Contemporary use of antimicrobial prophylaxis for surgical patients: an observational cohort study

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Abstract

Background: Antimicrobial prophylaxis is commonly used to prevent surgical site infection (SSI), despite concerns of overuse leading to antimicrobial resistance. However, it is unclear how often antimicrobials are used and whether guidelines are followed.

Objectives: To describe contemporary clinical practice for antimicrobial prophylaxis including guideline compliance, the rate of postoperative infection and associated side effects.

Design: Prospective multi-centre observational cohort study.

Setting: 12 United Kingdom National Health Service hospitals.

Participants: 1116 patients, aged ≥18 years undergoing specific colorectal, obstetric, gynaecological, urological or orthopaedic surgical procedures.

Exposure: Compliance with guidelines for antimicrobial prophylaxis.

Outcomes: The primary outcome was SSI within 30 days after surgery. Secondary outcomes were number of doses of antimicrobials for prophylaxis and to treat infection, incidence of antimicrobial-related side effects and mortality within 30-days after surgery. Data are presented as number with percentage (%) or median with interquartile range (IQR). Results of logistic regression analyses are presented as odds/rate ratios (OR/RR) with 95% confidence intervals (CI).

Results: 1102/1106 (99.6%) patients received antimicrobial prophylaxis, which was compliant with local guidelines in 929/1102 (84.3%) cases. 2169/5128 (42.3%) doses of antimicrobials were administered as prophylaxis (median 1 (1-2) doses) and 2959/5128 (57.7%) were administered to treat an infection (median 21 (11-28) doses). 56 patients (5.2%) developed surgical site infection. Antimicrobial prophylaxis administered according to local guidelines was not associated with a lower incidence of SSI compared with administration outside guidelines (OR 0.90 (0.35-2.29); *P*=0.823). 23/1072 (2.2%) patients experienced a side effect of antimicrobial therapy. 7/1082 (0.6%) patients died. The median hospital stay was 3 (1-5) days.

Conclusions: Antimicrobial prophylaxis was administered for almost all the surgical procedures under investigation. However, this was not always compliant with guidelines. Further research is required to determine whether the amount of prophylactic antimicrobials could be safely and effectively reduced without increasing the incidence of SSI.

Key points

1. Antimicrobial prophylaxis remains a common practice in preventing surgical site infections globally.
2. Antimicrobial use is the key driver of antimicrobial resistance increasing risk of untreatable infections.
3. In UK hospitals, perioperative antimicrobials were administered in majority of the surgical procedures under investigation.
4. No association was found between the use of guidelines and incidence of surgical site infection in the group of surgical procedures surgeries being studied.
5. Further work is urgently needed to ensure antimicrobial drugs are used in more efficient ways.

Introduction

Surgical site infections (SSI) are one of the most common postoperative complications affecting one in ten patients undergoing surgery.[1 2] SSIs are often a surrogate marker for illness following surgery with patients experiencing a range of poor health outcomes including pain, reduced quality of life, increased morbidity and a higher risk of mortality.[1-3] The healthcare costs associated with SSIs are substantial and can be attributed to longer lengths of hospital stay, additional treatments or procedures and more frequent hospital re-admissions.[4 5] In the context of an increasingly large surgical population,[6] the surveillance and prevention of SSI is an important component of good surgical care.

Antimicrobial prophylaxis, often administered by anaesthesiologists, has been a central component of strategies to minimise postoperative infections for over fifty years.[7 8] However, this is only one component of a multimodal care bundle which incorporates pre-operative showers, skin preparation, specialised operating theatre clothing for patients and staff, and carefully controlled environmental and air flow systems.[9 10] Despite this, there remains a perceived over reliance on antimicrobial drugs as a method for preventing SSI.[11 12] However, continued use of antimicrobial drugs increases the risk of antimicrobial resistance, which in turn reduces their effectiveness at preventing and treating SSI.[3 13-15] Current guidelines recommend a single pre-operative dose with a possible intraoperative dose depending on the duration of surgery.[9 10 16 17] However, there are frequent anecdotal reports of prophylaxis prolonged by several days after surgery without evidence of benefit in reducing the risk of SSI.[3 11 12 18 19] The use of antimicrobial drugs is not risk free. Adverse effects of antimicrobials include life-threatening allergic reactions, *C*. difficile colitis, acute kidney injury and diarrhoeal illness [20-22] while growing antimicrobial resistance threatens increased risk of untreatable infections.[13] Strategies to safely limit the use of antimicrobials is essential to ensure surgery remains a safe treatment in the future.[13 14 23]

Here we investigate the degree of compliance with guidelines for the administration of perioperative antimicrobial drugs and report the rates of SSI and side effects of antimicrobial drugs in 12 UK hospitals.

Methods

Reporting is consistent with the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) statement for observational studies.[24] The analysis was undertaken according to a pre-specified statistical analysis plan (https://www.qmul.ac.uk/ccpmg/sops--saps/statistical-analysis-plans-saps/).

Study design and setting

Multi-centre observational cohort study in 12 National Health Service (NHS) hospitals between the 1st September 2018 and 31st January 2019. We collected only anonymised data that was provided as part of routine clinical care, with no changes to patient care pathways.

Ethics

The study was conducted as a service evaluation or clinical audit, which was formally registered at each participating hospital. Informed consent from included patients was not required as no patient identifiable data were collected, which is consistent with current practice in the United Kingdom. We used only anonymised data provided as part of routine clinical care. At the lead hospital (The Royal London Hospital) of the study was registered as a service evaluation (9554: Antimicrobial prophylaxis for surgical patients).

Participants

We included adult patients aged ≥18 years undergoing any of the following surgical procedures: colorectal resection, elective caesarean section, hysterectomy, hip replacement, knee replacement, transurethral resection of prostate or bladder tumour, or open reduction of closed long bone fracture. This included open, robotic, laparoscopic, laparoscopically assisted and laparoscopic procedures.

Exposure of interest

The exposure of interest was compliance with local guidelines for antimicrobial prophylaxis. We also considered best practice recommendations for timing of antimicrobials, which include the first dose before the induction of anaesthesia and /or within the 60 minutes before surgical incision.

Outcome measures

The primary outcome was SSI (superficial, deep or body cavity) within 30 days after surgery.[25] SSI was categorised as mild (temporary harm without new medical treatment), moderate (requiring new medical treatment) or severe (significantly prolonged hospital stay and/or permanent functional limitation or death). Secondary outcomes within 30 days after surgery were: number of doses of antimicrobial given as prophylaxis, number of dose of antimicrobial given as treatment of infection, incidence of any infections, potential side effects of antimicrobials (anaphylaxis, acute kidney injury, angioedema, diarrhoeal illness or patient reported hearing loss) and mortality. Process outcome were admission to critical care to treat a complication and duration of hospital stay.

Data collection

We reviewed medical records documented as part of routine clinical care before, during and up to 30 days after surgery. We collected a standardised data set including demographic variables, past medical history and surgery-related factors. We considered administration of prophylactic antimicrobials (to prevent infection) separately to the administration of antimicrobials to treat infection. The follow-up period was within 30 days after surgery for all outcome variables. All patients with complete outcome measure data were included in the final analysis.

Sample size

Before starting this study, the incidence of antimicrobial prophylaxis across this range of procedures and hospitals was unclear. Therefore we were unable to undertake a formal sample size calculation before starting the study. Instead, we took a pragmatic approach based on the feasibility of inclusion at

individual centres. We aimed to include data for 1100 patients, which would give 80% power to detect a 50% reduction in the incidence of SSI comparing compliance with guidelines (5%) and without guidelines, assuming a 1:1 allocation ratio, and with a type one error rate of 5%.

Statistical methods

We used STATA version 14 (STATACorp LP, Texas, USA) to analyse the data. Baseline demographic and clinical data were summarised but not subjected to statistical testing. The primary analysis used a logistic regression model, adjusted for pre-specified baseline variables. We used the "10-percent-rule" and the "change-in-estimate" (CIE) approach to decide whether to include potential confounders in the causal model. We adjusted for duration of surgery as this was found to be associated with the outcome. Secondary analyses were performed using a mixed effects logistic regression model or mixed effects negative binomial regression model with a random intercept for site. We adjusted for duration of surgery for all models except for the analysis for the total number of antimicrobial prophylaxis doses which was also adjusted for surgical procedure. All p-values were two-sided with a significance level of 5%. For each outcome summary statistics (e.g. mean (SD), number (%) were presented for each category of the exposure. Effect estimates are reported as adjusted odds ratios (95% CI) or adjusted incidence rate ratios (95% CI).

Results

We included 1116 patients in the final analysis (Figure 1). The median (IQR) age was 56 (35-71) years and 775 (69.4%) patients were female. Elective caesarean section was the most common operation (345 [31%]). Baseline characteristics are presented in table 1.

Antimicrobial administration

The median number of doses of prophylactic antimicrobials was 1 (1-2) and the median number of doses given to treat an infection was 21 (11-28) for a median duration of 7 (5-10) days. The frequency of the total number of doses administered as antimicrobial prophylaxis is presented in figure 2. The commonest prophylactic antimicrobials were gentamicin (37.0%) and cefuroxime (36.5%), and the commonest therapeutic antimicrobial was co-amoxiclav (53.2%) (Table 2).

Postoperative infections

The frequency of postoperative infections is reported in table 3. Surgical site infection (SSI), including superficial SSI, deep SSI and body cavity infection, occurred in 56 (5.2%) patients within 30 days of their surgery.

Compliance with local guidelines

1102 patients received antimicrobial prophylaxis, which was consistent with local guidelines in 929 (84.3%) cases (Table 4). Antimicrobial prophylaxis administered according to local guidelines was not associated with a lower incidence of SSI (OR 0.90 [0.35-2.29]; *P*=0.823) (Table 5). Compliance with local guidelines was associated with a lower rate of prophylactic doses administered to those who complied versus those who did not (IRR: 0.84 (0.71, 0.98)) (Supplementary table 1). Compliance with local guidelines was not associated with a reduction in the number of doses used to treat infection, *P*=0.082 (Supplementary table 2).

Best practice guidance

Best practice was defined as having adhered to prophylaxis administered based on local guidelines, first dose of antibiotics administered before induction of anaesthesia and first dose administered within the 60 minutes before surgical incision (Supplementary table 3). Compliance with best practice guidance was not associated with a reduction in SSI (OR 0.56 [0.21-1.51]; *P=0*.251).

Side effects of antimicrobials

41 events among 23 patients were definitely or suspected to be side effects of antimicrobials (Supplementary table 4 and 5). The most common side effect was acute kidney injury (0.8%). There were four (0.4%) potential allergic reactions.

Process outcomes

The median (IQR) duration of the hospital stay after surgery was 3 (1-5) days. Five (0.5%) patients required repeat surgery to treat their SSI and 10 (0.9%) patients needed critical care stay to treat the complication of which three required reoperation. Seven (0.6%) patients died within 30 days of surgery (Supplementary table 6).

The overall effect of compliance with guidelines was borderline statistically associated with the incidence of postoperative infection (*P*=0.050). Those compliant to guidelines versus those who did not the OR (95% CI) was 2.01 [0.92-4.38] (Supplementary table 7).

Discussion

The principal finding of this study was the use of guidelines was not associated with a difference in the incidence of surgical site infection in 12 UK hospitals. However, this may be explained by unmeasured confounding or, if a difference does exist, it may be too small to detect with our current sample size. Around one in 20 surgical patients experienced a surgical site infection and one in five received antimicrobial prophylaxis that was inconsistent with local guidelines. In the context of antimicrobial stewardship strategies to reduce the use antimicrobial drugs, we found that, on average, fewer doses were administered in cases where guidelines were followed. However, there was no difference in the volume of antimicrobials used to treat postoperative infections.

Our findings add to the body of existing evidence in this area and draw together data from several surgical specialties.[1-3 26] In analysis of forty thousand surgical patients, Wan and colleagues reported that 3.8% of surgical patients developed a surgical site infection and around 10% developed an infection after surgery.[1] In this cohort, patients with postoperative infection had a three-fold increase in the risk of mortality within 30 days after surgery. The International Surgical Outcomes Study of over forty thousand surgical patients reported that 2.8% of patients experienced a surgical site infection,[2] while the global surgery study of twelve thousand patients reported that 9.8% of patients from high-income countries developed a surgical site infection after abdominal surgery.[3] Evidence from systematic reviews suggests that compliance with best practice guidance on the use of antimicrobial drugs is associated with reduced rates of infection.[11 12 27] However, we did not observe this finding. Emerging data from a very large systematic review suggests that the benefit of prophylactic antimicrobials is very small (<1% absolute risk difference) and it may be outweighed by the risk of side effects of antimicrobial drugs. This is supported by our data, which shows the incidence of confirmed or probable antimicrobial-related side effects is about 2%. It is possible that there may not be any benefit of antimicrobial drugs for some surgical procedures. However, further clinical effectiveness trials are required to confirm this hypothesis.

This study had several strengths. This was a prospective observational study in twelve hospitals nationwide. The results reflect a cross-section of UK perioperative practice and it is reasonable to generalise these findings to other centres. We collected data on potentially confounding variables and conducted adjusted analyses where indicated. We had a high rate of data completeness and a large sample size. There were also several limitations. First, we only collected data on eligible patients, so we are unable to provide data about the proportion of patients undergoing surgery that our sample represents. Given the high incidence of antimicrobial prophylaxis, we are cautious to consider a selection bias – that more patients receiving prophylaxis were included compared to patient that did not receive prophylaxis. However, our results seem consistent with our clinical experience and the risk of this bias seems low. The rates of patients being treated for postoperative infection are consistent with previously published data. Second, our follow-up period was limited to 30 days after surgery, so the outcomes of patients after this time is unknown. Third, given the very small effect size of prophylactic antimicrobials on the prevention of surgical site infection reported in emerging systematic reviews, our pragmatic sample size may not be large enough to detect a between group difference. This may be compounded by the unequal allocation ratio of patient that received prophylaxis compared to those that did not. Therefore, our study may be underpowered to detect a small between-group difference in the incidence of surgical site infection. Conversely, our observation of no association between antimicrobial prophylaxis and surgical site infection may be true, and may be further data to question the real-world efficacy of antimicrobial drugs for surgical prophylaxis. Fourth, we restricted our sample to a core group of surgical procedures that represent a wide spectrum of contemporary surgery. The rationale for including these procedures was to ensure the results provided a wide spectrum of NHS surgical activity. However, this may limit the external validity of our results in unrepresented surgical specialties. Finally, our study focused on the incidence of antimicrobial prophylaxis and compliance with guidelines for the provision of prophylaxis, rather than the composition of guidelines and/or differences between institutions. In order to fully understand the relationship between antimicrobial prophylaxis, the heterogeneity of guidelines for the provision of prophylaxis should be investigated further, perhaps using a mixed methods approach.

Conclusions

The results of this study demonstrate that perioperative antimicrobial drugs are commonly used in a generalisable sample of surgical patients. When these are administered in accordance with guidelines, the number of doses of antimicrobial drugs is lower. However, guidelines are not followed one out of five times. In this study we did not identify an association between the number of doses of antimicrobial drugs and lower incidence of surgical site infection. This is consistent with systematic reviews that demonstrate only a very small benefit of prophylactic antimicrobials, which may be outweighed by the risk of drug-related side effects.[28] Further research is needed to fully characterise the side effects prophylactic antimicrobial drugs and whether these outweigh the potential benefits of preventing infections after surgery.

Contributors

PD, TA and RP were responsible for study design. PD, WR, ME and TA were responsible for data collection. AP were responsible for data analysis. PD, AP and TA were responsible for data interpretation. PD and TA wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content and approved the final version. AP had full access to the data and act as guarantor. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Transparency declaration

TA affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing

The authors will consider requests for data sharing from bona fide researchers on a case by case basis.

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4. Presentation: None declared.

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1. **Tables and figures**

Figure 1 – CONSORT Diagram

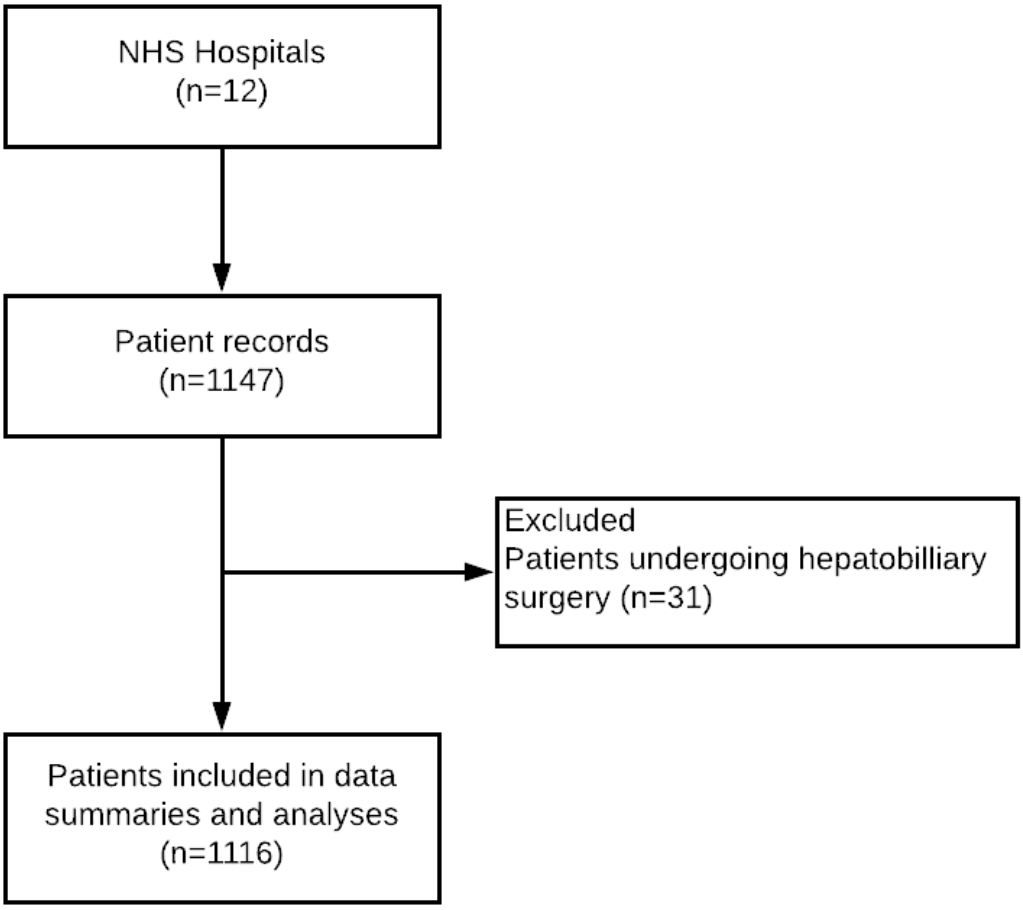
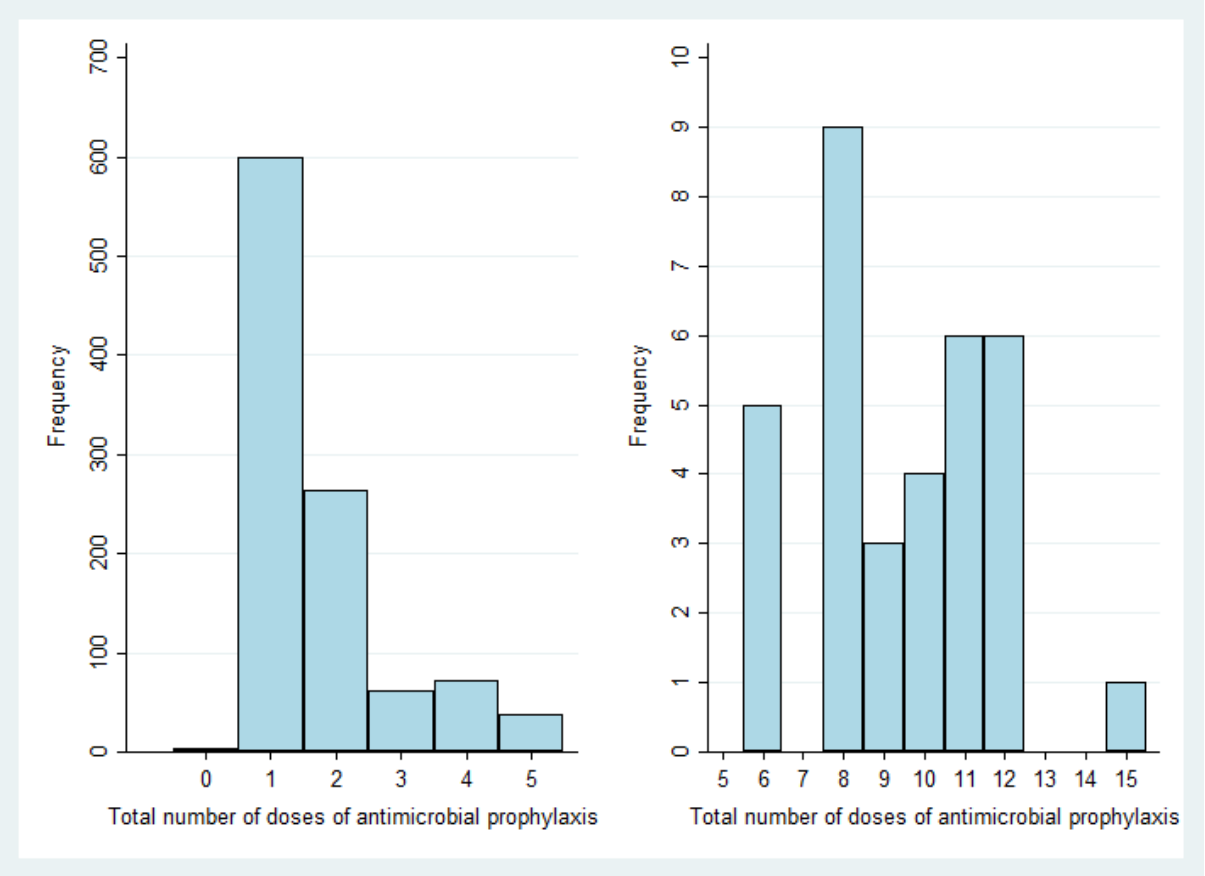


Figure 2: Histogram of total dose of antimicrobial prophylaxis



Note: This is based on antimicrobial prophylaxis administered at the start and/or during and/or after surgery

Table 1 – Baseline characteristics

Baseline Characteristics	Summary measure (*n*=1116)
Gender - no. (%)	
Male	341 (30.6)
Female	775 (69.4)
Age (years)	
Mean (SD)	54.3 (20.0)
Median (IQR)	56 (35-71)
American Society of Anaesthesiology Grade – no. (%)	
I	235 (21.1)
II	657 (59.1)
III	203 (18.3)
IV	17 (1.5)
Documented drug allergies - no. (%)	218 (19.5)
Risk factors - no. (%)	
Obesity (BMI>=30)	288 (25.8)
Antibiotics for pre-existing infection	34 (3.0)
Immunosuppressant disease	30 (2.7)
Active malignancy	198 (17.7)
Current smoker	80 (7.2)
Diabetes mellitus	125 (11.2)
Poor nutritional state	24 (2.2)
Immunosuppressant drugs	36 (3.2)
Known carrier of resistant organism	7 (0.6)
Chemo or Radiotherapy (within last 3 months)	14 (1.3)
Anaesthetic technique - no. (%)	
General	565 (50.6)
Spinal	612 (54.8)
Epidural	48 (4.3)
Other regional	88 (7.9)
Surgical procedure - no. (%)	
Colorectal resection	122 (11.0)
Elective Caesarean section	345 (31.0)
Abdominal hysterectomy	125 (11.2)
Vaginal hysterectomy	35 (3.1)
Primary hip replacement	103 (9.2)
Primary knee replacement	109 (9.8)
Transurethral resection of prostate	41 (3.7)
Transurethral resection of bladder tumour	107 (9.6)
Open surgery for closed long bone fracture (leg or arm)	127 (11.4)
Wound contamination - no. (%)	16 (1.5)
Duration of surgery – no. (%)	
<2 hours	744 (68.4)
2-<4 hours	259 (23.8)
4-<6 hours	57 (5.2)
≥6 hours	27 (2.5)

Abbreviations: SD, standard deviation; IQR, Interquartile range

Table 2 – Antimicrobial administration

Antimicrobial administration	**Summary measure (*n*=1116)**
Prophylactic antimicrobial use	
Start of surgery - no. (%)	1090 (98.9)
Number of doses	
Mean (SD)	1.4 (0.5)
Median (IQR)	1 (1-2)
During surgery - no. (%)	29 (2.7)
Number of doses	
Mean (SD)	1.5 (0.6)
Median (IQR)	1 (1-2)
After surgery - no. (%)	205 (18.6)
Number of doses	
Mean (SD)	3.2 (2.4)
Median (IQR)	2 (2-3)
Total number of doses of antimicrobial prophylaxis	
Mean (SD)	2.0 (1.8)
Median (IQR)	1 (1-2)
Antibiotic class - no. (%)	
Co-amoxiclav	226 (20.8)
Cefuroxime	396 (36.5)
Metronidazole	171 (15.8)
Gentamicin	401 (37.0)
Teicoplanin	144 (13.3)
Ceftriaxone	73 (6.7)
Other	148 (13.7)
Antibiotics given to treat infection within 30 days after surgery - no. (%)	143 (13.3)
Indication – no. (%)	
Surgical site infection/wound infection	49 (34.8)
Other infection	48 (34.0)
Pneumonia	17 (12.1)
Pyrexia - cause unconfirmed	16 (11.3)
Sepsis	9 (6.4)
Surgical prophylaxis	1 (0.7)
Pneumonia/sepsis/other infection	1 (0.7)
Antibiotic class - no. (%)	
Co-amoxiclav	74 (53.2)
Cefuroxime	6 (4.3)
Metronidazole	25 (18.0)
Gentamicin	11 (7.9)
Teicoplanin	1 (0.7)
Other	86 (61.9)
Total number of therapeutic doses	
Mean (SD)	23.7 (19.0)
Median (IQR)	21 (11-28)
Route of antimicrobial administration - no. (%)	
Intra-venous	85 (59.4)
Oral	94 (65.7)
Patient discharged with an antibiotic prescription - no. (%)	68 (50.0)
Total duration of all therapeutic antibiotics (calendar days)	

Mean (SD)	8.9 (6.2)
Median (IQR)	7 (5-10)
Total number of doses (prophylaxis and therapeutics)	
Mean (SD)	4.7 (10.3)
Median (IQR)	1 (1-3)

Abbreviations: SD, standard deviation; IQR, Interquartile range

Table 3 – Infection

Infection - no. (%)	Clavien-Dindo Grade		Summary measure (*n*=1116)				
	I-II	III-V	ISOS Grade				Total
			None	Mild	Moderate	Severe	
Superficial surgical site	35 (89.7)	4 (10.3)	39 (3.6)	16 (1.5)	20 (1.9)	3 (0.3)	39 (3.6)
Deep surgical site	6 (100.0)	0 (0.0)	6 (0.6)	0 (0.0)	5 (0.5)	1 (0.1)	6 (0.6)
Body cavity	12 (66.7)	6 (33.3)	18 (1.7)	0 (0.0)	7 (0.6)	11 (1.0)	18 (1.7)
Pneumonia	23 (79.3)	6 (20.7)	29 (2.7)	3 (0.3)	13 (1.2)	13 (1.2)	29 (2.7)
Urinary tract	36 (92.3)	3 (7.7)	39 (3.6)	11 (1.0)	21 (1.9)	7 (0.6)	39 (3.6)
Bloodstream	6 (50.0)	6 (50.0)	12 (1.1)	0 (0.0)	5 (0.5)	7 (0.6)	12 (1.1)
Other infection	22 (84.6)	4 (15.4)	26 (2.4)	7 (0.6)	13 (1.2)	6 (0.6)	26 (2.4)

Table 4 – Adherence to guidelines

Adherence to guidelines - no. (%)	Summary measure (*n*=1116)		
	No	Yes	Don't know
Prophylaxis administered based on local guidelines	86 (7.8)	929 (84.3)	87 (7.9)
First dose of antibiotics before induction of anaesthesia	688 (62.5)	227 (20.6)	186 (16.9)
First dose within the 60 minutes before surgical incision	124 (11.3)	913 (82.9)	64 (5.8)

Table 5 – Primary Analysis (Outcome: SSI)

Variable	Adjusted odds ratio (95% CI)	*P*-value
Prophylaxis administered based on local guidelines		
No	Reference	
Yes	0.90 (0.35, 2.29)	0.823
Don’t Know	1.73 (0.57, 5.24)	0.329
Duration of surgery (hours)	1.71 (1.48, 1.97)	<0.001

A logistic regression model was fitted.

Note: The overall effect of local guidelines (*P*=0.264)