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Prophylactic antibiotics to prevent surgical site infections in Botswana; findings and implications

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Key words: surgical site infection; antibiotic prophylaxis; timing of prophylaxis; organisms; Botswana

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Abstract

Background and aims: Antibiotic prophylaxis in surgery is known to reduce the rate of surgical site infections (SSI) as well as shorten hospital stay. However, there is currently a scarcity of data on antibiotic prophylaxis and SSIs among African countries including Botswana. Consequently, this study aimed to address this. Methods: A prospective study involving 400 patients was carried out at a leading tertiary hospital in Botswana from 2014-2015. Patients' demographic information, type of surgery performed and peri-operative use of antibiotics were documented. All enrolled patients were followed-up for 30 days post discharge to fully document the incidence of SSIs. Results: Median age of patients was 35.5 (25 – 50) years, with 52% female. There were 35.8% emergency and 64.2 % elective surgeries. The most common operations were exploratory laparotomy (25%), appendectomy (18.3%), excision and mastectomy (8%). Antibiotics were given in 73.3% of patients, mainly postoperatively (58.3%). The most commonly prescribed antibiotics were cefotaxime (80.7%), metronidazole (63.5%), cefradine (13.6%) and amoxicillin/clavulanate (11.6%). The incidence of SSI was 9%. The most common organisms were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and coagulase-negative staphylococci. Conclusion: The rate of SSI is a concern, and may be related to inappropriate antibiotic prophylaxis given post operatively. Interventions are in place to decrease SSI rates to acceptable levels in this leading hospital by improving for instance infection prevention practices including the timing of antibiotic prophylaxis. Research is also ongoing among other hospitals in Botswana to reduce SSI rates building on these findings.

Introduction

Surgical site infections (SSI) are infections related to the operative procedure that occurs at or near the surgical incision within 30 days of the procedure (up to one year if a prosthetic material is implanted), and affecting either the incision or deep tissue at the operation site or any part of the anatomy (e.g., organs and spaces) [1-3]. They are among the common causes of hospital acquired infections, which appreciably add to post-operative morbidity and mortality, prolong hospital stay by

up to 7 to 11 post-operative days, and increase costs [3-5]. Patients with SSIs can increase their mortality by up to 11-fold, with SSI costing up to US\$10bn/ year across countries [5, 6]. The incidence of SSI ranges from under 1% to over 50% depending on population studied, type of surgery, size of hospital, ventilation within the hospital, experience of the surgeon and surveillance method [3, 7-10]. In a meta-analysis, Ngaroua *et al* reported a pooled incidence rate of SSI of 14.8% in Africa [11], with SSIs appearing particularly problematic and common in lower and middle income countries (LMICs) versus high income countries [12].

The pattern of occurrence of SSI is based on the distribution and virulence of the offending organisms and host resistance [13]. Common causative organisms of SSI include *staphylococcus* species, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella* species [10, 14-16]. Polymicrobial existence is common in SSIs [15, 16]. Risk factors for development of SSI include the degree of tissue trauma, pre-operative infection, presence of a prosthesis or other foreign body, surgical technique, length of surgery and its complexity, re-interventions, reduced fitness, use of steroids, lack of adherence to agreed prescribing guidance and a prolonged duration of surgery [10, 13, 17-19].

Over the years, surgery has been made safer by modifying these factors through measures such as aseptic surgical techniques, skin cleansing prior to surgery, pre-operative patient preparation, optimization of co-morbid illnesses and by administering surgical antibiotic prophylaxis [13, 20]. Surgical antibiotic prophylaxis reduces the burden of microorganisms at the surgical site and has been shown to be a cost-effective strategy in reducing the rate of SSI and shortening hospital stay [13, 21, 22]. Overall, up to 60% of SSIs are preventable using evidence based approaches [6]. The use of antibiotics has been shown to decrease SSI by 39 % [23]. Guidelines recommend that antibiotic prophylaxis be given within 1-2 hours before incision, and in doses sufficient to achieve adequate serum and tissue drug levels for the interval during which the surgical site is open [6, 17, 20, 22, 24-26]. In cases where the duration of the surgery exceeds 2 half-lives of the antimicrobial or there is excessive blood loss, intraoperative re-dosing is needed to maintain adequate serum and tissue drug levels [27]. However, initiating antibiotics after the first incision is not advised as it almost doubles SSI rates [28]. Moreover, prolongation of antibiotic prophylaxis after the operation is not recommended as it predisposes to resistance [26, 29]. Continued surveillance and appropriate strategies can appreciably reduce the prevalence of SSIs, which include the monitoring of clinical practice against agreed guidance [30]. Such strategies are becoming increasingly important.

Antibiotic selection is often based on the risk of wound infection according to wound classification, the normal floral distribution of the site to be operated and the antibiotic resistance patterns in the hospital setting [1, 6, 17, 25, 27, 31, 32]. Generally, broad-spectrum antibiotics are preferred to narrow spectrum antibiotics and cephalosporin are commonly used [27]. Cefazolin is commonly recommended for gastroenterological, genito-urinary tract, and hepatobiliary surgeries [27]. The Botswana national guidelines recommend cefradine for cardiothoracic, neurosurgery, gastroenterological, vascular surgeries, breast, orthopaedic and gynaecological surgeries [33]. A combination of ampicillin, gentamicin and metronidazole is recommended for high risk biliary surgery, and a combination of gentamicin and ciprofloxacin for urological surgeries [33]. Despite these recommendations, studies have shown inconsistencies in administering surgical prophylaxis in for instance the proportion of surgical patients to whom prophylaxis is prescribed, type of the antibiotic chosen, time of administration and duration of the antibiotic course [17, 26]. In addition, there is paucity of information regarding the burden of SSI and prophylactic regimens used in developing countries; although, as mentioned, these are likely to be more problematic in LMICs [7, 12].

Aims

We sought to address the lack of knowledge regarding SSIs in Botswana by describing their current burden and the antibiotic surgical prophylactic patterns in a leading hospital in Botswana. The findings would act as a basis for developing future pertinent strategies to reduce the number of SSIs in this hospital and wider in Botswana. This is particularly important in Botswana with its high incidence of infectious diseases, e.g. 21.9% of the adult population currently have HIV although this rate is decreasing [34].

Methodology

Study setting and participants

This prospective cross-sectional study was conducted at Princess Marina Hospital (PMH) in Gaborone, between February 2014 and June 2015. PMH is the main public hospital in the country with a 560-bed capacity and an average of 12 general surgical operations every day. Consequently, if there were concerns with surgical prophylaxis in this hospital, such concerns or worse are highly likely at secondary hospitals in Botswana. We only included adult patients who underwent surgery, resided within a perimeter of 50 kilometres from PMH and with whom home visits were possible in view of our follow-up regime. We excluded children in this first study as adults are the largest population as well as patients with prostheses or implants.

Data collection

The information obtained from all enrolled patients included: demographic characteristics, anthropometric measurements, surgical diagnoses, comorbid conditions and the duration of antibiotics use. Other information included the type and time of prophylactic antibiotic administration. Enrolled patients were followed up for 30 days after the surgical procedure to assess the development of SSI. While in the wards, patients were assessed for the development of signs and symptoms of SSI once every two days until hospital discharge. We assessed for fever ($>38^{\circ}\text{C}$), abnormal wound discharge, increasing pain or tenderness, redness, heat or localized swelling/ abscess. Radiological, histological and clinical diagnoses of wound infection made by the attending doctor were also documented.

After discharge, patients were physically assessed for SSIs through home visits or an arranged hospital visit during the first week post-discharge the hospital. Thereafter, patients were contacted through telephone calls twice every week until the 30th day post discharge to determine the development of any SSIs. During the phone calls, patients were asked if they had any symptoms of a SSI as described above. For those with any of the SSI symptoms, we arranged physical examination and pus swabs for microbiological examination. The diagnosis of an SSI was made on the presence of one or more of the following: purulent exudate from a surgical site, positive fluid culture - from a surgical site that was closed primarily; reopened surgical site due to at least one clinical sign of infection (pain, swelling, erythema, warmth) - culture positive or not cultured; or surgeon's diagnosis of infection. Patients with SSIs were referred to the responsible unit at PMH where they were managed accordingly.

Statistical analysis

The sample size was calculated from the assumption that the incidence of SSIs in Botswana was 15%, and an expected loss to follow up of 30% [11]. We needed 400 patients to determine the true incidence with a margin of error of $\pm 4\%$ using a 95% confidence interval. Data were analysed using SPSS Version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Normally distributed variables were expressed as mean \pm standard deviation (SD) and asymmetrically distributed variables were presented as median [interquartile range (IQR)]. We present categorical and nominal variables as absolute and relative frequencies (%). The Pearson's χ^2 test was used to contrast categorical data. We considered a two sided p value of < 0.05 to be statistically significant.

Ethical consideration

The study was granted ethical clearance by the University of Botswana, Ministry of Health and PMH Institutional Review Boards. Written informed consent was obtained before data collection from all participants or their relatives in the cases where the patient was incapacitated to consent.

Results

In total, 400 patients with a median age of 35.5 (IQR 25-50) years were enrolled in the study. Demographic profile of the participants including their co-morbidities is shown in Table 1. There were 143 (35.8%) emergency and 257 (64.2 %) elective surgeries. The most common operations performed were explorative laparotomy (25%), appendectomy (18.3%), excisions and mastectomy (8%).

Table 1: Clinical and demographic characteristics of enrolled surgical patients at Princess Marina Hospital in Botswana, N=400

Characteristics		Emergency	Elective	Total
		143 cases	257 cases	400 cases
sex — n (%)	Female	<u>50 (35.0)</u>	<u>159 (61.9)</u>	<u>209(52.3)</u>
	Male	<u>90 (62.9)</u>	<u>98 (38.1)</u>	<u>191 (49.7)</u>
Age — years, median (IQR)		<u>43 (29-55)</u>	<u>26 (22-36)</u>	<u>35.5 (25-50)</u>
<u>Explorative laparotomy</u>		<u>74(51.7)</u>	<u>26(10.1)</u>	<u>100 (25.0)</u>
<u>Appendectomy</u>		<u>66(46.2)</u>	<u>7(2.7)</u>	<u>73 (18.3)</u>
<u>Excision</u>		<u>1(0.7)</u>	<u>49(19.1)</u>	<u>50 (12.5)</u>
<u>Mastectomy</u>		<u>0</u>	<u>32 (12.5)</u>	<u>32 (8.0)</u>
<u>Herniorraphy</u>		<u>3 (2.1)</u>	<u>25 (9.7)</u>	<u>28 (7.0)</u>
Surgeries— n (%)	<u>Hydrocoelectomy</u>	<u>2 (1.4)</u>	<u>19 (7.4)</u>	<u>21 (5.3)</u>
	<u>Cholecystectomy</u>	<u>1 (0.7)</u>	<u>20 (7.8)</u>	<u>21 (5.3)</u>
	<u>Orchiectomy</u>	<u>5(3.5)</u>	<u>12 (4.7)</u>	<u>17 (4.3)</u>
	<u>Mammoplasty</u>	<u>0</u>	<u>15 (5.8)</u>	<u>15 (3.8)</u>
	<u>Knee amputation</u>	<u>0</u>	<u>12 (4.7)</u>	<u>12 (3)</u>
	<u>Others</u>	<u>10 (7.0)</u>	<u>44 (17.1)</u>	<u>54 (11.3)</u>
	<u>HIV</u>	<u>21 (14.7)</u>	<u>56 (21.8)</u>	<u>77 (19.5)</u>
<u>Hypertension</u>		<u>7 (4.9)</u>	<u>55 (21.4)</u>	<u>62 (15.6)</u>
Co-morbidities— n (%)	<u>Cancer</u>	<u>0</u>	<u>41 (16.0)</u>	<u>41 (10.3)</u>
	<u>Tuberculosis</u>	<u>2 (1.4)</u>	<u>2 (0.8)</u>	<u>4 (1)</u>
	<u>Diabetes</u>	<u>2 (1.4)</u>	<u>20 (7.8)</u>	<u>22 (5.5)</u>

NB: IQR = Interquartile range

Antibiotic use

Overall, 293(73.3%) cases were prescribed antibiotics. Sixty (15%) patients received antibiotics pre-operatively, 233 (58.3%) patients post-surgery, and 107(26.8%) patients were not prescribed any antibiotics (Table 2).

Pre-operative antibiotics were prescribed in 31 (21.7%) emergency surgeries as compared to 29 (11.3%) elective surgeries (P= 0.005). Post-operative antibiotics were prescribed in 132 (92.3%) emergency surgeries as compared to 144 (56%) elective surgeries (P < 0.001). Of the patients who started antibiotics postoperatively, established infections was suspected in those with peritonitis (8 cases), abscesses (4 cases) and appendicitis (50 cases). The mean (SD) duration of post-operative antibiotic use was 5 (2.6) days. The most common prescribed antibiotics were cefotaxime (80.7%), metronidazole (63.5%), cefradine (13.6%) and amoxicillin/clavulanate (11.6%). Co-administration of cefotaxime and metronidazole was found in 134 (48.6%) patients post-operatively. Oral antibiotics such as cloxacillin, amoxicillin, doxycycline and metronidazole were also prescribed.

Table 2: Antibiotic prophylaxis among surgical patients at Princess Marina Hospital in Botswana.

<u>Antibiotics — n (%)</u>	<u>All</u>	<u>Pre-operative</u>		<u>Post-operative</u>	
		<u>Emergency</u>	<u>Elective</u>	<u>Emergency</u>	<u>Elective</u>
	<u>293 cases</u>	<u>31 cases</u>	<u>29 cases</u>	<u>104 cases</u>	<u>129 cases</u>
<u>Cefotaxime</u>	<u>220(80.7)</u>	<u>17(54.8)</u>	<u>16(55.2)</u>	<u>88(84.6)</u>	<u>99(76.7)</u>
<u>Metronidazole</u>	<u>186(63.5)</u>	<u>15(48.4)</u>	<u>6(20.7)</u>	<u>90(86.5)</u>	<u>75(58.1)</u>
<u>Cefradine</u>	<u>40(13.6)</u>	<u>8(25.8)</u>	<u>13(44.8)</u>	<u>11(10.6)</u>	<u>8(6.2)</u>
<u>Amoclav</u>	<u>34(11.6)</u>	<u>0</u>	<u>0</u>	<u>14(13.5)</u>	<u>20(15.5)</u>
<u>Amoxicillin</u>	<u>17(5.8)</u>	<u>0</u>	<u>0</u>	<u>2(1.9)</u>	<u>15(11.6)</u>
<u>Gentamicin</u>	<u>14(4.8)</u>	<u>1(3.2)</u>	<u>0</u>	<u>11(10.6)</u>	<u>2(1.6)</u>
<u>Tazocin</u>	<u>9(3.1)</u>	<u>0</u>	<u>0</u>	<u>4(3.8)</u>	<u>5(3.9)</u>
<u>Cefriaxone</u>	<u>3(1.0)</u>	<u>1(3.2)</u>	<u>0</u>	<u>0(1.9)</u>	<u>2(1.6)</u>

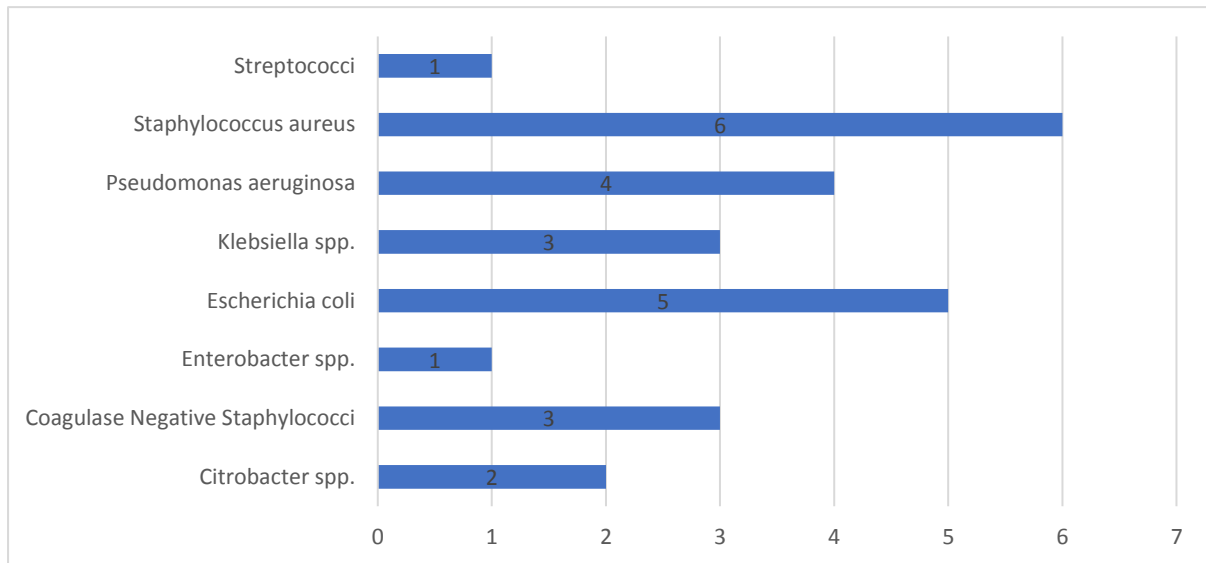
NB: Amoclav = amoxicillin- clavulanic

Surgical site infections

Fifty two (13%) patients self-reported purulent discharge from operation sites. The diagnosis of an SSI was made by the doctor in 36 (9%) patients and positive cultures were reported in 20 (5%) patients. The rate of SSI among patients who underwent emergency and elective surgeries were 22 (8.5%) and 14 (9.9%) respectively. Culture positive SSI occurred in 11 (55%) emergency and in 9 (45%) elective operations. The majority (88.2%) of patients with culture positive SSI had not received pre-operative antibiotics. Two thirds (65%) of the patients were women. Three of the patients who had positive culture results were HIV positive.

The most common types of organisms isolated from the SSIs are shown in figure 1. *Staphylococcus aureus*, *Pseudomonas auriginosa* and *Escherichia coli* were the most common isolated pathogens. All these organisms were sensitive to cefotaxime, the most commonly used antibiotic. *Escherichia coli*, *Klebsiella spp.* and *Citrobacter spp.*, were however resistant to cefotaxime. There was no sensitivity testing for metronidazole or cefradine.

Figure 1 - Organisms cultured from pus swabs of patients with SSI at PMH



Discussion

In this study, we found that approximately three-quarters (73%) of the patients received antibiotics peri-operatively, mostly after surgery. In addition, the majority of patients who had pre-operative antibiotics continued them post-operatively. The most frequently prescribed antibiotics were intravenous cefotaxime, cefradine and metronidazole. The incidence of SSIs was 8.8%, and about half (48.6%) of the patients with SSI had culture positive pus swabs.

The SSI rate in this hospital in Botswana is lower than the pooled incidence rate of SSI of 14.8% reported in Africa by Andersen *et al* [5]. It is, however, comparable to the incidence rate of 9.2% reported by Ntsama *et al* among surgical patients in three public hospitals in Yaounde [35]. While the SSI rate in Botswana is also lower than in other developing countries, where rates as high as 41% have been reported, it is higher than findings from developed countries where it is reported 0 - 3% of surgical patients develop SSIs [7-9]. Nevertheless, it is difficult to compare incidence rates across countries due to variations in populations including co-morbidities, types of surgery, hospital sizes, experience of the surgeons and surveillance methods [3, 4]. One of the reasons for the apparent lower rate of SSIs in Botswana could be the high uptake of antibiotics peri-operatively. The use of antibiotics is reported to decrease the incidence of SSI by 39 %, primarily in those patients who receive antibiotics pre-operatively [23, 26]. However, as the majority of our patients received antibiotics post-operatively in our study, the lower incidence of SSIs cannot fully be explained by antibiotic use.

Similar to findings from other studies, the most common organisms in the current study were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *coagulase-negative staphylococci* [36-38]. Generally, the causative pathogens for SSI originate from the patient's endogenous flora and depend on the type and site of surgery [38].

In addition to other measures, the World Health Organisation guidelines for the prevention of SSIs emphasize an optimal timing for preoperative antimicrobial prophylaxis when indicated [20]. In this study, we found that the timing of the initiation of antibiotics, antibiotic selection and duration of antibiotic prophylaxis were not according to the published guidelines [2, 13, 26]. The finding is consistent with previous studies which revealed heterogeneity in antibiotic choices, timing and duration of antibiotic prophylaxis among surgical patients [39]. To prevent SSIs, the guidelines advise that antibiotic prophylaxis should be given 1-2 hours before a surgical incision for adequate serum and tissue drug levels to be achieved during surgery [13, 17, 22, 24-26]. Similar to findings by Gans *et al.* where 59% of patients in selected American hospitals continued antibiotics postoperatively, the majority of our patients received antibiotics after surgery [39]. Largely, the majority of our patients were administered antibiotics for a mean duration of 5 days. This is contrary to the evidence showing

that the administration of antibiotics after the incision is associated with an increased predisposition to antibiotic resistance and hospital costs compared with administration of antibiotics prior to the incision [20,29]. In actual fact, post-operative initiation of antibiotics has the same effect on preventing SSI as placebo [29, 40]. For reasons which could not be ascertained in this study, we also found that most of those patients who received pre-operative antibiotics continued with them postoperatively for an average of five days. As mentioned above, postoperative antibiotic administration is no better than the preoperative administration alone and may enhance resistance rates [20,29, 41]. Pre-operative use of antibiotics should therefore be encouraged in Botswana and we are now encouraging this in our hospital. This will be the subject of future research.

Normally, selection of antibiotic prophylaxis should be based on multiple factors including the normal floral distribution of the site to be operated and the antibiotic resistance patterns in the hospital setting [1, 17, 27, 31, 32]. Usually, broad-spectrum antibiotics, especially cephalosporin, are preferred to narrow spectrum antibiotics [27]. Because of its longer half-life than other first-generation cephalosporin, a single dose of cefazolin has been ideal for many procedures [42]. As cefazolin is not available in our setting, the Botswana national guidelines recommend cefradine, a first-generation cephalosporin, for most procedures [33]. Despite this, cefradine was prescribed in only 13% of all patients who were administered antibiotics. The majority of our patients received cefotaxime, often in combination with metronidazole. This low compliance with the guideline not only increases hospital costs but also poses an increased risk of resistance to cefotaxime, increasing the occurrence of antibiotic resistance which we need to address [2].

Limitations

We are aware that our study was only undertaken in one hospital in Botswana. However, as mentioned, this is a leading tertiary hospital in the country; consequently, a similar or worse picture is likely to be seen in secondary hospitals in Botswana. Although the exclusion of patients with prosthetic implants may have underestimated the incidence of SSI in our study, we included most of the surgeries encountered in most general hospitals in Botswana for comparative purposes. Even so, surgical implantation of prostheses is not a common practice at PMH. Another limitation of the study was the reliance on surgeon's and anaesthetist's notes as evidence for pre-operative and intraoperative use of antibiotics. This is always a concern with such a methodology. Finally, we did not break SSI down into superficial, deep and organ/space related, and were unable to discuss the associated clinical consequences. Nevertheless, in view of our extensive methodology, we believe our findings are robust and provide guidance to this and other hospitals in Botswana as we seek to enhance the appropriate use of antibiotics in our country.

Conclusion

In conclusion, whilst our rate of SSIs at 8.8% appears lower than in other African countries, there are considerable areas for improvement to reduce the incidence of SSIs and potential AMR in Botswana. These include the timing of the prophylaxis, choice of antibiotics, and duration of prophylaxis beyond surgery. These findings call for interventions to improve the rational use of antibiotic prophylaxis to decrease the rate of SSIs in Botswana. We have already started these programmes in our hospital to address the concerns, and we will be following this up in future research projects. Research projects are also starting at other hospitals in Botswana building on these findings.

Key points

- Appropriate antibiotic prophylaxis is known to reduce the incidence of surgical site infections (SSIs), shorten hospital stay and reduce costs
- Current guidelines recommend that the first dose of antibiotic prophylaxis should be given 1 – 2 hours before the first incision and not after the first incision or post operatively for maximum impact to reduce SSIs and potentially resistance rates. To maintain adequate drug concentration at surgical site, re-dosing is advised for surgeries that exceed 2 half-lives of the antimicrobial or if there is excessive blood loss. However, there is variation in the use of prophylactic antibiotics across countries, with the need for prophylaxis greater in lower and middle income countries with more complex cases
- SSIs in this leading tertiary hospital in Botswana following antibiotic use and follow-up of patients up to 30 days post operatively was 8.8%

- Antibiotics were given in 73.3% of patients undergoing surgery, principally post-operatively (58.3%) with cefotaxime and metronidazole the most prescribed antibiotics
- Concerns that the low compliance with Botswana guidelines will increase costs as well as increase resistance rates. These concerns are already resulting in interventions to try and address this in this and other hospitals in Botswana, which is being followed up

Competing interest and acknowledgements.

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Author contributions

JCM, SS, MGMDM and MM designed the study and were principally involved in data collection and analysis. JCM, SS, AM and BG produced the initial draft manuscript. All authors critiqued successive drafts of the manuscript before submission.

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