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A multicenter Point Prevalence Survey of Antibiotic Use and Healthcare Acquired Infections in Ethiopian Hospitals

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Abstract

Objective: Effective antimicrobial containment strategies such as Antimicrobial stewardship programs (ASP) require comprehensive data on antibiotics use which is scarce in Ethiopia. We assessed antibiotics use and healthcare-associated infections (HCAIs) in Ethiopia.

Design: We conducted a cross-sectional study using the WHO point-prevalence survey protocol for systemic antibiotics use and HCAIs for low- and middle-income countries.

Setting: The study was conducted among 10 public hospitals in 2021.

Participants: All patients treated at adult and pediatrics inpatient and emergency wards were enrolled and a total of 1820 patients were included.

Outcome measure: The primary outcome measures were the proportion of antibiotic use, HCAIs, and the hospitals' readiness to implement ASP.

Results: None of the surveyed hospitals had functional ASP during the survey. The prevalence of HCAIs was 39.6% and pneumonia was the most common bacterial infection (28.6%) followed by clinical sepsis (17.8%). Most treatments were empiric (96.7%) and the overall prevalence of antibiotic use was 63.8% with antibiotics prescription per patient ratio of 1.77. Nearly half (45.8%) of the patients were prescribed ceftriaxone and metronidazole. Age, having a retroviral infection, ward type, catheterization and intubation history and type of hospital had significant association with antibiotic use. Patients who were treated in pediatric surgical wards were about four times more likely to be on antibiotics compared to patients treated at an adult emergency ward. Patients on urinary catheter (AOR: 2.74, 95%CI:2.04,3.68) and intubation device (AOR= 2.62, 95%CI:1.02,6.76) were more likely to be on antibiotics than their non-catheterized/non-intubated counterparts. Patients treated at secondary level hospitals had 0.34 times decreased odds of being on antibiotics compared to patients treated at tertiary level.

Conclusion: Antibiotic use across the surveyed hospitals was common and most were empiric which had both practical and policy implications for the needs of strengthening ASP to promote rational antibiotics use.

Strengths and limitations of the study

- Our study may not fully reflect long term antibiotic use patterns for Ethiopia as the point prevalence survey (PPS) was limited to selected secondary and tertiary public hospitals.
- This is the first multicenter PPS undertaken in Ethiopia using the standardized WHO PPS methodology thus allowing cross-country comparison.
- We generated valuable data for practitioners, hospital administrators and policymakers to strengthen implementation of antimicrobial stewardship programs.
- The findings can be used to guide future studies in Ethiopia and other low-middle income countries.

Introduction

Since their discovery, antimicrobials have saved millions of lives, substantially reduced disease burden, improved the quality of life, and helped to increase life expectancy since their discovery [1]. However, Antimicrobial Resistance (AMR) is becoming a growing global health, social and economic threat to humans, animals and the environment [2]. About 700,000 people per year die due to AMR and, unless urgent measures are taken, AMR will lead to 10 million deaths and would cost the global economy up to US$ 100 trillion by 2050. It is also predicted that AMR will disproportionately affect low- and middle-income countries (LMICs) [3]. As a result, containing and controlling AMR demands multi-sectoral collaboration and coordinated actions across diverse sectors and disciplines [4].

Although AMR is a complex problem with many interrelated contributors, the key drivers to the emergence of AMR are misuse and overuse of antimicrobials which are increasing globally [5,6]. There is also a strong correlation between antibiotic consumption and the emergence of resistant microbes [7–10]. To address this issue, the World Health Organization (WHO) has developed a Global Action Plan (GAP)[6], which included strategies for optimizing antimicrobial use and regular monitoring of antibiotic use and healthcare associated infections (HCAIs), using a standardized point prevalence survey (PPS) methodology [11].

Various Ethiopian studies had shown the problems of misuse and overuse of antibiotics [12–14] and widespread resistance of bacterias for locally available antibiotics including carbapenems [15,16]. Responding to this global health priority and in an attempt to optimize antibiotic use and contain AMR, the government of Ethiopia adapted the GAP and implemented different AMR prevention and containment strategies where Antimicrobial Stewardship Program (ASP) is one of them. Despite these high-level initiatives, both at regional and facility levels, a general picture of antibiotic use, rate of HCAIs, quality of prescribing, using a context-appropriate PPS methodology is lacking [11]. Hence, this multicenter PPS survey aimed to collect baseline information about antibiotic use, prevalence of HCAIs, distribution of these infections according to infection site and pathogen, and quality of antibiotic prescribing among selected public hospitals in Ethiopia.

The data could be utilized to raise antibiotic usage awareness, as well as to plan and support national and local stewardship initiatives.

Methods

Study design and setting

A multi-center cross-sectional study was conducted in Ethiopian hospitals in January 2021. We adopted a WHO methodology for PPS of HCAIs and systemic antibiotic use in LMICs Version 1.1[11]. Ethiopia has a three-tier healthcare system namely primary, secondary, and tertiary levels. The estimated numbers of hospitals in Ethiopia were about 439 at any level (353 public, 86 private) of which 25 were tertiary, 58 secondary and 381 primary hospitals. For this survey, we have included five secondary and five tertiary care level hospitals (Supplementary file).

Eligibility criteria

The inclusion criteria were first applied to the wards in 10 selected hospitals, then to patients in the selected wards, and finally to the antibiotics prescribed and dispensed to those patients as per the WHO PPS methodology in LMICs Version 1.1[11]. We included all patients who were admitted in acute care wards namely the adult and pediatric medical, emergency, gynecology/obstetrics, surgery, intensive care unit (ICU) and oncology-hematology wards at or before 08:00 AM on the day of the survey irrespective of whether they were receiving antibiotic treatment or not and with complete medical record.

We included only oral and parenteral antibiotics when the patient was on active antibiotic therapy at 08:00 AM on the day of the survey. For instance, if a patient was on treatment with antibiotic-A at 08:00 AM on the day of the survey but the treatment was changed to antibiotic-B at 10:00 AM, then only antibiotic-A was reported.

Outcome variables

The outcome variables were prevalence of antibiotic use, proportion of HCAIs among hospitalized patients and existence of functional ASP. We considered functional ASP when hospitals had been providing at least prospective audit and feedback, preauthorization or formulary restriction. The independent variables were types of the hospital and ward, patients' socio-demographics, clinical and treatment related characteristics.

Sample size determination and sampling technique

The 10 surveyed hospitals were purposively selected from 30 public hospitals currently implementing ASP. For hospitals with <500 bed capacity, all eligible participants were surveyed. For those with 500-800 bed capacity, every other patient was surveyed following an alphabetical listing of all eligible in-patients on the day of data collection. The next available record was included if a selected patient or medical record was not available. A consistent approach was employed across wards to ensure fidelity to predefined study procedures. Altogether, 2,209 eligible patients were admitted during the survey period, and a total of 1,820 patients were included in the survey and final data analyses (Figure 1).

Data collection and management

A total of 100 patients, 10 from each of the participating hospitals, were used to pilot test the survey instrument. Trained data collectors conducted the survey (one ASP chair/secretary and two clinical pharmacists per hospital). Data quality was assured through implementation of a field manual guiding data collectors, regular supervision, and daily checks on data completeness, accuracy, and clarity.

Data analysis and interpretation

Data were analyzed using SPSS version 26. Descriptive analyses such as frequency and percentage were used to summarize the data. A multivariable logistic regression analysis was used to explore factors affecting antimicrobial use. A *p*-value of <0.05 was considered statistically significant.

Results

Demographic characteristics of patients

The mean age of patients was 27.7±22.1 years and the majority (690, 37.9%) of patients were in the age group of 18-39 years. There were about 90 preterm babies and most (39, 43.3%) of them were late preterm. Out of the 1820 patients included in the survey, majority of them were from adult medical (340, 18.7%), adult surgical (330, 18.1%), and obstetrics/gynecology (309, 17.0%). Five hundred one (27.5%) patients were found to be transferred from other hospitals and 562 (30.9%) had a previous history of hospitalization in the last 90 days. Moreover, 194(10.7%) of the patients had retroviral infection, 76(4.2%) had active tuberculosis, and 277(15.2%) of patients were malnourished. A peripheral vascular catheter was secured in a significant number of patients (1535, 84.3%) (Table 1).

Table 1: Characteristics of patients

Variable, N= 1820	N(%)
Sex	
Male	848(46.6)
Female	972(53.4)
Age in years	
0-17	616(33.8)
18 – 39	690(37.9)
40-64	371(20.4)
≥ 65	143(7.9)
Type of preterm for pre-term babies, N=90	
Late preterm	39(43.3)
Moderate preterm	26(28.9)
Very preterm	24(26.7)
Extremely preterm	1(0.1)
Ward type	
Pediatric medical ward	146(8.0)
Pediatric emergency ward	120(6.6)
Pediatric surgical ward	56(3.1)
Pediatric Intensive Care Unit	13(0.7)
Pediatric high risk wards	42(2.3)
Neonatal intensive care unit	184(10.1)
Adult medical ward	340(18.7)

Adult emergency ward	181(9.9)
Adult surgical ward	330(18.1)
Adult intensive care unit	57(3.1)
Obstetrics & Gynecology	309(17.0)
Adult high risk wards	42(2.3)
Current hospitalization malarial status	
Yes	33(1.8)
No	1439(79.1)
Unknown	348(19.1)
Previous malarial treatment history	
Yes	41(2.3)
No	1517(83.3)
Unknown	262(14.4)
Active tuberculosis	
Yes	76(4.2)
No	1499(82.4)
Unknown	245(13.4)
Retroviral infection status	
Positive	194(10.7)
Negative	1421(78.0)
Unknown	205(11.3)
Patients having chronic obstructive pulmonary diseases	28(1.5)
Patients with Malnutrition	277(15.2)
Referred from another hospital	501(27.5)
Patients having hospitalization history within 90 days	562(30.9)
Patients on peripheral vascular catheter at 8:00 AM on the day of the survey	1535(84.3)
Patients on urinary catheter at 8:00 AM on the day of the survey	403(22.1)
Patients on intubation at 8:00 AM on the day of the survey	71(3.9)

Indications for Antibiotics

The most common indication for antibiotics was HCAI (461, 39.6%). Eight hundred eighty-seven patients had a documented infection, the most common being pneumonia (254,

28.6%) followed by bloodstream infection or clinical sepsis (158, 17.8%) and central nervous system (CNS) infections (118, 13.3%)(Table 2).

Table 2: Indication for antibiotics and types of infections.

Variable		N(%)
Indication, n= 1162	Healthcare associated infections	460(39.6)
	Community acquired infection	394(33.9)
	Surgical prophylaxis	218(18.8)
	Medical prophylaxis	71(6.1)
	HCAI and medical prophylaxis	6(0.5)
	CAI and medical prophylaxis	9(0.8)
	Unknown	4(0.3)
Types of infection, n=887	CNS infection	118(13.3)
	Clinical sepsis	158(17.8)
	Pneumonia	254(28.6)
	Gastro-intestinal infection	43(4.8)
	Cellulitis, wound, deep soft tissue infection; not related to surgery	61(6.9)
	Gynacological infection	30(3.4)
	Symptomatic upper urinary tract infection	59(6.7)
	Cardio-vascular infection	19(2.1)
	Intra-abdominal infection	35(3.9)
	Surgical site infection involving skin or soft tissue but not bone	39(4.4)
	Others*	71(8.0)

***Others:** Febrile neutropenia, sexually transmitted infection, Infection of ear, nose and throat, Cystic fibrosis, Symptomatic lower urinary tract infection, acute bronchitis and exacerbation of Asthma, Septic arthritis of surgical site, prostatitis, Systemic inflammatory response with no clear anatomical site, completely undefined site.

Microbiological tests

Microbiological diagnostics for patients treated for HCAIs and CAIs were rarely ordered during the survey period (119, 13.6%). If ordered, most of them were blood samples alone (53, 44.5%), followed by urine culture (26, 21.9%). Moreover, a great proportion of the results were unknown or not reported/collected (52, 43.7%). Out of 41 isolated microorganisms, about two-thirds (28, 68.3%) were gram-negative bacteria. *Escherichia coli* (8, 19.5%) and *Klebsiella pneumoniae* (7, 17.1%) were the commonest isolated bacteria. About 21 resistant phenotypes were reported and most (13, 61.9%) were third generation cephalosporin resistant Enterobacteriaceae followed by methicillin resistant *staphylococcus aureus* (3,14.3%) and Carbapenem Resistant Enterobacteriaceae (3, 14.3%) (Table 3).

Table 3: Microbiological diagnostics and culture and sensitivity results

Variable	N(%)
Sample collected for microbiological workup, N= 870 patients*	
Yes	119(13.6)
No	693(79.7)
Unknown	58(6.7)
Specimen type, N=119 patients	
Blood	53(44.5)
Urine	26(21.9)
Cerebrospinal Fluid	13(10.9)
Pus	11(9.2)
Blood and urine	8(6.7)
Blood and CSF	6(5.1)
Peritoneal fluid	2(1.7)
Culture result, N=119 patients	
Positive	38(31.9)
Negative	29(24.4)
Unknown	52(43.7)
Isolated microorganism, N=41 **	
Gram positive bacteria	13(31.7)
Gram negative bacteria	28(68.3)

Type of isolated bacteria, N=41**		
	Escherichia coli	8(19.5)
	Klebsiella pneumoniae	7(17.1)
	Klebsiella oxytoca	4(9.8)
	Acinetobacter	4(9.8)
	Staphylococcus aureus	4(9.8)
	Enterobacter aerogenes	3(7.3)
	Enterococcus	3(7.3)
	Coagulase negative *staphylococcus*, contaminant	3(7.3)
	Others#	5(12.2)
Resistant phenotype, N=21		
	3rd Generation Cephalosporin Resistant Enterobacteriaceae	13(61.9)
	Methicillin Resistant *Staphylococcus aureus*	3(14.3)
	Carbapenem Resistant *Enterobacteriaceae*	3(14.3)
	Carbapenem Resistant *Pseudomonas aeruginosa*	1(4.8)
	Carbapenem Resistant *Acinetobacter*	1(4.8)

*only for those whose indication type is for healthcare associated infection and community acquired infection. **for one patient *Klebsiella oxytoca* from blood and *Klebsiella pneumoniae* from urine, from another patient *streptococcus* from blood and *Klebsiella Pneumoniae* from blood and from another one *Klebsiella Pneumoniae* from urine and *Acinetobacter* from blood were isolated. #*Pseudomonas aeruginosa, Citrobacter*, Gram positive cocci, *Group A streptococcus*, *Group D streptococcus*.

Readiness to implement ASP

All surveyed hospitals had functional infection prevention and control committee and only eight hospitals had functional Drugs and Therapeutics Committee. Although a defined organizational structure for ASP was present in all the surveyed hospitals, formal ASP team was only available in seven (70%) of the hospitals and none of them were functional during the survey period. None of the hospitals were monitored antibiotic use as per defined daily dose or days of therapy and hospital activity denominator. Eight of the surveyed hospitals have microbiological services in the hospitals and the mean number blood cultures done in for the previous fisical year 2019/2020 were about 2625 ±3307. Different classes of broad and narrow spectrum antibiotics were stock out during the survey period (Supplementary file).

Antibiotics use prevalence and indication

Of the 1820 surveyed patients, 63.8% had at least one antibiotic prescription on the day of the survey. The prevalence of antibiotic use was higher in adult intensive care unit patients (49, 86.0%) followed by pediatric emergency (112, 76.7%) and pediatric medical (94, 78.3%) wards.

On the day of the survey, 2059 antibiotics were prescribed for 1162 patients with antibiotics prescribing ratio of 1.77 per patient. More than half (585, 50.3%) of patients were on two antibiotics. The largest shares of antibiotics were prescribed in their generic name (1998, 97.1%) and were administered parentally (1858, 90.2%). The mean duration of treatment from initiation to survey date was 7.72±7.9 days. A significantly higher proportion of treatments were empiric (837, 96.7%). As per the WHO definition of guideline compliance[11], only 54.8% (n=637) of the treatments were compliant with the guideline (Supplementary file).

As shown in Table 4, the most widely prescribed antibiotics across all surveyed hospitals were ceftriaxone (626, 30.4%) followed by metronidazole (317, 15.4%), ampicillin (249, 12.1%) and vancomycin (217, 10.5%).

Table 4: Proportion patients on antibiotics and types of antibiotics prescriptions

Antibiotics	N(%)
Proportion of patients on antibiotics	
Pediatric medical ward	112(76.7%)
Pediatric emergency ward	94(78.3%)
Pediatric surgical ward	41(73.2%)
Pediatric Intensive Care Unit	9(69.2%)
Pediatric high risk wards	32(76.2%)
Neonatal intensive care unit	140(76.1%)
Adult medical ward	199(58.5%)
Adult emergency ward	97(53.6%)
Adult surgical ward	219(66.4%)

Adult intensive care unit	49(86%)
Adult high risk ward	13(31%)
Obstetrics & Gynecology	157(50.8%)
Types of antibiotics prescribed	
Ceftriaxone	626(30.4)
Metronidazole	317(15.4)
Ampicillin	249(12.1)
Vancomycin	217(10.5)
Gentamycin	178(8.6)
Ceftazidime	116(5.6)
Trimethoprim/Sulphamethoxazole	72(3.5)
Cloxacillin	49(2.4)
Ciprofloxacin	42(2.0)
Cefepime	40(1.9)
Meropenam	39(1.9)
Azithromycin	25(1.2)
Amoxacillin	20(1.0)
Cefotaxime	13(0.6)
Amoxacillin-Clavulanate	12(0.6)
Cephalexin	9(0.4)
Others*	35(1.7)
Total	**2059(100)**

*Crystalline-penicillin= 6; Erythromycin= 6; Norfloxacin = 5; Benzanthine penicillin= 4; Clindamycin= 4; Doxycycline = 3; Chloramphenicol= 2; Clarithromycin = 1; Nitrofurantoin= 1; Cefixime = 1; Ampicillin-sulbactam = 1

Factors associated with antibiotic use

From the multivariable analysis, age, ward type, hospital type, catheterization and intubation history, and retroviral infection status were significantly associated with being on antibiotics. Patients aged between 18-39 years (AOR= 0.61, 95%CI: 0.38,0.86) and 40-64 years old (AOR=0.55, 95%CI: 0.39, 0.93) had a decreased odds of being on antibiotics

compared with patients from 0 to 17 years old. Moreover, patients treated at pediatrics medical and emergency ward were about four times more likely to be on antibiotics compared to patients treated in adult emergency ward. The study also found that being on urinary catheter and intubation device had a significant association with antibiotics use status, where they were nearly three times more likely to be on antibiotics as compared with their catheterized/intubated counterparts (Table 5).

Table 5: Univariate and multivariable binary logistic regression analysis of predictors of antibiotics use among the surveyed hospitals

Variables	Patient on antibiotics		COR, 95%CI	AOR, 95%CI
	Yes, n(%)	No, n(%)		
Age in years				
0-17	460(39.6)	156(23.7)	1.00	1.00
18-39	406(34.9)	284(43.6)	0.49(0.38,0.61)**	0.61(0.38,0.86)*
40-64	211(18.2)	160(24.3)	0.45(0.34, 0.59)*	0.55(0.39, 0.93)*
≥ 65	85(7.3)	58(8.8)	0.5(0.34, 0.73)**	1.45(0.31, 3.59)
Gender				
Female	584(50.3)	388(59.0)	1.00	1.00
Male	578(49.7)	270(41.0)	1.42(1.17, 1.73)*	1.18(0.93, 1.49)
Ward type				
Pediatric medical	112(9.6)	34(5.2)	2.85(1.76, 4.62)*	3.78(1.81, 7.9)**
Pediatric surgical	41(3.5)	15(2.3)	2.37(1.22, 4.58)	2.31(0.96, 5.51)
Pediatric high risk	32(27.5)	10(1.5)	2.77(1.29, 5.97)	4.15(1.59, 10.8)*
Pediatric ICU	9(0.8)	4(0.6)	1.95(0.58, 6.56)	1.57(0.38, 6.50)
Pediatric emergency	94(8.1)	26(4.0)	3.13(1.86, 5.28)*	4.22(1.98, 9.02)**
Neonatal ICU	140(12.0)	44(6.7)	2.76(1.76, 4.31)*	3.27(1.59, 6.67)*
Adult medical	199(17.1)	141(21.4)	1.22(0.85, 1.76)	1.31(0.89, 1.92)
Adult surgical	219(18.8)	111(16.9)	1.71(1.18, 2.48)	2.00(1.36, 2.95)**
Adult high risk	13(1.1)	29(4.4)	0.39(0.19, 0.79)	0.45(0.22, 0.96)*
Adult ICU	49(4.2)	8(1.2)	5.30(2.38, 11.83)*	2.68(1.05, 6.88)
Gyny/Obs	157(13.5)	152(23.1)	0.89(0.62, 1.29)	0.83(0.54, 1.27)
Adult emergency	97(8.3)	84(12.8)	1.00	1.00
Urinary catheterization status				
No	846(72.8)	571(86.8)	1.00	1.00
Yes	316(27.2)	87(13.2)	2.45(1.89, 3.18)*	2.74(2.04, 3.68)*
Intubation status				
No	1098(94.5)	650(98.8)	1.00	1.00
Yes	63(5.5)	8(1.2)	4.66(2.22, 9.79)*	2.62(1.02, 6.76)**
Retroviral infection status				
Yes	161(13.9)	33(5.0)	1.00	1.00
No	867(74.6)	554(84.2)	0.32(0.22,0.47)**	0.19(0.13,0.30)**
Unknown	134(11.5)	71(10.8)	0.39(0.24,0.62)**	0.24(0.15,0.40)**

Within 90 days hospitalization history				
Yes	366(31.5)	196(29.8)	1.00	1.00
No	796(68.5)	462(70.2)	0.93(0.75, 1.14)	0.85(0.67, 1.06)
Length of hospitalization in days			0.998(0.99, 1.00)	1.00(0.99, 1.01)
Hospital type				
Secondary care	623(53.6)	304(46.2)	1.00	1.00
Tertiary care	539(46.4)	354(53.8)	0.74(0.61, 0.90)*	0.66(0.53, 0.81)*

*p<0.05, **statistically significant at p<0.0001. AOR: Adjusted odds ratio; COR: Crude odds ratio

Discussion

Antimicrobial resistance is becoming a global threat exacting a major toll on human, animal, and environmental health [17–20]. Ethiopia, like many nations, has not been immune from the negative effects of AMR [16,21,22]. While there have been initiatives to address this pressing health challenge, the few national and institutional efforts have had limited success. Mounting an effective national response to combat AMR requires robust information on the scope of infections and antimicrobial agents being used in healthcare institutions. Using the WHO's standardized PPS methodology, this study assessed the burden of HCAIs and antibiotic use in selected public hospitals of Ethiopia.

Similar to studies done elsewhere [13,23,24], the most common indication for antibiotics therapy was for HCAIs (39.6%) where most of them were pneumonia and clinical sepsis. This high burden of infections might be a reason for misuse and overuse of antibiotics, potentially straining the already resource constrained hospitals, patients, and family caregivers[13]. Hence, efforts to effectively treat, prevent, and reduce HCAIs are needed. To achieve these, implementing interventions such as strengthening and integrating infection prevention and control practice, developing and enforcing the use of institution specific standard treatment guidelines, providing in-service trainings are needed. Strengthening microbiology laboratories to guided definitive treatment is also invaluable towards achievement of this goal.

Prescribing broad-spectrum antibiotics empirically (96.7%) was a common and persistent practice across the surveyed hospitals like other studies done in LMICs [24-27]. This could be owing to the hospital's inavailability and poor utilization of microbiology services, as seen by the hospitals' limited use of culture and sensitivity tests. Including this study (63.8%), this might also be a reason why overuse of antibiotics is common in LMICs, ranging from 70.6% to 80.1% [24-27] compared with studies from HICs (27.1-50.3%) [23,28–30]. An internet-based PPS done across 53 countries (LMICs and HICs) has also reported higher antimicrobial use in LMICs compared to HICs[31].

An enduring overuse of antibiotics for a prolonged duration in many LMICs compared to HICs [13,26,32] might be attributed to lack of a national and institutional antibiotic

guideline and poor diagnostic infrastructure which both can promote empiric as well as high rates of irrational antibiotic use. Although most of the surveyed hospitals had microbiological services, only one hospital developed institutional guideline as per the antibiogram data. This is also a clear sign of poor utilization of the microbiology services to guide empiric antibiotic use and highlights the missed opportunities in promoting rational antibiotic use [33]. Recently, a pharmacist-led ASP implemented in one of the tertiary care hospitals of Ethiopia was well received and shown to be beneficial [13]. Lessons from such programs, including knowledge of ongoing barriers to scale up and sustain these programs, should be leveraged to promote widespread adoption of ASP to decrease antibiotic consumption, save costs, and improve outcomes. Additionally, improving the infrastructure and capacity within hospitals to establish and support ASPs, and the policy framework to provide formal leadership and governance will be critical as these were identified to be deficient in the surveyed hospitals.

In this study, there was also a substantial difference in the prevalence of antibiotics use across different levels of surveyed hospitals where a statistically significant higher antibiotic use was reported in tertiary care hospitals. There were also disparities with respect to the type of prescribed antibiotics compared to other studies. Similar to the study done in Pakistan [26] and Ethiopia, the most widely prescribed antibiotic in this study was the 3rd generation cephalosporin, ceftriaxone (30.4%). In developed countries, the most commonly prescribed antibiotics were penicillins with β-lactamase inhibitors[23,31]. Nitroimidazole was the most commonly prescribed antibiotic in Nigeria [8].

Prolonged use of surgical prophylaxis (>24hours) in this study was high (82.6%), similar to studies from other LMICs (73% to 100%) [24,26,27,34–36]. The recommended duration of surgical prophylaxis is one day [37–39] since prolonging duration potentially increases rate of AMR, side effects, and costs for both the patient and the hospital [40–42]. Furthermore, average number of antibiotics prescribed per patient for surgical prophylaxis was 1.32 despite several studies and guidelines demonstrating the cost-effectiveness of single narrow-spectrum antibiotics, usually cefazolin [30,37,43–46]. However, in the current study, ceftriaxone (54.7%) was the widely prescribed antibiotic. The widespread use of broad-spectrum 3rd generation cephalosporin's in our survey might be due to

unavailability of cefazolin in all of the surveyed hospitals. Hence, due to proven safety and efficacy of Cefazolin, it's time for Ethiopia to include it on the essential medicine list, ensure its availability, develop guidelines and enforce use of cefazolin or other narrow-spectrum antibiotics for surgical prophylaxis.

Conclusion

Similar to studies from other LMICs, there was widespread use of antibiotics and a high burden of HCAIs. Moreover, prolonged use of broad-spectrum antibiotics was common practice for surgical prophylaxis suggesting an important target for ASP intervention. Almost all treatments were empiric and hospitals should be further stimulated to regularly monitor antibiotic use and set local targets to optimize their use.

Abbreviations

AMR: Antimicrobial resistance; **ASP:** Antimicrobial stewardship program; **CAIs:** Community acquired infections; **HCAIs:** Healthcare associated infections; **HICs:** High income countries; **LMICs:** Low- and middle-income countries; **PPS:** Point prevalence survey

Authors' contributions

AMF prepared the draft manuscript. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the manuscript or revising it critically for important intellectual content; gave final approval of the manuscript in its currently submitted form; and agree to be accountable for all aspects of the work.

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Ethical Considerations

Ethical clearance was obtained from the Ethiopian Federal Ministry of Health. Before data collection, permission was sought from respective hospital administration. Collected data were de-identified during data collection and data were analyzed in aggregate to maintain confidentiality and anonymity of information.

Competing interests: None

Patient consent for publication

Not required

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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References

1 Kardos N, Demain AL. Penicillin: The medicine with the greatest impact on therapeutic outcomes. Appl. Microbiol. Biotechnol. 2011. doi:10.1007/s00253-011-3587-6

2 Lobanovska M, Pilla G. Penicillin's Discovery and Antibiotic Resistance: Lessons for the Future? Yale J Biol Med. 2017 Mar 29;90(1):135-145. PMID: 28356901; PMCID: PMC5369031.

3 O'Neill J. Antimicrobial Resistance : Tackling a crisis for the health and wealth of nations. 2016.

4 The World Bank. Drug-resistant infections: A Threat to Our Economic Future. *World Bank Rep* 2017.

5 Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014 Sep 16;2:145. doi: 10.3389/fpubh.2014.00145. PMID: 25279369; PMCID: PMC4165128.

6 World Health Organization. Global Action Plan on Antimicrobial Resistance. *Microbe Mag* 2015;**10**:354–5. doi:10.1128/microbe.10.354.1

7 Centers for Disease Control and Prevention. Antibiotic Use in the United States, 2017. Progress and Opportunities Atlanta, GA: US Department of Health and Human Services, CDC; 2017. *J Antimicrob Chemother* 2017;:1–9.https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report.pdf

8 Abubakar U. Point-prevalence survey of hospital acquired infections in three acute care hospitals in Northern Nigeria. *Antimicrob Resist Infect Control* 2020;**9**:1–7. doi:10.1186/s13756-020-00722-9

9 Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: Causes and control strategies. *Antimicrob Resist Infect Control*

2017;**6**:1–8. doi:10.1186/s13756-017-0208-x

10 Mboya EA, Sanga LA, Ngocho JS. Irrational use of antibiotics in the moshi municipality Northern Tanzania: A cross sectional study. *Pan Afr Med J* 2018;**31**:1–10. doi:10.11604/pamj.2018.31.165.15991

11 World Health Organization. WHO Methodology for Point Prevalence Survey on Antibiotics Use in Hospitals. 2018;**Version 1.**

12 Alemkere G, Tenna A, Engidawork E. Antibiotic use practice and predictors of hospital outcome among patients with systemic bacterial infection: Identifying targets for antibiotic and health care resource stewardship. *PLoS One* Published Online First: 2019. doi:10.1371/journal.pone.0212661

13 Gebretekle GB, Haile Mariam D, Abebe Taye W, *et al.* Half of Prescribed Antibiotics Are Not Needed: A Pharmacist-Led Antimicrobial Stewardship Intervention and Clinical Outcomes in a Referral Hospital in Ethiopia. *Front Public Heal* Published Online First: 2020. doi:10.3389/fpubh.2020.00109

14 Argaw, N.A., Shumbash, K.Z., Asfaw, A.A. *et al.* Assessment of surgical antimicrobial prophylaxis in Orthopaedics and Traumatology Surgical Unit of a Tertiary Care Teaching Hospital in Addis Ababa. *BMC Res Notes* **10,** 160 (2017). https://doi.org/10.1186/s13104-017-2475-2

15 Abebe W, Alemayehu T, Kong L, *et al.* Alarming rates of drug-resistant Gram-negative bloodstream infections among hospitalized patients in Ethiopia : an urgent call to strengthen diagnostic bacteriology and antimicrobia ... *28th Eur Congr Clin Microbiol Infect Dis* 2018.

16 Alemayehu, T., Ali, M., Mitiku, E. *et al.* The burden of antimicrobial resistance at tertiary care hospital, southern Ethiopia: a three years' retrospective study. *BMC Infect Dis* **19,** 585 (2019). https://doi.org/10.1186/s12879-019-4210-1.

17 Mouiche, M.M.M., Moffo, F., Akoachere, JF.T.K. *et al.* Antimicrobial resistance from a one health perspective in Cameroon: a systematic review and meta-analysis. *BMC*

Public Health **19,** 1135 (2019). https://doi.org/10.1186/s12889-019-7450-5

18 Nellums LB, Thompson H, Holmes A, *et al.* Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. *Lancet Infect Dis* 2018;**18**:796–811. doi:10.1016/S1473-3099(18)30219-6

19 Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. Front Microbiol. 2010 Dec 8;1:134. doi: 10.3389/fmicb.2010.00134. PMID: 21687759; PMCID: PMC3109405.

20 Midega J. Estimating the global burden of antimicrobial resistance: Reflections on current methods and data needs. *Wellcome Open Res* 2020;**5**:48. doi:10.12688/wellcomeopenres.15680.1

21 Muhie OA. Antibiotic Use and Resistance Pattern in Ethiopia: Systematic Review and Meta-Analysis. Int J Microbiol. 2019; 2019: 2489063. doi: 10.1155/2019/2489063*Int*

22 Ibrahim RA, Teshale AM, Dinku SF, *et al.* Erratum: Antimicrobial resistance surveillance in Ethiopia: Implementation experiences and lessons learned. *Afr J Lab Med* 2019;**8**:1–4. doi:10.4102/ajlm.v7i2.770

23 Frenette C, Sperlea D, German GJ, *et al.* The 2017 global point prevalence survey of antimicrobial consumption and resistance in Canadian hospitals. *Antimicrob Resist Infect Control:* 2020. doi:10.1186/s13756-020-00758-x

24 Anand Paramadhas BD, Tiroyakgosi C, Mpinda-Joseph P, *et al.* Point prevalence study of antimicrobial use among hospitals across Botswana; findings and implications. *Expert Rev Anti Infect Ther* 2019;**17**:535–46. doi:10.1080/14787210.2019.1629288

25 Gutema G, Håkonsen H, Engidawork E, *et al.* Multiple challenges of antibiotic use in a large hospital in Ethiopia - A ward-specific study showing high rates of hospital-acquired infections and ineffective prophylaxis. *BMC Health Serv Res*: 2018. doi:10.1186/s12913-018-3107-9

26 Saleem Z, Saeed H, Hassali MA, *et al.* Pattern of inappropriate antibiotic use among

hospitalized patients in Pakistan: A longitudinal surveillance and implications. *Antimicrob Resist Infect Control*: 2019. doi:10.1186/s13756-019-0649-5

27 Abubakar U. Antibiotic use among hospitalized patients in northern Nigeria: A multicenter point-prevalence survey. *BMC Infect Dis* 2020;**20**:1–9. doi:10.1186/s12879-020-4815-4

28 Ciofi Degli Atti ML, D'Amore C, Ceradini J, *et al.* Prevalence of antibiotic use in a tertiary care hospital in Italy, 2008-2016. *Ital J Pediatr*: 2019. doi:10.1186/s13052-019-0645-7

29 Sorensen H. Trends in U. S. Antibiotic Use. *Pew Charit Trust* 2018;:1–9.

30 Vandael E, Latour K, Goossens H, *et al.* Point prevalence survey of antimicrobial use and healthcare-associated infections in Belgian acute care hospitals: Results of the Global-PPS and ECDC-PPS 2017. *Antimicrob Resist Infect Control* 2020;**9**:1–13. doi:10.1186/s13756-019-0663-7

31 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal*: 2018. doi:10.1016/S2214-109X(18)30186-4

32 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal:* 2018;**6**:e619–29. doi:10.1016/S2214-109X(18)30186-4

33 de With K, Allerberger F, Amann S, *et al.* Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. *Infection:* 2016;**44**:395–439. doi:10.1007/s15010-016-0885-z

34 Afriyie DK, Sefah IA, Sneddon J, *et al.* Antimicrobial point prevalence surveys in two Ghanaian hospitals: opportunities for antimicrobial stewardship. *JAC-Antimicrobial Resist:* 2020;**2**:1–9. doi:10.1093/jacamr/dlaa001

35 Horumpende PG, Mshana SE, Mouw EF, *et al.* Point prevalence survey of antimicrobial use in three hospitals in North-Eastern Tanzania. *Antimicrob Resist Infect Control:* 2020;**9**:1–6. doi:10.1186/s13756-020-00809-3

36 Van Der Sandt N, Schellack N, Mabope LA, *et al.* Surgical antimicrobial prophylaxis among pediatric patients in south africa comparing two healthcare settings. *Pediatr Infect Dis J*: 2019. doi:10.1097/INF.0000000000002072

37 Berriós-Torres SI, Umscheid CA, Bratzler DW, *et al.* Centers for disease control and prevention guideline for the prevention of surgical site infection. JAMA Surg. 2017. doi:10.1001/jamasurg.2017.0904

38 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt):* 2013;**14**:73–156. doi:10.1089/sur.2013.9999

39 Jocum J. Surgical antibiotic prophylaxis: Are you doing it right? *South African J Anaesth Analg:* 2018;**24**:S49–53.

40 Roberts SA, Morris AJ. Surgical antibiotic prophylaxis: more is not better. *Lancet Infect Dis:* 2020;**20**:1110–1. doi:10.1016/S1473-3099(20)30290-5

41 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Balancing the Risks and Benefits of Surgical Prophylaxis Timing and Duration Do Matter. *Am J Heal Pharm:* 2013;**70**:195–283. doi:10.2146/ajhp120568

42 Branch-Elliman W, O'Brien W, Strymish J, *et al.* Association of Duration and Type of Surgical Prophylaxis with Antimicrobial-Associated Adverse Events. In: *JAMA Surgery*: 2019. doi:10.1001/jamasurg.2019.0569

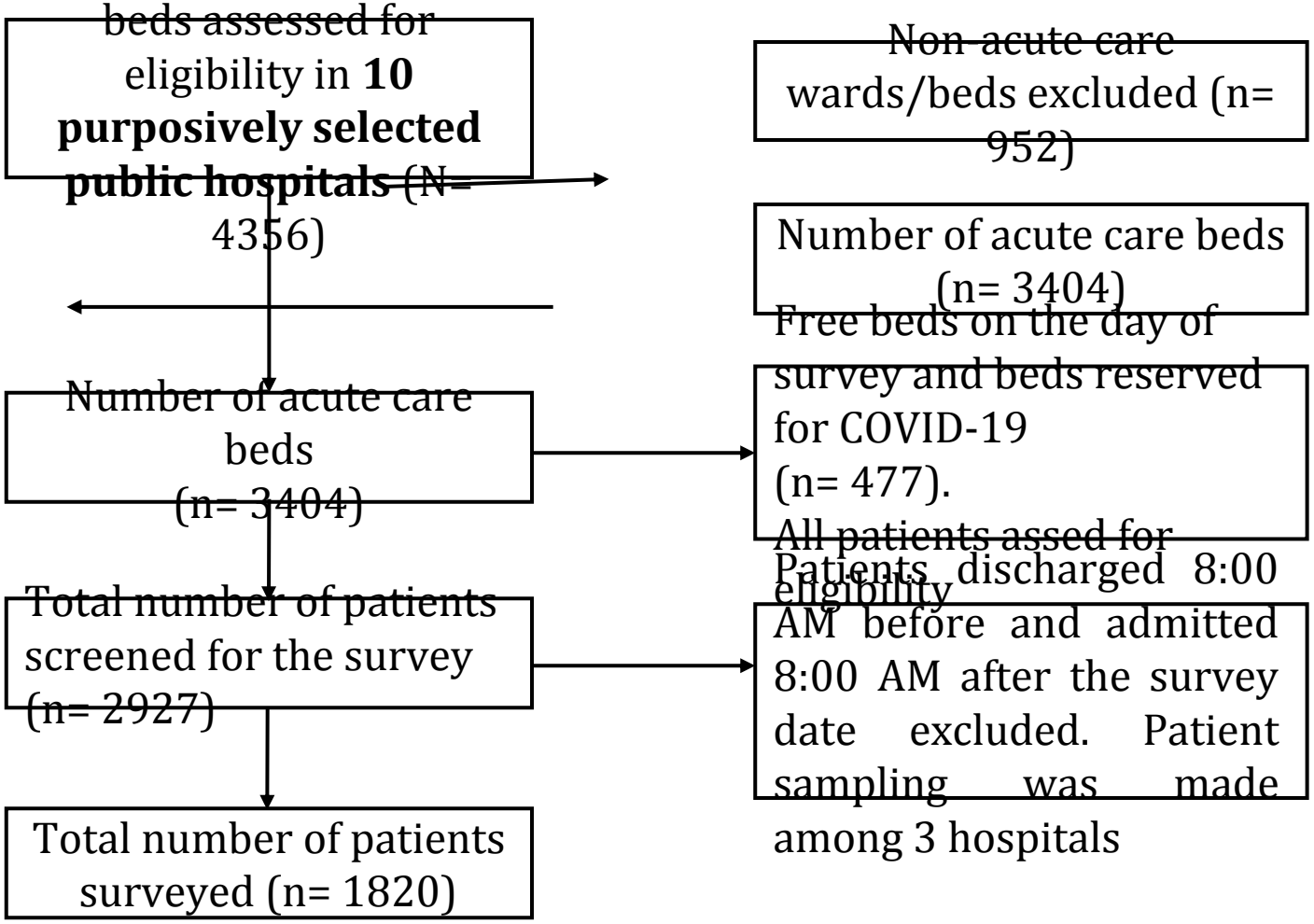
43 Pinto-Lopes R, Sousa-Pinto B, Azevedo LF. Single dose versus multiple dose of antibiotic prophylaxis in caesarean section: a systematic review and meta-analysis. BJOG An Int. J. Obstet. Gynaecol: 2017; 124(4): doi:10.1111/1471-0528.14373

44 Slobogean GP, Kennedy SA, Davidson D, O'Brien PJ. Single- versus multiple-dose

antibiotic prophylaxis in the surgical treatment of closed fractures: a meta-analysis. J Orthop Trauma. 2008 Apr;22(4):264-9. doi: 10.1097/BOT.0b013e31816b7880. PMID: 18404036.

45 Ierano C, Nankervis JM, James R, Rajkhowa A, Peel T, Thursky K. Surgical antimicrobial prophylaxis. *Aust Prescr*. 2017;40(6):225-229. doi:10.18773/austprescr.2017.073

46 Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013 Feb;14(1):73-156. doi: 10.1089/sur.2013.9999. Epub 2013 Mar 5. PMID: 23461695.


Total number hospital beds assessed for eligibility in **10 purposively selected public hospitals** (N= 4356)
Non-acute care wards/beds excluded (n= 952)
Number of acute care beds (n= 3404)
Number of acute care beds (n= 3404)
Free beds on the day of survey and beds reserved for COVID-19 (n= 477).
Total number of patients screened for the survey (n= 2927)
All patients assed for eligibility
Patients discharged 8:00 AM before and admitted 8:00 AM after the survey date excluded. Patient sampling was made among 3 hospitals
Total number of patients surveyed (n= 1820)

Supplementary file

Ethiopia's profile

S.N	Variable	Response
1.	ISO code of Ethiopia	ETH
2.	Total number of hospitals at any level (tertiary, secondary, primary and specialized) in the country.	439
3.	Number of public hospitals in the country.	353
4.	Estimated number of private hospitals in the country	86
5.	Estimated number of tertiary level (university teaching and specialized hospital) hospitals in the country.	25
6.	Number of secondary level (General) hospitals in the country.	58
7.	Estimated number of primary hospitals in the country.	381
8.	Is Hospital grouping exist in the country	No
9.	Hospital survey sampling strategy	Convenience sampling
10.	Number of hospitals for the survey	**10**
11.	Does a national treatment guideline exist?	Yes
12.	Does facility-based treatment guidelines exist	No
13.	Does a national hospital ASP exists	Yes

The 10 surveyed hospitals profile

S.N	Variable	Mean ± SD	Median(Range)
1.	Number of beds in the surveyed hospitals	443 ± 164	410(223-700)
2.	Number of acute care beds	349 ± 134	314(186-600)
3.	Number of ICU beds	34 ± 24	32(6-82)
4.	Number of high risk beds	22 ± 19	18(0-51)
5.	Annual overall admissions in the hospitals in the previous physical year, i.e. 2012 E.C.#	16471 ± 7405	13885 (7025-30456)
6.	Overall patient days in the hospitals for the previous physical year i.e. 2012 E.C.*	94679 ± 45583	79254(48931-176,742)
7.	Average length of hospital stay in days	6 .53 ± 1.48	6.0(4.8-10.2)
8.	Sum of the number of beds of the wards included in the survey (Total= 2927 beds)	293 ± 153	214(103-541)
9.	Number of patients eligible for inclusion in the survey. (Total= 2209 patients)	240 ± 115	203(103-474)
10.	Number of patients included in the survey (Total= 1820).	182± 61	161(103-325)

#emergency admission over 24 hours was not included. * **Patient days:** over all admission * average length of hospital stay.

Existing surveyed hospitals capacity to promote rational use of antibiotics

Variable	Yes, N(%)
Hospital infrastructure	
Functioning Drugs and Therapeutics Committee	8(80.0)
Functioning Infection Prevention & Control Committee	10(100.0)
Microbiological laboratory service	8(80.0)
Availability of a formal organizational structure responsible for ASP	10(100.0)
A physician ASP leader	10(100.0)
Availability of a ASP team	7(70.0)
Availability of functional ASP in the hospital	0(0.0)
Availability of pharmacist responsible for ensuring appropriate antibiotic use	9(90.0)
Incentive package for dedicated staff for ASP	0(0.0)
IT support for ASP	0(0.0)
Availability of outpatient parenteral antibiotic therapy (OPAT) unit	0(0.0)
Policy and practice	
Availability of antibiotic formulary (including unrestricted and restricted antibiotics) updated continuously	0(0.0)
Antibiotic formulary based on the Essential Drug List	0(0.0)
Institutional antibiotic guideline	3(30.0)
Institutional antibiotic guidelines based on local Antibiogram	1(10.0)

A written policy that requires prescribers to document an indication in the medical records		2(20.0)
Preauthorization policy		1(10.0)
Post-prescription review service		7(70.0)
Monitoring and feedback		
Monitoring of antibiotics indications on medical record		5(50.0)
Monitoring of surgical antibiotic prophylaxis choice and duration		2(20.0)
Results of antibiotic audits are communicated directly with prescribers		7(70.0)
Monitor of antibiotic use		1(10.0)
Monitoring of antibiotic use by DDD or DOT		0(0.0)
Antibiotic use reported by hospital activity denominator		0(0.0)
Annual report focused on ASP in the past year		2(20.0)
A cumulative antibiotic susceptibility report in the past year		3(30.0)
A national antibiotic resistance surveillance program participation		4(40.0)
A national antibiotic use surveillance program participation		0(0.0)
Number of blood cultures done in the past year, N= 7- hospitals	Mean ± SD	2625 ± 3307
	Median(Range)	1707(452-9860)
List of antibiotics out of stock at the facility during the survey period.	Cefepime 1g, Meropenam 1g and 0.5g, Piperacillin-Tazobactam 4.5g, Ciprofloxacin 0.4mg , ceftazidime 1gm, Metronidazole 0.5g and Gentamycin 80mg injections were stock out in all of the surveyed hospitals. Vancomycin 1g and 0.5g was also stock out at two surveyed hospitals.	

Antibiotics prescription and indication

Variable		Number	Percentage
Total number of antibiotics prescribed since admission		3192	
Number of antibiotics prescribed/ patient since admission: **N= 1410 patients**			
	1	379	26.9
	2	632	44.8
	3	203	14.3
	4	117	8.3
	5	42	3.0
	6	19	1.3
	Others*	18	1.2
Overall antibiotics prescribed on the day of survey		2058	
Number of antibiotics given/patient at a time of survey: **N= 1162 patients**			
	1	432	37.1
	2	585	50.4
	3	124	10.7
	4	18	1.6
	5	3	0.3
Route of administration: **N= 2059 antibiotics**			
	Oral	201	9.8
	Parenteral	1858	90.2
Antibiotics prescription note: **N= 2059 antibiotics**			
	Brand	61	2.9
	Generic	1998	97.1
Indication of antibiotics written on patient notes: **N= 1162 patients**			
	No	51	4.4
	Yes	1111	95.6
Antibiotics duration in days (From time of initiation to survey date): Mean ± SD: 7.72 ± 7.9			
Type of treatment**, N=866 patients			
	Empiric	837	96.7
	Definitive	29	3.3
Guideline compliance			
	Yes	637	54.8
	No	255	21.9
	Not assessable	237	20.4
	No information	33	2.8
Prescriber type			
	General practitioner	178	15.3
	Resident	949	81.7
	Specialist	35	3.0

***Others:** 7 antibiotics= 5 patients; 8 antibiotics=8 patients; 9 antibiotics=3 patients; 10 antibiotics= 1 patient; 12 antibiotics=1 patient; **Is only for patients whose antibiotics indication is for HCAIs and CAIs

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Last paragraph on 3/4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	10 and 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	15-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A multicenter point prevalence survey of antibiotic use and healthcare-associated infections in Ethiopian hospitals

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A multicenter point prevalence survey of antibiotic use and healthcare associated infections in Ethiopian hospitals

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Abstract

Objective: Effective antimicrobial containment strategies such as Antimicrobial Stewardship programs (ASP) require comprehensive data on antibiotics use which is scarce in Ethiopia. This study sought to assess antibiotics use and healthcare-associated infections (HCAIs) in Ethiopian public hospitals.

Design: We conducted a cross-sectional study using the WHO point-prevalence survey protocol for systemic antibiotics use and HCAIs for low- and middle-income countries (LMICs).

Setting: The study was conducted among 10 public-hospitals in 2021.

Participants: All patients admitted to adult and pediatrics inpatient and emergency wards at or on 8:00AM on the survey date were enrolled.

Outcome measure: The primary outcome measures were the proportion of antibiotic use, HCAIs, and the hospitals' readiness to implement ASP.

Results: Data were collected from 1820 patient records. None of the surveyed hospitals had functional ASP. The common indication for antibiotics was for HCAIs (40.3%). Pneumonia was the most common bacterial infection (28.6%) followed by clinical sepsis (17.8%). Most treatments were empiric (96.7%) and the overall prevalence of antibiotic use was 63.8% with antibiotics prescription per patient ratio of 1.77. Ceftriaxone was the most commonly prescribed antibiotic (30.4%) followed by metronidazole (15.4%). Age, having HIV infection, ward type, type of hospital, catheterization and intubation history had significant association with antibiotic use. Patients who were treated in pediatric surgical wards were about four times more likely to be on antibiotics compared to patients treated at an adult emergency ward. Patients on urinary catheter (AOR:2.74,95%CI:2.04,3.68) and intubation device (AOR=2.62,95%CI:1.02,6.76) were more likely to be on antibiotics than their non-intubated/non catheterized counterparts. Patients treated at secondary-level hospitals had 0.34 times lower odds of being on antibiotics compared to those in tertiary-hospitals.

Conclusions: Antibiotic use across the surveyed hospitals was common and most were empiric which has both practical and policy implications for strengthening ASP and promoting rational antibiotics use.

Strengths and limitations of the study

- This is the first multicenter point prevalence survey in Ethiopia using the standardized WHO tool, thus allowing cross-country comparisons.
- The findings are valuable in strengthening implementation of antimicrobial stewardship programs and can be used to guide future studies in Ethiopia and other low and middle-income countries.
- The findings may have limited generalizability given the study's focus on selected secondary and tertiary public hospitals of Ethiopia.
- Surgical prophylaxis may have been switched to empiric treatment without documentation, potentially inflating rate of prophylactic antibiotic use and underestimating rate of health care associated infection.

Introduction

Since their discovery, antimicrobials have saved millions of lives, substantially reduced disease burden, improved the quality of life, and helped increase life expectancy [1]. However, Antimicrobial Resistance (AMR) is becoming a growing threat to the health of humans, animals, and the environment [2]. Every year, about 700,000 deaths are attributable to AMR and, unless urgent measures are taken, AMR will lead to 10 million deaths and would cost the global economy up to US$ 100 trillion by 2050. It is also predicted that AMR will disproportionately affect low- and middle-income countries (LMICs) [3]. Containing and controlling AMR demands multi-sectoral collaboration and coordinated efforts across diverse sectors [4].

Although AMR is a complex problem with many interrelated contributors, the key drivers to the emergence of AMR are misuse and overuse of antimicrobials [5,6]. There is a strong correlation between antibiotic consumption and the emergence of resistant microbes [7–10]. To address this issue, the World Health Organization (WHO) has developed a Global Action Plan (GAP)[6], which includes a standardized point prevalence survey (PPS) methodology to guide optimization of antimicrobial use and AMR containment [11].

Various Ethiopian studies have shown the problems of misuse and overuse of antibiotics [12–14] and widespread resistance of microbes against locally available antibiotics including carbapenems [15,16]. Responding to this global health priority, the government of Ethiopia adopted the GAP and implemented strategies, including Antimicrobial Stewardship Program (ASP), to prevent and contain AMR. However, a general picture of antibiotic use, rate of HCAIs, and quality of prescribing is lacking [11]. Hence, this multicenter PPS survey aimed to collect baseline information about antibiotic use, prevalence of HCAIs, distribution of these infections according to infection site and pathogen, and quality of antibiotic prescribing among selected public hospitals in Ethiopia.

Methods

Study design and setting

A multi-center cross-sectional study was conducted in Ethiopian public hospitals in January 2021. We adopted the WHO methodology for PPS of HCAIs and systemic antibiotic use for LMICs Version 1.1[11]. Ethiopia has a three-tier public healthcare system that broadly classifies its facilities as primary, secondary and tertiary level service providers. At the time of this survey, the estimated number of hospitals in Ethiopia was about 439 at any level (353 public, 86 private) of which 25 were tertiary, 58 secondary, and 381 primary hospitals. As part of its strategic initiatives, the Ethiopian Ministry of Health identified selected secondary and tertiary public hospitals to serve as the first cohort of facilities that will implement new ASP or strengthen existing programs. In alignment with the Ministry's programmatic priorities, we have included five secondary and five tertiary care level hospitals. The hospitals were selected based on their readiness to implement the antimicrobial stewardship program, location and catchment area of service (Supplementary file).

Eligibility criteria

The inclusion criteria were first applied to the wards in 10 purposively selected hospitals, then to patients in the selected wards, and finally to the antibiotics prescribed and dispensed to those patients as per the WHO PPS methodology in for LMICs Version 1.1[11]. We included all hospitalized patients with a complete medical record admitted in the following acute care wards at or before 08:00 AM on the day of the survey regardless of antibiotic treatment status: adult and pediatric medical, emergency, gynecology/obstetrics, surgery, intensive care unit (ICU) and oncology-hematology. Excluded patients included: those seen in outpatient departments, outpatient dialysis centers, patients who were discharged before 8:00 AM of the day of survey but remaining in wards while awaiting transportation, undergoing treatment or surgery and were discharged or expected to be discharged on the same day, and patients receiving outpatient parenteral antibiotic therapy.

We included only oral and parenteral antibiotics when the patient was on active antibiotic therapy at 08:00 AM on the day of the survey. For instance, if a patient was on treatment

with antibiotic-A at 08:00 AM on the day of the survey but the treatment was changed to antibiotic-B at 10:00 AM, then only antibiotic-A was reported.

Outcome variables

The outcome variables were prevalence of antibiotic use, proportion of HCAIs among hospitalized patients and existence of functional ASP. We considered functional ASP when hospitals had been providing at least prospective audit and feedback, preauthorization and/or formulary restriction. The independent variables were types of the hospital and ward, patients' socio-demographics, clinical and treatment related characteristics.

Sample size determination and sampling technique

For hospitals with <500 bed capacity, all eligible participants were surveyed. For those with 500-800 bed capacity, every other patient was surveyed following an alphabetical listing of all eligible in-patients on the day of data collection. The next available record was included if a selected patient or medical record was not available. A consistent approach was employed across wards to ensure fidelity to predefined study procedures. Altogether, 2,209 eligible patients were admitted during the survey period, and a total of 1820 patients were included in the survey and final data analyses. As per the WHO PPS methodology, 389 patients were excluded from the survey because they were either (i) undergoing treatment or surgery and were discharged or expected to be discharged on the same day, or (ii) admitted to the ward after 08:00AM or discharged before 8:00AM of the survey date (Figure 1).

Data collection and management

A total of 100 patients, 10 from each of the participating hospitals, were used to pilot test the survey instrument. Trained data collectors fielded the survey instrument (one ASP chair/secretary and two clinical pharmacists per hospital). Data quality was assured through the implementation of a field manual guiding data collectors, regular supervision, and daily checks on data completeness, accuracy, and clarity. A validation workshop was also

conducted to review findings with infectious disease specialists, data collectors, and other key stakeholders from the surveyed hospitals and Ethiopian Ministry of Health.

Patient and Public involvement

The survey was designed for public health surveillance purposes; it was non-experimental, did not involve any patient examination nor did it introduce interventions. There was no direct patient and public involvement in the design, recruitment and conduct of the study. Collected data were de-identified during data collection and it can therefore be considered to be a minimal risk study. All the data were extracted from the respective patient's medical records. Procedures for data collection, data management, analysis and interpretation were in accordance with the ethical and data safety regulations of the country.

Data analysis and interpretation

Data were analyzed using SPSS version 26. Descriptive analyses using frequency and percentage were used to summarize the data. A multivariable logistic regression analysis was used to explore factors affecting antimicrobial use. During univariate analysis, all variables with $p < 0.25$ and other clinically significant variables (e.g. length of hospital stay and within 90 days hospitalization history) were included for multivariable logistic regression model. A *p*-value of <0.05 was considered statistically significant.

Results

Demographic characteristics of patients

The mean age of patients was 27.7±22.1 years and the majority (690, 37.9%) of patients were in the age group of 18-39 years. There were about 90 preterm babies. Out of the 1820 patients included in the survey, a large proportion of them were from adult medical (340, 18.7%), adult surgical (330, 18.1%), and obstetrics/gynecology (309, 17.0%). Five hundred one (27.5%) patients were found to be transferred from other hospitals and 562 (30.9%) had a previous history of hospitalization in the last 90 days. Moreover, 194(10.7%) of the patients had HIV infection, 76(4.2%) had active tuberculosis, and 277(15.2%) of patients were malnourished. A peripheral vascular catheter was secured in a significant number of patients (1535, 84.3%) (Table 1).

Table 1: Characteristics of patients

Variable, N= 1820	N(%)
Sex	
Male	848(46.6)
Female	972(53.4)
Age in years	
0-17	616(33.8)
18 – 39	690(37.9)
40-64	371(20.4)
≥ 65	143(7.9)
Type of preterm for pre-term babies, N=90	
Late preterm	39(43.3)
Moderate preterm	26(28.9)
Very preterm	24(26.7)
Extremely preterm	1(0.1)
Ward/unit type	
Adult medical ward	340(18.7)
Adult surgical ward	330(18.1)
Obstetrics/Gynecology ward	309(17.0)
Neonatal intensive care unit	184(10.1)
Adult emergency ward	181(9.9)
Pediatric medical ward	146(8.0)
Pediatric emergency ward	120(6.6)

Adult intensive care unit	57(3.1)
Pediatric surgical ward	56(3.1)
Pediatric high risk wards	42(2.3)
Adult high risk wards	42(2.3)
Pediatric intensive care unit	13(0.7)
Current hospitalization malarial status	
Yes	33(1.8)
No	1439(79.1)
Unknown	348(19.1)
Previous malarial treatment history	
Yes	41(2.3)
No	1517(83.3)
Unknown	262(14.4)
Active tuberculosis	
Yes	76(4.2)
No	1499(82.4)
Unknown	245(13.4)
HIV infection status	
Positive	194(10.7)
Negative	1421(78.0)
Unknown	205(11.3)
Patients having chronic obstructive pulmonary disease	28(1.5)
Patients with malnutrition	277(15.2)
Referred from another hospital	501(27.5)
Patients having hospitalization history within 90 days	562(30.9)
Patients with peripheral vascular catheter at 8:00 AM on the day of the survey	1535(84.3)
Patients with urinary catheter at 8:00 AM on the day of the survey	403(22.1)
Patients that were intubated at 8:00 AM on the day of the survey	71(3.9)

HIV: Human immunodeficiency virus

Indications for Antibiotics

From the 1820 enrolled patients, there were about 1191 (65.4%) antibiotics indications on the day of survey. The most common indication for antibiotics was HCAI (480, 40.3%). Eight

hundred eighty-seven patients had a documented infection, the most common being pneumonia (254, 28.6%) followed by clinical sepsis (158, 17.8%) and central nervous system (CNS) infections (118, 13.3%) (Table 2).

Table 2: Indication for antibiotics and types of infections

Variable		N(%)
Indication of antibiotics among 1191 indications	Healthcare-associated infections	480(40.3)
	Community-acquired infection	403(33.8)
	Surgical prophylaxis	218(18.3)
	Medical prophylaxis	86(7.2)
	Unknown	4(0.3)
Types of infection among the 887 patients	Pneumonia	254(28.6)
	Clinical sepsis	158(17.8)
	CNS infection	118(13.3)
	Cellulitis, wound, deep soft tissue infection; not related to surgery	61(6.9)
	Symptomatic upper urinary tract infection	59(6.7)
	Gastro-intestinal infection	43(4.8)
	Surgical site infection involving skin or soft tissue but not bone	39(4.4)
	Intra-abdominal infection	35(3.9)
	Gynecological infection	30(3.4)
	Cardio-vascular infection	19(2.1)
	Others*	71(8.0)

***Others:** Febrile neutropenia, sexually transmitted infection, Infection of ear, nose and throat, Cystic fibrosis, Symptomatic lower urinary tract infection, acute bronchitis and exacerbation of Asthma, Septic arthritis of surgical site, prostatitis, Systemic inflammatory response with no clear anatomical site, completely undefined site. HCAI: Healthcare associated infection; CAI: Community acquired infection; CNS: Central nervous system

Microbiological tests

Microbiological diagnostics for patients treated for HCAIs and CAIs were rarely ordered during the survey period (119, 13.6%). If ordered, most of them were blood samples alone (53, 44.5%), followed by urine culture (26, 21.9%). Moreover, a high proportion of the results were unknown or not reported/collected (52, 43.7%). Out of 41 isolated microorganisms, about two-thirds (28, 68.3%) were gram-negative bacteria. *Escherichia coli* (8, 19.5%) and *Klebsiella pneumoniae* (7, 17.1%) were the most commonly isolated microbes. About 21 resistant phenotypes were reported and most (13, 61.9%) were third generation cephalosporin resistant Enterobacteriaceae followed by Methicillin Resistant *Staphylococcus aureus* (3,14.3%) and Carbapenem Resistant Enterobacteriaceae (3, 14.3%) (Table 3).

Table 3: Microbiological diagnostics and culture and sensitivity results

Variable	N(%)
Sample collected for microbiological workup, N= 870 patients*	
Yes	119(13.6)
No	693(79.7)
Unknown	58(6.7)
Specimen type, N=119 patients	
Blood	53(44.5)
Urine	26(21.9)
Cerebrospinal Fluid	13(10.9)
Pus	11(9.2)
Blood and urine	8(6.7)
Blood and Cerebrospinal fluid	6(5.1)
Peritoneal fluid	2(1.7)
Culture result, N=119 patients	
Positive	38(31.9)
Negative	29(24.4)
Unknown	52(43.7)
Isolated microorganism, N=41 **	
Gram positive bacteria	13(31.7)
Gram negative bacteria	28(68.3)

Type of isolated bacteria, N=41**		
	Escherichia coli	8(19.5)
	Klebsiella pneumoniae	7(17.1)
	Klebsiella oxytoca	4(9.8)
	Acinetobacter	4(9.8)
	Staphylococcus aureus	4(9.8)
	Enterobacter aerogenes	3(7.3)
	Enterococcus	3(7.3)
	Coagulase negative staphylococcus, contaminant	3(7.3)
	Others[#]	5(12.2)
Resistant phenotype, N=21		
	3rd Generation Cephalosporin Resistant Enterobacteriaceae	13(61.9)
	Methicillin Resistant *Staphylococcus aureus*	3(14.3)
	Carbapenem Resistant *Enterobacteriaceae*	3(14.3)
	Carbapenem Resistant *Pseudomonas aeruginosa*	1(4.8)
	Carbapenem Resistant *Acinetobacter*	1(4.8)

*only for those whose indication type is for healthcare associated infection and community acquired infection. **for one patient *Klebsiella oxytoca* from blood and *Klebsiella pneumoniae* from urine, from another patient *streptococcus* from blood and *Klebsiella Pneumoniae* from blood and another one *Klebsiella Pneumoniae* from urine and *Acinetobacter* from blood were isolated. [#]*Pseudomonas aeruginosa, Citrobacter*, Gram positive cocci, *Group A streptococcus*, *Group D streptococcus*.

Readiness to implement antimicrobial stewardship program

All surveyed hospitals had functional infection prevention and control committee and only eight hospitals had functional Drugs and Therapeutics Committee. Although a defined organizational structure for ASP was present in all surveyed hospitals, a formal ASP team was only available in seven (70%) hospitals and none were functional during the survey period. None of the hospitals monitored antibiotic use per defined daily dose or days of therapy and hospital activity denominator. Microbiological services were available in eight of the surveyed hospitals, and the average number of blood cultures performed in the previous fiscal year 2019/2020 was 2625 ±3307. Different classes of broad- and narrow-spectrum antibiotics were stock out during the survey period (Supplementary file).

Antibiotics use prevalence and indication

Of the 1820 surveyed patients, 63.8% had at least one antibiotic prescription on the day of the survey. The prevalence of antibiotic use was higher in adult intensive care unit patients (49, 86.0%) followed by pediatric emergency (112, 76.7%) and pediatric medical wards (94, 78.3%)(Table 4).

On the day of the survey, 2059 antibiotics were prescribed for 1162 patients with antibiotics prescribing ratio of 1.77 per patient. More than half (585, 50.3%) patients were on two antibiotics. Most antibiotics were prescribed in their generic name (1998, 97.1%) and were administered parenterally (1858, 90.2%). The mean duration of treatment from initiation to survey date was 7.72±7.9 days. A significantly higher proportion of treatments were empiric (837, 96.7%). As per the WHO definition of guideline compliance[11], only 637 (54.8%) of the treatments were compliant with the guideline (Supplementary file).

As shown in Table 4, the most widely prescribed antibiotics across all surveyed hospitals were ceftriaxone (626, 30.4%) followed by metronidazole (317, 15.4%), ampicillin (249, 12.1%) and vancomycin (217, 10.5%). Ceftriaxone (157, 54.7%) was the most widely prescribed antibiotic for surgical prophylaxis followed by metronidazole (64, 22.3%). A significantly higher proportion of patients (180, 82.6%) were on prolonged duration of antibiotics for surgical prophylaxis.

Table 4: Proportion patients on antibiotics and types of antibiotics prescriptions

Antibiotics	N(%)
Proportion of patients on antibiotics per surveyed wards, n= 1162	
Adult surgical ward	219(66.4%)
Adult medical ward	199(58.5%)
Obstetrics & Gynecology	157(50.8%)
Neonatal intensive care unit	140(76.1%)
Pediatric medical ward	112(76.7%)
Adult emergency ward	97(53.6%)
Pediatric emergency ward	94(78.3%)
Adult intensive care unit	49(86%)
Pediatric surgical ward	41(73.2%)
Pediatric high risk wards	32(76.2%)

Adult high risk ward	13(31%)
Pediatric Intensive Care Unit	9(69.2%)
Types of antibiotics prescribed for therapeutic use, n= 2059	
Ceftriaxone	626(30.4)
Metronidazole	317(15.4)
Ampicillin	249(12.1)
Vancomycin	217(10.5)
Gentamycin	178(8.6)
Ceftazidime	116(5.6)
Trimethoprim/Sulphamethoxazole	72(3.5)
Cloxacillin	49(2.4)
Ciprofloxacin	42(2.0)
Cefepime	40(1.9)
Meropenam	39(1.9)
Azithromycin	25(1.2)
Others*	89(4.3)
Type of antibiotics prescribed for surgical prophylaxis, n= 287	
Ceftriaxone	157(54.7)
Metronidazole	64(22.3)
Ampicillin	55(19.2)
Cephalexin	4(1.4)
Amoxicillin	3(1.0)
Others **	4(1.4)
Dosage for surgical prophylaxis, n= 218 patients	
Single dose	7(3.2)
Multiple doses over 24 hours only	31(14.2)
Multiple doses for more than 24 hours	180(82.6)
Ratio of antibiotics per surgical procedure (number of antibiotics used for surgery/total number of patients who were on SP) =**1.32**	

* Amoxacillin=20; Cefotaxime=13; Amoxacillin-clavulanic acid=12; Cephalexin=9; Crystalline-penicillin= 6; Erythromycin= 6; Norfloxacin = 5; Benzanthine penicillin= 4; Clindamycin= 4; Doxycycline = 3; Chloramphenicol= 2; Clarithromycin = 1; Nitrofurantoin= 1; Cefixime = 1; Ampicillin-sulbactam = 1, **Amoxicillin-clavulanate, Ciprofloxacin, Cloxacillin and Gentamycin.

Factors associated with antibiotic use

From the multivariable analysis, age, ward type, hospital type, history of being catheterized, history of being intubated, and HIV infection status were significantly associated with being on antibiotics. Patients aged between 18-39 years (AOR= 0.61, 95%CI: 0.38,0.86) and 40-64 years old (AOR=0.55, 95%CI: 0.39, 0.93) had a lower odds of being on antibiotics compared with patients 17 years or younger. Moreover, patients treated in pediatric medical and emergency wards were about four times more likely to be on antibiotics compared to

patients in an adult emergency ward. The study also found that being on urinary catheter and intubation device had a significant association with antibiotics use status, where they were nearly three times more likely to be on antibiotics compared to non-catheterized and non-intubated patients (Table 5).

Table 5: Univariate and multivariable binary logistic regression analysis of predictors of antibiotics use among the surveyed hospitals

Variables	Patient on antibiotics		COR, 95%CI	AOR, 95%CI
	Yes, n(%)	No, n(%)		
Age in years				
0-17	460(39.6)	156(23.7)	1.00	1.00
18-39	406(34.9)	284(43.6)	0.49(0.38,0.61)**	0.61(0.38,0.86)*
40-64	211(18.2)	160(24.3)	0.45(0.34, 0.59)*	0.55(0.39, 0.93)*
≥ 65	85(7.3)	58(8.8)	0.5(0.34, 0.73)**	1.45(0.31, 3.59)
Gender				
Female	584(50.3)	388(59.0)	1.00	1.00
Male	578(49.7)	270(41.0)	1.42(1.17, 1.73)*	1.18(0.93, 1.49)
Ward type				
Pediatric medical	112(9.6)	34(5.2)	2.85(1.76, 4.62)*	3.78(1.81, 7.9)**
Pediatric surgical	41(3.5)	15(2.3)	2.37(1.22, 4.58)	2.31(0.96, 5.51)
Pediatric high risk	32(27.5)	10(1.5)	2.77(1.29, 5.97)	4.15(1.59, 10.8)*
Pediatric ICU	9(0.8)	4(0.6)	1.95(0.58, 6.56)	1.57(0.38, 6.50)
Pediatric emergency	94(8.1)	26(4.0)	3.13(1.86, 5.28)*	4.22(1.98, 9.02)**
Neonatal ICU	140(12.0)	44(6.7)	2.76(1.76, 4.31)*	3.27(1.59, 6.67)*
Adult medical	199(17.1)	141(21.4)	1.22(0.85, 1.76)	1.31(0.89, 1.92)
Adult surgical	219(18.8)	111(16.9)	1.71(1.18, 2.48)	2.00(1.36, 2.95)**
Adult high risk	13(1.1)	29(4.4)	0.39(0.19, 0.79)	0.45(0.22, 0.96)*
Adult ICU	49(4.2)	8(1.2)	5.30(2.38, 11.83)*	2.68(1.05, 6.88)
Gyny/Obs	157(13.5)	152(23.1)	0.89(0.62, 1.29)	0.83(0.54, 1.27)
Adult emergency	97(8.3)	84(12.8)	1.00	1.00
Urinary catheterization status				
No	846(72.8)	571(86.8)	1.00	1.00
Yes	316(27.2)	87(13.2)	2.45(1.89, 3.18)*	2.74(2.04, 3.68)*
Intubation status				
No	1098(94.5)	650(98.8)	1.00	1.00
Yes	63(5.5)	8(1.2)	4.66(2.22, 9.79)*	2.62(1.02, 6.76)**
HIV infection status				
Yes	161(13.9)	33(5.0)	1.00	1.00
No	867(74.6)	554(84.2)	0.32(0.22,0.47)**	0.19(0.13,0.30)**
Unknown	134(11.5)	71(10.8)	0.39(0.24,0.62)**	0.24(0.15,0.40)**
Within 90 days hospitalization history				
Yes	366(31.5)	196(29.8)	1.00	1.00

No	796(68.5)	462(70.2)	0.93(0.75, 1.14)	0.85(0.67, 1.06)
Length of hospitalization in days			0.998(0.99, 1.00)	1.00(0.99, 1.01)
Hospital type				
Secondary care	623(53.6)	304(46.2)	1.00	1.00
Tertiary care	539(46.4)	354(53.8)	0.74(0.61, 0.90)*	0.66(0.53, 0.81)*

*p<0.05, **statistically significant at p<0.0001. AOR: Adjusted odds ratio; COR: Crude odds ratio

Discussion

Antimicrobial resistance is becoming a global threat exacting a major toll on human, animal, and environmental health [17–20]. Ethiopia, like many nations, has not been immune from the negative effects of AMR [16,21,22]. While there have been initiatives to address this pressing health challenge, the few national and institutional efforts have had limited success. Mounting an effective national response to combat AMR requires robust information on the scope of infections and antimicrobial agents being used in healthcare institutions. Using the WHO's standardized PPS methodology, this study assessed the burden of HCAIs and antibiotic use in selected public hospitals of Ethiopia.

Similar to studies done elsewhere [13,23,24], the most common indication for antibiotics therapy was for HCAIs (40.3%), with pneumonia and clinical sepsis accounting for the lion share of indications. This high burden of infections might be a reason for misuse and overuse of antibiotics, potentially straining the already resource constrained hospitals, patients, and family caregivers [13]. Hence, efforts to effectively treat, prevent, and reduce HCAIs are needed. To achieve these, implementing interventions such as strengthening and integrating infection prevention and control practice, developing and enforcing the use of institution specific standard treatment guidelines, and providing in-service trainings are needed. Strengthening microbiology laboratories to guide definitive treatment is also invaluable towards the achievement of this goal.

Empiric prescribing for broad-spectrum antibiotics (96.7%) was a common finding across the surveyed hospitals, something that has been reported in studies from other LMIC countries [24-27]. This may have resulted from lack of– and poor utilization of microbiology services, as seen by the hospitals' limited use of culture and sensitivity tests. This also parallels overuse of antibiotics in general (63.8%), consistent with findings from countries with similar economic contexts (use ranging from 70.6% to 80.1%) [24-27] but contrasting with those from HICs (27.1-50.3%) [23,28–30]. An internet-based PPS done across 53 countries (LMICs and HICs) has also reported higher antimicrobial use in LMICs compared to HICs[31].

An enduring overuse of antibiotics for a prolonged duration in many LMICs compared to HICs [13,26,32] might be attributed to lack of a national and institutional antibiotic guideline and poor diagnostic infrastructure which can promote empiric but also high rates of irrational antibiotic use. Although most of the surveyed hospitals had microbiological services, only one hospital developed institutional guideline as per the antibiogram data. This suggests poor utilization of microbiology services to guide empiric antibiotic use and highlights the missed opportunities in promoting rational antibiotic use [33]. Recently, a pharmacist-led ASP implemented in one of the tertiary care hospitals of Ethiopia was well received and shown to be beneficial [13]. Lessons from such programs should be leveraged to promote widespread adoption of ASP to decrease antibiotic consumption, save costs, and improve outcomes. Additionally, enhancing capacity of existing ASPs through leadership and governance support will be critical as these were identified to be deficient in the surveyed hospitals.

In this study, there was also a substantial difference in the prevalence of antibiotics use across different levels of surveyed hospitals where a statistically significant higher antibiotic use was reported in tertiary care hospitals compared to secondary hospitals. There were also disparities with respect to the type of prescribed antibiotics compared to other studies. Similar to studies done in Pakistan [26] and Ethiopia [12,13,25], the most widely prescribed antibiotic was the 3rd-generation cephalosporin, ceftriaxone (30.4%) which is included under the WHO watch category of Access, Watch and Reserve(AWaRe) classification of antibiotics [6]. In developed countries however, the most commonly prescribed antibiotics were penicillins with β-lactamase inhibitors[23,31]. Nitroimidazole was the most commonly prescribed antibiotic in Nigeria [8].

Prolonged use of surgical prophylaxis (>24hours) was high in this study (82.6%), similar to studies from other LMICs (73% to 100%) [24,26,27,34–36]. The recommended duration of surgical prophylaxis is one day [37–39] since prolonging duration potentially increases the rate of AMR, side effects, and costs for both the patient and the hospital [40–42]. Furthermore, average number of antibiotics prescribed per patient for surgical prophylaxis was 1.32 despite several studies and guidelines demonstrating the cost-effectiveness of single narrow-spectrum antibiotics, usually cefazolin [30,37,43–46]. However, in the current

study, ceftriaxone (54.7%) was the widely prescribed antibiotic for surgical prophylaxis. The widespread use of broad-spectrum 3rd generation cephalosporin's in our survey might be due to unavailability of cefazolin in all of the surveyed hospitals. Hence, due to proven safety and efficacy of Cefazolin, it is time for Ethiopia to include it on the essential medicine list, ensure its availability, and develop guidelines to promote use of cefazolin or other narrow-spectrum antibiotics for surgical prophylaxis.

Our study has some limitations. First, the study only included purposely-selected tertiary and secondary hospitals. Hence, the findings may not be generalizable to all settings. Second, because this was a point prevalence survey (i.e., cross-sectional study), patients were not followed-up in time. As a result, it was not possible to measure outcomes that had a temporal element such as AMR, duration of antibiotic use and length of hospital stay. Some surgical prophylaxis orders might have been changed to empiric treatment for suspected infection without proper documentation reflecting such change. This would inflate the rate of prolonged surgical prophylaxis, but underestimate the true rate of HCAI. Third, the reported microbiology finding may not be representative of the hospital population as a whole and could overestimate rate of AMR. This is because microbiologic investigations are mostly conducted for patients with severe diseases and those who failed first-line therapy. Hence, the reported microbiology finding may not be representative of the hospital population as a whole and could overestimate rate of AMR.

Despite these limitations, the study is the first multicenter study in Ethiopia using a standardized PPS methodology from the WHO. The findings are based on large sample size and are robust enough to guide similar studies to be conducted in Ethiopia and other LMICs. Furthermore, the findings could aid policymakers and other concerned bodies in strengthening ASP, optimizing antibiotics use, and containing and preventing AMR.

Conclusions

Similar to studies from other LMICs, there was widespread use of antibiotics and a high burden of HCAIs. Moreover, prolonged use of broad-spectrum antibiotics was a common practice for surgical prophylaxis suggesting an important target for ASP intervention. Almost

all treatments were empiric and hospitals should be further stimulated to regularly monitor antibiotic use and set local targets to optimize their use.

Abbreviations

AMR: Antimicrobial resistance; **ASP:** Antimicrobial stewardship program; **CAIs:** Community-acquired infections; **HCAIs:** Healthcare-associated infections; **HICs:** High-income countries; **LMICs:** Low- and middle-income countries; **PPS:** Point prevalence survey

Authors' contributions

AMF: prepared the draft manuscript; **YD and MW:** funding acquisition: **AMF, YD, GA, WS and MW**: research planning, conduct and organization of data collection; **AMF, YD, GA, WS, MW, EA and GBG:** supervision, visualization, conception, design, acquisition of data, analysis and interpretation of the results; **AMF, YD, WS, MW, GA, EA and GBG:** took part in revising it critically for important intellectual content. All authors gave final approval of the manuscript and agree to be accountable for all aspects of the work.

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Ethical Considerations

Ethical clearance was obtained from the Ethiopian Federal Ministry of Health. Before data collection, permission was sought from respective hospital administration. Collected data

were de-identified during data collection and data were analyzed in aggregate to maintain confidentiality and anonymity of information.

Competing interests: None

Patient consent for publication

Not required

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Acknowledgments

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References

1 Kardos N, Demain AL. Penicillin: The medicine with the greatest impact on therapeutic outcomes. Appl. Microbiol. Biotechnol. 2011; **92**(4):677-87. doi:10.1007/s00253-011-3587-6

2 Lobanovska M, Pilla G. Penicillin's Discovery and Antibiotic Resistance: Lessons for the Future? Yale J Biol Med. 2017;**90**(1):135-145.

3 O'Neill J. Antimicrobial Resistance : Tackling a crisis for the health and wealth of nations. 2016.

4 The World Bank. Drug-resistant infections: A Threat to Our Economic Future. *World Bank Rep.* 2017.

5 Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014 ;**2**:145. doi: 10.3389/fpubh.2014.00145.

6 World Health Organization. Global Action Plan on Antimicrobial Resistance. *Microbe Mag.* 2015;**10**:354–5. doi:10.1128/microbe.10.354.1

7 Centers for Disease Control and Prevention. Antibiotic Use in the United States. Progress and Opportunities. Atlanta, GA: US Department of Health and Human Services. CDC; 2017.

8 Abubakar U. Point-prevalence survey of hospital acquired infections in three acute care hospitals in Northern Nigeria. *Antimicrob Resist Infect Control.* 2020;**9**:1–7. doi:10.1186/s13756-020-00722-9

9 Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: Causes and control strategies. *Antimicrob Resist Infect Control.* 2017;**6**:1–8. doi:10.1186/s13756-017-0208-x

10 Mboya EA, Sanga LA, Ngocho JS. Irrational use of antibiotics in the moshi municipality Northern Tanzania: A cross sectional study. *Pan Afr Med J.* 2018;**31**:1–10.

doi:10.11604/pamj.2018.31.165.15991

11 World Health Organization. WHO Methodology for Point Prevalence Survey on Antibiotics Use in Hospitals. 2018;**Version 1.**

12 Alemkere G, Tenna A, Engidawork E. Antibiotic use practice and predictors of hospital outcome among patients with systemic bacterial infection: Identifying targets for antibiotic and health care resource stewardship. *PLoS One.* 2019; 14(2):e0212661. doi:10.1371/journal.pone.0212661

13 Gebretekle GB, Haile Mariam D, Abebe Taye W, *et al.* Half of Prescribed Antibiotics Are Not Needed: A Pharmacist-Led Antimicrobial Stewardship Intervention and Clinical Outcomes in a Referral Hospital in Ethiopia. *Front Public Heal.* 2020; **8**:109. doi:10.3389/fpubh.2020.00109

14 Argaw, N.A., Shumbash, K.Z., Asfaw, A.A. *et al.* Assessment of surgical antimicrobial prophylaxis in Orthopaedics and Traumatology Surgical Unit of a Tertiary Care Teaching Hospital in Addis Ababa. *BMC Res Notes.* 2017; **10:**160 (2017). doi: https://doi.org/10.1186/s13104-017-2475-2

15 Abebe W, Alemayehu T, Kong L, *et al.* Alarming rates of drug-resistant Gram-negative bloodstream infections among hospitalized patients in Ethiopia : an urgent call to strengthen diagnostic bacteriology and antimicrobia. *28th Eur Congr Clin Microbiol Infect Dis.* 2018.

16 Alemayehu, T., Ali, M., Mitiku, E. *et al.* The burden of antimicrobial resistance at tertiary care hospital, southern Ethiopia: a three years' retrospective study. *BMC Infect Dis.* 2017; **19:**585 (2019). doi: https://doi.org/10.1186/s12879-019-4210-1.

17 Mouiche, M.M.M., Moffo, F., Akoachere, JF.T.K. *et al.* Antimicrobial resistance from a one health perspective in Cameroon: a systematic review and meta-analysis. *BMC Public Health.* 2019; **19:** 1135 (2019). doi: https://doi.org/10.1186/s12889-019-7450-5

18 Nellums LB, Thompson H, Holmes A, *et al.* Antimicrobial resistance among migrants in

Europe: a systematic review and meta-analysis. *Lancet Infect Dis.* 2018;**18**:796–811. doi:10.1016/S1473-3099(18)30219-6

19 Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol*. 2010;**1**:134. doi: 10.3389/fmicb.2010.00134.

20 Midega J. Estimating the global burden of antimicrobial resistance: Reflections on current methods and data needs. *Wellcome Open Res.* 2020;**5**:48. doi:10.12688/wellcomeopenres.15680.1

21 Muhie OA. Antibiotic Use and Resistance Pattern in Ethiopia: Systematic Review and Meta-Analysis. *Int J Microbiol.* 2019; **2019**: 2489063. doi: 10.1155/2019/2489063*Int*

22 Ibrahim RA, Teshale AM, Dinku SF, *et al.* Erratum: Antimicrobial resistance surveillance in Ethiopia: Implementation experiences and lessons learned. *Afr J Lab Med.* 2019;**8**:1–4. doi:10.4102/ajlm.v7i2.770

23 Frenette C, Sperlea D, German GJ, *et al.* The 2017 global point prevalence survey of antimicrobial consumption and resistance in Canadian hospitals. *Antimicrob Resist Infect Control.* 2020. **9**(104). doi:10.1186/s13756-020-00758-x

24 Anand Paramadhas BD, Tiroyakgosi C, Mpinda-Joseph P, *et al.* Point prevalence study of antimicrobial use among hospitals across Botswana; findings and implications. *Expert Rev Anti Infect Ther.* 2019;**17**:535–46. doi:10.1080/14787210.2019.1629288

25 Gutema G, Håkonsen H, Engidawork E, *et al.* Multiple challenges of antibiotic use in a large hospital in Ethiopia - A ward-specific study showing high rates of hospital-acquired infections and ineffective prophylaxis. *BMC Health Serv Res*. 2018. doi:10.1186/s12913-018-3107-9

26 Saleem Z, Saeed H, Hassali MA, *et al.* Pattern of inappropriate antibiotic use among hospitalized patients in Pakistan: A longitudinal surveillance and implications. *Antimicrob Resist Infect Control*. 2019. doi:10.1186/s13756-019-0649-5

27 Abubakar U. Antibiotic use among hospitalized patients in northern Nigeria: A

multicenter point-prevalence survey. *BMC Infect Dis.* 2020;**20**:1–9. doi:10.1186/s12879-020-4815-4

28 Ciofi Degli Atti ML, D'Amore C, Ceradini J, *et al.* Prevalence of antibiotic use in a tertiary care hospital in Italy, 2008-2016. *Ital J Pediatr*. 2019. doi:10.1186/s13052-019-0645-7

29 Sorensen H. Trends in U. S. Antibiotic Use. *Pew Charit Trust.* 2018:1–9.

30 Vandael E, Latour K, Goossens H, *et al.* Point prevalence survey of antimicrobial use and healthcare-associated infections in Belgian acute care hospitals: Results of the Global-PPS and ECDC-PPS 2017. *Antimicrob Resist Infect Control.* 2020;**9**:1–13. doi:10.1186/s13756-019-0663-7

31 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal*. 2018. doi:10.1016/S2214-109X(18)30186-4

32 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal.* 2018;**6**:e619–29. doi:10.1016/S2214-109X(18)30186-4

33 de With K, Allerberger F, Amann S, *et al.* Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. *Infection:* 2016;**44**:395–439. doi:10.1007/s15010-016-0885-z

34 Afriyie DK, Sefah IA, Sneddon J, *et al.* Antimicrobial point prevalence surveys in two Ghanaian hospitals: opportunities for antimicrobial stewardship. *JAC-Antimicrobial Resist.* 2020;**2**:1–9. doi:10.1093/jacamr/dlaa001

35 Horumpende PG, Mshana SE, Mouw EF, *et al.* Point prevalence survey of antimicrobial use in three hospitals in North-Eastern Tanzania. *Antimicrob Resist Infect Control.* 2020;**9**:1–6. doi:10.1186/s13756-020-00809-3

36 Van Der Sandt N, Schellack N, Mabope LA, *et al.* Surgical antimicrobial prophylaxis among pediatric patients in south africa comparing two healthcare settings. *Pediatr Infect Dis J*. 2019. doi:10.1097/INF.0000000000002072

37 Berriós-Torres SI, Umscheid CA, Bratzler DW, *et al.* Centers for disease control and prevention guideline for the prevention of surgical site infection. JAMA Surg. 2017. doi:10.1001/jamasurg.2017.0904

38 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt).* 2013;**14**:73–156. doi:10.1089/sur.2013.9999

39 Jocum J. Surgical antibiotic prophylaxis: Are you doing it right? *South African J Anaesth Analg.* 2018;**24**:S49–53.

40 Roberts SA, Morris AJ. Surgical antibiotic prophylaxis: more is not better. *Lancet Infect Dis.* 2020;**20**:1110–1. doi:10.1016/S1473-3099(20)30290-5

41 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Balancing the Risks and Benefits of Surgical Prophylaxis Timing and Duration Do Matter. *Am J Heal Pharm.* 2013;**70**:195–283. doi:10.2146/ajhp120568

42 Branch-Elliman W, O'Brien W, Strymish J, *et al.* Association of Duration and Type of Surgical Prophylaxis with Antimicrobial-Associated Adverse Events. In: *JAMA Surgery*. 2019. doi:10.1001/jamasurg.2019.0569

43 Pinto-Lopes R, Sousa-Pinto B, Azevedo LF. Single dose versus multiple dose of antibiotic prophylaxis in caesarean section: a systematic review and meta-analysis. BJOG An Int. J. Obstet. Gynaecol. 2017; **124**(4): doi:10.1111/1471-0528.14373

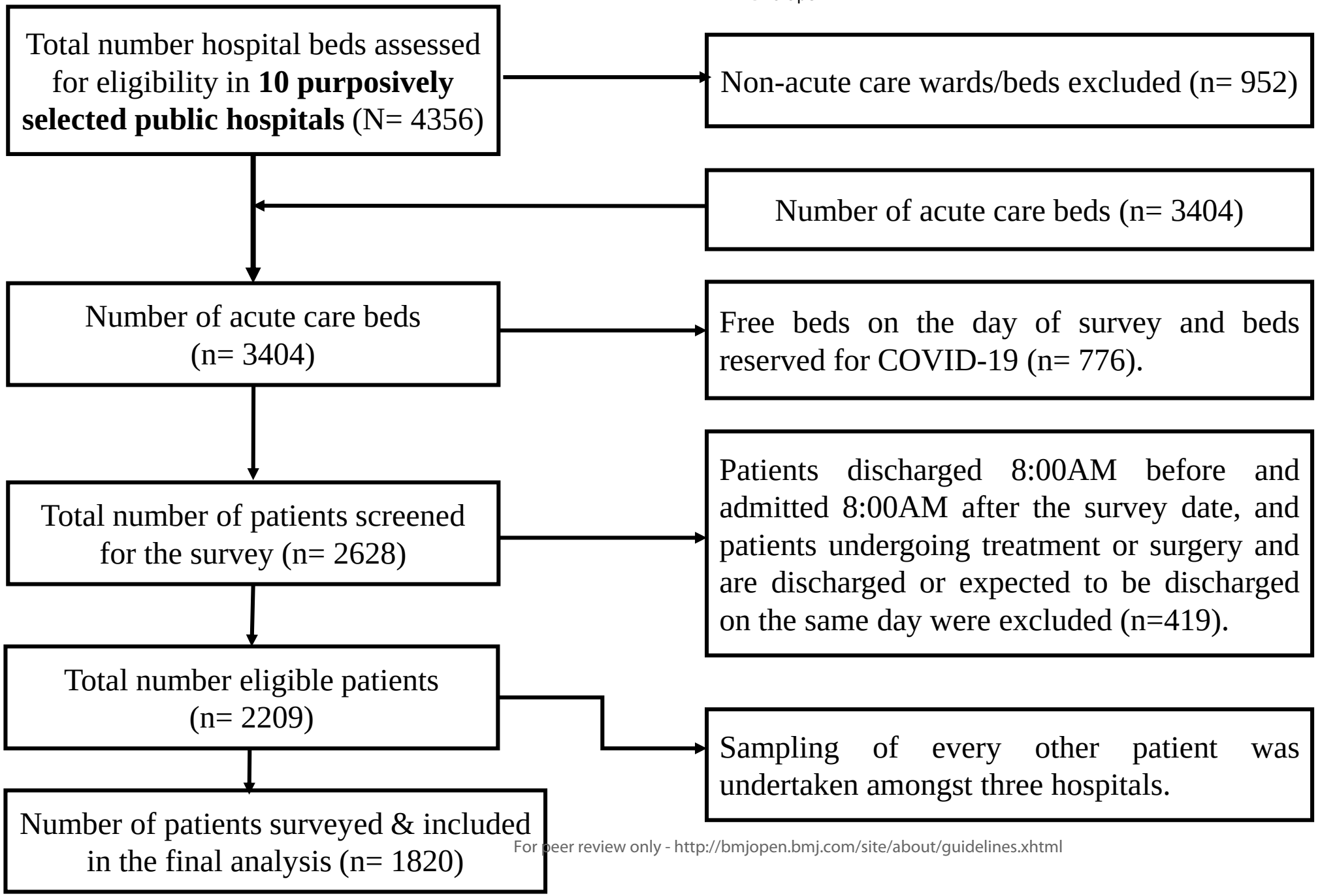
44 Slobogean GP, Kennedy SA, Davidson D, O'Brien PJ. Single- versus multiple-dose antibiotic prophylaxis in the surgical treatment of closed fractures: a meta-analysis. J Orthop Trauma. 2008;**22**(4):264-9. doi: 10.1097/BOT.0b013e31816b7880. PMID: 18404036.

45 Ierano C, Nankervis JM, James R, Rajkhowa A, Peel T, Thursky K. Surgical antimicrobial prophylaxis. *Aust Prescr*. 2017;**40**(6):225-229. doi:10.18773/austprescr.2017.073

46 Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013;**14**(1):73-156. doi: 10.1089/sur.2013.9999.

Figure legend

Figure 1: Diagrammatic scheme of study participant recruitment process



Supplementary file

Table 1: Ethiopia's healthcare system profile

S.N	Variable	Response
1.	ISO code of Ethiopia	ETH
2.	Total number of hospitals at any level (tertiary, secondary, primary and specialized) in the country.	439
3.	Number of public hospitals in the country.	353
4.	Estimated number of private hospitals in the country	86
5.	Estimated number of tertiary level (university teaching and specialized hospital) hospitals in the country.	25
6.	Number of secondary level (General) hospitals in the country.	58
7.	Estimated number of primary hospitals in the country.	381
8.	Is Hospital grouping exist in the country	No
9.	Hospital survey sampling strategy	Convenience sampling
10.	Number of hospitals for the survey	**10**
11.	Does a national treatment guideline exist?	Yes
12.	Does facility-based treatment guidelines exist	No
13.	Does a national hospital ASP exists	Yes

Table 2: The 10 surveyed hospitals profile

S.N	Variable	Mean ± SD	Median(Range)
1.	Number of beds in the surveyed hospitals	443 ± 164	410(223-700)
2.	Number of acute care beds	349 ± 134	314(186-600)
3.	Number of ICU beds	34 ± 24	32(6-82)
4.	Number of high risk beds	22 ± 19	18(0-51)
5.	Annual overall admissions in the hospitals in the previous physical year, i.e. 2012 E.C.#	16471 ± 7405	13885 (7025-30456)
6.	Overall patient days in the hospitals for the previous physical year i.e. 2012 E.C.*	94679 ± 45583	79254(48931-176,742)
7.	Average length of hospital stay in days	6 .53 ± 1.48	6.0(4.8-10.2)
8.	Sum of the number of beds of the wards included in the survey (Total= 2927 beds)	293 ± 153	214(103-541)
9.	Number of patients eligible for inclusion in the survey. (Total= 2209 patients)	240 ± 115	203(103-474)
10.	Number of patients included in the survey (Total= 1820).	182± 61	161(103-325)

#emergency admission over 24 hours was not included. * **Patient days:** over all admission * average length of hospital stay.

Current and past medical history, January 7-29, 2021 G.C.

Variable		Number of patients	Percentage
Current hospitalization malarial status	Yes	33	1.8
	No	1439	79.1
	Unknown	348	19.1
Previous malarial treatment history	Yes	41	2.3
	No	1517	83.3
	Unknown	262	14.4
Active tuberculosis	Yes	76	4.2

	No	1499	82.4
	Unknown	245	13.4
COPD	Yes	28	1.5
	No	1792	98.5
Malnutrition	Yes	277	15.2
	No	1543	84.8
McCabe Score	RF	86	4.7
	UF	258	14.2
	NF	1476	81.1
Referred from another hospital		501	27.5
Referred from another facility other than hospital		447	25.1
Hospitalization history within 90 days		562	30.9

RF= Rapidly fatal, UF= Ultimately fatal, NF= Non-fatal, COPD= Chronic obstructive pulmonary disease, RVI= Retroviral infection

Table 3: Existing surveyed hospitals capacity to promote rational use of antibiotics

Variable	Yes, N(%)
Hospital infrastructure	
Functioning Drugs and Therapeutics Committee	8(80.0)
Functioning Infection Prevention & Control Committee	10(100.0)
Microbiological laboratory service	8(80.0)
Availability of a formal organizational structure responsible for ASP	10(100.0)
A physician ASP leader	10(100.0)
Availability of a ASP team	7(70.0)
Availability of functional ASP in the hospital	0(0.0)
Availability of pharmacist responsible for ensuring appropriate antibiotic use	9(90.0)
Incentive package for dedicated staff for ASP	0(0.0)
IT support for ASP	0(0.0)
Availability of outpatient parenteral antibiotic therapy (OPAT) unit	0(0.0)
Policy and practice	
Availability of antibiotic formulary (including unrestricted and restricted antibiotics) updated continuously	0(0.0)
Antibiotic formulary based on the Essential Drug List	0(0.0)
Institutional antibiotic guideline	3(30.0)
Institutional antibiotic guidelines based on local Antibiogram	1(10.0)

A written policy that requires prescribers to document an indication in the medical records		2(20.0)
Preauthorization policy		1(10.0)
Post-prescription review service		7(70.0)
Monitoring and feedback		
Monitoring of antibiotics indications on medical record		5(50.0)
Monitoring of surgical antibiotic prophylaxis choice and duration		2(20.0)
Results of antibiotic audits are communicated directly with prescribers		7(70.0)
Monitor of antibiotic use		1(10.0)
Monitoring of antibiotic use by DDD or DOT		0(0.0)
Antibiotic use reported by hospital activity denominator		0(0.0)
Annual report focused on ASP in the past year		2(20.0)
A cumulative antibiotic susceptibility report in the past year		3(30.0)
A national antibiotic resistance surveillance program participation		4(40.0)
A national antibiotic use surveillance program participation		0(0.0)
Number of blood cultures done in the past year, N= 7- hospitals	Mean ± SD	2625 ± 3307
	Median(Range)	1707(452-9860)
List of antibiotics out of stock at the facility during the survey period.	Cefepime 1g, Meropenam 1g and 0.5g, Piperacillin-Tazobactam 4.5g, Ciprofloxacin 0.4mg , ceftazidime 1gm, Metronidazole 0.5g and Gentamycin 80mg injections were stock out in all of the surveyed hospitals. Vancomycin 1g and 0.5g was also stock out at two surveyed hospitals.	

Table 5: Antibiotics prescription and indication

Variable		Number	Percentage
Total number of antibiotics prescribed since admission		3192	
Number of antibiotics prescribed/ patient since admission: **N= 1410 patients**			
	1	379	26.9
	2	632	44.8
	3	203	14.3
	4	117	8.3
	5	42	3.0
	6	19	1.3
	Others*	18	1.2
Overall antibiotics prescribed on the day of survey		2058	
Number of antibiotics given/patient at a time of survey: **N= 1162 patients**			
	1	432	37.1
	2	585	50.4
	3	124	10.7
	4	18	1.6
	5	3	0.3
Route of administration: **N= 2059 antibiotics**			
	Oral	201	9.8
	Parenteral	1858	90.2
Antibiotics prescription note: **N= 2059 antibiotics**			
	Brand	61	2.9
	Generic	1998	97.1
Indication of antibiotics written on patient notes: **N= 1162 patients**			
	No	51	4.4
	Yes	1111	95.6
Antibiotics duration in days (From time of initiation to survey date): Mean ± SD: 7.72 ± 7.9			
Type of treatment**, N=866 patients			
	Empiric	837	96.7
	Definitive	29	3.3
Guideline compliance			
	Yes	637	54.8
	No	255	21.9
	Not assessable	237	20.4
	No information	33	2.8
Prescriber type			
	General practitioner	178	15.3
	Resident	949	81.7
	Specialist	35	3.0

***Others:** 7 antibiotics= 5 patients; 8 antibiotics=8 patients; 9 antibiotics=3 patients; 10 antibiotics= 1 patient; 12 antibiotics=1 patient; **Is only for patients whose antibiotics indication is for HCAIs and CAIs

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Last paragraph on 3/4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	10 and 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	15-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A multicenter point prevalence survey of antibiotic use and healthcare associated infections in Ethiopian hospitals

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Abstract

Objective: Effective antimicrobial containment strategies such as Antimicrobial Stewardship programs (ASP) require comprehensive data on antibiotics use which is scarce in Ethiopia. This study sought to assess antibiotics use and healthcare associated infections (HCAIs) in Ethiopian public hospitals.

Design: We conducted a cross-sectional study using the WHO point-prevalence survey protocol for systemic antibiotics use and HCAIs for low- and middle-income countries.

Setting: The study was conducted among 10 public hospitals in 2021.

Participants: All patients admitted to adult and pediatric inpatient and emergency wards before or at 8:00AM on the survey date were enrolled.

Outcome measure: The primary outcome measures were the prevalence of antibiotic use, HCAIs, and the hospitals' readiness to implement ASP.

Results: Data were collected from 1,820 patient records. None of the surveyed hospitals had functional ASP. The common indication for antibiotics was for HCAIs (40.3%). Pneumonia was the most common bacterial infection (28.6%) followed by clinical sepsis (17.8%). Most treatments were empiric (96.7%) and the overall prevalence of antibiotic use was 63.8% with antibiotics prescription per patient ratio of 1.77. Ceftriaxone was the most commonly prescribed antibiotic (30.4%) followed by metronidazole (15.4%). Age, having HIV infection, ward type, type of hospital, catheterization and intubation history had significant association with antibiotic use. Patients who were treated in pediatric surgical wards were about four times more likely to be on antibiotics compared to patients treated at an adult emergency ward. Patients on urinary catheter (AOR:2.74,95%CI:2.04,3.68) and intubation device (AOR=2.62,95%CI:1.02,6.76) were more likely to be on antibiotics than their non-intubated/non-catheterized counterparts. Patients treated at secondary-level hospitals had 0.34 times lower odds of being on antibiotics compared to those in tertiary hospitals.

Conclusions: Antibiotic use across the surveyed hospitals was common and most were empiric which has both practical and policy implications for strengthening ASP and promoting rational antibiotics use.

Strengths and limitations of the study

- This is the first multicenter point prevalence survey in Ethiopia using the standardized WHO tool, thus allowing cross-country comparisons.
- The findings are valuable in strengthening the implementation of antimicrobial stewardship programs and can be used to guide future studies in Ethiopia and other low- and middle-income countries.
- The findings may have limited generalizability given the study's focus on selected secondary and tertiary public hospitals of Ethiopia.
- Surgical prophylaxis may have been switched to empiric treatment without documentation, potentially inflating rate of prolonged prophylactic antibiotic use and underestimating rate of healthcare associated infection.

Introduction

Since their discovery, antimicrobials have saved millions of lives, substantially reduced disease burden, improved patients' quality of life, and helped increase life expectancy [1]. However, Antimicrobial Resistance (AMR) is becoming a growing threat to the health of humans, animals, and the environment [2]. Every year, more than 700,000 deaths are attributable to AMR and, unless urgent measures are taken, AMR will lead to 10 million deaths and would cost the global economy up to US$ 100 trillion by 2050. It is also predicted that AMR will disproportionately affect low- and middle-income countries (LMICs) [3]. Hence, containing and controlling AMR demands multi-sectoral collaboration and coordinated efforts across diverse sectors [4].

Although AMR is a complex problem with many interrelated contributors, the key drivers to the emergence of AMR are misuse and overuse of antimicrobials [5,6]. There is a strong correlation between antibiotic consumption and the emergence of resistant microbes [7–10]. To address this issue, the World Health Organization (WHO) has developed a Global Action Plan (GAP)[6], which includes a standardized point prevalence survey (PPS) methodology to guide optimization of antimicrobial use and AMR containment [11].

Prior studies from Ethiopia have shown widespread misuse and overuse of antibiotics [12–14] as well as emergence of microbes that are resistant against locally available antibiotics including carbapenems [15,16]. Responding to this global health priority, the government of Ethiopia adopted the GAP and implemented strategies, including Antimicrobial Stewardship Program (ASP), to prevent and contain AMR. However, a general picture of antibiotic use, prevalence of HCAIs, and quality of prescribing at a national level is lacking [11]. Hence, this multicenter PPS survey aimed to collect baseline information about antibiotic use, prevalence of HCAIs, distribution of these infections according to infection site and pathogen, and quality of antibiotic prescribing among selected public hospitals in Ethiopia.

Methods

Study design and setting

A multi-center cross-sectional study was conducted in Ethiopian public hospitals in January 2021. We adopted the WHO methodology for PPS of HCAIs and systemic antibiotic use for LMICs Version 1.1[11]. Ethiopia has a three-tier public healthcare system that broadly classifies its facilities as primary, secondary and tertiary level service providers. At the time of this survey, the estimated number of hospitals in Ethiopia was about 464 at any level (378 public, 86 private) of which 25 were tertiary, 58 secondary, and 381 primary hospitals. As part of its strategic initiatives, the Ethiopian Ministry of Health identified selected secondary and tertiary public hospitals to serve as the first cohort of facilities that will implement new ASP or strengthen existing programs. In alignment with the Ministry's programmatic priorities, we have included five secondary and five tertiary care level hospitals. The hospitals were selected based on their readiness to implement the antimicrobial stewardship program, location and catchment area of service (Supplementary file).

Eligibility criteria

The inclusion criteria were first applied to the wards in 10 purposively selected hospitals, then to patients in the selected wards, and finally to the antibiotics prescribed and dispensed to those patients as per the WHO PPS methodology for LMICs Version 1.1[11]. We included all hospitalized patients with a complete medical record admitted in the following acute care wards before or at 08:00 AM on the day of the survey regardless of antibiotic treatment status: adult and pediatric medical, emergency, gynecology/obstetrics, surgery, intensive care unit (ICU) and oncology-hematology. Excluded patients included: those seen in outpatient departments, outpatient dialysis centers, patients who were discharged before 8:00 AM of the day of survey but remaining in wards while awaiting transportation, undergoing treatment or surgery and were discharged or expected to be discharged on the same day, and patients receiving outpatient parenteral antibiotic therapy.

We included only oral and parenteral antibiotics when the patient was on active antibiotic therapy at 08:00 AM on the day of the survey. For instance, if a patient was on treatment

with antibiotic-A at 08:00 AM on the day of the survey but the treatment was changed to antibiotic-B at 10:00 AM, then only antibiotic-A was reported.

Outcome variables

The outcome variables were prevalence of antibiotic use and HCAIs among hospitalized patients and existence of functional ASP. We considered functional ASP when hospitals had been providing either prospective audit and feedback or preauthorization and/or formulary restriction. The independent variables were types of the hospital and ward, patients' socio-demographics, clinical and treatment related characteristics.

Sample size determination and sampling technique

For hospitals with <500 bed capacity, all eligible participants were surveyed. For those with 500-800 bed capacity, every other patient was surveyed following an alphabetical listing of all eligible in-patients on the day of data collection. The next available record was included if a selected patient or medical record was not available. A consistent approach was employed across wards to ensure fidelity to predefined study procedures. Altogether, 2,209 eligible patients were admitted during the survey period, and a total of 1,820 patients were included in the survey and final data analyses. As per the WHO PPS methodology, 389 patients were excluded from the survey because they were either (i) undergoing treatment or surgery and were discharged or expected to be discharged on the same day, or (ii) admitted to the ward after 08:00 AM or discharged before 8:00 AM of the survey date (Figure 1).

Data collection and management

A total of 100 patients, 10 from each of the participating hospitals, were used to pilot test the survey instrument. Trained data collectors fielded the survey instrument (one ASP chair/secretary and two clinical pharmacists per hospital). Data quality was assured through the implementation of a field manual guiding data collectors, regular supervision, and daily checks on data completeness, accuracy, and clarity. A validation workshop was also

conducted to review findings with infectious disease specialists, data collectors, and other key stakeholders from the surveyed hospitals and the Ethiopian Ministry of Health.

Patient and public involvement

The survey was designed for public health surveillance purposes; it was non-experimental, did not involve any patient examination nor did it introduce interventions. There was no direct patient and public involvement in the design, recruitment and conduct of the study. Collected data were de-identified during data collection and it can therefore be considered to be a minimal risk study. All the data were extracted from the respective patient's medical records. Procedures for data collection, data management, analysis and interpretation were in accordance with the ethical and data safety regulations of the country.

Data analysis and interpretation

Data were analyzed using SPSS version 26. Descriptive analyses such as frequency and percentage were used to summarize the data. A multivariable logistic regression analysis was used to explore factors affecting antimicrobial use. During univariate analysis, all variables with $p < 0.25$ and other clinically significant variables (e.g. length of hospital stay and within 90 days hospitalization history) were included for multivariable logistic regression model. A *p*-value of <0.05 was considered statistically significant.

Results

Demographic characteristics of patients

The mean age of patients was 27.7±22.1 years and the majority (690, 37.9%) of patients were in the age group of 18-39 years. There were about 90 preterm babies. Out of the 1820 patients included in the survey, a large proportion of them were from adult medical (340, 18.7%), adult surgical (330, 18.1%), and obstetrics/gynecology (309, 17.0%) wards. Five hundred one (27.5%) patients were found to be transferred from other hospitals and 562 (30.9%) had a previous history of hospitalization in the last 90 days. Moreover, 194(10.7%) of the patients had HIV infection, 76(4.2%) had active tuberculosis, and 277(15.2%) of patients were malnourished. A peripheral vascular catheter was secured in a significant number of patients (1535, 84.3%) (Table 1).

Table 1: Characteristics of patients

Variable, N= 1820	N(%)
Sex	
Male	848(46.6)
Female	972(53.4)
Age in years	
0-17	616(33.8)
18 – 39	690(37.9)
40-64	371(20.4)
≥ 65	143(7.9)
Type of preterm for pre-term babies, N=90	
Late preterm	39(43.3)
Moderate preterm	26(28.9)
Very preterm	24(26.7)
Extremely preterm	1(0.1)
Ward/unit type	
Adult medical ward	340(18.7)
Adult surgical ward	330(18.1)
Obstetrics/Gynecology ward	309(17.0)
Neonatal intensive care unit	184(10.1)
Adult emergency ward	181(9.9)
Pediatric medical ward	146(8.0)
Pediatric emergency ward	120(6.6)
Adult intensive care unit	57(3.1)

Pediatric surgical ward	56(3.1)
Pediatric high risk wards	42(2.3)
Adult high risk wards	42(2.3)
Pediatric intensive care unit	13(0.7)
Current hospitalization malarial status	
Yes	33(1.8)
No	1439(79.1)
Unknown	348(19.1)
Previous malarial treatment history	
Yes	41(2.3)
No	1517(83.3)
Unknown	262(14.4)
Active tuberculosis	
Yes	76(4.2)
No	1499(82.4)
Unknown	245(13.4)
HIV infection status	
Positive	194(10.7)
Negative	1421(78.0)
Unknown	205(11.3)
Patients having chronic obstructive pulmonary disease	28(1.5)
Patients with malnutrition	277(15.2)
Referred from another hospital	501(27.5)
Patients having hospitalization history within 90 days	562(30.9)
Patients with peripheral vascular catheter at 8:00 AM on the day of the survey	1535(84.3)
Patients with urinary catheter at 8:00 AM on the day of the survey	403(22.1)
Patients that were intubated at 8:00 AM on the day of the survey	71(3.9)

Indications for antibiotics

From the 1,820 enrolled patients, there were about 1,191 (65.4%) antibiotic indications on the day of survey. The most common indication for antibiotics was HCAI (480, 40.3%). Eight hundred eighty-seven patients had a documented infection, the most common being

pneumonia (254, 28.6%) followed by clinical sepsis (158, 17.8%) and central nervous system infections (118, 13.3%) (Table 2).

Table 2: Indication for antibiotics and types of infections

Variable		N(%)
Indication of antibiotics among 1191 indications	Healthcare associated infections	480(40.3)
	Community-acquired infection	403(33.8)
	Surgical prophylaxis	218(18.3)
	Medical prophylaxis	86(7.2)
	Unknown	4(0.3)
Types of infection among the 887 patients	Pneumonia	254(28.6)
	Clinical sepsis	158(17.8)
	Central nervous system infection	118(13.3)
	Cellulitis, wound, deep soft tissue infection; not related to surgery	61(6.9)
	Symptomatic upper urinary tract infection	59(6.7)
	Gastro-intestinal infection	43(4.8)
	Surgical site infection involving skin or soft tissue but not bone	39(4.4)
	Intra-abdominal infection	35(3.9)
	Gynecological infection	30(3.4)
	Cardio-vascular infection	19(2.1)
	Others*	71(8.0)

***Others:** Febrile neutropenia, sexually transmitted infection, Infection of ear, nose and throat, Cystic fibrosis, Symptomatic lower urinary tract infection, acute bronchitis and exacerbation of Asthma, Septic arthritis of surgical site, prostatitis, Systemic inflammatory response with no clear anatomical site, completely undefined site.

Microbiological tests

Microbiological diagnostics for patients treated for HCAIs and CAIs were rarely ordered during the survey period (119, 13.6%). If ordered, most of them were blood samples alone

(53, 44.5%), followed by urine culture (26, 21.9%). Moreover, a high proportion of the results were unknown or not reported/collected (52, 43.7%). Out of 41 isolated microorganisms, about two-thirds (28, 68.3%) were gram-negative bacteria. *Escherichia coli* (8, 19.5%) and *Klebsiella pneumoniae* (7, 17.1%) were the most commonly isolated microbes. About 21 resistant phenotypes were reported and most (13, 61.9%) were third-generation cephalosporin resistant Enterobacteriaceae followed by methicillin resistant *Staphylococcus aureus* (3,14.3%) and carbapenem resistant Enterobacteriaceae (3, 14.3%) (Table 3).

Table 3: Microbiological diagnostics and culture and sensitivity results

Variable	**N(%)**
Sample collected for microbiological workup, N= 870 patients*	
Yes	119(13.6)
No	693(79.7)
Unknown	58(6.7)
Specimen type, N=119 patients	
Blood	53(44.5)
Urine	26(21.9)
Cerebrospinal Fluid	13(10.9)
Pus	11(9.2)
Blood and urine	8(6.7)
Blood and Cerebrospinal fluid	6(5.1)
Peritoneal fluid	2(1.7)
Culture result, N=119 patients	
Positive	38(31.9)
Negative	29(24.4)
Unknown	52(43.7)
Isolated microorganism, N=41	
Gram positive bacteria	13(31.7)
Gram negative bacteria	28(68.3)
Type of isolated bacteria, N=41**	
Escherichia coli	8(19.5)
Klebsiella pneumoniae	7(17.1)
Klebsiella oxytoca	4(9.8)

	Acinetobacter	4(9.8)
	Staphylococcus aureus	4(9.8)
	Enterobacter aerogenes	3(7.3)
	Enterococcus	3(7.3)
	Coagulase negative staphylococcus, contaminant	3(7.3)
	Others[#]	5(12.2)
Resistant phenotype, N=21		
	Third-generation cephalosporin resistant Enterobacteriaceae	13(61.9)
	Methicillin resistant *Staphylococcus aureus*	3(14.3)
	Carbapenem resistant *Enterobacteriaceae*	3(14.3)
	Carbapenem resistant *Pseudomonas aeruginosa*	1(4.8)
	Carbapenem resistant *Acinetobacter*	1(4.8)

*only for those whose indication type is for healthcare associated infection and community acquired infection. **for one patient *Klebsiella oxytoca* from blood and *Klebsiella pneumoniae* from urine, from another patient *streptococcus* from blood and *Klebsiella Pneumoniae* from blood and another one *Klebsiella Pneumoniae* from urine and *Acinetobacter* from blood were isolated. [#]*Pseudomonas aeruginosa, Citrobacter*, Gram positive cocci, *Group A streptococcus*, *Group D streptococcus*.

Readiness to implement antimicrobial stewardship program

All surveyed hospitals had functional infection prevention and control committee and only eight hospitals had functional Drugs and Therapeutics Committee. Although a defined organizational structure for ASP was present in all surveyed hospitals, a formal ASP team was only available in seven (70%) hospitals and none were functional during the survey period. None of the hospitals monitored antibiotic use per defined daily dose or days of therapy and hospital activity denominator. Microbiological services were available in eight of the surveyed hospitals, and the median number of blood cultures performed in the previous fiscal year 2019/2020 was 1,707(Inter-quartile range (IQR):680-2,786). Different classes of broad- and narrow-spectrum antibiotics were stocked out during the survey period (Supplementary file).

Antibiotics use prevalence and indication

Of the 1,820 surveyed patients, 63.8% had at least one antibiotic prescription on the day of the survey. The prevalence of antibiotic use was higher in adult intensive care unit patients (49, 86.0%) followed by pediatric emergency (112, 76.7%) and pediatric medical wards (94, 78.3%) (Table 4).

On the day of the survey, 2,059 antibiotics were prescribed for 1,162 patients with antibiotics prescribing ratio of 1.77 per patient. More than half (585, 50.3%) patients were on two antibiotics. Most antibiotics were prescribed in their generic name (1998, 97.1%) and were administered parenterally (1858, 90.2%). The median duration of treatment from initiation to survey date was 5 days (IQR: 3-10 days). A significantly higher proportion of treatments were empiric (837, 96.7%). As per the WHO definition of guideline compliance[11], only 637 (54.8%) of the treatments were compliant with the national guideline (Supplementary file).

As shown in Table 4, the most widely prescribed antibiotics across all surveyed hospitals were ceftriaxone (626, 30.4%) followed by metronidazole (317, 15.4%), ampicillin (249, 12.1%) and vancomycin (217, 10.5%). Additionally, ceftriaxone (157, 54.7%) was the most widely prescribed antibiotic for surgical prophylaxis followed by metronidazole (64, 22.3%). A significantly higher proportion of patients (180, 82.6%) were on prolonged duration of antibiotics for surgical prophylaxis (defined as >24 hours use).

Table 4: Proportion patients on antibiotics and types of antibiotics prescriptions

Antibiotics	N(%)
Proportion of patients on antibiotics per surveyed wards, n= 1162	
Adult surgical ward	219(66.4%)
Adult medical ward	199(58.5%)
Obstetrics & Gynecology	157(50.8%)
Neonatal intensive care unit	140(76.1%)
Pediatric medical ward	112(76.7%)
Adult emergency ward	97(53.6%)
Pediatric emergency ward	94(78.3%)
Adult intensive care unit	49(86%)
Pediatric surgical ward	41(73.2%)

Pediatric high risk wards	32(76.2%)
Adult high risk ward	13(31%)
Pediatric Intensive Care Unit	9(69.2%)
Types of antibiotics prescribed for therapeutic use, n= 2059	
Ceftriaxone	626(30.4)
Metronidazole	317(15.4)
Ampicillin	249(12.1)
Vancomycin	217(10.5)
Gentamycin	178(8.6)
Ceftazidime	116(5.6)
Trimethoprim/Sulphamethoxazole	72(3.5)
Cloxacillin	49(2.4)
Ciprofloxacin	42(2.0)
Cefepime	40(1.9)
Meropenam	39(1.9)
Azithromycin	25(1.2)
Others*	89(4.3)
Type of antibiotics prescribed for surgical prophylaxis, n= 287	
Ceftriaxone	157(54.7)
Metronidazole	64(22.3)
Ampicillin	55(19.2)
Cephalexin	4(1.4)
Amoxicillin	3(1.0)
Others **	4(1.4)
Dosage for surgical prophylaxis, n= 218 patients	
Single dose	7(3.2)
Multiple doses over 24 hours only	31(14.2)
Multiple doses for more than 24 hours	180(82.6)
Ratio of antibiotics per surgical procedure	
(number of antibiotics used for surgery/total number of patients who were on SP) =**1.32**	

*Amoxacillin=20; Cefotaxime=13; Amoxacillin-clavulanic acid=12; Cephalexin=9; Crystalline-penicillin= 6; Erythromycin= 6; Norfloxacin = 5; Benzanthine penicillin= 4; Clindamycin= 4; Doxycycline = 3; Chloramphenicol= 2; Clarithromycin = 1; Nitrofurantoin= 1; Cefixime = 1; Ampicillin-sulbactam = 1, **Amoxicillin-clavulanate, Ciprofloxacin, Cloxacillin and Gentamycin.

Factors associated with antibiotic use

From the multivariable logistic regression analysis, age, ward type, hospital type, history of being catheterized, history of being intubated, and HIV infection status were significantly associated with being on antibiotics. Patients aged between 18-39 years (AOR= 0.61, 95%CI: 0.38,0.86) and 40-64 years old (AOR=0.55, 95%CI: 0.39, 0.93) had lower odds of being on antibiotics compared with 17 years old or younger patients. Moreover, patients treated in

pediatric medical and emergency wards were about four times more likely to be on antibiotics compared to patients in an adult emergency ward. The study also found that being on urinary catheter and intubation device had a significant association with antibiotics use status, where they were nearly three times more likely to be on antibiotics compared to non-catheterized and non-intubated counterparts (Table 5).

Table 5: Univariate and multivariable binary logistic regression analysis of predictors of antibiotics use among the surveyed hospitals

Variables	Patient on antibiotics		COR, 95%CI	AOR, 95%CI
	Yes, n(%)	No, n(%)		
Age in years				
0-17	460(39.6)	156(23.7)	1.00	1.00
18-39	406(34.9)	284(43.6)	0.49(0.38,0.61)**	0.61(0.38,0.86)*
40-64	211(18.2)	160(24.3)	0.45(0.34, 0.59)*	0.55(0.39, 0.93)*
≥ 65	85(7.3)	58(8.8)	0.5(0.34, 0.73)**	1.45(0.31, 3.59)
Gender				
Female	584(50.3)	388(59.0)	1.00	1.00
Male	578(49.7)	270(41.0)	1.42(1.17, 1.73)*	1.18(0.93, 1.49)
Ward type				
Pediatric medical	112(9.6)	34(5.2)	2.85(1.76, 4.62)*	3.78(1.81, 7.9)**
Pediatric surgical	41(3.5)	15(2.3)	2.37(1.22, 4.58)	2.31(0.96, 5.51)
Pediatric high risk	32(27.5)	10(1.5)	2.77(1.29, 5.97)	4.15(1.59, 10.8)*
Pediatric ICU	9(0.8)	4(0.6)	1.95(0.58, 6.56)	1.57(0.38, 6.50)
Pediatric emergency	94(8.1)	26(4.0)	3.13(1.86, 5.28)*	4.22(1.98, 9.02)**
Neonatal ICU	140(12.0)	44(6.7)	2.76(1.76, 4.31)*	3.27(1.59, 6.67)*
Adult medical	199(17.1)	141(21.4)	1.22(0.85, 1.76)	1.31(0.89, 1.92)
Adult surgical	219(18.8)	111(16.9)	1.71(1.18, 2.48)	2.00(1.36, 2.95)**
Adult high risk	13(1.1)	29(4.4)	0.39(0.19, 0.79)	0.45(0.22, 0.96)*
Adult ICU	49(4.2)	8(1.2)	5.30(2.38, 11.83)*	2.68(1.05, 6.88)
Gynecology/Obstetrics	157(13.5)	152(23.1)	0.89(0.62, 1.29)	0.83(0.54, 1.27)
Adult emergency	97(8.3)	84(12.8)	1.00	1.00
Urinary catheterization status				
No	846(72.8)	571(86.8)	1.00	1.00
Yes	316(27.2)	87(13.2)	2.45(1.89, 3.18)*	2.74(2.04, 3.68)*
Intubation status				
No	1098(94.5)	650(98.8)	1.00	1.00
Yes	63(5.5)	8(1.2)	4.66(2.22, 9.79)*	2.62(1.02, 6.76)**
HIV infection status				
Yes	161(13.9)	33(5.0)	1.00	1.00
No	867(74.6)	554(84.2)	0.32(0.22,0.47)**	0.19(0.13,0.30)**
Unknown	134(11.5)	71(10.8)	0.39(0.24,0.62)**	0.24(0.15,0.40)**
Within 90 days hospitalization history				

Yes	366(31.5)	196(29.8)	1.00	1.00
No	796(68.5)	462(70.2)	0.93(0.75, 1.14)	0.85(0.67, 1.06)
Length of hospitalization in days			0.998(0.99, 1.00)	1.00(0.99, 1.01)
Hospital type				
Secondary care	623(53.6)	304(46.2)	1.00	1.00
Tertiary care	539(46.4)	354(53.8)	0.74(0.61, 0.90)*	0.66(0.53, 0.81)*

*p<0.05, **statistically significant at p<0.0001. AOR: Adjusted odds ratio; COR: Crude odds ratio. ICU: Intensive care unit, HIV: Human immune deficiency virus

Discussion

Antimicrobial resistance is becoming a global threat exacting a major toll on human, animal, and environmental health [17–20]. Ethiopia, like many nations, has not been immune from the negative effects of AMR [16,21,22]. While there have been initiatives to address this pressing health challenge, the few national and institutional efforts have had limited success. Mounting an effective national response to combat AMR requires robust information on the scope of infections and antimicrobial agents being used in healthcare institutions. Using the WHO's standardized PPS methodology, this study assessed the burden of HCAIs and antibiotic use in selected public hospitals of Ethiopia.

Similar to studies done elsewhere [13,23,24], the most common indication for antibiotics therapy was for HCAIs (40.3%), with pneumonia and clinical sepsis accounting for the lion share of indications. This high burden of infections might be a reason for misuse and overuse of antibiotics, potentially straining the already resource constrained hospitals, patients, and family caregivers [13]. Hence, efforts to effectively treat, prevent, and reduce HCAIs are needed. To achieve these, implementing interventions such as strengthening and integrating infection prevention and control practice, developing and enforcing the use of institution specific standard treatment guidelines, and providing in-service trainings are needed. Strengthening microbiology laboratories to guide definitive treatment is also invaluable towards the achievement of this goal.

Empiric prescribing for broad-spectrum antibiotics (96.7%) was a common finding across the surveyed hospitals, something that has been reported in studies from other LMIC [24-27]. This may have resulted from lack of– and poor utilization of microbiology services, as seen by the hospitals' limited use of culture and sensitivity tests. This also parallels the overuse of antibiotics in general (63.8%), consistent with findings from countries with similar economic contexts (use ranging from 70.6% to 80.1%) [24-27] but contrasting with those from HICs (27.1-50.3%) [23,28–30]. An internet-based PPS done across 53 countries (LMICs and HICs) has also reported higher antimicrobial use in LMICs compared to HICs [31].

A high prevalence of empiric antibiotics use in many LMICs compared to HICs [13,26,32] might be attributed to lack of a national and institutional antibiotic guideline and poor

diagnostic infrastructure which can promote empiric but also high rates of irrational antibiotic use. Although most of the surveyed hospitals had microbiological services, only one hospital developed institutional guideline as per the antibiogram data. This suggests poor utilization of microbiology services to guide empiric antibiotic use and highlights the missed opportunities in promoting rational antibiotic use [33]. Recently, a pharmacist-led ASP implemented in one of the tertiary care hospitals of Ethiopia was well received and shown to be beneficial [13]. Lessons from such programs should be leveraged to promote widespread adoption of ASP to decrease antibiotic consumption, save costs, and improve outcomes. Additionally, enhancing capacity of existing ASPs through leadership and governance support will be critical as these were identified to be deficient in the surveyed hospitals.

In this study, there was also a substantial difference in the prevalence of antibiotics use across different levels of surveyed hospitals where a statistically significant higher antibiotic use was reported in tertiary care hospitals compared to secondary hospitals. There were also disparities with respect to the type of prescribed antibiotics compared to other studies. Similar to studies done in Pakistan [26] and Ethiopia [12,13,25], the most widely prescribed antibiotic was the third-generation cephalosporin, ceftriaxone (30.4%) which is included under the WHO watch category of Access, Watch and Reserve(AWaRe) classification of antibiotics [6]. In developed countries, however, the most commonly prescribed antibiotics were penicillins with β-lactamase inhibitors [23,31]. Nitroimidazoles were the most commonly prescribed antibiotics in Nigeria [8].

Prolonged use of surgical prophylaxis (>24hours) was high in this study (82.6%), similar to studies from other LMICs (73% to 100%) [24,26,27,34–36]. The recommended duration of surgical prophylaxis is one day [37–39] since prolonging duration potentially increases the rate of AMR, side effects, and costs for both the patient and the hospital [40–42]. Furthermore, average number of antibiotics prescribed per patient for surgical prophylaxis was 1.32 despite several studies and guidelines demonstrating the cost-effectiveness of single narrow-spectrum antibiotics, usually cefazolin [30,37,43–46]. However, in the current study, ceftriaxone (54.7%) was the widely prescribed antibiotic for surgical prophylaxis. The widespread use of broad-spectrum third-generation cephalosporins in our survey might be

due to unavailability of cefazolin in all of the surveyed hospitals. Hence, due to proven safety and efficacy of Cefazolin, it is time for Ethiopia to include it on the essential medicine list, ensure its availability, and develop guidelines to promote use of cefazolin or other narrow-spectrum antibiotics for surgical prophylaxis.

Our study has some limitations. First, the study only included purposely-selected tertiary and secondary hospitals. Hence, the findings may not be generalizable to all settings. Second, because this was a point prevalence survey (i.e., cross-sectional study), patients were not followed-up in time. As a result, it was not possible to measure outcomes that had a temporal element such as AMR, duration of antibiotic use and length of hospital stay. Third, some surgical prophylaxis orders might have been changed to empiric treatment for suspected infection without proper documentation reflecting such change. This would inflate the rate of prolonged surgical prophylaxis, but underestimate the true rate of HCAIs. Fourth, the reported microbiology finding may not be representative of the hospital population as a whole and could overestimate rate of AMR. This is because microbiologic investigations are mostly conducted for patients with severe diseases and those who failed first-line therapy.

Despite these limitations, the study is the first multicenter study in Ethiopia using a standardized PPS methodology from the WHO. The findings are based on large sample size and are robust enough to guide similar studies to be conducted in Ethiopia and other LMICs. Furthermore, the findings could aid policymakers and other concerned bodies in strengthening ASP, optimizing antibiotics use, and containing and preventing AMR.

Conclusions

Similar to studies from other LMICs, there was widespread use of antibiotics and a high burden of HCAIs. Moreover, prolonged use of broad-spectrum antibiotics was a common practice for surgical prophylaxis suggesting an important target for ASP intervention. Almost all treatments were empiric and hospitals should be further stimulated to regularly monitor antibiotic use and set local targets to optimize their use.

Abbreviations

AMR: Antimicrobial resistance; **ASP:** Antimicrobial stewardship program; **CAIs:** Community-acquired infections; **HCAIs:** Healthcare associated infections; **HICs:** High-income countries; **LMICs:** Low- and middle-income countries; **PPS:** Point prevalence survey

Authors' contributions

AMF: prepared the draft manuscript; **YD and MW:** funding acquisition: **AMF, YD, GA, WS and MW**: research planning, conduct and organization of data collection; **AMF, YD, GA, WS, MW, EA and GBG:** supervision, visualization, conception, design, acquisition of data, analysis and interpretation of the results; **AMF, YD, WS, MW, GA, EA and GBG:** took part in revising it critically for important intellectual content. All authors gave final approval of the manuscript and agree to be accountable for all aspects of the work.

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Ethical approval statement

Ethical approval was obtained from the Ethiopian Federal Ministry of Health (Approval ID: SOM/21/10/13). Before data collection, permission was sought from respective hospital administration. Collected data were de-identified during data collection and data were analyzed in aggregate to maintain confidentiality and anonymity of information.

Competing interests: None

Patient consent for publication

Not required

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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References

1 Kardos N, Demain AL. Penicillin: The medicine with the greatest impact on therapeutic outcomes. Appl. Microbiol. Biotechnol. 2011; **92**(4):677-87. doi:10.1007/s00253-011-3587-6

2 Lobanovska M, Pilla G. Penicillin's Discovery and Antibiotic Resistance: Lessons for the Future? Yale J Biol Med. 2017;**90**(1):135-145.

3 O'Neill J. Antimicrobial Resistance : Tackling a crisis for the health and wealth of nations. 2016. Available at: https://wellcomecollection.org/works/rdpck35v

4 The World Bank. Drug-resistant infections: A Threat to Our Economic Future. *World Bank Rep.* 2017. Available at: *https://openknowledge.worldbank.org/handle/10986/26707*

5 Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014 ;**2**:145. doi: 10.3389/fpubh.2014.00145.

6 World Health Organization. Global Action Plan on Antimicrobial Resistance. *Microbe Mag.* 2015;**10**:354–5. doi:10.1128/microbe.10.354.1

7 Centers for Disease Control and Prevention. Antibiotic Use in the United States. Progress and Opportunities. Atlanta, GA: US Department of Health and Human Services. CDC; 2017.

8 Abubakar U. Point-prevalence survey of hospital acquired infections in three acute care hospitals in Northern Nigeria. *Antimicrob Resist Infect Control.* 2020;**9**:1–7. doi:10.1186/s13756-020-00722-9

9 Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: Causes and control strategies. *Antimicrob Resist Infect Control.* 2017;**6**:1–8. doi:10.1186/s13756-017-0208-x

10 Mboya EA, Sanga LA, Ngocho JS. Irrational use of antibiotics in the moshi municipality

Northern Tanzania: A cross sectional study. *Pan Afr Med J.* 2018;**31**:1–10. doi:10.11604/pamj.2018.31.165.15991

11 World Health Organization. WHO Methodology for Point Prevalence Survey on Antibiotics Use in Hospitals. 2018;**Version 1.** Available at: https://apps.who.int/iris/handle/10665/280063.

12 Alemkere G, Tenna A, Engidawork E. Antibiotic use practice and predictors of hospital outcome among patients with systemic bacterial infection: Identifying targets for antibiotic and health care resource stewardship. *PLoS One.* 2019; 14(2):e0212661. doi:10.1371/journal.pone.0212661

13 Gebretekle GB, Haile Mariam D, Abebe Taye W, *et al.* Half of Prescribed Antibiotics Are Not Needed: A Pharmacist-Led Antimicrobial Stewardship Intervention and Clinical Outcomes in a Referral Hospital in Ethiopia. *Front Public Heal.* 2020; **8**:109. doi:10.3389/fpubh.2020.00109

14 Argaw, N.A., Shumbash, K.Z., Asfaw, A.A. *et al.* Assessment of surgical antimicrobial prophylaxis in Orthopaedics and Traumatology Surgical Unit of a Tertiary Care Teaching Hospital in Addis Ababa. *BMC Res Notes.* 2017; **10:**160 (2017). doi: https://doi.org/10.1186/s13104-017-2475-2

15 Abebe W, Alemayehu T, Kong L, *et al.* Alarming rates of drug-resistant Gram-negative bloodstream infections among hospitalized patients in Ethiopia : an urgent call to strengthen diagnostic bacteriology and antimicrobia. *28th Eur Congr Clin Microbiol Infect Dis.* 2018.

16 Alemayehu, T., Ali, M., Mitiku, E. *et al.* The burden of antimicrobial resistance at tertiary care hospital, southern Ethiopia: a three years' retrospective study. *BMC Infect Dis.* 2017; **19:**585 (2019). doi: https://doi.org/10.1186/s12879-019-4210-1.

17 Mouiche, M.M.M., Moffo, F., Akoachere, JF.T.K. *et al.* Antimicrobial resistance from a one health perspective in Cameroon: a systematic review and meta-analysis. *BMC Public Health.* 2019; **19:** 1135 (2019). doi: https://doi.org/10.1186/s12889-019-

7450-5

18 Nellums LB, Thompson H, Holmes A, *et al.* Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. *Lancet Infect Dis.* 2018;**18**:796–811. doi:10.1016/S1473-3099(18)30219-6

19 Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol*. 2010;**1**:134. doi: 10.3389/fmicb.2010.00134.

20 Midega J. Estimating the global burden of antimicrobial resistance: Reflections on current methods and data needs. *Wellcome Open Res.* 2020;**5**:48. doi:10.12688/wellcomeopenres.15680.1

21 Muhie OA. Antibiotic Use and Resistance Pattern in Ethiopia: Systematic Review and Meta-Analysis. *Int J Microbiol.* 2019; **2019**: 2489063. doi: 10.1155/2019/2489063*Int*

22 Ibrahim RA, Teshale AM, Dinku SF, *et al.* Erratum: Antimicrobial resistance surveillance in Ethiopia: Implementation experiences and lessons learned. *Afr J Lab Med.* 2019;**8**:1–4. doi:10.4102/ajlm.v7i2.770

23 Frenette C, Sperlea D, German GJ, *et al.* The 2017 global point prevalence survey of antimicrobial consumption and resistance in Canadian hospitals. *Antimicrob Resist Infect Control.* 2020. **9**(104). doi:10.1186/s13756-020-00758-x

24 Anand Paramadhas BD, Tiroyakgosi C, Mpinda-Joseph P, *et al.* Point prevalence study of antimicrobial use among hospitals across Botswana; findings and implications. *Expert Rev Anti Infect Ther.* 2019;**17**:535–46. doi:10.1080/14787210.2019.1629288

25 Gutema G, Håkonsen H, Engidawork E, *et al.* Multiple challenges of antibiotic use in a large hospital in Ethiopia - A ward-specific study showing high rates of hospital-acquired infections and ineffective prophylaxis. *BMC Health Serv Res*. 2018. doi:10.1186/s12913-018-3107-9

26 Saleem Z, Saeed H, Hassali MA, *et al.* Pattern of inappropriate antibiotic use among hospitalized patients in Pakistan: A longitudinal surveillance and implications.

Antimicrob Resist Infect Control. 2019. doi:10.1186/s13756-019-0649-5

27 Abubakar U. Antibiotic use among hospitalized patients in northern Nigeria: A multicenter point-prevalence survey. *BMC Infect Dis.* 2020;**20**:1–9. doi:10.1186/s12879-020-4815-4

28 Ciofi Degli Atti ML, D'Amore C, Ceradini J, *et al.* Prevalence of antibiotic use in a tertiary care hospital in Italy, 2008-2016. *Ital J Pediatr*. 2019. doi:10.1186/s13052-019-0645-7

29 Sorensen H. Trends in U. S. Antibiotic Use. *Pew Charit Trust.* 2018:1–9.

30 Vandael E, Latour K, Goossens H, *et al.* Point prevalence survey of antimicrobial use and healthcare-associated infections in Belgian acute care hospitals: Results of the Global-PPS and ECDC-PPS 2017. *Antimicrob Resist Infect Control.* 2020;**9**:1–13. doi:10.1186/s13756-019-0663-7

31 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal*. 2018. doi:10.1016/S2214-109X(18)30186-4

32 Versporten A, Zarb P, Caniaux I, *et al.* Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Heal.* 2018;**6**:e619–29. doi:10.1016/S2214-109X(18)30186-4

33 de With K, Allerberger F, Amann S, *et al.* Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. *Infection:* 2016;**44**:395–439. doi:10.1007/s15010-016-0885-z

34 Afriyie DK, Sefah IA, Sneddon J, *et al.* Antimicrobial point prevalence surveys in two Ghanaian hospitals: opportunities for antimicrobial stewardship. *JAC-Antimicrobial Resist.* 2020;**2**:1–9. doi:10.1093/jacamr/dlaa001

35 Horumpende PG, Mshana SE, Mouw EF, *et al.* Point prevalence survey of antimicrobial

use in three hospitals in North-Eastern Tanzania. *Antimicrob Resist Infect Control.* 2020;**9**:1–6. doi:10.1186/s13756-020-00809-3

36 Van Der Sandt N, Schellack N, Mabope LA, *et al.* Surgical antimicrobial prophylaxis among pediatric patients in south africa comparing two healthcare settings. *Pediatr Infect Dis J*. 2019. doi:10.1097/INF.0000000000002072

37 Berriós-Torres SI, Umscheid CA, Bratzler DW, *et al.* Centers for disease control and prevention guideline for the prevention of surgical site infection. JAMA Surg. 2017. doi:10.1001/jamasurg.2017.0904

38 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt).* 2013;**14**:73–156. doi:10.1089/sur.2013.9999

39 Jocum J. Surgical antibiotic prophylaxis: Are you doing it right? *South African J Anaesth Analg.* 2018;**24**:S49–53.

40 Roberts SA, Morris AJ. Surgical antibiotic prophylaxis: more is not better. *Lancet Infect Dis.* 2020;**20**:1110–1. doi:10.1016/S1473-3099(20)30290-5

41 Bratzler DW, Dellinger EP, Olsen KM, *et al.* Balancing the Risks and Benefits of Surgical Prophylaxis Timing and Duration Do Matter. *Am J Heal Pharm.* 2013;**70**:195–283. doi:10.2146/ajhp120568

42 Branch-Elliman W, O'Brien W, Strymish J, *et al.* Association of Duration and Type of Surgical Prophylaxis with Antimicrobial-Associated Adverse Events. In: *JAMA Surgery*. 2019. doi:10.1001/jamasurg.2019.0569

43 Pinto-Lopes R, Sousa-Pinto B, Azevedo LF. Single dose versus multiple dose of antibiotic prophylaxis in caesarean section: a systematic review and meta-analysis. BJOG An Int. J. Obstet. Gynaecol. 2017; **124**(4): doi:10.1111/1471-0528.14373

44 Slobogean GP, Kennedy SA, Davidson D, O'Brien PJ. Single- versus multiple-dose antibiotic prophylaxis in the surgical treatment of closed fractures: a meta-analysis. J

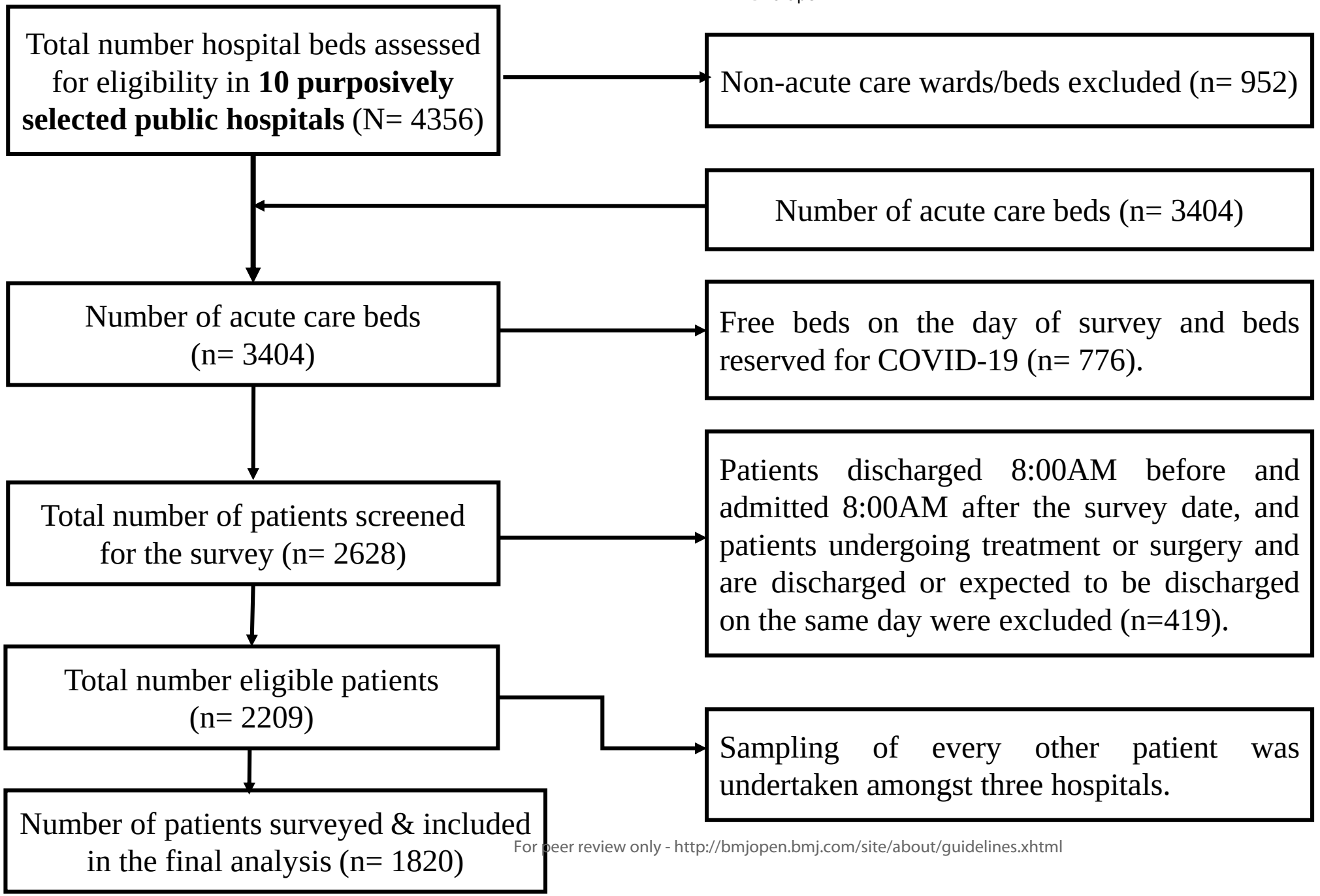
Orthop Trauma. 2008;**22**(4):264-9. doi: 10.1097/BOT.0b013e31816b7880. PMID: 18404036.

45 Ierano C, Nankervis JM, James R, Rajkhowa A, Peel T, Thursky K. Surgical antimicrobial prophylaxis. *Aust Prescr*. 2017;**40**(6):225-229. doi:10.18773/austprescr.2017.073

46 Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013;**14**(1):73-156. doi: 10.1089/sur.2013.9999.

Figure legend

Figure 1: Diagrammatic scheme of study participant recruitment process



Supplementary file

Table 1: Ethiopia's healthcare system profile

S.N	Variable	Response
1.	ISO code of Ethiopia	ETH
2.	Total number of hospitals at any level (tertiary, secondary, primary and specialized) in the country.	464
3.	Number of public hospitals in the country.	378
4.	Estimated number of private hospitals in the country	86
5.	Estimated number of tertiary level (university teaching and specialized hospital) hospitals in the country.	25
6.	Number of secondary level (General) hospitals in the country.	58
7.	Estimated number of primary hospitals in the country.	381
8.	Is Hospital grouping exist in the country	No
9.	Hospital survey sampling strategy	Convenience sampling
10.	Number of hospitals for the survey	**10**
11.	Does a national treatment guideline exist?	Yes
12.	Does facility-based treatment guidelines exist	No
13.	Does a national hospital ASP exists	Yes

Table 2: The 10 surveyed hospitals profile

S.N	Variable	Mean ± SD	Median(Range)
1.	Number of beds in the surveyed hospitals	443 ± 164	410(223-700)
2.	Number of acute care beds	349 ± 134	314(186-600)
3.	Number of intensive care unit beds	34 ± 24	32(6-82)
4.	Number of high risk beds	22 ± 19	18(0-51)
5.	Annual overall admissions in the hospitals in the previous physical year, i.e. 2012 E.C.#	16471 ± 7405	13885 (7025-30456)
6.	Overall patient days in the hospitals for the previous physical year i.e. 2012 E.C.*	94679 ± 45583	79254(48931-176,742)
7.	Average length of hospital stay in days	6 .53 ± 1.48	6.0(4.8-10.2)
8.	Sum of the number of beds of the wards included in the survey (Total= 2628 beds)	293 ± 153	214(103-541)
9.	Number of patients eligible for inclusion in the survey. (Total= 2209 patients)	240 ± 115	203(103-474)
10.	Number of patients included in the survey (Total= 1820).	182± 61	161(103-325)

#emergency admission over 24 hours was not included. * **Patient days:** over all admission * average length of hospital stay.

Current and past medical history, January 7-29, 2021 G.C.

Variable		Number of patients	Percentage
Current hospitalization malarial status	Yes	33	1.8
	No	1439	79.1
	Unknown	348	19.1
Previous malarial treatment history	Yes	41	2.3
	No	1517	83.3
	Unknown	262	14.4
Active tuberculosis	Yes	76	4.2

	No	1499	82.4
	Unknown	245	13.4
COPD	Yes	28	1.5
	No	1792	98.5
Malnutrition	Yes	277	15.2
	No	1543	84.8
McCabe Score	RF	86	4.7
	UF	258	14.2
	NF	1476	81.1
Referred from another hospital		501	27.5
Referred from another facility other than hospital		447	25.1
Hospitalization history within 90 days		562	30.9

RF= Rapidly fatal, UF= Ultimately fatal, NF= Non-fatal, COPD= Chronic obstructive pulmonary disease, RVI= Retroviral infection

Table 3: Existing surveyed hospitals capacity to promote rational use of antibiotics

Variable	Yes, N(%)
Hospital infrastructure	
Functioning Drugs and Therapeutics Committee	8(80.0)
Functioning Infection Prevention & Control Committee	10(100.0)
Microbiological laboratory service	8(80.0)
Availability of a formal organizational structure responsible for ASP	10(100.0)
A physician ASP leader	10(100.0)
Availability of a ASP team	7(70.0)
Availability of functional ASP in the hospital	0(0.0)
Availability of pharmacist responsible for ensuring appropriate antibiotic use	9(90.0)
Incentive package for dedicated staff for ASP	0(0.0)
IT support for ASP	0(0.0)
Availability of outpatient parenteral antibiotic therapy (OPAT) unit	0(0.0)
Policy and practice	
Availability of antibiotic formulary (including unrestricted and restricted antibiotics) updated continuously	0(0.0)
Antibiotic formulary based on the Essential Drug List	0(0.0)
Institutional antibiotic guideline	3(30.0)
Institutional antibiotic guidelines based on local Antibiogram	1(10.0)

A written policy that requires prescribers to document an indication in the medical records		2(20.0)
Preauthorization policy		1(10.0)
Post-prescription review service		7(70.0)
Monitoring and feedback		
Monitoring of antibiotics indications on medical record		5(50.0)
Monitoring of surgical antibiotic prophylaxis choice and duration		2(20.0)
Results of antibiotic audits are communicated directly with prescribers		7(70.0)
Monitor of antibiotic use		1(10.0)
Monitoring of antibiotic use by DDD or DOT		0(0.0)
Antibiotic use reported by hospital activity denominator		0(0.0)
Annual report focused on ASP in the past year		2(20.0)
A cumulative antibiotic susceptibility report in the past year		3(30.0)
A national antibiotic resistance surveillance program participation		4(40.0)
A national antibiotic use surveillance program participation		0(0.0)
Number of blood cultures done in the past year, N= 7- hospitals	Mean ± SD	2625 ± 3307
	Median(Range) IQR	1707(452-9860), 680-2786
List of antibiotics out of stock at the facility during the survey period.	Cefepime 1g, Meropenam 1g and 0.5g, Piperacillin-Tazobactam 4.5g, Ciprofloxacin 0.4mg , ceftazidime 1gm, Metronidazole 0.5g and Gentamycin 80mg injections were stock out in all of the surveyed hospitals. Vancomycin 1g and 0.5g was also stock out at two surveyed hospitals.	

Table 5: Antibiotics prescription and indication

Variable		Number	Percentage
Total number of antibiotics prescribed since admission		3192	
Number of antibiotics prescribed/ patient since admission: **N= 1410 patients**			
	1	379	26.9
	2	632	44.8
	3	203	14.3
	4	117	8.3
	5	42	3.0
	6	19	1.3
	Others*	18	1.2
Overall antibiotics prescribed on the day of survey		2058	
Number of antibiotics given/patient at a time of survey: **N= 1162 patients**			
	1	432	37.1
	2	585	50.4
	3	124	10.7
	4	18	1.6
	5	3	0.3
Route of administration: **N= 2059 antibiotics**			
	Oral	201	9.8
	Parenteral	1858	90.2
Antibiotics prescription note: **N= 2059 antibiotics**			
	Brand	61	2.9
	Generic	1998	97.1
Indication of antibiotics written on patient notes: **N= 1162 patients**			
	No	51	4.4
	Yes	1111	95.6
Antibiotics duration in days (From time of initiation to survey date):Median: 5 days; IQR: 3-10 days			
Type of treatment**, N=866 patients			
	Empiric	837	96.7
	Definitive	29	3.3
Guideline compliance			
	Yes	637	54.8
	No	255	21.9
	Not assessable	237	20.4
	No information	33	2.8
Prescriber type			
	General practitioner	178	15.3
	Resident	949	81.7
	Specialist	35	3.0

***Others:** 7 antibiotics= 5 patients; 8 antibiotics=8 patients; 9 antibiotics=3 patients; 10 antibiotics= 1 patient; 12 antibiotics=1 patient; **Is only for patients whose antibiotics indication is for HCAIs and CAIs

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Last paragraph on 3/4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	NA
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	10 and 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	15-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	18-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.