Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study

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Summary

Background Surgical site infection (SSI) is one of the most common infections associated with health care, but its importance as a global health priority is not fully understood. We quantified the burden of SSI after gastrointestinal surgery in countries in all parts of the world.

Methods This international, prospective, multicentre cohort study included consecutive patients undergoing elective or emergency gastrointestinal resection within 2-week time periods at any health-care facility in any country. Countries with participating centres were stratified into high-income, middle-income, and low-income groups according to the UN's Human Development Index (HDI). Data variables from the GlobalSurg 1 study and other studies that have been found to affect the likelihood of SSI were entered into risk adjustment models. The primary outcome measure was the 30-day SSI incidence (defined by US Centers for Disease Control and Prevention criteria for superficial and deep incisional SSI). Relationships with explanatory variables were examined using Bayesian multilevel logistic regression models. This trial is registered with ClinicalTrials.gov, number NCT02662231.

Findings Between Jan 4, 2016, and July 31, 2016, 13 265 records were submitted for analysis. 12 539 patients from 343 hospitals in 66 countries were included. 7339 (58·5%) patient were from high-HDI countries (193 hospitals in 30 countries), 3918 (31·2%) patients were from middle-HDI countries (82 hospitals in 18 countries), and 1282 (10·2%) patients were from low-HDI countries (68 hospitals in 18 countries). In total, 1538 (12·3%) patients had SSI within 30 days of surgery. The incidence of SSI varied between countries with high (691 [9·4%] of 7339 patients), middle (549 [14·0%] of 3918 patients), and low (298 [23·2%] of 1282) HDI (p<0·001). The highest SSI incidence in each HDI group was after dirty surgery (102 [17·8%] of 574 patients in high-HDI countries; 74 [31·4%] of 236 patients in middle-HDI countries; 72 [39·8%] of 181 patients in low-HDI countries). Following risk factor adjustment, patients in low-HDI countries were at greatest risk of SSI (adjusted odds ratio 1·60, 95% credible interval 1·05–2·37; p=0·030). 132 (21·6%) of 610 patients with an SSI and a microbiology culture result had an infection that was resistant to the prophylactic antibiotic used. Resistant infections were detected in 49 (16·6%) of 295 patients in high-HDI countries, in 37 (19·8%) of 187 patients in middle-HDI countries, and in 46 (35·9%) of 128 patients in low-HDI countries (p<0·001).

Interpretation Countries with a low HDI carry a disproportionately greater burden of SSI than countries with a middle or high HDI and might have higher rates of antibiotic resistance. In view of WHO recommendations on SSI prevention that highlight the absence of high-quality interventional research, urgent, pragmatic, randomised trials based in LMICs are needed to assess measures aiming to reduce this preventable complication.

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Introduction

Surgical site infection (SSI) is a large health burden for patients and health-care providers. It is the most common postoperative complication and causes pain and suffering to patients.[1,2] SSI is universally expensive[3] and could result in catastrophic health expenditure and impoverishment to patients who are required to pay for their own treatment.[4] In low-income and middle-income countries (LMICs), single-centre retrospective series have suggested that SSI could be the most common infection associated with health care.[1] However, prospective, standardised,

and internationally comparable data on the incidence of SSI and adverse events associated with SSI are lacking.[5–8]

These knowledge gaps make allocation of resources to tackle SSI in LMICs challenging. The WHO Guideline Development Group recently published 29 preoperative, intraoperative, and postoperative recommendations about SSI prevention.[6,9,10] These recommendations are welcomed but are necessarily based in large part on data extrapolated from high-income countries and, consequently, might lack validity in resource-limited settings. Strategic planning to tackle

Research in context

Evidence before this study
We searched for evidence of multinational research assessing surgical site infection (SSI) after abdominal surgery, focusing on low-income and middle-income countries (LMICs). We searched PubMed, MEDLINE, Google Scholar, and ClinicalTrials.gov for articles published between Jan 1, 1997, and June 1, 2017, with the terms "wound infection" OR "surgical site infection" AND "developing countries" OR "low income" OR "middle income" OR "low and middle income", without language restrictions. We reviewed related articles, references, and citations of eligible texts. Several low-volume, single-centre studies to characterise SSI in LMICs have been done in the past 20 years, but the research quality is low to medium. These studies were systematically reviewed in 2011 and included 57 studies of abdominal surgery, with reported SSI incidence ranging from 0·4% to 30·9% (between 1·5% and 81·0% for clean–contaminated surgery, 0·5% to 65·5% for contaminated surgery, and 0·2% to 100% for dirty surgery). The methodological quality of individual studies was low and heterogeneity was high, preventing meta-analysis. One multinational study has been done since 2010, and included patients from seven high-income, 17 upper-middle-income, and six lower-middle-income countries. The low observed SSI incidence (4·1%) after abdominal

surgery could relate to the passive 30-day follow-up strategy; additional limitations include a lack of data from lowest-income countries and exclusion of children.

Added value of this study
We identified the burden and clinical impact of SSI in patients undergoing gastrointestinal surgery in multiple income settings. We used standardised, validated, prospective methodology to provide global, contemporaneous data. SSI is most common after dirty surgery in LMICs. Even after casemix adjustment, patients in LMICs have a disproportionate burden of infection. A large proportion of SSIs are caused by organisms resistant to prophylactic antibiotics with the greatest apparent burden in LMICs.

Implications of all the available evidence
The burden of SSI is disproportionately greater on patients and health services in LMICs. Recent WHO recommendations on preoperative and intraoperative measures for SSI prevention highlight an absence of high-quality evidence. Urgent, pragmatic, randomised trials based in LMICs are needed to assess measures aiming to reduce this preventable complication and associated antibiotic use.

SSI has been hindered by a lack of high-quality global data. Microbiological data describing antimicrobial resistance in SSI and information on the likely origin of causative organisms are also needed to help refine prevention strategies and quality-improvement interventions.[6,10]

The GlobalSurg Collaborative designed and conducted an international, multicentre, prospective cohort study aimed at closing knowledge gaps in the incidence of SSI in global health settings. The primary aim was to determine variability in SSI rates in high-income, middle-income, and low-income settings.

Methods
Study design and participants
This international, multicentre, prospective cohort study used a published protocol[11] and was done by teams of local investigators who were coordinated by a national lead investigator. Investigators were recruited via the GlobalSurg network, social media, and personal contacts. Any health-care facility in any country treating patients who fulfilled the inclusion criteria could participate. The collaborative network methodology has been described in detail elsewhere.[12] Ethical and institutional approval was sought and obtained by each contributing institution as per local regulations. A UK National Health Service Research Ethics review considered this study exempt from formal research registration (South East Scotland Research Ethics Service, reference NR/1510AB5). Individual centres obtained their own audit or

institutional approval, and ethical approval was obtained in countries where local research ethics committees deemed it a requirement. This study is reported according to the STROBE and SAMPL guidelines.

Investigators included patients from at least one 2-week period that was chosen a priori by the local team. Consecutive sampling of patients undergoing elective or emergency gastrointestinal resection was done during the chosen 2-week period or periods. Consecutive sampling is a common non-probability sampling strategy in which all patients fulfilling the inclusion criteria within a defined time period are enrolled. A 2-week period was chosen to balance sample size requirements and pragmatism for the working clinicians who were enrolling patients and contributing data. The inclusion criteria were based on two considerations. First, the procedures were required to be relevant to the general surgeons who form the collaborative. Second, a reasonable baseline incidence of SSI was required so meaningful comparisons could be made with the predicted cohort size. So-called clean general surgery cases, such as simple hernia repair, were excluded on this basis. There was an absolute requirement for all cases in the chosen period to be included, but no minimum number was set to avoid bias against smaller centres. Gastrointestinal resection was defined as complete transection and removal of a segment of the oesophagus, stomach, small bowel, colon, rectum, appendix, or gallbladder and included formation or reversal of a gastrointestinal stoma. Emergency

procedures were defined as unplanned, non-elective operations and included procedures for trauma and reoperation after previous surgery. Open or minimally invasive procedures (eg, laparoscopic or robotic) were eligible. No age restrictions were included. Patients were excluded if the primary indication for surgery was vascular, gynaecological, obstetric, urological, or transplantation because the gastrointestinal tract is not typically opened.

Data variables from the GlobalSurg 1 study[13] and other studies that have been found to affect the likelihood of SSI were entered into risk adjustment models. Patient variables included age, sex, physical status according to the American Society of Anesthesiologists classification system, existence of immune suppression (eg, HIV status, active malarial infection, diabetes, use of steroid therapies, chemotherapy or other immunosuppressive drugs), and smoking status. Disease-related variables included diagnostic category, timing of surgery (elective *vs* emergency), use of the WHO surgical safety checklist,[14] use of laparoscopy, use of epidural anaesthesia, use of prophylactic antibiotics, and intraoperative contamination. Contamination level[2,15] was defined by the operating surgeon as clean (an incision in which no inflammation is encountered in a surgical procedure, without a break in sterile technique, and during which the respiratory, alimentary, and genitourinary tracts are not entered; inclusion criteria for this study excluded this group), clean–contaminated (an incision through which the respiratory, alimentary, or genitourinary tract is entered under controlled conditions but with no contamination encountered), contaminated (an incision undertaken during an operation in which there is a major break in sterile technique or gross spillage from the gastrointestinal tract, or an incision in which acute, non-purulent inflammation is encountered; open traumatic wounds more than 12–24 h old also fall into this category), or dirty (an incision undertaken during an operation in which the viscera are perforated or when acute inflammation with pus is encountered during the operation [eg, emergency surgery for faecal peritonitis], and for traumatic wounds where treatment is delayed, and faecal contamination or devitalised tissue is present).

Data were collected on the incidence and length of antimicrobial treatment before and after surgery. A pragmatic view was taken in the use of local protocols and techniques for collecting and processing microbiological specimens. Antimicrobial resistance was defined as resistance in the species presumed to be pathological to the antimicrobial used for prophylaxis. To aid in the communication of findings, organisms were broadly categorised as bowel-derived if cultures contained only Gram-negative bacilli, *Enterococcus* species, or anaerobic organisms, as skin-derived if cultures only contained skin-derived organisms such as *Staphylococcus* species, and as of mixed origin if cultures contained both bowel-derived and skin-derived cultures.

Data variables were selected to be objective, standardised, easily transcribed, and internationally relevant to maximise record completion and accuracy. Local investigators uploaded records to a secure online website, provided using the Research Electronic Data Capture (REDCap) system.[16] The lead investigator at each site checked the accuracy of all cases before data submission. The submitted data were then checked centrally and when missing data were identified, the local lead investigator was contacted and asked to complete the record. Once vetted, the record was accepted into the dataset for analysis. Records that were vetted but remained incomplete were included in the patient flowchart but excluded from analysis.

Data validation was done in three parts across a representative sample of centres according to a pre-specified protocol (appendix). First, centres self-reported the key processes used to identify and follow up patients. Second, independent validators (ie, doctors, nurses, or medical students who were not part of the recruiting teams) quantitatively reported case ascertainment and sampled data accuracy. Third, teams were interviewed to qualitatively assess collaborator engagement and data collection processes.

Outcomes

The primary outcome measure was the 30-day SSI incidence, defined using the US Centers for Disease Control and Prevention criteria for superficial and deep incisional SSI.[2] These criteria require the patient to have at least one of the following: (1) purulent drainage from the superficial or deep (fascia or muscle) incision but not from within the organ or space component of the surgical site; (2) pain or tenderness, localised swelling, redness, heat, or fever, or several of these symptoms, and the incision is opened deliberately or spontaneously dehisces; or (3) abscess within the wound (clinically or radiologically detected).

Organ space infections were recorded separately and defined as intra-abdominal or pelvic infections detected clinically or symptomatically, radiologically, or intra-operatively. A mandatory online SSI training module was completed by all collaborators before data collection.

The secondary outcome measures were designed to describe the clinical effect of SSI and included: (1) 30-day postoperative mortality, defined as death any time after skin closure until 30 days after surgery;[17] (2) prevalence in perioperative antibiotic administration; (3) 30-day postoperative reintervention incidence (operative, radio-logical, or endoscopic reintervention any time after skin closure until 30 days after surgery); (4) the prevalence of antimicrobial resistance for SSI (microbiological culture of wound swabs from site of SSI done according to local protocols, with a pragmatic definition of antimicrobial resistance defined a priori as resistance to the anti-microbial drug used for prophylaxis for that procedure in that particular patient); and (5) in-hospital SSI incidence

(patients were reviewed for SSI during their stay and at the time of hospital discharge); and (6) overall 30-day SSI incidence (patients were assessed at 30 days to determine whether an SSI had occurred; follow-up was done in person, by telephone, or by review of medical/readmission records, dependent on local practices).

Statistical analysis

As described in the protocol,[11] consideration was given to the sample size needed to compare HDI groups. This was approximated because data describing SSI incidence internationally are lacking. Taken with data from the GlobalSurg 1 study,[13] for a baseline SSI incidence of 15%, 550 patients per group (1350 patients in total after accounting for potential missing data and loss to follow-up) would allow for a 6·5 percentage point difference to be detected with a power of 80% at an α significance level of 0·05.

Variation between different international health settings was assessed by stratifying countries with participating centres into tertiles according to the Human Development Index (HDI). The HDI is the UN's composite statistic of life expectancy, education, and income indices. Differences between HDI tertiles were tested with the Pearson χ^2 test for categorical variables and with the Kruskal-Wallis test for continuous variables. Bayesian multilevel logistic regression models were constructed to account for casemix (differing patient, disease, and operative characteristics), as previously described.[18] Briefly, non-informative priors were used with sensitivity analyses done on alternative priors and different chain initiation points or chain lengths. Models were constructed using the following principles: (1) variables associated with outcome measures in previous studies were accounted for; (2) demographic variables were included in model exploration; (3) population stratification by hospital and country of residence was incorporated as random effects with constrained gradients; (4) all first-order interactions were checked and included in final models if found to be influential; (5) final model selection was done using a criterion-based approach by minimising the widely applicable information criterion (WAIC) and discrimination determined using the c-statistic (area under the receiver operator curve). Model coefficients are presented as odds ratio (OR) and 95% credible intervals (CI; analogous to confidence intervals in frequentist statistics, but philosophically distinct). In a further analysis, a restricted cubic spline transformation was applied to the continuous representation of the HDI to account for potential non-linearity (three knots distributed equally across the range of HDI rank). This was substituted into the final multilevel model (generalised additive model) and posterior predictions were made for specified covariate levels with 95% CI determined. All analyses were done using the R Foundation Statistical Program version 3.1.1 and Stan A C++ Library for Probability and Sampling version 2.10.0. This trial is registered with ClinicalTrials.gov, number NCT02662231.

Data sharing

The dataset can be explored using an online visualisation application at http://ssi.globalsurg.org.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. 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

Between Jan 4, 2016, and July 31, 2016, 13 265 patient records were submitted for analysis. 726 (5·5%) records remained incomplete after quality control, leaving 12 539 records for the final analysis (figure 1). These patients were from 343 centres across 66 countries (15 countries in Africa, 16 countries in Asia, 22 countries in Europe, eight countries in North America, one country in Oceania, and four countries in South America; table 1). 7339 (58·5%) patients were from countries with high HDI, 3918 (31·2%) patients were from countries with middle HDI, and 1282 (10·2%) patients were from countries with low HDI. 1291 (10·3%) patients were children (aged 16 years or younger). Missing data were uncommon (appendix p 12), and no patterns were seen when comparing included and missing data (appendix pp 13, 14).

The most common operations were cholecystectomy (4412 [35·2%] of 12 539 patients) and appendicectomy (4179 [33·3%]; appendix p 1). 6117 (48·8%) patients had emergency surgery, 5887 (46·9%) patients had an open approach, and a surgical safety checklist was used before 8843 (70·5%) cases (table 1). Overall, 9922 (79·1%) operations were clean–contaminated, 1540 (12·3%) operations were contaminated, and 991 (7·9%) operations were dirty.
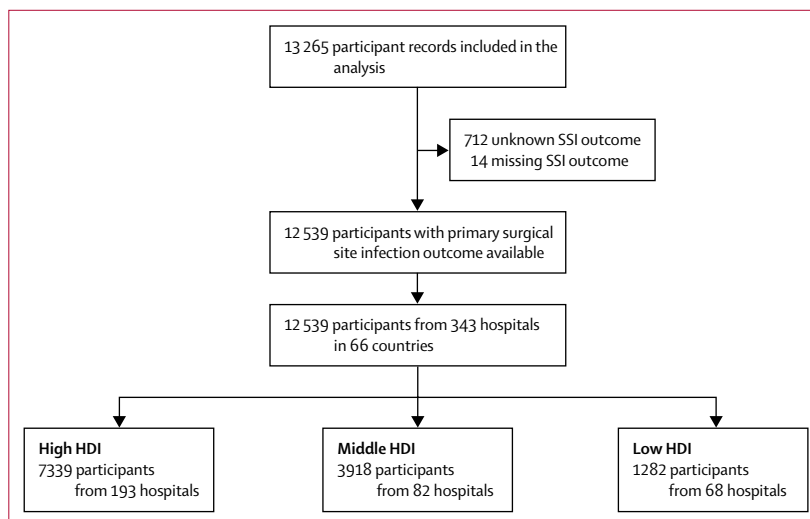
For the **Human Development Index** see http://hdr.undp.org/en/content/human-development-index-hdi

Figure 1: **Patient flowchart**
SSI=surgical site infection. HDI=Human Development Index.

	High HDI (n=7339)*	Middle HDI (n=3918)†	Low HDI (n=1282)‡	Total (n=12 539)§	p value
Mean age (SD), years	48·7 (21·5)	37·3 (18·5)	32·4 (19·1)	43·5 (21·3)	<0·001
Sex					
Male	3248 (44·3%)	1508 (38·5%)	678 (52·9%)	5434 (43·3%)	<0·001
Female	3683 (50·2%)	2215 (56·5%)	562 (43·8%)	6460 (51·5%)	..
Missing	408 (5·6%)	195 (5·0%)	42 (3·3%)	645 (5·1%)	..
ASA					
I	2498 (34·0%)	2299 (58·7%)	687 (53·6%)	5484 (43·7%)	<0·001
II	3191 (43·5%)	1106 (28·2%)	409 (31·9%)	4706 (37·5%)	..
III+	1543 (21·0%)	293 (7·5%)	178 (13·9%)	2014 (16·1%)	..
Unknown	107 (1·5%)	220 (5·6%)	7 (0·5%)	334 (2·7%)	..
Missing	0	0	1 (0·1%)	1 (<0·1%)	..
HIV					
No	6773 (92·3%)	3573 (91·2%)	1097 (85·6%)	11 443 (91·3%)	<0·001
Yes	13 (0·2%)	39 (1·0%)	5 (0·4%)	57 (0·5%)	..
Unknown	553 (7·5%)	306 (7·8%)	179 (14·0%)	1038 (8·3%)	..
Missing	0	0	1 (0·1%)	1 (<0·1%)	..
Malaria					
No	7243 (98·7%)	3845 (98·1%)	1157 (90·2%)	12 245 (97·7%)	<0·001
Yes	8 (0·1%)	3 (0·1%)	10 (0·8%)	21 (0·2%)	..
Unknown	87 (1·2%)	69 (1·8%)	115 (9·0%)	271 (2·2%)	..
Missing	1 (<0·1%)	1 (<0·1%)	0	2 (<0·1%)	..
Diabetes					
No	6484 (88·3%)	3564 (91·0%)	1184 (92·4%)	11 232 (89·6%)	<0·001
Yes	745 (10·2%)	309 (7·9%)	73 (5·7%)	1127 (9·0%)	..
Unknown	110 (1·5%)	44 (1·1%)	25 (2·0%)	179 (1·4%)	..
Missing	0	1 (<0·1%)	0	1 (<0·1%)	..
Immunosuppressive medication					
No	6893 (93·9%)	3789 (96·7%)	1243 (97·0%)	11 925 (95·1%)	<0·001
Yes	446 (6·1%)	129 (3·3%)	39 (3·0%)	614 (4·9%)	..
Current smoker					
No	6190 (84·3%)	3353 (85·6%)	1170 (91·3%)	10 713 (85·4%)	<0·001
Yes	1149 (15·7%)	565 (14·4%)	112 (8·7%)	1826 (14·6%)	..
Pathology					
Appendicitis	2061 (28·1%)	1516 (38·7%)	502 (39·2%)	4079 (32·5%)	<0·001
Gallstone disease	2505 (34·1%)	1493 (38·1%)	290 (22·6%)	4288 (34·2%)	..
Malignancy	1510 (20·6%)	287 (7·3%)	104 (8·1%)	1901 (15·2%)	..
Benign foregut	446 (6·1%)	220 (5·6%)	49 (3·8%)	715 (5·7%)	..
Benign midgut or hindgut	570 (7·8%)	150 (3·8%)	121 (9·4%)	841 (6·7%)	..
Infection	46 (0·6%)	41 (1·0%)	63 (4·9%)	150 (1·2%)	..
Congenital	47 (0·6%)	49 (1·3%)	85 (6·6%)	181 (1·4%)	..
Trauma or injury	18 (0·2%)	47 (1·2%)	45 (3·5%)	110 (0·9%)	..
Complication of previous procedure	67 (0·9%)	23 (0·6%)	14 (1·1%)	104 (0·8%)	..
Other	33 (0·4%)	9 (0·2%)	6 (0·5%)	48 (0·4%)	..
No disease	36 (0·5%)	80 (2·0%)	3 (0·2%)	119 (0·9%)	..
Missing	0	3 (0·1%)	0	3 (<0·1%)	..
Procedure start-time					
0800 h to 1759 h	5788 (78·9%)	2753 (70·3%)	865 (67·5%)	9406 (75·0%)	<0·001
1800 h to 2159 h	724 (9·9%)	381 (9·7%)	180 (14·0%)	1285 (10·2%)	..
2200 h to 0759 h	821 (11·2%)	782 (20·0%)	237 (18·5%)	1840 (14·7%)	..
Missing	6 (0·1%)	2 (0·1%)	0 (0·0%)	8 (0·1%)	..

(Table 1 continues on next page)

	High HDI (n=7339)*	Middle HDI (n=3918)†	Low HDI (n=1282)‡	Total (n=12 539)§	p value
(Continued from previous page)					
Admission to procedure time, h					
<6	2291 (31·2%)	1052 (26·9%)	308 (24·0%)	3651 (29·1%)	<0·001
6–11	722 (9·8%)	366 (9·3%)	128 (10·0%)	1216 (9·7%)	..
12–23	1364 (18·6%)	675 (17·2%)	217 (16·9%)	2256 (18·0%)	..
24–47	1330 (18·1%)	552 (14·1%)	230 (17·9%)	2112 (16·8%)	..
≥48	1358 (18·5%)	1033 (26·4%)	338 (26·4%)	2729 (21·8%)	..
Missing	274 (3·7%)	240 (6·1%)	61 (4·8%)	575 (4·6%)	..
Urgency					
Elective	3941 (53·7%)	1997 (51·0%)	483 (37·7%)	6421 (51·2%)	<0·001
Emergency	3397 (46·3%)	1921 (49·0%)	799 (62·3%)	6117 (48·8%)	..
Missing	1 (<0·1%)	0	0	1 (<0·1%)	..
Operative approach					
Open	2679 (36·5%)	2153 (55·0%)	1055 (82·3%)	5887 (46·9%)	<0·001
Laparoscopic	4660 (63·5%)	1765 (45·0%)	227 (17·7%)	6652 (53·1%)	..
Epidural					
No	6554 (89·3%)	3666 (93·6%)	1230 (95·9%)	11 450 (91·3%)	<0·001
Yes	646 (8·8%)	210 (5·4%)	48 (3·7%)	904 (7·2%)	..
Unknown	139 (1·9%)	42 (1·1%)	4 (0·3%)	185 (1·5%)	..
Antibiotic: pre-procedural or prophylactic					
No	848 (11·6%)	472 (12·0%)	50 (3·9%)	1370 (10·9%)	<0·001
Yes	6446 (87·8%)	3392 (86·6%)	1224 (95·5%)	11 062 (88·2%)	..
Missing	45 (0·6%)	54 (1·4%)	8 (0·6%)	107 (0·9%)	..
Intraoperative contamination					
Clean–contaminated	5918 (80·6%)	3126 (79·8%)	878 (68·5%)	9922 (79·1%)	<0·001
Contaminated	779 (10·6%)	542 (13·8%)	219 (17·1%)	1540 (12·3%)	..
Dirty	574 (7·8%)	236 (6·0%)	181 (14·1%)	991 (7·9%)	..
Missing	68 (0·9%)	14 (0·4%)	4 (0·3%)	86 (0·7%)	..
Safety checklist used					
No, not available	837 (11·4%)	1114 (28·4%)	308 (24·0%)	2259 (18·0%)	<0·001
No, but available	238 (3·2%)	690 (17·6%)	363 (28·3%)	1291 (10·3%)	..
Yes	6194 (84·4%)	2049 (52·3%)	600 (46·8%)	8843 (70·5%)	..
Unknown	69 (0·9%)	65 (1·7%)	11 (0·9%)	145 (1·2%)	..
Missing	1 (<0·1%)	0	0	1 (<0·1%)	..

Numbers are n (%), unless otherwise indicated. All tests are Pearson's χ^2 test, except for the comparison of mean age, where a Kruskall-Wallis test has been applied. ASA=American Society of Anesthesiologists classification grade. *Included 30 countries and 193 hospitals. †Included 18 countries and 82 hospitals. ‡Included 18 countries and 68 hospitals. §Included 66 countries and 343 hospitals.

Table 1: Patient and operative characteristics by human development index (HDI) rank

1538 (12·3%) patients had SSI within 30 days of surgery, and 842 (6·7%) had SSI before discharge from hospital (appendix p 5). The unadjusted SSI incidence varied between countries with high HDI (691 [9·4%] of 7339 patients), middle HDI (549 [14·0%] of 3918 patients) and low HDI (298 [23·2%] of 1282 patients). Intraoperative contamination was more likely to be classed as dirty in countries with low HDI (181 [14·1%] of 1282 patients) than in countries with middle HDI (236 [6·0%] of 3918 patients) or high HDI (574 [7·8%] of 7339; table 1). SSI rates increased significantly with dirty surgery compared with clean–contaminated surgery; however, there was no significant interaction for SSI between HDI and intraoperative contamination

(appendix pp 3, 4). After multivariable adjustment for confounders (including contamination), a significantly higher SSI rate was seen in countries with low HDI (adjusted OR 1·60, 95% CI 1·05–2·37; p=0·030) but not in middle-HDI settings (1·12, 0·77–1·61; p=0·539) compared with high-HDI countries (figure 2; appendix p 4). When adjusted for patient and hospital factors, SSI increased markedly at the threshold between countries with middle and low HDI (rank 100; figure 3). The increase was observed for both clean–contaminated and dirty surgery because there was no significant interaction between contamination and HDI, suggesting that HDI is an independent risk factor for SSI, irrespective of intraoperative contamination.
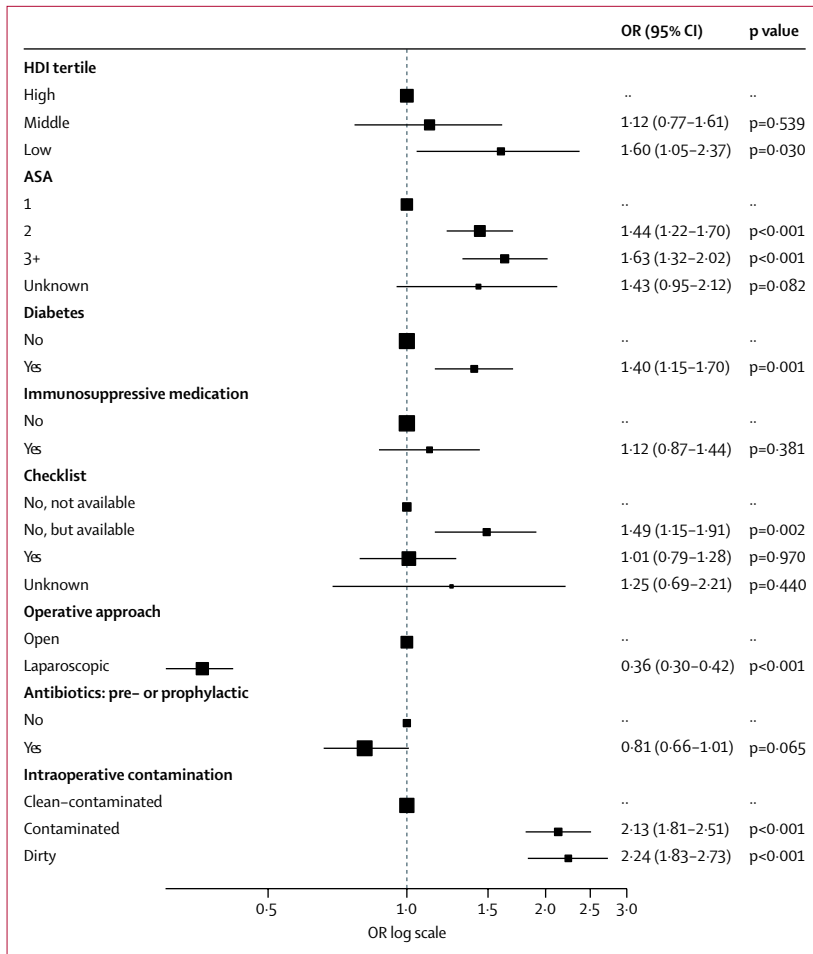
Figure 2: **Multilevel model for factors associated with surgical site infection**
Full model includes HDI tertile, age, American Society of Anesthesiologists (ASA) classification grade, diabetes status, immunosuppressive medication treatment, current smoker, pathology, operative approach, antibiotic use before surgery, intraoperative contamination, and WHO checklist used. Error bars are 95% credible interval. Full data are in the appendix (p 4). OR=odds ratio. HDI=Human Development Index. CI=credible interval.

235 (1·9%) patients died within 30 days of surgery, but mortality varied between countries with high HDI (110 [1·5%] of 7339 patients), middle HDI (64 [1·6%] of 3918 patients), and low HDI (61 [4·8%] of 1282 patients; appendix p 5). Patients with SSI were more likely than patients without SSI to die, to have a reintervention, to have an organ space infection, or to have another health-care-associated infection (table 2). The median length of hospital stay was three times longer for patients with an SSI than for patients without (median 7·0 days [IQR 11·0] *vs* 2·0 days [4·0]; p<0·001).

Patients in LMICs were more likely to receive presurgery antibiotic courses than patients in high-HDI settings (appendix p 6). Prophylactic antibiotic administration was generally high (10 225 [81·5%] of 12 539 patients), with slight variation between HDI groups. Overall, administration of preoperative or prophylactic antibiotics, or both, was higher in groups with low HDI (1224 [95·5%] of 1282) than in

countries with middle HDI (3392 [86·6%] of 3918 patients) and high HDI (6446 of 87·8%] of 7339 patients; p<0·001).

Patients in LMICs were more likely to receive postoperative antibiotics than those in high-HDI countries (3376 [46·0%] of 7339 patients in high-HDI countries *vs* 3135 [80·0%] of 3918 patients in middle-HDI countries *vs* 1098 [85·6%] of 1282 patients in low-HDI countries; p<0·001; appendix p 7). The increased tendency to use antibiotics after surgery in low-HDI countries persisted despite adjustment for confounding factors (adjusted OR 4·37, 95% CI 1·65–11·85, p=0·002), including contamination of surgery (appendix pp 8, 9). Courses of postoperative antibiotics were longer in patients in LMICs than in high-income countries, with the number of patients receiving antibiotics for 5 days or more increasing from countries with high HDI to low HDI (1830 [24·9%] of 7339 patients in high-HDI countries *vs* 1837 [46·9%] of 3918 patients in middle-HDI countries *vs* 650 [50·7%] of 1282 patients in low-HDI countries; p<0·001; appendix p 7).

A microbiological wound culture was available for 610 (39·7%) of 1538 patients with an SSI (table 3). A summary and full lists of causative organisms are available in the appendix (pp 10, 11). 301 [63·8%] of 472 patients had bowel-derived infections, 97 (20·6%) patients had skin-derived infections, and 53 (11·2%) patients had infections of mixed origin. Organisms with resistance to the actual prophylactic antibiotic used were isolated from 132 (21·6%) of the 610 patients with SSI who had a wound culture (table 3). The prevalence of resistance varied between countries with high, middle, and low HDI (table 3).

Patients were identified for inclusion predominantly using theatre logbooks or computer systems (5771 [78·6%] of 7339 patients in high-HDI countries; 2349 [60·0%] of 3918 patients in middle-HDI countries; 759 [59·2%] of 1282 patients in low-HDI countries) and operating lists (1318 [18·0%] of 7339 patients in high-HDI countries; 823 [21·0%] of 3918 patients in middle-HDI countries; 278 [21·7%] of 1282 patients in low-HDI countries; appendix p 16). Many patients across HDI strata were followed up by telephone (2708 [36·9%] of 7339 patients in high-HDI countries; 2582 [65·9%] of 3918 patients in middle-HDI countries; 483 [37·7%] of 1282 patients in low-HDI countries; appendix p 17). Validators identified 1476 cases that fulfilled inclusion criteria, and 1378 (93%) cases were ascertained (appendix p 18). Accuracy was high for the validated continuous predictor (Pearson's correlation coefficient 0·99; appendix p 20), categorical predictors (Cohen's κ coefficients >0·90; appendix p 21), and mortality (κ 0·91). The agreement for 30-day reintervention was lower (κ 0·65).

Discussion

We identified both the burden and clinical effect of SSI on patients undergoing gastrointestinal surgery in many parts of the world. SSI affected 12·3% of patients worldwide, and the incidence increased across HDI groups, reaching 39·8% of patients undergoing dirty

surgery in low-HDI settings. The incidence of SSI remained higher in low-HDI countries than in middle-HDI or high-HDI countries, despite adjustment for factors describing patients, diseases (including contamination), procedures, safety, and hospitals. Length of hospital stay was three times longer for patients affected by SSI than for patients with no SSI. Delayed return to work or school carries a societal burden, which is likely to be greater in LMICs.

These findings begin to characterise the relationship between SSI and global antimicrobial resistance. Where microbiological cultures were available, SSIs were more likely to be caused by bowel-derived organisms. Large amounts of antibiotics were consumed to prevent and treat SSI, yet in 21·6% of cases with a positive culture, the causative microorganism was resistant to the prophylactic antibiotics that had been administered. The prevalence of antimicrobial resistance increased to one of three isolates in low-HDI countries. Postoperative courses of antibiotics were longest for patients in low-HDI countries, and this was not explained by casemix. Although there is randomised evidence that short postoperative antibiotic courses are as safe as long antibiotic courses, this evidence was not derived in LMICs, and caution is needed before changing practice.[19] The high prevalence of SSIs that were resistant to the initial prophylactic antibiotic illustrates a potentially important area for improvement worldwide. Complete microbiological analysis of all SSIs was not possible within this observational study, so the problem might be even larger that estimated here.

The focus in global surgery to date has been directed towards mortality. The 30-day mortality in this study was similar to that in the GlobalSurg 1 study (1·9% and 1·6% respectively).[13] This generally low mortality highlights the importance of studying more common outcomes such as SSI across health systems, given the impact on patients. We found an association between SSI and death, with a three-fold increase from 1·5% in patients without SSI to 4·7% in patients with SSI within this study. This is an association, and no causal link can be made with these data; it is likely that patients died with an SSI rather than from an SSI. Since SSI was also associated with deep organ space infection and other health-care-associated infections, this supports its use as a severity marker of illness.

Interest in the use of surgical safety checklists has increased in the past 5 years, and they are now part of clinical routine in many surgical units. In this study, the failure to use an available surgical safety checklist was associated with a high SSI rate. This association was not explained by an omission of prophylactic antibiotics, nor was it particular to emergency surgery, when haste might improperly trump safety measures. The scientific literature describing checklists and SSI is contrasting and includes a recent systematic review of 14 studies.[14] The data in this systematic review showed a decrease in
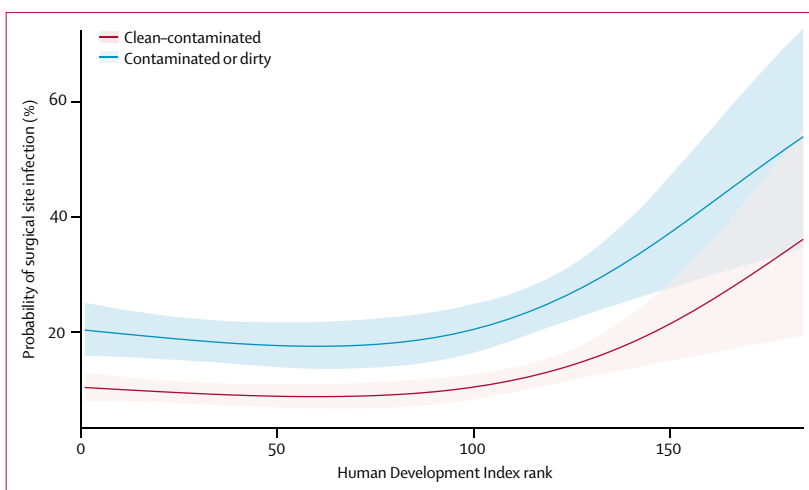

Figure 3: **Probability of surgical site infection (SSI) by human development index (HDI) rank**
Adjusted predicted probability of SSI across HDI rank by intraoperative contamination. In the most developed countries (rank 1), patients had a low probability of SSI. At rank 100, the probability of SSI increases linearly through the least developed countries. This absolute difference between clean–contaminated and contaminated or dirty surgery is shown, with no interaction between HDI and intraoperative contamination found. Shaded area is the credible interval.

	No SSI (n=11 001)	SSI (n=1538)	p value
30-day mortality			
Alive	10 665 (96·9%)	1438 (93·5%)	<0·001
Dead	162 (1·5%)	73 (4·7%)	··
Missing	174 (1·6%)	27 (1·8%)	··
30-day reintervention			
No	10 674 (97·0%)	1202 (78·2%)	<0·001
Yes	235 (2·1%)	316 (20·5%)	··
Missing	92 (0·8%)	20 (1·3%)	··
Organ space infection (abscess)			
No	10 759 (97·8%)	1229 (79·9%)	<0·001
Yes	146 (1·3%)	276 (17·9%)	··
Missing	96 (0·9%)	33 (2·1%)	··
Other health-care-associated infection			
No	10 546 (95·9%)	1292 (84·0%)	<0·001
Yes	388 (3·5%)	214 (13·9%)	··
Missing	67 (0·6%)	32 (2·1%)	··
Median length of stay (IQR)	2·0 (4·0)	7·0 (11·0)	<0·001*

Numbers are n (%), unless otherwise indicated. All tests are χ² tests, except when indicated by*, where a Kruskall-Wallis test has been applied.

Table 2: **Associations between surgical site infection (SSI) and other outcomes**

	High HDI (n=295)	Middle HDI (n=187)	Low HDI (n=128)	Total (n=610)	p value
Antibiotic not used	27 (9·2%)	6 (3·2%)	0 (0·0%)	33 (5·4%)	<0·001
Sensitive to antibiotic	92 (31·2%)	56 (29·9%)	40 (31·2%)	188 (30·8%)	··
Resistant to antibiotic	49 (16·6%)	37 (19·8%)	46 (35·9%)	132 (21·6%)	··
Sensitivity not available	127 (43·1%)	88 (47·1%)	42 (32·8%)	257 (42·1%)	··

Numbers are n (%), unless otherwise indicated. All tests are χ² tests.

Table 3: **Sensitivity of organism by Human Development Index (HDI) from patients with a surgical site infection who had a wound swab taken**

SSI with checklist use (range within individual studies from 3·2% to 10·2% absolute risk reduction). The GlobalSurg studies provide novel checklist data from LMIC settings. The explanation for the observed effect is unclear but probably describes a broader attitude to safety in hospital systems that require further investigation.

A major strength of this study is its provision of prospective patient-level SSI data from a wide breadth of settings around the world. In particular, outcome assessment was standardised and training provided through our online tool. Several small and generally single-centre studies have been done in the past 20 years in attempts to characterise SSI in LMICs. These were systematically reviewed in a 2010 study[1] that included 57 reports focusing on SSI. General methodological quality was low and heterogeneity was high, with reported SSI rates varying from 0·4% to 30·9%. Since then, SSI outcomes from several single-centre and national multicentre studies in LMICs have been published.[20–24] The lower than expected rates emphasise the difficulty in robustly determining SSI, which, together with the between-study variability, make international comparisons difficult. The present study contributes to closing this knowledge gap and allows meaningful comparison from multiple income settings with accurate casemix adjustment and standardised training in outcome assessment. Reliability was increased through the vetting of incomplete records and was demonstrated in a parallel validation study.

A major limitation of this study was the inability to follow up every patient 30 days after surgery. SSI detection within randomised trials is higher when proactively followed up as a primary endpoint than when followed up as a secondary outcome.[25] Within our study, collaborators were trained and encouraged to directly determine 30-day outcomes whenever possible. Overall, this was successful; however, complete, in-person, 30-day follow-up for thousands of patients would not have been possible, particularly in resource-limited settings. Nevertheless, we did assess SSI as a primary endpoint, used a mandatory training package, and did a sensitivity analysis using in-hospital SSI rates. The variation in incidence of SSI before discharge from hospital and within 30 days was similar between countries of high, middle, and low HDI. Since these incidence data are already comparable to those from high-quality randomised trials, this provides some measure of validity.[26] Other limitations apply. First, with respect to microbiological analysis, we did not standardise specimen collection, laboratory assessment, techniques, or definitions. A pragmatic view was taken to use local protocols and techniques for collecting and processing specimens and for determining antimicrobial resistance. These measures were therefore recognised in advance as being an exploratory analysis to describe the prevalence of organisms with antimicrobial resistance against the particular prophylactic antibiotic administered. Second, although we did validation, there is still the potential for missed cases or inaccurate data.[13,27,28] The large number of patients, a prospective protocol, and the use of local coordinators might have minimised the potential bias.

Reducing SSI will contribute to ensuring safe and essential surgery around the world.[29] Costs to patients in LMICs in terms of expenditure and time off work have not been measured but are probably considerable. The costs of preventive measures might be offset by the realised cost-savings. WHO has published recommendations to help reduce the incidence of SSI that include global perspectives relevant to LMICs.[9] Despite inclusion of strongly graded recommendations, none of these could be based on high-quality evidence, which is lacking in support of most interventions. Virtually none of the existing evidence is derived from LMICs, leading to uncertainty about future performance of these measures.[8] SSI research is complex, and bundles of measures have been seen to paradoxically increase SSI incidence.[30] Implementation therefore necessitates careful consideration and meticulous attention to longer-term evaluation. In resource-limited settings, the development of robust policy will remain difficult without high-quality evidence. Our findings provide the rationale to plan, fund, and perform high-quality surgical research that can effect change in health policy. There are no multicentre, multi-country randomised trials on SSI prevention in LMICs at a time when efforts to combat SSI should be informed by high-quality research derived in these settings.[8]

Central & Southern Africa, Cutting Edge Manipal, Egyptian Medical Student Research Association, International Collaboration For Essential Surgery, International Federation of Medical Student Associations, Italian Society of Colorectal Surgery, Lifebox Foundation, School of Surgery, Student Audit and Research in Surgery, The Electives Network, United Kingdom National Research Collaborative, World Society of Emergency Surgery, World Surgical Association.

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