

Key Issues Surrounding Appropriate Antibiotic Use for Prevention of Surgical Site Infections in Low- and Middle-Income Countries: A Narrative Review and the Implications

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Julius C Mwita ¹
Olayinka O Ogunleye ^{2,3}
Adesola Olalekan ^{4,5}
Aubrey C Kalungia ⁶
Amanj Kurdi ^{7,8}
Zikria Saleem ⁹
Jacqueline Sneddon ¹⁰
Brian Godman ^{7,11,12}

¹Department of Internal Medicine, Faculty of Medicine, University of Botswana, Gaborone, Botswana; ²Department of Pharmacology, Therapeutics and Toxicology, Lagos State University College of Medicine, Lagos, Nigeria; ³Department of Medicine, Lagos State University Teaching Hospital, Lagos, Nigeria; ⁴Department of Medical Laboratory Science, University of Lagos, Lagos, Nigeria; ⁵Centre for Genomics of Non-Diseases and Personalized Healthcare (CGNPH), University of Lagos, Lagos, Nigeria; ⁶Department of Pharmacy, University of Zambia, Lusaka, Zambia; ⁷Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK; ⁸Department of Pharmacology, College of Pharmacy, Hawler Medical University, Erbil, Iraq; ⁹Department of Pharmacy Practice, Faculty of Pharmacy, The University of Lahore, Lahore, Pakistan; ¹⁰Healthcare Improvement Scotland, Glasgow, UK; ¹¹School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa; ¹²School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

Correspondence: Brian Godman
Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK
Tel +44 141 548 3825
Email Brian.godman@strath.ac.uk

Background: There is a concern with the growing use of antimicrobials across countries increasing antimicrobial resistance (AMR) rates. A key area within hospitals is their use for the prevention of surgical site infections (SSI) with concerns with timing of the first dose, which can appreciably impact on effectiveness, as well as duration with extended prophylaxis common among low- and middle-income countries (LMICs). This is a concern as extended duration increases utilization rates and AMR as well as adverse events. Consequently, there is a need to document issues of timing and duration of surgical antibiotic prophylaxis (SAP) among LMICs together with potential ways forward to address current concerns.

Methods: Narrative review of timings and duration of SAP among LMICs combined with publications documenting successful approaches to improve SAP to provide future direction to all key stakeholder groups.

Results: There were documented concerns with the timing of the first dose of antibiotics, with appropriate timing as low as 6.7% in Egypt, although as high as 81.9% in Turkey. There was also an extensive duration of SAP, ranging from long duration times in all patients in a study in Nigeria with a mean of 8.7 days and 97% of patients in Egypt to 42.9% of patients in Pakistan and 35% in Turkey. Successful interventions to improve SAP typically involved multiple approaches including education of all key stakeholder groups, monitoring of usage against agreed guidelines, as well as quality targets. Multiple approaches typically improved timing and duration as well as reduced costs. For instance, in one study appropriateness increased from 30.1% to 91.4%, prolonged duration reduced to 5.7% of patients, and mean costs of antibiotics decreased 11-fold.

Conclusion: There are considerable concerns with the timing and duration of SAP among LMICs. Multiple interventions among LMICs can address this providing future directions.

Keywords: surgical site infections, antibiotic prophylaxis, timing of prophylaxis, duration of prophylaxis, LMICs, quality indicators

Introduction

Globally, utilization of antibiotics rose by 39% between 2000 and 2015, which has been driven mainly by increasing consumption in lower- and middle-income (LMIC) countries.¹⁻³ This is a concern as rising rates will increase antimicrobial resistance (AMR), increasing morbidity, mortality, and costs.⁴⁻⁷

One of the key areas to reduce inappropriate prescribing of antibiotics in hospitals surrounds their use in preventing surgical site infections (SSIs).⁸ SSIs

are categorized as infections related to a given operative procedure that occurs at or near the surgical incision within 30 days of the procedure or longer if a prosthesis is implanted, and affects either the incision or deep tissue at the operation site or any part of the surrounding anatomy such as pertinent organs or spaces.^{9–11} They are currently the most common infectious complications seen among hospitalized patients in developing countries,^{12,13} and are among the most common and costly causes of hospital acquired infections (HAIs), especially in LMICs.^{14–22} SSIs can also account for appreciable antibiotic use in hospitals.^{23–26} Costs associated with SSIs are enhanced by associated increases in the length of hospital stay, which is in addition to increasing morbidity and mortality.^{15,–27–29} Published studies suggest consolidated incidence figures for SSIs for Nigeria and across Africa at between 14.5–14.8% of all operations,^{12,30} with rates typically higher in LMICs vs high-income countries.^{13,–30–35} Consequently, there is an urgent need to improve their prevention in LMICs.

Recognized measures to reduce SSIs include surgical hand preparation, antiseptic preparation, coated sutures, wound protector devices, and negative-pressure wound dressings.^{18,–29,–36–38} In addition, improving the quality of surgery through increased education as well as the development and monitoring of pertinent quality indicators (QIs).^{39–41} Measures also include administering antimicrobial prophylaxis, which is seen as the single most effective intervention to reduce SSI rates.⁴² The selection of antibiotics for SSIs is often based on the risk of wound infection according to the wound classification, ie, clean, clean–contaminated, contaminated, or dirty–infected, the normal floral distribution of the site to be operated on, and local antibiotic resistance patterns.^{14,43,44} Broad-spectrum antibiotics are often preferred to narrow spectrum antibiotics, and cephalosporins are commonly used.^{27,–45–47} For instance, cefazolin is commonly recommended for the gastrointestinal, genitourinary tract, and hepatobiliary surgeries.⁴⁸ Ideally, administration of the first antibiotic dose should be within 60 minutes of the first incision, longer for vancomycin and the fluoroquinolones, with a second dose administered for long procedures.^{18,–42,–49–51} Vicentini et al⁸ found that adequate antibiotic choices and length of administration were associated with significantly reduced risks of SSIs. Overall, published studies have shown that the risk of SSIs is almost 5-times higher when antibiotics are administered more than 120 minutes prior to the first incision and almost doubled when

antibiotics are administered after the first incision.⁵² Extending prophylaxis beyond 1 day also does not appear to improve patient outcomes, whilst at the same time increasing the chances of acute kidney injury, *Clostridium difficile* infections, AMR, and costs.^{13,–42,–53–56}

We are aware that there can be poor compliance to current guidelines when available to prevent SSIs across LMICs and wider.^{45,–57–62} This is in addition to the lack of antibiotic guidelines generally in some hospitals.⁶³ For instance, Madubueze et al⁵⁹ found that compliance with surgical antibiotic prophylaxis (SAP) protocols among orthopedic surgeons in Nigeria was only 30.3% of situations. Reasons for poor compliance to guidelines included following old practices (25%), concerns that the hospitals were not sufficiently clean (27.3%), and proper aseptic techniques were not being followed (27.3%).⁵⁹ Other reasons for poor compliance include overcrowding in hospitals, resistance to change among physicians, poor knowledge regarding antibiotics among physicians, and concerns with malnutrition in some patients.^{45,50,64} Patient expectations may also play an important factor in decision-making.^{50,65}

Principal areas of concern with current SAP approaches across countries including LMICs include timing of administration as well as prolonged use post-surgery.^{23,45,66,67} Consequently, we believe there is a need to document issues regarding the current timing of administration and the duration of antibiotic administration for SAP among LMICs as well as debate potential ways forward to improve this. This is because reducing the length of post-operative administration will reduce the extent of broad-spectrum antibiotic use for SAP, which in turn should reduce AMR as well as adverse events. Improved SAP can be part of the agreed National Action Plans as countries move to reduce their AMR rates.^{68–70} This was the objective behind this review article.

Materials and Methods

We have chosen LMICs as they typically have the highest rates of AMR with concerns with antibiotic prescribing common across countries and sectors.^{68,–71–73} We are also aware of the challenges involved with implementing quality improvement programs among hospitals in LMICs to improve future antibiotic prescribing, which include manpower and resource issues as well as physician resistance as part of any antibiotic stewardship program(ASP).^{74,75} ASPs are important as they can appreciably improve

antibiotic use in hospitals and reduce costs.^{74,76} These challenges with improving the appropriate use of antibiotics in hospitals are exacerbated by variable knowledge regarding antibiotics, AMR, and ASPs among clinicians in LMICs.^{73,-77-85} Consequently, we will look to build upon successful approaches to improve SAP instigated among LMICs to give guidance on potential ways forward to address concerns where these continue to exist.^{50,86}

The first step will be to document timings and the duration of antibiotic administration for SAP among a range of LMICs before documenting interventions that have been successful with improving SAP among LMICs. This will involve a narrative review of the published literature. The findings will be combined with the extensive experience of the senior-level co-authors to provide future guidance on potential ways to enhance SAP among LMICs including lessons generally from a range of former Soviet Union Republics that have variably instigated initiatives to reduce inappropriate prescribing of antibiotics. We have chosen former Soviet Union Republics as they typically have less Gross Domestic Product (GDP) per capita than among higher income Western European countries,⁸⁷ ie, more akin to LMICs.

We did not undertake a systematic review since we were aware that there had been a number of reviews surrounding the use of antibiotic prophylaxis as well as other potential interventions to reduce SSIs.^{29,-50,-52,-86,-88-93} In addition, our aim was to provide possible guidance for key stakeholder groups within LMICs based on our experiences for potential debate. We have successfully used this approach across LMICs to stimulate debate in different key disease areas and topics.^{68,-94-97}

The interventions that have been undertaken and proposed will be broken down into the 4Es where pertinent, namely Education, Engineering, Economics, and Enforcement,^{98,99} to enhance understanding and comparisons given the range of potential interventions that could be instigated. Education includes developing guidelines or formularies, with adherence to well-constructed guidelines increasingly seen as indicating good quality care.^{25,-100-103} Activities within hospitals to enhance the rational use of medicines are typically co-ordinated by Drug and Therapeutic Committees (DTCs).¹⁰⁴⁻¹⁰⁶ Antimicrobial stewardship groups may be part of DTCs; alternatively, separate groups working in the hospital as part of infection, prevention, and control groups.^{107,108} In addition, the development and dissemination of the WHO AWaRe list of antibiotics to improve future antibiotic prescribing and

dispensing.^{109,110} Engineering includes organizational or managerial interventions such as instigating and monitoring prescribing targets and quality targets.^{99,100} Quality targets could include the percentage of antibiotics prescribed according to agreed guidance, the percentage of antibiotics prescribed within a specified time and for an agreed length to prevent SSIs, as well as monitoring drug and therapeutic committee (DTC) activities against agreed performance indicators.^{59,102,111} Economics includes financial incentives to hospitals, physicians, pharmacists, or patients, ie, providing financial incentives to hospitals to improve patient safety and not pay for preventable errors, to physicians for attaining agreed prescribing targets, and fining pharmacists for illegally dispensing an antibiotic without a prescription.^{99,100,112,113} Enforcement includes regulations by law.⁹⁹ Examples include laws banning the dispensing of antibiotics in pharmacies without a prescription as well as national policies outlining the existence of DTCs in hospitals as currently seen in South Africa.^{105,114}

Results

Timing and Duration of Administration for SAP Among LMICs

Table 1 documents a range of timings and duration of administration for SAP among LMICs across continents. Ideally, administration of the first antibiotic dose should be within 60 minutes of the first incision and only for 1 day. However, wide variations were seen with only a limited number of patients across a range of LMICs generally receiving SAP within this time (Table 1). Documented rates for staying within agreed timings of the first incision ranged from as low as 6.7% of patients in Egypt, up to 81.9% in Turkey.

There were similar concerns regarding the extent of prophylactic antibiotics given for longer than 1 day across LMICs. Rates of extended prophylaxis ranged from all patients in Nigeria in the study by Abubakar et al (2018) with a mean of 8.7 days, to 97% of patients in Egypt and Pakistan (Saied et al 2015 and Saleem et al 2019, respectively), and 86.3% among surgical patients in Eastern Europe (part of the Global PPS study). Extended prophylaxis was seen in 42.9% of patients in Pakistan (Butt et al 2019) and 35% in Turkey (Ozgun et al 2020) (Table 1).

Interventions to Enhance Adherence to SAPs Among Countries

A number of interventions have been instigated across many LMICs to improve SAP broken down into

Table 1 Published Rates Regarding Inappropriate Timing and Length of Administration of Antibiotics for SAP Among LMICs

Country	Author and Year	Findings
Global PPS including many LMICs	Versporten et al, 2018 ²⁵	<ul style="list-style-type: none"> • Prolonged surgical prophylaxis, ie, >1 day was very common in all regions of the world • The highest rates of extended prophylaxis were seen in Eastern Europe (LMICs) – 86.3% of patients
Botswana	Mwita et al, 2018 ¹¹	<ul style="list-style-type: none"> • Poor timing of prophylaxis was common, with only 15% of surgical patients receiving antibiotics pre-operatively, 58.3% post-surgery, and 26.8% of patients were not prescribed any antibiotics • Prolonged surgical prophylaxis was common, with the mean (SD) duration of post-operative antibiotic use being 5 (2.6) days
	Anand Paramadhas et al, 2019 ¹¹⁵	<p>Extended prophylaxis (>1 day) was common. However, the extent among patients varied across hospital types:</p> <ul style="list-style-type: none"> • Specialist – 66.7% of patients • Tertiary – 100% of patients • District – 90.3% of patients • Primary – 100% of patients
China	Yang et al, 2014 ⁵¹	Poor timing of the initial antibiotic dose, ie, outside of 30 minutes to 2 hours pre-incision, was common and seen in 67.1% of patients
Egypt	Talaat et al, 2014 ¹¹⁶	<p>Poor timing and prolonged use of antibiotics was common among surgical patients in this PPS study:</p> <ul style="list-style-type: none"> • 72% of surgical patients did not receive their first dose of antibiotics within 2 hours before the incision • 75% of patients received surgical prophylaxis for >24 hours
	Saied et al, 2015 ¹¹⁷	<ul style="list-style-type: none"> • Poor timing of SAP was common, with 92.3% of patients receiving the first dose of antibiotics outside of the agreed optimal time among three hospitals surveyed prior to educational and other interventions • All hospitals surveyed showed a significant improvement in the optimal duration of SAP post-intervention – increasing from 3% of patients to 28% ($P<0.01$)
Ethiopia	Halawi et al, 2018 ⁴⁷	<ul style="list-style-type: none"> • 62.2% of patients received SAP longer than 1 hour pre-operatively • 88.9% of patients received antimicrobial prophylaxis for greater than 24 hours after surgery
Ghana	Afriyie et al, 2020 ⁶³	The duration of antibiotic use for SAP was generally more than 1 day – 69.0% in one hospital and 77.0% in another
Kenya	Ntumba et al, 2015 ¹¹⁸	50% of patients in this study received post-operative antibiotics before an active intervention to address high rates
	Opanga et al, 2017 ⁶⁷	The duration of prophylaxis from the onset of surgery for patients with neurotrauma ranged from 1–3 days
	Okoth et al, 2018 ¹¹⁹	The average number of antibiotic doses in this PPS study for SAP was 19.1 doses
India	Shankar, 2018 ⁶¹	All patients operated on on a particular day were administered antibiotics in the morning, irrespective of the timing of their surgery
Iran	Mahmoudi et al, 2019 ²⁷	92.1% of patients received SAP for more than 48 hours
Nigeria	Madubueze et al, 2015 ⁵⁹	57.6% of orthopedic surgeons gave antibiotic administration outside of 1 hour prior to surgery
	Abubakar et al, 2018 ⁶⁴	<ul style="list-style-type: none"> • Timing of SAP was suboptimal, with 83.5% of patients administered their first dose outside of the 60 minute window prior to the first incision • Prolonged SAP was seen in all patients with a mean duration of 8.7±1.0 days

(Continued)

Table 1 (Continued).

Country	Author and Year	Findings
	Oshikoya et al, 2019 ¹²⁰	<ul style="list-style-type: none"> 97.7% of surgical patients received SAP However complete compliance to current guidelines on issues such as timing and duration of antibiotic use was suboptimal in 94.4% of patients
	Umeokonkwo et al, 2019 ⁴⁶	Typically, prolonged use of antibiotics for surgical prophylaxis was common
	Fowotade et al, 2020 ¹²¹	98.7% of all antibiotic prescriptions for SAP were given for more than 1 day
Pakistan	Butt et al, 2019 ⁴⁵	<ul style="list-style-type: none"> Pre-intervention – incorrect choice of antibiotic – 88.4% of occasions Duration of antibiotic use >60 hours – 42.9% of occasions
	Saleem et al, 2019 ¹²²	97.4% of antibiotics prescribed for SAP in this PPS study in the Punjab region were given for more than 1 day
	Satti et al, 2019 ¹²³	Duration of post-operative prophylaxis for SAP was suboptimal with 47.3% prescribed antibiotics for >24 hours
Rwanda	Nkurunziza et al, 2019 ⁶⁰	92% of SAP patients received post-operative antibiotics for more than 3 days
Turkey	Ozgun et al, 2010 ¹³¹	There was prolonged use of antibiotics post-operatively in 35% of patients
	Kaya et al, 2016 ¹²⁴	Duration of antibiotic use for SAP was inappropriate in 29.1% of cases
	Karaali et al, 2019 ²³	<ul style="list-style-type: none"> Surgical prophylaxis >24 hours – 60.2% of patients Antibiotic prescribed after discharge – 80.6% of patients

Abbreviations: LMICs, lower- and middle-income countries; PPS, Point Prevalence Survey; SAP, surgical antibiotic prophylaxis.

Education, Engineering, Economics, and Enforcement where pertinent and by year to provide guidance.

Interventions principally centred around educational inputs. In addition, monitoring subsequent prescribing against agreed guidance (QIs) and providing feedback to help improve subsequent SAP (Engineering – Table 2). Multiple interventions resulted in appreciable improvements in SAP across LMICs. For instance, Bozkurt et al (2014) found that multiple interventions improved the duration of prophylaxis from 10.3% to 59.4% of cases, Saied et al (2015) that optimal timing of the first dose can be appreciably improved (6.7% to 38.7%), and Brink et al (2017) that the choice of antibiotic, consistent with agreed guidelines, can be improved to 95.9% of patients (Table 2).

However, we are aware there are cases where interventions have not always been effective. In their study, Ozgun et al¹³¹ instigated a number of measures including analyzing key concerns regarding SAP with individual surgical teams, as well as educational meetings with all key stakeholders during which concerns including timing and duration of antibiotic use were discussed. However,

compliance to agreed guidelines actually decreased post-intervention, and the number of patients receiving prolonged SAP was higher after the intervention than before, increasing from 34% of patients (Table 1) to 52%, which was statistically significant ($P < 0.01$), with surgeons comfortable at the time with prolonged administration.¹³¹

Discussion and Recommendations

We have shown that there can be considerable concerns regarding the current use of SAP among LMICs to reduce SSIs. These include concerns with both the timing and duration of administration of antibiotics (Table 1). Both need to be addressed to enhance the effectiveness of appropriate SAP to prevent SSIs, reduce the extent of any adverse events including *Clostridium difficile* infections and AMR, as well as reduce costs.^{8,52–55}

Encouragingly, typically multifaceted interventions appear to be successful in addressing concerns with timing and duration of antibiotic prophylaxis providing direction to others (Table 2). This mirrors the successful impact of multiple interventions instigated by health authorities and others in different disease areas and situations, including

Table 2 Summary of Published Studies Across Countries Documenting the Impact of Interventions on Subsequent Timing and Length of Antibiotic Administration Among a Range of LMICs

Author and Year	Intervention	Impact
Gomez et al, 2006 ¹²⁵	<ul style="list-style-type: none"> • Education: Intervention based on education/training • Engineering/Enforcement: Introduction of a protocol with an automatic stop for antimicrobial prophylaxis 	<ul style="list-style-type: none"> • Timing of prophylaxis improved from 55% to 88% of patients ($P<0.01$) • Adequate duration of prophylaxis increased from 44% to 55% of patients ($P<0.01$) • Overall expenditure decreased from US\$10,679 per 1,000 patient-days to US\$7,686
Aitken et al, 2013 ⁶⁵	Education and Engineering: Developing and implementing a SAP policy within the hospital	<ul style="list-style-type: none"> • Appreciable improvement in lack of post-operative prophylactic antibiotics to 60% of patients in week 1 and 90% in week 6 following policy implementation ($P<0.0001$) • Net reduction in the costs for IV antibiotics and associated consumables of approximately US\$2.50/operation
Bozkurt et al, 2014 ¹²⁶	Educational interventions including: <ul style="list-style-type: none"> • Series of meetings with physicians from each clinic organized by the Infection Control Committee • Daily visits from the Infection Control Nurse as well as regular visits (twice per week) from an Infectious Diseases Control Specialist – more if compliance with agreed guidelines was low • Observations regularly shared with the physicians 	<ul style="list-style-type: none"> • Use of appropriate antibiotics increased from 51% to 63.4% of cases • Duration of use improved from 10.3% to 59.4% of cases • Total cost of antibiotics in the medical units, surgical units, and ICUs decreased by 32.5%, 38.6%, and 11.1%, respectively
Yang et al, 2014 ⁵¹	Education and Engineering: Introduction of a Drug Rational Usage Guideline System (DRUGS) vs paper-based guidelines to enhance adherence to surgical prophylaxis guidelines	<ul style="list-style-type: none"> • Timing of the initial dose improved from 32.9% instigated within 30 minutes to 2 hours pre-incision to 85.8% (statistically significant) post-intervention • Average length of stay decreased from 7.00 days with paper-based guidelines to 2.55 days with DRUGS • Average cost of antibiotics decreased from ¥3,481 with paper-based guidelines to ¥1,693 with DRUGS
Kim et al, 2015 ¹²⁷	Education and Engineering: <ul style="list-style-type: none"> • Introduction of a surgical safety checklist in the operating theater over a week-long period • Data collection team developed and randomly assigned to observe 30% of the surgical cases and collect process adherence measures, and feedback the findings 	<ul style="list-style-type: none"> • 12.7% increase in the appropriate use of prophylactic antibiotics
Ntumba et al, 2015 ¹¹⁸	Education and Engineering: <ul style="list-style-type: none"> • Local adaptation of guidelines • Creation and tools for advocacy, training, and leadership around appropriate SAP 	<ul style="list-style-type: none"> • Patients receiving antibiotics post-operatively decreased from 50% to 26% • Crude SSI rates significantly decreased from 9.3% to 5% of patients
Saied et al, 2015 ¹¹⁷	Education and Engineering: <ul style="list-style-type: none"> • 2-day training curriculum • On-the-job training provided to junior surgeons and residents • Wall-mounted poster developed to remind prescribers of the optimal timing and duration of antibiotic administration for SAP • Regular audit and feedback meetings orchestrated by the senior surgeon in the hospital (three of five participating hospitals) 	<ul style="list-style-type: none"> • The optimal timing of the first dose improved significantly in three hospitals, increasing from 6.7% to 38.7% ($P<0.01$) • All hospitals showed a significant rise in the optimal duration of surgical prophylaxis – overall increase of 3–28% ($P<0.01$)

(Continued)

Table 2 (Continued).

Author and Year	Intervention	Impact
Brink et al, 2017 ¹²⁸	<p>Education and Engineering. Key activities driven by hospital pharmacists included:</p> <ul style="list-style-type: none"> Recording current SSI rates and developing a SAP “toolkit” Testing and revising the SAP guidelines and toolkits at pilot sites prior to their launch at regional training and institutional workshops Obtaining consensus and endorsement from key professionals in the hospital through adapting and modifying guidelines where appropriate Choosing at least one or more surgical procedures to audit, including recording pre-intervention SAP practices and trends for the chosen surgeries Subsequently measure compliance to agreed four process measures over a 4-week period and feedback 	<ul style="list-style-type: none"> Timely administration of antibiotics increased to 56.4% of surgical patients ($P<0.0001$) Antibiotic choice consistent with the guidelines increased to 95.9% of patients and the duration of prophylaxis was now appropriate among 93.9% of patients
Allegranzi et al, 2018 ¹²⁹	<p>Education and Engineering:</p> <ul style="list-style-type: none"> 5 planned visits to each hospital during the study period supported by a range of tools Local teams identified key areas of concern with preventing SSIs to concentrate on through monitoring an agreed range of SAP indicators (six pre-identified ones including skin preparation and optimal timing of prophylaxis) Subsequent launch activities of tools and indicators and monitoring/feedback 	<ul style="list-style-type: none"> Appropriate use of SAP improved from 12.8% (baseline) to 39.1% of patients ($P<0.0001$) Cumulative SSI incidence decreased from a baseline of 8.0% to 3.8% post-intervention ($P<0.0001$)
Shankar, 2018 ⁶¹	<p>Education and Engineering:</p> <ul style="list-style-type: none"> Agreement among key stakeholders of the key elements of the WHO checklist to help reduce SSIs The designated checklist coordinator to confirm that the surgical team has completed its tasks before proceeding to the next steps 	<ul style="list-style-type: none"> Prior to implementation all patients operated on on a particular day were administered antibiotics in the morning, irrespective of the timing of their surgery The correct practice of administration within 1–2 hours of the incision was seen following the intervention In addition, rectification of any concerns that appropriate surgical patients were not given SAP
Abubakar et al, 2019 ¹³⁰	<p>Education and Engineering:</p> <ul style="list-style-type: none"> Development and dissemination of an agreed departmental protocol for SAP, presented and agreed before adoption to enhance adoption rates Educational meetings with key clinicians to enhance uptake of agreed protocols Audit and feedback meetings using baseline data Reminders with wall mounted posters 	<ul style="list-style-type: none"> Patients in the post-intervention period were 5.6-times more likely to receive SAP within 60 minutes before the incision vs pre-intervention ($P<0.001$) Rate of redundant antibiotic prescriptions was reduced by 19.1%
Butt et al, 2019 ⁴⁵	<p>Education and Engineering:</p> <ul style="list-style-type: none"> Results of pre-intervention studies shared with physicians and nurses Subsequently general and specific problems regarding appropriate SAP were discussed with concerned personal and committees to enhance future adherence rates Training programs over 10–15 days were conducted by hospital pharmacists for physicians and nurses 	<ul style="list-style-type: none"> Appropriateness of prophylactic antibiotics increased from 11.6% to 28% Only 33% of patients received extended prophylaxis, ie, >60 hours, down from 42.9% of patients pre-intervention ($P=0.032$) significantly reducing antibiotic costs ($P=0.023$) Average length of hospitalization also fell to an average of 4.50 days post-intervention vs 5.4 days pre-intervention, further reducing costs

(Continued)

Table 2 (Continued).

Author and Year	Intervention	Impact
Karaali et al, 2019 ²³	<p>Education, Engineering, and Enforcement:</p> <ul style="list-style-type: none"> Local guidelines updated by two members of the infection control committee One general surgery team leader was appointed to be responsible for improving SAP as part of ASPs in their group Periodic training sessions were planned to supervise and regulate SAP by surgical team leaders It was decided that clean and clean-contaminated cases would not be given SAP for longer than 24 hours and that discharge prescriptions would not include antibiotics. However, no verbal or written sanctions were imposed for abuse 	<ul style="list-style-type: none"> Compliance with the indication of surgical prophylaxis significantly increasing from 55.6% to 64.5% of patients ($P<0.05$) – despite differences between surgical types Significant reduction in the extent of prolonged antibiotic prophylaxis, ie, beyond 24 hours, to just 7.5% post-intervention from 60.2% of patients pre-intervention ($P<0.05$) Extent of antibiotic prescribing after discharge improved, ie, from 80.6% of patients pre-intervention down to 9.4% post-intervention ($P<0.05$) However limited impact on the timing of first antibiotic dose – appropriate timing increasing from 81.9% of patients to 83.7%
Mahmoudi et al, 2019 ²⁷	<p>Education and Engineering:</p> <ul style="list-style-type: none"> Revising SAP guidelines following meetings between a clinical pharmacist and the surgical department, with senior clinical pharmacists delivering lectures about SAP to key members of the surgical departments Clinical pharmacists participating in ward rounds, attending recovery rooms, and communicating with surgeons when guidelines not followed Clinical pharmacists providing educational material on SAP to enhance future care Rationality of SAP continually evaluated during the perioperative period in accordance with agreed guidelines, with clinical pharmacists communicating any concerns directly to relevant physicians to improve future SAP 	<ul style="list-style-type: none"> Rate of antibiotic prescribing beyond 48 hours appreciably improved to just 5.7% of patients, down from 92.1% of patients pre-intervention Appropriateness of antibiotic use increased to 91.4% of patients, up from 30.1% The mean cost of antibiotics decreased more than 11-fold and length of stay from an average of 5.14 days to 4.33 days ($P<0.001$) post-intervention

Abbreviations: LMICs, lower- and middle-income countries; ASPs, antimicrobial stewardship programs; PPS, Point Prevalence Survey; SAP, surgical antibiotic prophylaxis; SSIs, surgical site infections.

antibiotics as well as medicines for acid-related stomach disorders, depression, hypertension, and hypercholesterolemia, to improve their prescribing.^{132–140} There have been limited changes in physician prescribing behavior in the absence of such interventions.^{141–143} In addition, we are aware that multiple demand-side measures in former Soviet Union Republics have improved appropriate use of antibiotics. In Azerbaijan, initiatives including Education, Economics, and Enforcement resulted in antibiotic utilization decreasing by 47% between 2011 and 2015.¹⁴⁴ In Slovenia, multiple activities including all the 4Es also resulted in antibiotic utilization falling by 31% between 1999 to 2012,¹³⁷ with multiple activities in the Republic of Srpska including all the 4Es resulting in a decreasing trend in antibiotic consumption in recent years, with utilization rates comparable or lower than those seen in neighboring countries.¹⁴⁵ This contrasts with Poland, where limited activities among the authorities and other

groups between 2007 and 2016 resulted in Poland continuing to have one of the highest rates of antibiotic consumption across Europe.¹⁴⁶ However, we are aware of situations where multiple interventions have not improved SAP.¹³¹

Potential future activities to improve SAP center around the development of antimicrobial stewardship activities including ASPs which can be part of DTCs within countries and hospitals if not already instigated to address concerns and misconceptions (Table 3). This may include the need for additional educational activities surrounding antibiotics and concerns with hygiene, AMR, and SAP if pertinent, along with the development of any local guidelines and QIs. The outputs from subsequent monitoring of SAP post-intervention, including changes in any agreed QIs, can be used to develop and instigate additional pertinent interventions. This is because we have seen that multiple activities including Education,

Table 3 Potential Strategies to Improve SAP Within Hospitals in LMICs

Potential Strategies (if Not Being Enacted)
<p>Health authority/Government – the following (if not already done so):</p> <p>a) General/Economics</p> <ul style="list-style-type: none"> • Commitment to reducing inappropriate antibiotic prescribing in hospitals as part of any ongoing/planned NAPs. This will involve resources being made available for instigating/implementing ASPs within hospitals with the appropriate use of SAP a key priority. This could be part of DTC or other activities <p>b) Education/Engineering</p> <ul style="list-style-type: none"> • As part of this: <ul style="list-style-type: none"> ○ Contact key universities within countries concerning current physician, pharmacy, and nurse training regarding antibiotics, AMR, ASPs, and SAP, and seek to address concerns where identified. Subsequently, monitor the situation ○ Ascertain current knowledge of key stakeholders within hospitals regarding antibiotics, AMR, ASPs, and SAP, using both quantitative and qualitative approaches to guide future activities – which could include the need for further education and training ○ Ascertain current SAP practices within hospitals, especially around key issues of timing and length of administration to guide future activities • Use the findings from any research activities to develop additional educational and other programs where needed among all key stakeholder groups to further improve SAP as part of any NAP – recognizing that multiple interventions are likely to have greater success (Table 2). This includes the introduction/expansion of ASPs that will be culture- and country-specific, as well as multidisciplinary given concerns in some LMICs^{75,77,79} • Develop or update current guidelines for SAP with key stakeholder groups and make these readily accessible and easy to use. This could include the availability of guidelines on smartphones and other electronic media where pertinent and possible • As part of this, seek to introduce routine monitoring of antibiotic resistance patterns within hospitals to refine future SAP guidelines • Instigate active communication and dissemination of any guidelines – key to enhancing adherence rates along with their ease of use.^{50,86,103,157,158} • Subsequently, monitor SAP prescribing against current guidelines and NAPs, enhanced by auditing current practices based on WHO and other checklists • Pertinent additional programs could include developing/refining QIs for the setting/country building on WHO checklists as well as other quality initiatives for the prevention of SSIs mindful of the requirements needed to develop robust quality indicators^{40,41,61,147,159} <p>c) Economics/Enforcement</p> <ul style="list-style-type: none"> • Potentially review funding for hospitals based on avoidable SSIs and their subsequent impact on morbidity, mortality, and costs <p>Physicians</p> <p>a) Education</p> <ul style="list-style-type: none"> • Ascertain current knowledge and beliefs about antibiotics, SAP, and AMR as well as current SAP practices to ascertain gaps in knowledge/current practices. This includes attitudes and beliefs that lead to prolonged antibiotic administration for SAP • Subsequently seek to instigate additional educational and other activities to address concerns with SAP where these exist, as well as help instigate ASPs within the hospital if these are lacking – recognizing that multiple interventions including educational interventions are typically more successful than single ones (Table 2)^{50,86} • Seek to instigate/enhance CPD activities once healthcare professionals qualify with the help of relevant societies and the government¹⁶⁰ • Make sure current national guidelines are readily available and easily accessible in facilities and regularly updated as this is not always the case. This can include the availability of guidelines on smart phones • In addition, encourage physicians through auditing and other practices to regularly consult national/hospital guidelines about optimal approaches to SAP including timing and duration where there are concerns, as well as monitor their performance. • Work with microbiologists to regularly update resistance patterns within the hospital to help refine SAP guidelines if needed <p>b) Engineering</p> <ul style="list-style-type: none"> • Encourage physicians through auditing and other practices to regularly consult national/hospital guidelines about optimal approaches to SAP including timing where there are concerns, as well as monitor their performance • Use their knowledge to develop meaningful QIs for their specific setting to improve SAP in the future – building on checklists from the WHO and others together with key stakeholder groups – including other physicians, physician societies, nurse practitioners, hospital pharmacists, and health authorities • Subsequently introduce agreed QIs, monitor prescribing against agreed targets, refine QIs if needed, as well as seek to instigate additional activities if needed to further enhance adherence to agreed QIs to improve SAP within the hospital <p>c) Economics</p> <ul style="list-style-type: none"> • Potentially seek to reward physicians for adherence to agreed SAP guidelines similar to activities with prescribing in a number of countries as well as achieving agreed QIs^{100,134,161}

(Continued)

Table 3 (Continued).

Potential Strategies (if Not Being Enacted)
<p>d) Enforcement</p> <ul style="list-style-type: none"> Potential activities could surround stopping antimicrobial prescribing for SAP after 24 hours, with potential sanctions for abuse – similar to the situation for self-purchasing of antibiotics in community pharmacies^{113,114} <p>Hospital Pharmacists</p> <p>a) Education</p> <ul style="list-style-type: none"> Conduct activities within hospitals to ascertain current knowledge regarding antibiotic use, AMR, and ASPs given concerns that exist including concerns with hygiene, etc., leading to extended prophylaxis to prevent SSIs Advocate for additional educational activities among pharmacy students surrounding antibiotics, AMR, ASPs, and SAP where pertinent, as well as seek to instigate/enhance CPD activities among hospital pharmacies with the help of relevant pharmaceutical societies and the government <p>b) Education/Engineering</p> <ul style="list-style-type: none"> Play an active role in the instigation/development of ASPs within hospitals as well as seek to actively research current antibiotic use for SAP and generally regarding antibiotic use including PPS studies.^{115,162} This could be part of DTC activities Educate key stakeholders regarding appropriate SAP and pertinent antibiotics including alternatives if drug shortages exist.¹⁶³ Such activities can also be part of DTC activities within hospitals or separate depending on the hospital Be involved with the development of pertinent QIs within the hospital to improve future SAP, as well as future monitoring and refining activities. This can include disseminating the findings from current antimicrobial resistance patterns within the hospital to refine future SAP guidelines if needed <p>Infection, prevention, and control co-ordinating personnel (if different, eg, nurses)</p> <p>a) Education/Engineering</p> <ul style="list-style-type: none"> Help instigate ASPs and research into current SAP activities if not already enacted – including addressing current beliefs that lead to extended use of antibiotics for SAP post-surgery, eg, concerns with hygiene Help physicians and hospital pharmacists to improve the use of antibiotics for SAP within the hospital, including pertinent educational activities as well as the development/refinement/monitoring of QI activities Use the findings from any research/monitoring activities including those surrounding any developed QIs to further educate and co-ordinate activities within hospitals to improve future SAP. This can also include updated findings regarding resistance patterns within the hospital Continue to monitor the impact of any activities on the dose, timing, and length of administration of any antibiotics for SAP and introduce further campaigns if needed <p>HTA Organizations (where these exist)</p> <ul style="list-style-type: none"> Can help with the local development of any SAP guidelines building on evidence-based principles and subsequently with the monitoring of adherence to SAP guidelines that are developed Potentially research the cost-effectiveness of different potential campaigns to improve SAP within hospitals, building on current information regarding the cost benefits of different activities to improving timings/reduce prolonged administration of antibiotics within hospitals – especially if increased resistance increases the costs of antibiotics used. This includes any QIs developed <p>Patients and the public (education)</p> <ul style="list-style-type: none"> Instigate health education programs regarding the appropriate use of antibiotics and AMR within in schools, communities and patient groups where needed Potentially educate patients and households that extensive use of antibiotics is not necessary to reduce SSIs and can be counter-productive, including enhancing future AMR rates

Abbreviations: AMR, antimicrobial resistance; ASPs, antimicrobial stewardship programs; CPD, continual professional development; DTCs, Drug and Therapeutic Committees; LMICs, lower- and middle-income countries; NAP, National Action Plans; PPS, Point Prevalence Survey; QIs, quality indicators; SAP, surgical antibiotic prophylaxis; WHO, World Health Organization.

Engineering, and Enforcement can have a significant impact on both the timing and duration of antibiotic use as part of SAP, impacting on future prevalence and morbidity of SSIs as well as costs (Table 2).

More studies are needed though to assess the cost-effectiveness of different interventions as opposed to studies that principally measure individual cost components before and after interventions to provide future guidance (Table 3). In addition, any QI developed needs to be robust, appropriate, measurable, and

improve future care, building on examples in other situations as well as suggestions from the WHO and others.^{25,–61,–147–149}

We are aware that Health Technology Assessment (HTA) units are less developed in LMICs vs high-income countries and there can be concerns with implementing the findings of HTA analyses.^{150,151} However, this is starting to change in some countries, with suggestions for a more integrative approach.^{152,153} This is important as the outputs from HTA units can help hospitals and governments

prioritize resources and personnel, with the situation becoming even more imperative post the current COVID-19 and its consequences.⁹⁷ This is important to enhance the rational use of SAP in LMICs. However, HTA as a strategy to curb AMR requires appropriate legislative and institutional frameworks, as well as human and financial resources, to translate any findings into effective implementation and monitoring of health interventions.¹⁵⁴

In addition, physicians, nurses, and pharmacists must confidently trust any STGs produced to enhance their acceptability and success in curbing AMR.^{155,156} This, complemented by enhancing healthcare worker's knowledge regarding antibiotic use, AMR, and ASPs within hospitals through targeted educational interventions, can improve the rational use of antibiotics.

We are aware of some limitations with this paper. These include the fact that we did not undertake a systematic review for the reasons discussed. We have, though, contextualized the findings to provide direction to key stakeholder groups to improve SAP in LMICs based on the considerable experience of the co-authors. We believe these recommendations are robust based on their experience and knowledge across LMICs.

Conclusion

We believe this is the first review study to combine a narrative review of the timings and duration of antibiotic use for SAP among LMICs as well as approaches that have been successful in addressing current concerns with SAP to provide future direction. We have shown that there are considerable concerns with current SAP among LMICs, including timing and duration, which is important given rising antimicrobial consumption rates and AMR among LMICs. However, multiple interventions can appreciably improve the situation and reduce costs. As a result, there are multiple activities that all key stakeholder groups can undertake to improve future SAP where important issues have been identified, and we will be monitoring this.

Author Contributions

All authors contributed to the design and development of the paper through their extensive activities to improve the use of antibiotics within hospitals and wider. All authors critically evaluated the first and subsequent drafts and approved the final version before submission.

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