistance is the use of antimicrobial drugs.[3,4] Worldwide, there are 53 million prescriptions of antimicrobial prophylaxis for the 315 million surgical procedures that occur each year.[5,14]

Antimicrobial prophylaxis is widely, and often liberally, used in surgical care. However, it is only one of many perioperative infection control interventions. Advanced surgical techniques, especially laparoscopic and robotic surgery, leave smaller wounds that reduce the risk of surgical site infection. In addition, contemporary multi-modal prevention strategies include specialised operating theatre clothing, face coverings, antiseptic skin preparation, hypothermia prevention, novel suture materials and postoperative wound cleansing.[7,9–11,15] Given that many trials of antimicrobial prophylaxis were undertaken more than 20 years ago, the net contribution of this practice to a wider strategy for prevention of surgical site infection may now have changed. Two recent meta-analyses suggest that timely antimicrobial administration before surgery, with repeat dosing during long procedures, may render postoperative doses unnecessary.[13,14,18] However, the most recent analysis compared only a single preoperative dose to postoperative continuation, and did not evaluate the many other dosing strategies used globally, including no prophylaxis at all. Meanwhile as many as 40% of surgical patients receive prolonged administration of antimicrobial prophylaxis.[10,19] The frequency and impact of the side effects of antimicrobial prophylaxis (e.g. acute kidney injury, anaphylaxis, *clostridium difficile*) remain unclear, and are not reported in widely cited guidelines.[20]

There is a need for an evidence synthesis describing the clinical effectiveness and safety of antimicrobial prophylaxis across different surgical specialties. A clear understanding of this evidence base is needed to balance the risks of surgical site infection against the individual patient harms of antimicrobial drugs and the societal risk of antimicrobial resistance.[21] We performed a systematic review and meta-analysis of randomised trials comparing liberal antimicrobial prophylaxis regimens to restrictive approaches involving fewer or no doses of antimicrobial drugs.

METHODS

Systematic review and meta-analysis of randomised trials conducted according to a prospectively registered protocol (PROSPERO CRD: 42018116946). Our findings are reported according to PRISMA guidelines.[22]

Search strategy and selection criteria

We searched MEDLINE, Embase, the Cochrane Controlled Register of Trials and the World Health Organisation International Clinical Trials Registry Platform for trials published from 1st January 1990 to 1st January 2020. The full search strategy is included in the supplementary file. Reports were eligible for inclusion if they described a trial in which participants aged ≥16 years undergoing a surgical procedure were randomised to a differing number of doses of antimicrobial drugs for the purpose of prophylaxis against surgical site infection.[23] Trials reported in any language were eligible for inclusion. We excluded trials where a full trial report was not available; non-randomised studies; those where the antimicrobial regimen was the same in both arms but the drugs differed; those where antimicrobials administered were not systemic; those where antimicrobials were administered as treatment not prophylaxis; those which did not report infection outcomes; studies of non-surgical procedures; those studying solid organ transplant recipients; and trials using anti-fungal, anti-helminth or anti-viral agents. Record screening, full text eligibility and data extraction for each study was undertaken independently by two investigators (AF, RC, PD, SH, AA, RL, YW). Records (title and abstract) were screened within the Mendeley Reference Manager (Elsevier, Amsterdam, Netherlands). We then obtained the full text for records selected by either reviewer. Authors were contacted if we were unable to find full trial reports or if we were unable to translate the full trial report into English. We screened reference lists of included trials and prior systematic reviews. A Google Form (Google Docs, Alphabet Inc, California, USA) was used for full text eligibility and data extraction. Discrepancies were resolved by discussion with a third investigator (TA).

Data analysis

Data were extracted individually for each trial arm using a piloted form. Duplicate trial reports were included as a single trial. If data were unclear, authors were contacted directly for clarification. Risk of bias was assessed using the Cochrane Risk of Bias Tool.[24] The number of antimicrobial doses was calculated for each randomisation arm of each trial. If the number of doses was not reported for a given agent, we assumed the dosing strategy reported in the British National Formulary (BNF) (BNF 78; British Medical Association & Royal Pharmaceutical Society, 2019). The BNF is provided by the UK National Institute for Health and Care Excellence to provide key information about selecting, prescribing, dispensing, and administering medications. We extracted data describing trial

characteristics including number of trial centres, surgical procedure category, urgency of surgery and income status of the host nation based on World Bank categorisations in 2018-2019.[25] The primary outcome measure was surgical site infection within 30 days after surgery or before hospital discharge according to the investigator's definition. For urological surgery we used the analogous outcome of bacteriuria which included urinary tract infection.

The primary analysis compared patients receiving a liberal antimicrobial prophylaxis regimen to those receiving a restrictive regimen involving fewer or no doses of antimicrobial drug. We use the terms liberal and restrictive for ease of understanding as they indicate an intervention group receiving more, and a control group receiving less, antimicrobial prophylaxis. We conducted a series of pre-specified sub-group analyses: 1) elective OR emergency surgery; 2) different surgical procedure categories; 3) surgery performed in low and middle-income countries (LMICs) OR high-income countries (HIC);[25] 4) alternative dosing regimens (no dose versus ≥1 doses OR 1 dose versus ≥2 doses OR ≥2 doses versus ≥3 doses); and 5) trials with a low risk of bias in two or more domains according to the Cochrane Risk of Bias Tool.[24] The assignment of trials to different alternative dosing regimens is summarised in supplementary figure 1. We calculated risk difference using an inverse variance random effects model with zeroes included in the model, and also present relative risks. Tau was calculated using the Der Simonian-Laird estimator. Consistency was measured using the I^2 statistic and prediction intervals, which provide a forecasted range for the true treatment effect that may be observed in a future study by combining the summary effect measure with the observed heterogeneity.[26] Heterogeneity measures are reported from models calculating risk difference. A sensitivity analysis restricting to trials using the United States Centers for Disease Control (CDC) definition of surgical site infection was performed.[27] We did a post-hoc dose-response meta-analysis using the two step model described by Crippa and incorporated splines with five degrees of freedom.[28] We performed a series of meta-regressions to determine the influence of the year of publication, timing of surgical site infection measurement and administration of at least one dose prior to skin incision. We measured reduction in heterogeneity using Tau^2 to determine the proportion of explained heterogeneity relative to the base model. For the purposes of meta-regressions, we used a risk-ratio based model as these excluded studies that had zero events in both arms.

For the overall result, we used the median number of doses administered to the intervention arms to calculate the number of doses needed to prevent one infection and present 95% confidence intervals. Risk of bias plots were generated. Eggers test and visual assessment of funnel plots were used to identify small study effects which may indicate publication bias. Where we detected asymmetry, we estimated the number and outcome of missing trials using the trim-and-fill method of Duval and

Tweedie.[15] Evidence certainty was assessed by two authors using the GRADE criteria (AF, TA).[15] We present the frequency with which important harms are reported. All analyses were performed in R (version 3.6.1, R Core Team, Vienna, Austria) using the *robvis*, *meta* and *metafor* packages.[29–31] Deviations from our pre-specified protocol are summarised in supplementary table 6. Results are presented as average risk difference (RD) with 95% confidence intervals, I^2, p-value and prediction intervals (PI). There was no direct patient and public involvement in this project.

RESULTS

Main analysis

Electronic searches yielded 8,272 records and we identified 1,981 records from other sources. Of these, 1,799 were selected for full text assessment and 2954 met the inclusion criteria (figure 1). Included trials are summarised by surgical procedure categories in table 1, and the characteristics of each trial are described in supplementary tables 1-3. Most trials were single-centre (239 of 294 trials [81%]) and the median number of participants per trial was 167 (IQR: 98-332, range: 18 to 3,670). 235 of 294 trials (80%) included patients undergoing elective surgery. Surgical site infection was the primary outcome measure in 266 of 294 trials (90%) and bacteriuria was the primary outcome in the remaining 28 trials (10%). 121 of 294 trials (41%) were performed in LMICs. The primary infection outcome occurred in 5,126 of 86,146 (6.0%) patients. Surgical site infection occurred in 4,548 of 78,188 patients (5.8%) and bacteriuria in 578 of 7,958 Patients (7.3%). The timing of infection was inconsistently recorded (supplementary table 1). In the primary analysis there was a small reduction in surgical site infection associated with liberal antimicrobial prophylaxis when compared with restrictive regimens (RD -0.01 [-0.02 to -0.01]; RR 0.72 [0.67 to 0.77]; I^2=52%; p<0.01; PI: -0.05 to 0.02) (figure 2). When we did a dose-response analysis, we found that there was no additional benefit beyond two doses of antimicrobials, which were associated with the greatest reduction in relative risk of infection (Supplementary figure 2).

Sub-group analyses

Liberal antimicrobial prophylaxis was associated with fewer infections in 236 trials of elective surgery (RD -0.01 [-0.02 to -0.01]; RR 0.75 [0.69 to 0.75]; I^2=50%; p<0.01; PI: -0.05 to 0.02) and also in 51 trials of emergency or mixed urgency surgery (RD -0.01 [-0.2 to 0.00]; RR 0.88 [0.71 to 1.09]; I^2=49%; p=0.03; PI: -0.05 to 0.03) (supplementary figures 3 and 4). Around 1% of the observed heterogeneity was explained by the urgency of surgery and 4% by the surgical setting (Supplementary table 4). However, the treatment effects of liberal antimicrobial prophylaxis varied widely across different surgical specialities, with evidence of benefit in breast, cardiac, lower gastrointestinal, obstetrics, urology or kidney, and maxillofacial or dental surgeries. There was no benefit with liberal prophylaxis among ear, nose and throat, endocrine, gynaecological, head and neck, hepato-pancreatobiliary, neurosurgical or spinal, orthopaedic, plastics and cutaneous, thoracic, trauma or vascular surgeries (figure 2). The largest risk difference reduction was observed in 34 studies of urology & kidney surgery (RD -0.04 [-0.06 to -0.02]; RR 0.53 [0.40 to 0.69]; I^2=71%; p<0.01; PI: -0.1 to 0.05]).

The rate of surgical site infection was lower in trials performed in LMICs (1,598 of 30,225 participants [5.3%]) than HICs (3,528 of 55,921 participants [6.3%]). This is possibly due to under-reporting but

may also relate to differing case-mix. Patients enrolled in trials performed in LMICs had a pooled mean age of 41 years compared to 52 years in HICs. There remained a small treatment benefit for liberal antimicrobial prophylaxis regimens, both in 121 LMIC trials (RD -0.01 [-0.02 to -0.01]; RR 0.70 [0.61 to 0.79]; I^2=44%; p<0.01; PI: -0.05 to 0.02) and in 173 HIC trials (RD -0.02 [-0.02 to -0.01]; RR 0.73 [0.66 to 0.80]; I^2=57%; p<0.01; PI: -0.05 to 0.02) (supplementary figures 5 and 6). There was no reduction in heterogeneity when we included income status in a meta-regression model (table 4). There was a modest treatment effect amongst the sub-group of 161 trials comparing no doses with ≥1 doses (RD -0.02 [-0.03 to -0.02]; RR 0.58 [0.52 to 0.65]; I^2=62%; p<0.01; PI: -0.06 to 0.02), and the sub-group of 92 trials comparing one dose to ≥2 doses (RD -0.01 [-0.01 to 0.00]; RR 0.82 [0.72 to 0.93]; I^2=39%; p<0.01; PI: -0.04 to 0.03), but not in the sub-group of 60 trials comparing ≥2 doses versus ≥3 doses (RD 0.0 [-0.01 to 0.01]; RR 0.99 [0.89 to 1.11]; I^2=13%; p=0.96; PI: -0.02 to 0.02) (table 3). Our findings were unchanged when we repeated the comparison in a pre-specified sensitivity analysis of 42 trials using the CDC definition of surgical site infection (RD -0.02 [-0.03 to -0.01]; RR 0.75 [0.63 to 0.88]; I^2=53%, p<0.01, PI: -0.05 to 0.02). There was no significant change in either the frequency of surgical site infection or antimicrobial prophylaxis treatment effect over time from 1990 to 2020 (supplementary table 4 & supplementary figure 5). Around 16% of the observed heterogeneity was due to variable timing of outcome measurement (Supplementary table 4). The influence of prophylactic antibiotics was greatest in reducing bacteriuria, and 6% of the heterogeneity we identified was due to differences between studies reporting bacteriuria or surgical site infection.

Only 43 of 294 (14.6%) trials reported pre-specified harms associated with antimicrobial prophylaxis. Diarrhoeal illness was reported in 29 trials (9.8%), anaphylaxis in 19 trials (6.4%), acute kidney injury in three trials (1.0%) and hearing loss in only one trial (0.3%). Sensitivities of infecting bacteria were reported in 45 of 294 (15.3%) trials, pneumonia was reported in 49 (16.7%) trials and death in 47 (16.0%). Some 44 (95% CI: 36 to 59) antimicrobial doses were required to prevent one surgical site infection, ranging from 8 doses (95% CI: 5 to 21) in upper gastrointestinal surgery, to 1082 doses (95% CI: 149 to infinity) in thoracic surgery (table 2).

Certainty and quality of evidence

The risk of bias was high or unclear in all domains in 16.3% of trials (48 of 294) and low in all domains in 9% of trials (27 of 294) (supplementary figure 7). Blinding was the domain most frequently at high or unclear risk of bias (178 of 294 trials [60.1%]). Our principal findings were unchanged when restricting the analysis to 214 trials with low risk of bias in two or more domains (RD -0.02 [-0.02 to -0.01]; RR 0.71 [0.65 to 0.77]; I^2 = 56%; p<0.01; PI: -0.05 to 0.02). Visual assessment of funnel plots for the primary analysis indicated possible publication bias with up to 62 unreported clinical trials (figure

3); Eggers test confirmed asymmetry ($p<0.01$). The prediction interval range included zero for all analyses indicating that, when trial heterogeneity was accounted for, the range of possible treatment effects included no effect for all comparisons. The certainty of evidence assessed using the GRADE approach was very low (supplementary table 5).

DISCUSSION

The principal finding of this comprehensive systematic review and meta-analysis is that liberal antimicrobial prophylaxis regimens were associated with a small (approximately 1%) absolute reduction in the risk of surgical site infection in comparison to restrictive regimens. However, this small treatment effect must be interpreted with caution because of important limitations in the quality and certainty of the evidence. Most trials were single-centre with small sample sizes. Only one in ten trials were at low risk of bias in all domains and funnel plots indicate possible publication bias with up to 62 unreported trials. When we accounted for trial heterogeneity using prediction intervals, we found liberal antimicrobial prophylaxis is unlikely to be associated with a true treatment effect in future studies. This finding was consistent across all sub-group analyses. To prevent one infection, 44 doses of antimicrobial prophylaxis must be administered. Antimicrobial harms were reported in only 15% of trials preventing any meaningful comparison of harm and benefit. There have been widespread improvements in infection control for surgical patients since many trials were reported, and the overall benefit of perioperative antimicrobial prophylaxis may now be marginal for many patient groups. Given the global importance of antimicrobial resistance, the clinical effectiveness of antimicrobial prophylaxis should now be re-evaluated.

This is the first comprehensive meta-analysis of liberal versus restrictive antimicrobial prophylaxis that we are aware of. Our finding that there is a modest benefit with liberal regimens aligns with smaller meta-analyses restricted to specific surgical settings.[32–36] Many of these smaller analyses also report concerns regarding the high risk of trial bias, publication bias and overall low certainty of evidence.[17,32,33,36] There are a wide variety of antimicrobial regimens for prophylaxis against surgical site infection, which we explored with pre-specified sub-group analyses. A recent review found there was no benefit from additional postoperative doses of antibiotics compared to a single dose if best practices were followed.[13,14] A recent multi-centre study suggested that antibiotic prophylaxis guidelines were not followed for one in five patients.[37] Our findings contrast with the recent review due to our inclusion of a broader range of surgical procedures and a variety of dosing strategies. We also identified a benefit from antimicrobial prophylaxis when compared to a control group receiving no drugs, however the absolute risk reduction was very small in every analysis. Recent high-quality meta-analyses excluded these treatment comparisons. We found no evidence of a change in infection rates over time, which is consistent with prior analyses.[38] The overall rate of surgical site infection in the reported trials is comparable to the incidence of 5-10% reported in recent international epidemiological studies.[4,7,8,27] We did a meta-regression including the year of the study and found minimal change in the rate of surgical site infection, or the influence of liberal antimicrobial

prophylaxis. While the effectiveness of infection control measures may have improved over time, patient risk factors (e.g. advanced age) may now be more significant resulting in little overall change in reported surgical site infection rates.[27]

We observed a lower incidence of surgical site infection amongst trials performed in LMICs, which contrasts with the GlobalSurg II epidemiological study that described higher incidences of infection in LMICs compared to HICs.[28] This may be due to under-reporting but could also be explained by differing case-mix. Patients enrolled in trials performed in LMICs were on average ten years younger than those in HICs and may have undergone different surgical procedures. Despite undergoing surgery at a younger age, the effectiveness of prophylaxis was similar in both HIC and LMIC settings. This suggests that antimicrobial prophylaxis may have a greater potential benefit amongst patients undergoing surgery in LMICs which may be due to the lack of other infection control measures available. Trials of patients undergoing emergency surgery reported a lower rate of surgical site infection than trials of patients undergoing elective procedures. This may be due to publication bias or reluctance of investigators to enrol emergency patients considered very likely to develop surgical site infection in trials. Only one in ten trials had a low risk of bias in all domains. Many used non-standardised outcome measures and enrolled small numbers of patients.

Antimicrobial drugs have side effects, which have both direct impact on patients and indirect impact on society through antimicrobial resistance. Despite the worldwide use of antimicrobial prophylaxis for surgery, the incidence of side effects is unclear and poorly reported in existing guidelines.[20] A conservative estimate from observational studies suggests one in every 100 patients experiences significant antimicrobial side-effects, including diarrhoea, acute kidney injury and hearing loss.[40] Perhaps the most serious side-effect of antimicrobial drugs is anaphylaxis, a life-threatening drug reaction that occurs as often as once in 350 surgical procedures.[36] While diarrhoea and acute kidney injury may occur in up to one in three patients.[40] Serious diarrhoeal illness caused by infection with *clostridium difficile* is strongly related to the use of antimicrobial prophylaxis.[41] However, in the absence of reliable data reporting the incidence of these side-effects, it is not possible to balance the risks of antimicrobial prophylaxis with the marginal benefit in preventing surgical site infection. Poor data on side effects of antimicrobial prophylaxis, in conjunction with variable adherence to clinical practice guidelines, may contribute to persisting liberal use of antimicrobials for surgery.[37] Further research is urgently needed to re-evaluate both the risks and benefits of antimicrobial prophylaxis in contemporary perioperative practice, which will support anaesthetists in guaranteeing safe and effective perioperative care.

Our analysis has a number of strengths. We undertook a comprehensive search including a hand search of included trials and prior systematic review citations. Our protocol was pre-specified and pre-registered, with analyses to explore treatment effects in important sub-groups. Article selection and data extraction were performed in duplicate with detailed review of any discrepancies by a senior author. Risk differences are presented in line with Cochrane guidance to ease interpretation and we present findings divided by analysis and by surgical specialty for clarity.[42] There are also limitations. There was substantial variation in reported outcomes, including the definition and timing of infection, with some trials reporting infections up to one year following surgery. However, in our post-hoc meta-regression of studies reporting infection timing, a moderate amount of the observed heterogeneity was explained by the timing of outcome measurement. This finding enforces the importance of consistent outcome reporting in trials. Only 42 trials used the standard CDC criteria for surgical site infection, and the severity of infection was infrequently reported. There was a variable baseline infection rate between trials, even within the same surgical groupings. We report greater heterogeneity than other recent systematic reviews, possibly due to the use of risk difference as a summary effect measure and our inclusion of a broader range of surgical procedures.[13,33]

Conclusions

In this systematic review and meta-analysis we found that patients receiving liberal antimicrobial prophylaxis regimens may experience a 1% absolute risk reduction for surgical site infection. However, this small apparent benefit is sensitive to the low quality and certainty of the published evidence. Given the widespread advances in perioperative infection control over the past 20 years, it is entirely possible that antimicrobial prophylaxis no longer offers incremental value over other infection control measures in routine use. However, it is important to note that the potential benefit of antimicrobial prophylaxis in LMICs may be greater than in settings where comprehensive infection control measures are routinely available. Meanwhile, antimicrobial drug use may cause direct harm to individual patients and promote global antimicrobial resistance.[7] In light of these findings, the clinical effectiveness of antimicrobial prophylaxis during and after surgery should be re-evaluated.

Competing interests: All authors have completed the unified competing interest form which is available on request from the corresponding author. Dr Fowler reports grants from National Institutes of Health Research (NIHR) and Barts Charity, outside the submitted work. Ms Hui, Drs Das, Cashmore, Lalloo, Ahmad and Wan have nothing to disclose. Dr Gillies reports grants from NIHR and the Chief Scientific Officer (Scotland), outside the submitted work. Prof Pearse is a member of the editorial board of the British Journal of Anaesthesia, and reports grants and personal fees from NIHR, Edwards Life Sciences, Intersurgical and GlaxoSmithkline outside the submitted work. Dr Abbott reports he an editor of the British Journal of Anaesthesia, has received research grants from the National Institute for Health Research, the National Institute for Academic Anaesthesia and Barts Charity, and has received consultancy fees from MSD, outside the submitted work.

Contributors:
Protocol development: AJF, PD, MAG, RMP, TEFA
Electronic searches: AJF, PD
Selection and data extraction: AJF, PD, SH, RC, RL, ANA, YIW, TEFA
Data analysis: AJF, TEFA
Drafting manuscript, guarantors: AJF, RMP, TEFA
Approval of final version: All authors

Transparency declaration: We declare that this manuscript is an honest, accurate and transparent account of the study we conducted. No important aspects have been omitted, and discrepancies from the originally planned protocol have been accounted for.

Funding/Sponsorship: No funding was received, there was no organisational study sponsorship.

Ethical approval: Not applicable (systematic review)

Acknowledgements: We thank authors of trials who provided additional information and full texts of the articles where we were unable to locate these.

Data sharing: All data used for this study is freely available on request, study level data is available in the supplementary files. We plan to disseminate these findings to relevant professional organisations involved in the care of surgical patients.

REFERENCES

1 Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA, Crosby C. Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries. *J Hosp Infect* 2017; **96**: 1–15.

2 Wan YI, Patel A, Abbott TEF, *et al.* Prospective observational study of postoperative infection and outcomes after noncardiac surgery: analysis of prospective data from the VISION cohort. *Br J Anaesth* 2020; **125**: 87–97.

3 International Surgical Outcomes Study Group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016; **117**: 601–9.

4 Wan Y, Patel A, Achary C, Hewson R, Phull M, Pearse R. Prospective observational cohort study of post-operative infection and mortality following elective surgery: International Surgical Outcomes Study (ISOS) sub-study. *Br J Surg* 2020; **Accepted 1**: Forthcoming.

5 Chief Medical Officer. Antimicrobial Resistance. London, 2011.

6 de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? *PLoS Med* 2016; **13**: e1002184.

7 Internatinal coordination group on antimicrobial resistance. No time to wait: securing the future from drug-resistant infections. 2019.

8 Chatterjee A, Modarai M, Naylor NR, *et al.* Quantifying drivers of antibiotic resistance in humans: a systematic review. *Lancet Infect Dis* 2018; **18**: e368–78.

9 Holmes AH, Moore LSP, Sundsfjord A, *et al.* Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet (London, England)* 2016; **387**: 176–87.

10 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal* 2018; **6**: e619–29.

11 Weiser TG, Haynes AB, Molina G, *et al.* Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet (London, England)* 2015; **385 Suppl**: S11.

12 Caroff DA, Chan C, Kleinman K, *et al.* Association of Open Approach vs Laparoscopic Approach With Risk of Surgical Site Infection After Colon Surgery. *JAMA Netw open* 2019; **2**: e1913570.

13 World Health Organisation. Global guidelines for the prevention of surgical site infection. Geneva, Switzerland, 2016.

14 Gachabayov M, Senagore AJ, Abbas SK, Yelika SB, You K, Bergamaschi R. Perioperative hyperglycemia: an unmet need within a surgical site infection bundle. *Tech Coloproctol* 2018; **22**: 201–7.

15 National Institutes for Health and Care Excellence. NICE Guideline [NG125] Surgical site infections: prevention and treatment. 2019.

16 de Jonge SW, Boldingh QJJ, Solomkin JS, *et al.* Effect of postoperative continuation of antibiotic prophylaxis on the incidence of surgical site infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2020; **20**: 1182–92.

17 de Jonge S, Gans S, Atema J, Solomkin J, Dellinger P, Boermeester M. Timing of preoperative antibiotic prophylaxis in 54,552 patients and the risk of surgical site infection. *Med (United States)* 2017; **96**: e6903.

18 Allegranzi B, Zayed B, Bischoff P, *et al.* New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016; **16**: e288–303.

19 Ansari F, Erntell M, Goossens H, Davey P. The European surveillance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. *Clin Infect Dis an Off Publ Infect Dis Soc Am* 2009; **49**: 1496–504.

20 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Heal Pharm AJHP Off J Am Soc Heal Pharm* 2013; **70**: 195–283.

21 Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv drug Saf* 2014; **5**: 229–41.

22 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.

23 Abbott TEF, Fowler AJ, Dobbs TD, Harrison EM, Gillies MA, Pearse RM. Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics. *Br J Anaesth* 2017; **119**: 249–57.

24 Higgins JPT, Altman DG, Gøtzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.

25 World Bank. World Bank Country And Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

26 Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011; **342**: d549.

27 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999; **27**: 97–132; quiz 133–4; discussion 96.

28 Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: the dosresmeta R package. *J*

Stat Softw 2016; **72**: 1–15.

29 Viechtbauer W. Conducting meta-analyses in {R} with the {metafor} package. *J Stat Softw* 2010; **36**: 1–48.

30 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with {R}: a practical tutorial. *Evid Based Ment Health* 2019.

31 McGuinness LA, Higgins JPT. robvis: An R package and web application for visualising risk-of-bias assessments. *Res Synth Methods* 2020; : 1–7.

32 Siddiqi A, Forte SA, Docter S, Bryant D, Sheth NP, Chen AF. Perioperative Antibiotic Prophylaxis in Total Joint Arthroplasty: A Systematic Review and Meta-Analysis. *J Bone Joint Surg Am* 2019; **101**: 828–42.

33 Pinto-Lopes R, Sousa-Pinto B, Azevedo LF. Single dose versus multiple dose of antibiotic prophylaxis in caesarean section: a systematic review and meta-analysis. *BJOG* 2017; **124**: 595–605.

34 Zhang Y, Dong J, Qiao Y, *et al.* Efficacy and safety profile of antibiotic prophylaxis usage in clean and clean-contaminated plastic and reconstructive surgery: a meta-analysis of randomized controlled trials. *Ann Plast Surg* 2014; **72**: 121–30.

35 Liang B, Dai M, Zou Z. Safety and efficacy of antibiotic prophylaxis in patients undergoing elective laparoscopic cholecystectomy: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016; **31**: 921–8.

36 Mertz D, Johnstone J, Loeb M. Does duration of perioperative antibiotic prophylaxis matter in cardiac surgery? A systematic review and meta-analysis. *Ann Surg* 2011; **254**: 48–54.

37 Dias P, Patel A, Rook W, Edwards MR, Pearse RM, Abbott TEF. Contemporary use of antimicrobial prophylaxis for surgical patients: An observational cohort study. *Eur J Anaesthesiol* 2021; published online Nov. DOI:10.1097/EJA.0000000000001619.

38 Gandra S, Trett A, Alvarez-Uria G, Solomkin JS, Laxminarayan R. Is the efficacy of antibiotic prophylaxis for surgical procedures decreasing? Systematic review and meta-analysis of randomized control trials. *Infect Control Hosp Epidemiol* 2019; **40**: 133–41.

39 Bhangu A, Ademuyiwa A, Aguilera M, *et al.* Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. *Lancet Infect Dis* 2018; **18**: 516–25.

40 Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of Duration and Type of Surgical Prophylaxis With Antimicrobial-Associated Adverse Events. *JAMA Surg* 2019; **154**: 590–8.

41 Southern WN, Rahmani R, Aroniadis O, *et al.* Postoperative Clostridium difficile-associated diarrhea. *Surgery* 2010; **148**: 24–30.

42 Higgins JPT, Thomas J, Chandler J, *et al.* Cochrane Handbook for Systematic Reviews of Interventions, Versin 6.0. Cochrane, 2019.

Tables

Surgical setting	n	Patients	Rate of surgical infection		Number of LMIC trials
			Intervention	Control	
Mixed	10	7078	126 of 3553 (3.5%)	130 of 3525 (3.7%)	7 (70%)
Neurosurgical & spinal	7	3072	74 of 1516 (4.9%)	98 of 1556 (6.3%)	2 (29%)
Thoracic	4	713	8 of 360 (2.2%)	9 of 353 (2.5%)	1 (25%)
Cardiac	10	7041	141 of 3551 (4.0%)	224 of 3490 (6.4%)	3 (30%)
Orthopaedic	14	6286	151 of 3150 (4.8%)	144 of 3136 (4.6%)	4 (29%)
Urology & kidney	34	8835	291 of 5055 (5.8%)	369 of 3780 (9.8%)	18 (53%)
Obstetric	22	5797	136 of 2950 (4.6%)	212 of 2847 (7.4%)	14 (64%)
Gynaecological	19	8128	148 of 4042 (3.7%)	190 of 4086 (4.7%)	6 (32%)
Lower gastrointestinal	36	9067	315 of 4669 (6.7%)	388 of 4398 (8.8%)	15 (42%)
Breast	9	2647	118 of 1318 (9.0%)	169 of 1329 (12.7%)	3 (33%)
Hepato-pancreatobiliary	28	7090	136 of 3710 (3.7%)	137 of 3380 (4.1%)	16 (57.1%)
Maxillofacial & dental	53	6581	148 of 3332 (4.4%)	255 of 3249 (7.8%)	23 (43%)
Trauma	5	1135	84 of 570 (14.7%)	81 of 565 (14.3%)	1 (20%)
Plastics & cutaneous	11	4088	99 of 2032 (4.9%)	144 of 2056 (7.0%)	2 (18%)
Upper gastrointestinal	13	2660	144 of 1335 (10.8%)	165 of 1325 (12.5%)	0 (0%)
Head and neck	6	531	18 of 272 (6.6%)	30 of 259 (11.6%)	1 (17%)
Vascular	4	1580	70 of 784 (8.9%)	100 of 796 (12.6%)	0 (0%)
Ear, nose & throat	8	1653	29 of 832 (3.5%)	41 of 821 (5.0%)	5 (63%)
Endocrine	1	2164	1 of 1082 (0.1%)	3 of 1082 (0.3%)	0 (0%)
Overall	**294**	**86146**	**2237 of 44113 (5.1%)**	**2889 of 42033 (6.9%)**	**121 (41.2%)**

Table 1. Characteristics of included trials grouped by surgical setting. Data are presented as number (%). We present the number of trials conducted in low and middle-income country (LMIC) settings.

Specialty	Median number of doses in ≥1 dose arms	Risk difference		Number of doses needed to prevent one infection	
		Average	95% CI	Average	95% CI
Mixed	1 (1 to 1)	-0.03	-0.05 to -0.01	34	19 to 163
Neurosurgical & spinal	1 (1 to 1)	-0.02	-0.03 to 0	65	34 to 718
Thoracic	4 (2 to 5)	0	-0.03 to 0.02	1082	149 to ∞
Cardiac	2 (2 to 3)	-0.03	-0.05 to -0.01	66	43 to 137
Orthopaedic	1 (1 to 1)	0	-0.04 to 0.03	219	25 to ∞
Urology & kidney	1 (1 to 1)	-0.07	-0.1 to -0.04	14	11 to 24
Obstetric	1 (1 to 1.5)	-0.03	-0.06 to -0.01	30	18 to 84
Gynaecological	1 (1 to 2)	-0.01	-0.01 to 0	149	77 to 2029
Lower gastrointestinal	1 (1 to 1)	-0.03	-0.04 to -0.01	37	24 to 93
Breast	1 (1 to 1)	-0.04	-0.06 to -0.01	26	16 to 70
Hepato-pancreatobiliary	1 (1 to 2)	-0.01	-0.01 to 0	165	76 to ∞
Maxillofacial & dental	9 (1 to 11)	-0.03	-0.05 to -0.01	322	194 to 718
Plastics & cutaneous	4 (1 to 9)	-0.03	-0.06 to 0	124	64 to 2360
Upper gastrointestinal	1 (1 to 1)	-0.13	-0.22 to -0.05	8	5 to 21
Head and neck	1 (1 to 1)	-0.12	-0.3 to 0.07	9	4 to ∞
Vascular	1 (1 to 1)	-0.08	-0.15 to -0.02	12	7 to 57
Ear, nose & throat	3 (2 to 7)	-0.04	-0.09 to 0	74	36 to ∞
Endocrine	1 (1 to 1)	0	-0.01 to 0	541	183 to ∞
Overall	1 (1 to 3)	-0.02	-0.03 to -0.02	44	36 to 59

Table 2. Number of antimicrobial doses needed to prevent one surgical site infection across surgical specialties. Calculations made using data from the no dose vs. ≥1 dose comparison. Data are presented as median (IQR), risk difference (RD) with 95% confidence intervals (CI). Where the 95% CI of the risk difference spans zero, the 95% CI of the doses needed to prevent one infection crosses from a number needed to benefit to a number needed to harm in two disjointed regions via infinity (∞). Presence of infinity indicates the number needed to harm is ≥1. Trauma trials were excluded as none reported strategies comparing no doses to ≥1 dose.

	Primary analysis	Dosing subgroup analyses		
Specialty	**Restrictive vs Liberal**	**0 vs ≥1 dose**	**1 vs ≥2 doses**	**≥2 vs ≥3 doses**
Mixed	0 [-0.01 to 0.01]	-0.03 [-0.05 to -0.01]	0 [0 to 0.01]	-0.02 [-0.06 to 0.02]
Neurosurgical & spinal	-0.01 [-0.02 to 0]	-0.02 [-0.03 to 0]	-0.03 [-0.07 to 0.02]	0 [-0.02 to 0.03]
Thoracic	0 [-0.02 to 0.02]	0 [-0.03 to 0.02]	0.01 [-0.04 to 0.06]	0 [-0.03 to 0.03]
Cardiac	-0.02 [-0.03 to -0.01]	-0.03 [-0.05 to -0.01]	-0.02 [-0.04 to 0]	0 [-0.01 to 0.01]
Orthopaedic	-0.01 [-0.02 to 0.01]	0 [-0.04 to 0.03]	-0.03 [-0.09 to 0.03]	0 [-0.02 to 0.01]
Urology & kidney	-0.04 [-0.06 to -0.02]	-0.07 [-0.1 to -0.04]	-0.01 [-0.03 to 0.02]	-0.04 [-0.1 to 0.01]
Obstetric	-0.02 [-0.03 to -0.01]	-0.03 [-0.06 to -0.01]	-0.01 [-0.03 to 0.01]	0.02 [-0.04 to 0.08]
Gynaecological	0 [-0.01 to 0]	-0.01 [-0.01 to 0]	0 [-0.04 to 0.04]	0 [-0.01 to 0.01]
Lower gastrointestinal	-0.02 [-0.03 to -0.01]	-0.03 [-0.04 to -0.01]	-0.01 [-0.04 to 0.01]	-0.01 [-0.04 to 0.03]
Breast	-0.04 [-0.06 to -0.01]	-0.04 [-0.06 to -0.01]	NA	0.03 [-0.12 to 0.18]
Hepato-pancreatobiliary	-0.01 [-0.01 to 0]	-0.01 [-0.01 to 0]	0.02 [-0.02 to 0.06]	0.03 [-0.03 to 0.09]
Trauma	0 [-0.06 to 0.06]	NA	NA	0 [-0.06 to 0.06]
Maxillofacial & dental	-0.02 [-0.04 to -0.01]	-0.03 [-0.05 to -0.01]	-0.01 [-0.02 to 0]	-0.01 [-0.03 to 0.02]
Plastics & cutaneous	-0.02 [-0.05 to 0.01]	-0.03 [-0.06 to 0]	0.01 [-0.07 to 0.08]	NA
Upper gastrointestinal	-0.03 [-0.07 to 0.01]	-0.13 [-0.22 to -0.05]	0 [-0.04 to 0.05]	0.02 [-0.02 to 0.05]
Head & neck	-0.02 [-0.07 to 0.02]	-0.12 [-0.3 to 0.07]	-0.16 [-0.3 to -0.02]	0 [-0.03 to 0.03]
Vascular	-0.03 [-0.08 to 0.02]	-0.08 [-0.15 to -0.02]	-0.03 [-0.12 to 0.07]	0 [-0.05 to 0.05]
Ear, nose & throat	-0.01 [-0.03 to 0.01]	-0.04 [-0.09 to 0]	0.01 [-0.01 to 0.02]	0.03 [-0.03 to 0.09]
Endocrine	0 [-0.01 to 0]	0 [-0.01 to 0]	NA	NA

Table 3. Risk difference and associated 95% confidence intervals of the primary analysis and three dosing subgroup comparisons, divided by surgical specialty. Data are presented as Risk Difference [95% Confidence Interval]. NA; not applicable as no studies included this comparison for the given surgical specialty.

Figure legends

Figure 1. Article selection flow diagram (PRISMA) diagram.

Figure 2. Forest plot of the effect of liberal versus restrictive antimicrobial prophylaxis on subsequent development of surgical infection, presented by surgical specialty grouping. A random effects model was used to derive the risk difference, which is presented with associated 95% confidence interval.

Figure 3. Funnel plot for the primary comparison of liberal versus restrictive antimicrobial prophylaxis indicating up to 62 unreported trials (red dots). Eggers test confirmed substantial asymetry in the plot ($t = -8.0$, $df=297$, $p<0.01$).