A Case Study of Antibiotic Use, Variability Across Antibiotic Groups, Prescribers, and Prescription Habits in Rwanda

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Abstract

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Misuse and overuse of antibiotics are the main causes of antimicrobial resistance (AMR), a palpable threat to global health. In Rwanda, data on AMR is inadequate due to various factors, including but not limited to the lack of adequate AMR surveillance systems. The WHO Point Prevalence Surveys (PPS) are a resource-limited, appropriate tool for surveillance that can provide accurate and timely information on antibiotic use and prevalence in health facility settings. The WHO AWaRe classification tool further offers a framework for consumption using categorization based on the spectrum of antibiotic use activity and the potential to develop resistance to promote the prudent use of antibiotics. We deployed the two tools to estimate the prevalence of antibiotic use, understand the distribution of antibiotic agents used, and identify prescribing patterns among providers to identify the scope of interventions to enhance antimicrobial stewardship. A cross-sectional study was conducted in 2021 involving inpatient departments of the three district

hospitals in Kirehe, Butaro, and Rwinkwavu in Rwanda. Patients were enrolled if they were on at least one antibiotic agent at 0800 on the day of the survey. Using study-adapted questionnaires, we collected data on patient demographics, prescribed antibiotics, and clinical indications. Additionally, prescribing providers were interviewed, and data on the field of practice, training, and rationale for prescriptions were collected.

Antibiotic use prevalence was 67.2%. Among the 314 enrolled patients from three district hospitals, 147 (46.8%) were from Kirehe, 95 (29.9%) from Butaro, and 73 (23.2%) from Rwinkwavu District hospitals. Of those enrolled, 187 (59.5%) were female; 140 (45.5%) were under 5 years old at admission; 6 (1.9%) were HIV positive; and 1 (0.3%) was positive for malaria. Overall, 81 (25.8%) reported they had received one antibiotic, while the majority, 157 (50.2%), received two antibiotics, 55 (17.5%) received three antibiotics, 17 (5.4%) received four antibiotics, and 3 (1%) received a maximum of five antibiotics. Of all the 314 participants, 121 (39%) received penicillin, 81 (26%) received third-generation cephalosporins, and 53 (17%) received aminoglycosides. According to the WHO AWaRe category, of total prescriptions, 69.0% were from the Access group, 30.9% were from the Watch group of antibiotics, and no antibiotics from the Reserve group were prescribed at any of the three hospitals. Of total prescriptions, the use of Access and Watch group antibiotics was high in neonatology (80.1% and 9.9%) and obstetrics and gynecology units (71.8% and 28.2%), respectively. A total of 51 prescribing providers participated in the interview survey, 23 (45.1%) were from Butaro, 15 (29.4%) from Rwinkwavu, and 13 (25.5%) from Kirehe hospitals. The majority, 36 (70.6%), were under thirty years of age, and 46 (90.2%) were male. 40 (78.4%) of the providers were general practitioners. 46 (90.2%) of providers identified prescribing antibiotics before obtaining laboratory results in situations of common clinical presentation of infections and 38 (74.5%) in pre-operative conditions. Our findings point to the high use of a wide range of antibiotics. This underscores the urgent need for public health facility-based interventions to enhance appropriate antibiotic stewardship - including the need for enhanced surveillance of antibiotic use as part of a strong antimicrobial stewardship (AMS) program at national and health facility levels. Corresponding activities in AMS at the health facility level include the implementation of appropriate guidelines, continued in-service review of use, and training on recommended prescription practices.

INTRODUCTION:

The discovery of penicillin in 1928 revolutionized the treatment of infectious diseases worldwide.[1] Although antibiotics have since delivered on their promise of positively impacting the burden of disease, specifically, infectious diseases, the contemporary era is confronted with a significant threat of antimicrobial resistance (AMR).[1,2]

Bacterial AMR consists of resistance across various classes of antimicrobial agents.[3] According to the first comprehensive global assessment of bacterial AMR burden, as of 2019, bacterial AMR was directly responsible for 1.27 million deaths and associated with 4.95 million deaths[3, 4] Notably, the burden was found to be disproportionately higher in sub-Saharan Africa (SSA), with all-age death rates attributable to and associated with bacterial AMR.[3] In another study, the estimated burden for the WHO Africa region was 1.05 million deaths associated with AMR and 250,000 deaths attributable to bacterial AMR.[5] Although there is a strong relationship between suboptimal use of antibiotics and AMR,[4, 6, 7] there are multifaceted challenges countries in SSA face that complicate the AMR crisis. These include lack of surveillance systems, lack of access to effective antibiotics, limited institutional and human resource capacity, lack of and/or limited implementation of national action plans on combating AMR, and lack of stewardship programs, among others. In 2015, the World Health Assembly endorsed the global action plan on antimicrobial resistance,[8] which underscored five objectives, one of which solidified the need to strengthen surveillance, research, and optimize antimicrobial use, the latter being the first aim of Antimicrobial Stewardship (AMS).[8] However, more data is urgently needed to inform the implementation of AMS in respective countries, especially in low-income countries. Key aspects of priority include dispensing and prescribing patterns of antibiotics in health facilities, antibiograms and availability, and use of essential medicines.

In Rwanda, there is a paucity of data on antimicrobial use, prevalence, and resistance or susceptibility profiles of common pathogens. The limited evidence indicates an alarming increase in AMR, particularly in primary health settings. A 5-year longitudinal study on temporal trends of antimicrobial susceptibility conducted at King Faisal Hospital (a tertiary hospital) revealed alarming resistance rates of gram-negative pathogens and reduced susceptibility to some of the commonly used antimicrobial agents in Rwanda. [9] A total of 5296 isolates were included, 46.7% of which were *E. coli* (18.4%), *Klebsiella* spp. (18.4%), *S. aureus* (11.7%), *Enterococcus* spp. (10.3%), *Pseudomonas* spp. (7.1%), *and Acinetobacter* spp. (5.9%). [9] *E. coli* was least susceptible (most resistant) to ampicillin (14.8%) and amoxicillin-clavulanate (36.0%). *Enterococcus* spp. was least susceptible (most resistant) to gentamicin (27.0%) and levofloxacin (54.6%). [9] The study revealed a rise in *E. coli*'s resistance to various antibiotics, including amoxicillin-clavulanate, gentamicin, nalidixic acid, cefuroxime, piperacillin, imipenem, and colistin. [9] Subsequent studies in Rwanda confirm this increase in resistance to commonly used and available agents. [10, 11, 12] Researchers found that *E. coli* was significantly resistant to penicillin (ampicillin, 96%; amoxicillin/clavulanate, 88%), third- generation cephalosporins (ceftriaxone, 30%; ceftazidime, 33%), gentamicin (37%), and imipenem (8%), in a prospective observational study carried out in 2015 at CHUK, a teaching and tertiary health facility. [10] Furthermore, *Klebsiella* spp., showed higher resistance rates to most third-generation cephalosporins (ceftazidime, 58%; ceftriaxone, 55%; cefotaxime, 44%), and gentamicin (53%). [10] In 2017, at CHUK, Sutherland and colleagues found that 75% of gram-negative isolates (of 90% total positive culture specimens) were resistant to third or fourth cephalosporins. [11] This study tested for the extended-spectrum beta-lactamase (ESBL) positive phenotype, and of the 92 tested, 66 (71.7%) were positive. [11] These findings are key because ESBL detection is a concerning indicator of colonization and potential carriage of

ESBL-producing gram-negative bacteria. This coupled with the high resistance to third- and fourth cephalosporins which are commonly used, renders need for the restricted and expensive treatment options for ESBL-positive infection from the carbapenem class (meropenem). In 2020, another study exploring community versus hospital-acquired infections in surgical patients at CHUK, corroborated the increase of ESBL production and resistance to third- generation cephalosporins was common among the isolates. [12] For instance, in *E. coli* and *Klebsiella* spp. isolates, 58% and 67% were resistant to third- generation cephalosporins, respectively, while 52% and 38% were ESBL producers. [12] The above studies paint a concerning snapshot of increasing AMR in Rwanda. Moreover, the available data remains concentrated at tertiary facilities such as CHUK due to their significant referral base, making it important to assess district-level burden of AMR to ensure timely intervention. Despite Rwanda's national strategic action plan on AMR, [13] the absence of a national surveillance system remains a crucial limitation that would otherwise provide evidence for programmatic and scientific intervention design.

We adapted the WHO-adopted ECDC protocol for Point Prevalence Surveys (PPS)[14] on antimicrobial use and WHO AWaRe (Access, Watch, and Reserve) [15] antibiotic classification resources to collect systematic data working at three rural district hospitals in Rwanda. The WHO-PPS collects information relevant to treating and managing infectious diseases among hospitalized patients at specific times, providing meaningful insights into the prescribing behaviors and overall facility-based use of antibiotics. The WHO AWaRe classification guides antibiotic choice vis a vis commonly seen infections and is based on the antibiotics' impact on resistance. [15] According to the tool, Access antibiotics, with a narrow spectrum of activity, are recommended for common infections due to their lower resistance selection and costs. Watch antibiotics, with a higher resistance risk, which are reserved for severe conditions, and need careful monitoring. Lastly, Reserve antibiotics are last-resort options for critical situations, highlighting the need to restrict Watch and Reserve category usage.

Specific aims of the study include:

1. Describe the proportion of antibiotic use (frequency, classes, and indications) among admitted patients in three rural district hospitals
2. Assess the relationship between provider characteristics and antibiotic prescribing patterns in the three hospitals

To characterize antibiotic profile using validated tools, this study provides the prevalence of antibiotic use, distribution of antimicrobial agents used, provider prescribing patterns, and indications for antibiotic use among hospitalized patients. The body of evidence generated here will inform the design of the relevant and the scope of intervention for promoting the rational use of antibiotics within the study context.

METHODS:

Study design

We conducted a cross-sectional point prevalence survey (PPS) from March to April 2021 at three MOH district hospitals in Rwanda. Our survey adapted the WHO Methodology for PPS on Antibiotic Use in Hospital Settings, version 1.1.[14] Additionally, we administered a prescriber survey adapted from a validated tool from the American College of Oral and Maxillofacial Surgeons, [16] to assess prescribing patterns, for on-call prescribing providers.

Site and Population

The PPS was administered in three purposively selected district hospitals of Butaro (BDH) in the northern province, Kirehe (KDH), and Rwinkwavu (RDH) in the eastern province. In terms of inpatient capacity, BDH had 155 beds, KDH had 218 beds, and RDH had 150 beds. Partners In

Health/Inshuti Mu Buzima, a key collaborator of this study, has supported the three health facilities since 2005. Each facility has basic laboratory capacity and infrastructure, with BDH housing the country's first histopathology laboratory due to its oncology services.

Questionnaire-based data were collected from the inpatient units of internal medicine, surgery, obstetrics and gynecology, pediatric wards, and intensive care units. Only hospitalized patients from the respective facilities as of 8:00 AM on the day of the survey were included. Data using interviews was also collected from on-call prescribing providers.

Data collection procedures and measures

Data were abstracted from patients' medical records on a single weekday starting at 0800. When all the data from the inpatient wards was not captured in a day, the individual collecting data would return to collect the same date's information and validate missing information from the medical records by asking the nursing staff. Data collection occurred on a single day and only on weekdays. Additionally, prescribing providers were interviewed to capture their background, practice, training, and rationale for prescriptions.

Inclusion criteria*:*

- Records of all hospitalized patients with in-patient status by 0800 on the survey day
- Records of all hospitalized patients on antimicrobials by 0800 on the survey day
- All willing and consenting prescribing providers at the respective health facilities

Exclusion criteria:

- Outpatient and ambulatory services and patients seeking care in those services
- Admitted patients who were not on any antimicrobials on the day of the survey
- Discharged or patients who are being planned to be admitted on the day of the survey Data collected from medical records of patients on the day of the survey:

- Demographic information: Age, weight, gender, marital status
- Medical history: HIV status with CD4 results and ARV status, malaria status,
- Admission and clinical information: Date and reason for admission, diagnosis, antimicrobial(s) name, dosage units, frequency of intake, route of administration, indication for prescribed antimicrobial, the start date of antimicrobial administration, and whether there was a change in prescription (with the accompanying date of the new drug)

Data collected on the wards on the day of the survey:

- Ward/Department type
- Total number of admitted patients
- Inpatient bed capacity

Data collected from prescribing provider surveys:

- Demographic information: Age, gender
- Hospitals the provider practices and the primary department
- Education, experience, and specialization in medicine
- Antibiotic prescription practices against the availability of laboratory results

All collected data were de-identified and all other study protocols and case record forms used in the study were submitted and approved by the Rwanda National Ethics Committee (RNEC). All study data were collected, managed, and stored in REDCap, a web-based electronic database enabled to capture both online and offline data. All study-employed data collectors were trained in the use of REDCap and the abstraction of data from patient charts. REDCap was installed on a limited password-protected tablet. Each participant was assigned a unique study identification number (ID) to input relevant information. In addition, all study tablets were stored in limited-access lockers in department-only offices at each study site. At the end of a single day of data collection, the study coordinator conducted data quality audits, and any issues were resolved within 1-2 working days. In this study, "Diagnoses" and "indications" were considered similar in meaning.

STATISTICAL ANALYSIS:

Descriptive statistics, hospital and ward information, demographic and clinical information of patients, and antimicrobial agents were reported as frequencies and percentages for categorical variables. We define the prevalence of antibiotic use as the number of patients prescribed an antibiotic agent divided by the total number of admitted patients. Data from the prescriber survey permitted an estimate of the proportion and frequency of antibiotic prescription rationales based on provider practice in prescribing scenarios. Categorical data was presented per hospital to allow identification of inter-facility differences. Using the 2021 WHO AWaRe classification, we estimate the distribution of prescribed antibiotics per antibiotic class to determine proxy appropriate use. Statistical tests such as Pearson's chi-square tests of relevant categorical variables on both surveys was conducted to estimate associations of relevant variables. Analysis was carried out in Stata/BE 18.0.

ETHICAL CONSIDERATIONS

Primary study procedures were approved by Partners In Health/Inshuti Mu Buzima Research Committee, and subsequent approval from the Rwanda National Ethics Committee (RNEC) was obtained on October 27th, 2020 (No. 989/RNEC /2020). Prior to secondary data analysis for purposes of the thesis, the necessary training (CITI- Human Subjects) and the form of use of UW Human and Animal Subjects for UW Graduate Student Theses and Dissertations were completed.

RESULTS:

Hospital and Demographic Characteristics

A total of 314 admitted patients were enrolled; 147 (46.8%) were from KDH, 94 (29.9%) from BDH, and 73 (23.2%) from RDH (Table 1). The total number of admissions at the respective facilities on the day of the survey was BDH (166), KDH (202), and RDH (99). Among the enrolled, 187 (59.5%) were female, 150 (47.7%) were aged 15 years or older, and 140 (44.5%) were under-five. The study participants' median age was 10 years (SD: ± 21.5). Of the enrolled, 6 (1.9%) were living with HIV and on ART, except for one who had been recently diagnosed and was yet to begin treatment; 1 individual tested positive for malaria and was on antimalarial treatment. By clinical department, 91 (29.0%) were from the neonatology department, 85 (27.1%) from the obstetrics and gynecology units (OB/GYN), 62 (19.8%) from pediatric units, 46 (14.4%) from internal medicine units, 26 (8.3%) from surgery units, and 4 (1.3%) from oncology units. The median duration of patient hospitalization by study enrollment was 4 days at KDH, 7 days at BDH, and 5 days at RDH.

Clinical Characteristics and Indications

Of the 314 patients on antibiotics, 213 (67.8%) had one diagnosis, 78 (24.8%) had two diagnoses, 17 (5.4%) had three diagnoses, and 6 (1.9%) had four diagnoses (Fig. 1). From the chart review, antibiotics were prescribed for prophylactic or therapeutic intent. Indications for total prescribed antibiotics (649) were infection (and risk of) among neonates (n=144, 22.2%), obstetric complications (n=187, 29.0%), including C-section surgery (n=112, 17.3%), and non-surgical delivery complications (n=75, 11.7%). Other indications included pneumonia (n=73, 11.3%), gastritis (n=26, 3.9%), meningitis and presumed meningitis (n=20, 3.1%), malnutrition (n=17, 2.6%), and fractures (n=15, 2.3%) (Table 2a). Respiratory distress (2.2%), bronchiolitis (1.9%), convulsions (1.4%), syphilis (1.1%), and sepsis (0.8%) were among the other documented indications and diagnoses.

Antimicrobial Use: Antibiotic use prevalence and class distribution

Among 314 patients who were prescribed antimicrobial agents, totaling 649 prescriptions, 645 (99.3%) were prescribed antibiotic, 3 (0.46%) were prescribed antifungals, and 1 (0.15%) were prescribed an antimalarial (Table 3a).

Prevalence of antibiotic use

The prevalence of antibiotic use was 67.2% (314/467). Antibiotic use prevalence per facility was 72.8% at Kirehe DH, 56.6% at Butaro DH and 73.7% at Rwinkwavu DH.

Antibiotics and class distribution

Among the 314 enrolled patients, 81 (25.8%) were prescribed at least one antibiotic; nearly half, 157 (50.16%) were prescribed two antibiotics, and 55 (17.57%), 17 (5.4%), and 3 (1%) were prescribed three, four, and five antibiotics, respectively (Table 3c). Of all prescriptions, in terms of classes, 249 (38.4%) and 160 (24.7%) were for penicillin and third- generation cephalosporins, respectively. Aminoglycosides made up 121 (18.8%) and imidazole 71 (11.0%). Ceftriaxone and cefotaxime were equally prescribed cephalosporins, each with 80 (12.3%) prescriptions, while ampicillin was the most prescribed penicillin among 178 (27.5%), followed by gentamicin (n=121 18.7%) (Table 3b). Overall, there was a significant difference in distribution of total prescriptions across departments, with a higher numbers seen in neonatology (n=91, 29.0%), obstetrics and gynecology departments (n=85, 27.1%), and pediatric department (n=62, 19.8%). Other departments such as internal medicine department accounted for 46 (14.4%), surgery units 26 (8.3%), and the oncology unit 4 (1.3%).

Distribution of Antibiotics using the AWaRe Classification

According to the WHO AWaRe categorization, Access group antibiotics comprised the majority of total prescriptions, accounting for 70.7%, while Watch group antibiotics represented 29.3% of prescriptions. Notably, no antibiotics were prescribed from the Reserve group (Table 3e).

Furthermore, an analysis of antibiotic prescription patterns across departments revealed significant variations. The highest use of the Watch group (total 189) was seen in the OB/GYN units (n=57, 30.2%), followed by internal medicine wards (n=42, 22.2%) and neonatology units (n=40, 21.2%) (Table 3f). Overall, high use of both Access and Watch antibiotic groups was observed at KDH (50.4% and 41.27%) (Table 3g). There was a statistically significant relationship between departments and antibiotic categories (Pearson chi-square = 39.2648, p< 0.000), suggesting a correlation between the department in which the prescription is made and the choice of antibiotic category. Similarly, for age, chi-square test results indicate that there may be a statistically significant association between age and the antibiotic AWaRe category (Pearson chi-square (1) = 7.139, p = 0.008). Assuming the first documented diagnosis, which was documented under indication as well, was the primary reason for treatment, there was a significant relationship between indication and antibiotic category of choice based on a chi-square test result (Pearson chi2(1) = 5.189, p = 0.023).

Prescriber Characteristics and Rationale

A total of 51 physicians were interviewed. Of the participating providers, 23 (45.1%) were based at BDH, 15 (29.4%) at RDH, and 13 (25.5%) at KDH. A majority 46 (90.2%) were male, while 36 (70.6%) were under 30 years of age. 30 (58.8%) had practiced medicine for less than a year, 43 (84.3%) had completed their medical training in Rwanda and the remainder had completed their medical degrees within the region (Uganda, Congo, and Burundi), whilst 7 (13.7%) had received additional training such as residency and masters. In terms of specialization, the majority were general practitioners 40 (78.4%), 5 (9.8%) were internal medicine specialists and 3 (5.9%) were pediatric specialists. Despite rotational servicing, providers reported the following as their primary departments: obstetrics and gynecology (n=18, 35.3%), internal medicine (n=11, 21.6%), pediatric ward (n=8, 15.7%), surgery (n=5, 9.8%), neonatology (n=4, 7.8%), oncology (n=2, 3.9%), emergency medicine (n=2, 3.9%), and clinical services/admin (n=1, 1.9%).

In the review of prescription practices, providers varied in the spectrum of antibiotics prescribed relative to the timing of diagnostic testing. Patient files could not be consistently connected to a single provider due to routine provider rotations in departments. Among the prescribers, 25 (49.0%) indicated a tendency to sometimes prescribe antibiotics before ordering laboratory tests, while 23 (45.1%) reported to rarely engage in this practice. Only 3 (5.9%) of the providers stated that they refrain from prescribing antibiotics before ordering diagnostic tests. Among providers who sometimes prescribe antibiotic before ordering of lab tests (25), 72% were 30 years old and younger compared to other age groups. However, there was no statistically significant association between age and this practice (p=0.724). In the medical charts, concurrent placement of laboratory tests and prescribing was observed among 36 (70.6%) and 11 (21.6%) providers who reported doing so either sometimes or always, respectively. In a clinical scenario of prescribing antibiotics after receiving laboratory results, 36 (70.6%) providers reported to sometimes practice this, while 13 (25.5%) reported to always do so to adjust for optimal treatment.

Indications for prescribing antibiotics before ordering laboratory tests varied based on clinical presentation, surgical considerations, anticipated delays, and the urgency of clinical situations. In a number of scenarios, providers reported writing prescriptions because their patients displayed signs/symptoms of infection (n=46, 90.2%), in preoperative prophylactic situations (n=38, 74.5%), due to the expected delay of laboratory results (n=16, 31.4%), and in emergencies (n=6, 11.8%) where administering antibiotics was critical. Regarding surgery-related care, 41 providers (80.4%) indicated administering antibiotics both before and after surgery, among whom 18 (43.9%) did so at least one hour before the procedure.

DISCUSSION:

There is limited published data on antibiotic use in Rwanda. Using the PPS tool to delve into the patterns of antibiotic use in three rural district hospitals offers critical baseline insights into the prevalence, indications, and prescription practices in this setting. The high estimated antibiotic use prevalence at Kirehe, Rwinkwavu, and Butaro district hospitals suggests that antibiotic therapy is a critical part of patient care management. In the study, 2 in 3 admitted patients received an antibiotic as part of their treatment course. Although our study is limited in concluding whether prescriptions were appropriate or indicated due to unlinked documentation (antibiotic- indication- diagnosis), this finding is slightly higher than the 50% estimated for the Africa continent. [17] It is however comparable with findings in from similar countries in their healthcare settings. In Kenya, two study reported prevalence of 55% and 68% in leading referral and teaching hospitals.[18,19] Other studies in Ghana, Uganda, Zambia, and Tanzania reported an overall prevalence ranging from 30%-57%.[20]

Clinical indications and risk factors for which high rates of antibiotics were prescribed include cesarean sections, neonatal infection (and risk of), and non-surgical pregnancy indications such as delivery, episiotomy, preterm labor, and pneumonia. Antibiotics in the beta-lactam group, such as penicillin and cephalosporins (third- generation; ceftriaxone, cefotaxime), were the most observed in this survey across the three facilities, as has been reported from other studies in Rwanda, in different clinical indications. [21, 22] and in other African countries. [16] The widespread use of penicillin and third- generation cephalosporins is concerning, as it has been reported to lead to the selection and proliferation of antibiotic-resistant strains of bacteria, including critical pathogens such as Enterobacteriaceae, Acinetobacter, and Pseudomonas. [23] Additionally, the capacity of these strains to acquire and disseminate plasmid-mediated resistance determinants add to the concern.[23] Similarly, excessive use of third generation cephalosporins has been reported as one of the key risk factors for extended spectrum beta-lactamase (ESBL) producing bacteria.[24] In Rwanda, there is already evidence of exacerbating resistance to these drugs by common pathogens, such as *E. coli, Klebsiella.*[10, 11]

According to the AWaRe classification, the most used antibiotics in our study were Access and Watch antibiotic groups – Access group are considered first or second line agents in treatment of most infections and therefore are recommended for use and should be available whereas those in Watch group have a high risk of selecting for resistance and are to be used as first and second line treatment for a limited number of indications – respectively. The use of Access group antibiotics was observed in 70.7% of total prescriptions made, which aligns with the WHO target recommendation that 60% of the antibiotic prescriptions should belong to the Access group.[15] However, there was a notable predominance of Watch group antibiotics, which underscored the reliance on broad-spectrum agents, offering an opportunity for urgent and targeted interventions promoting rational use, as this group is also to be carefully used. Similarly, the observed correlation in department-based prescriptions warrants further investigation and emphasizes the importance of considering department-specific interventions in antimicrobial efforts. On the other hand, the absence of Reserve group antibiotics in our study hospitals suggests a favorable scenario for antimicrobial efforts, emphasizing the importance of preserving last-resort antibiotics for critical cases.

Notably, the 3 hospitals in Rwanda reflect a young generalist physician population in primary care. There was substantial evidence of suboptimal use of antibiotics based on reduced reliance on laboratory results to guide therapy and a high number of prescriptions per patient, with 76% of patients prescribed one-two antibiotics and the maximum number of antibiotics prescribed reaching five for a few patients. On average, 2.1 drugs were prescribed per admission, which is slightly higher than the WHO recommended optimal 1.6-1.8 per encounter. [25] Important to note the recommendation lacks an update. [25] While our study could not assess the appropriateness of prescriptions due to inconsistent documentation of diagnosis and indications per antibiotic among other determinants, it is critical to review use tendencies, which – overuse, misuse, abuse – is one of the main drivers of AMR. Moreover, the high burden of antibiotic use was observed in OB/GYN, neonatology, and pediatric wards, which may be hypothesized to relate to the heavy reliance on empiric treatment, and providers may be proactive with this patient population due to the high susceptibility to infection, and hospital-acquired infections. This could be due to the groups majority sample size and hence limited power to detect true association. Furthermore, 70% of providers reported a concurrent approach, prescribing and ordering of diagnostic laboratory tests, with 21.6% always doing so, which indicates a recognition of importance of diagnostic testing. Despite the risk it poses, the concurrent approach, prompted by delays in laboratory results before starting antibiotics, underscores the delicate balance providers must strike between timely intervention and antimicrobial stewardship. Similarly, there is an evident reliance on clinical judgement that points to the critical role of provider experience and expertise in managing infections, especially in settings where diagnostic resources may be limited, or delay of results is common due to limited laboratory capacity. In surgical care, there is evidence of practice of administering antibiotics before and after surgery, consistent with WHO guidelines, and a significant number of providers err on the side of preventing postsurgical infections by prophylactic prescription of antibiotics at least one hour before the procedure, especially in caesarean section cases, which were predominant in our findings. [26]

Our findings highlight key gaps needing remedial interventions in antimicrobial stewardship.

AMS aims to optimize use of antibiotics, promote behavior change in prescribing and dispensing, prolong lifespan of existing antibiotics, and build best-practice capacity of healthcare providers regarding rational use to avoid unnecessary costs. [8] To achieve this, core elements at the health facility level focus on establishing leadership commitment, accountability, and responsibilities, followed by actions related to ensuring availability of laboratory capacity, updated guidelines, standardized prescription charts, presence of formulary of approved antibiotics, and accompanying policies. [8]

The empirical use of antibiotics, especially in cases of unconfirmed laboratory findings, suggests a need for enhanced diagnostic capacity and an efficient turnaround time for laboratory test results to inform patient care plans. The establishment of antimicrobial stewardship programs within hospitals, including implementation of activities such as the development of contextually adapted guidelines, feedback to prescribers on antibiotic use, monitoring of AMR patterns, and optimizing the use of diagnostic testing, is essential in the fight against AMR.

Our study had limitations. The primary constraint lies in the cross-sectional method of the survey, which involves the interpretation of data captured at a point in time. This restricts our capacity to establish associations between antibiotic use and specific patient outcomes, in addition to assessing trends. The included facilities were government hospitals, whose data may not be generalizable to other facilities, such as private ones with varying capacities (infrastructure and personnel). Secondly, we did not collect data from all the wards, therefore, it is important not to extrapolate these findings to excluded wards (emergency and ambulatory). It is also worth noting that patient charts could not be linked to specific providers who prescribed all the antibiotics the patient may have been taking. Similarly, for diagnosis, a patient could have several clinical indications listed for which making a direct link to a specific antibiotic was not possible. Future studies should deploy robust designs to explore the underlying determinants of antibiotic use, evaluate the appropriateness of prescribing practices, and impact on AMR in the setting, in addition to assessing the impact of stewardship on clinical outcomes.

CONCLUSION:

Our study contributes to the wide body of evidence of the high use and misuse of antibiotics at three rural district hospitals in Rwanda. Prescription variability varied by age and type of indication. The findings underscore the importance of targeted interventions to optimize antimicrobial stewardship and promote judicious antibiotic use in healthcare settings.

TABLES AND FIGURES:

Table 1: Demographic and setting characteristics of enrolled patients in the PPS at facilities of Butaro, Rwinkwavu, and Kirehe District Hospitals in Rwanda from March-April 2021

Characteristic	**N**	**%**
Hospital		
Kirehe	147	46.8
Butaro	94	29.9
Rwinkwavu	73	23.2
Gender		
Male	127	40.4
Female	187	59.5
Age at Admission		
25 years	140	44.5
5-14 years	18	5.7
≥ 15 years	150	47.7
Missing/Unknown	6	1.9
Median (SD)	10(21.5)	
Malaria Status		
Positive	1	0.3
Negative	77	24.5
Missing/Unknown	236	75.2
HIV Status4		
Positive	6	1.9
Negative	126	40.1
Unknown	182	57.9
HIV Positive on ART (N=6)		
Yes	5	83.3
No	1	16.6
Department distribution		
Internal medicine	46	14.4
OB/GYN	85	27.1
Neonatology	91	29.0
Surgery	26	8.3
Pediatrics	62	19.8
Oncology	4	1.3
Total admissions (N=467)		
Kirehe	202	
Butaro	166	
Rwinkwavu	99	

Fig1. Number of diagnoses per patient on antibiotics (N=314)

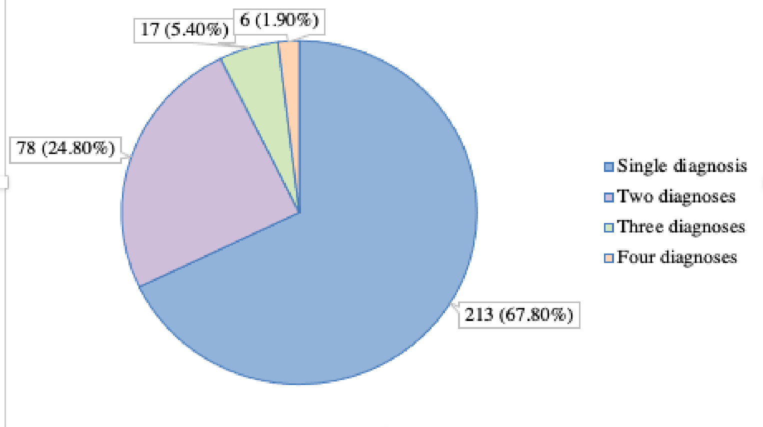

Table 2: Diagnosis and Common Indications Profile Among Patients

a. Most Common Indications (overall)

Diagnosis/Indications	**n**	**%**
Neonatal infection (and risk of neonatal infection)	144	22.2
Surgery- Cesarean section	112	17.3
Non-surgical maternity (including prophylactic)	75	11.7
Pneumonia	73	11.3
Gastritis	26	4.1
Meningitis (and presumed meningitis)	20	3.1
Malnutrition	17	2.6
Fracture	15	2.3
Respiratory distress	14	2.2
Bronchiolitis	12	1.9
Hysterectomy	9	1.4
Convulsion	9	1.4
Syphilis (and suspected syphilis)	7	1.1
Sepsis	5	0.8

Prematurity	5	0.8
Others (combined)	93	14.5

[a] It was possible for one patient to have more than one indications/diagnosis per reason notes

b. Most Common Indications (Based on Single diagnosis cohort, N=213)

Diagnosis/Indications	**n**	**%**
Neonatal infection (and risk of neonatal infection)	41	19.2
Surgery- Cesarean section	40	18.8
Non-surgical maternity (including prophylactic)	27	12.7
Pneumonia	17	8.0
Fracture	8	3.8
Gastritis	7	3.3
Meningitis (and presumed meningitis)	7	3.3
Respiratory distress	6	2.8
Bronchiolitis	5	2.6
Others (combined)	27	13.3

Table 3: Antimicrobials, Antibiotics, and AWaRe classification distributions

a. Most prescribed antimicrobial classes (N=649)

Treatment	**Freq**	**%**
Penicillin	249	38.4
Third generation cephalosporins	160	24.7
Aminoglycosides	121	18.6
Imidazole	71	10.9
Fluoroquinolones	23	3.5
Tetracyclines	8	1.2

Macrolides	6	0.9
Beta-lactam/beta-lactamase-inhibitor	3	0.5
Sulfonamide	3	0.5

Antifungal	3	0.5
Antimalarial	1	0.2
Nitrofuran-derivatives	1	0.2

b. Total prescription antimicrobial agents

Antibiotics[a] (N=649)	**N (%)**
Ampicillin	178 (27.43)
Gentamicin	121 (18.64)
Cefotaxime	80 (12.33)
Ceftriaxone	80 (12.33)
Flagyl (Metronidazole)	71 (10.94)
Cloxacillin	40 (6.16)
Ciprofloxacin	23 (3.45)
Amoxicillin	17 (2.62)
Penicillin G benzathine	9 (1.39)
Doxycycline	8 (1.23)
Erythromycin	6 (0.92)
Penicillin V (Phenoxymethylpenicillin)	4 (0.62)
Amoxicillin/clavulanic acid (Augmentin)	3 (0.46)
Sulfamerazine/trimethoprim (Bactrim)	3 (0.46)
Nystatin syrup (Antifungal)	3 (0.46)

Antibiotic agents prescribed- individual patients

Antibiotics (N=313)	**N (%)**
Ampicillin	83 (26.52)
Gentamicin	53 (16.93)
Ceftriaxone	45 (14.38)
Cefotaxime	36 (11.50)
Flagyl (Metronidazole)	32 (10.22)
Cloxacillin	22 (7.03)
Ciprofloxacin	13 (4.15)
Penicillin G benzathine	8 (2.56)
Amoxicillin	7 (2.24)
Amoxicillin/clavulanic acid (Augmentin)	3 (0.96)
Erythromycin	3 (0.96)
Doxycycline	2 (0.64)
Penicillin V	2 (0.64)
Sulfamerazine/trimethoprim (Bactrim)	2 (0.64)
Ampicillin +Amoxicillin	1 (0.32)
Nitrofurantoin	1 (0.32)

Ampicillin +Amoxicillin	1 (0.15)
Coartem (anti-malarial)	1 (0.15)
Nitrofurantoin	1 (0.15)

[a]It was possible for one patient to be given more than one type of antibiotic and/or receive an additional antimicrobial agent besides an antibiotic.

c. Antibiotics per patient N=313

Number of antibiotics	**freq**	**%**
1	81	25.8
2	157	50.16
3	55	17.57
4	17	5.43
5	3	0.96

d. Facility and Department distribution (N=314)

Department	**Hospital name**			**N**	**%**
	Butaro DH	Rwinkwavu DH	Kirehe DH		
Neonatology	12	27	52	91	28.9
OB/ GYN	19	30	36	85	27.1
Pediatrics	35	6	21	62	19.8
Internal medicine	14	4	28	46	14.6
Surgery	10	6	10	26	8.3
Oncology	4	0	0	4	1.3
	94	73	147	314	

e. AWaRe class distribution (total prescription)

AWaRe classification	freq	(%)	cum (%)
Access	456	70.7	70.7
Watch	18	29.3	100.0

f. AWaRe class distribution (total prescriptions) per department

freq
row percent

Name of department	AWaRe classification Access	Watch	Total
Internal medicine	33 44.0%	42 56.0%	75 100%

Neonatology	161 80.1%	40 19.9%	201 100%
OB/GYN	145 71.8%	57 28.2%	202 100%
Oncology	2 33.3%	4 66.6%	6 100%
Pediatrics	85 73.3%	31 26.7	116 100%
Surgery	30 66.7%	15 33.3%	45 100%

g. AWaRe class distribution (total prescriptions) per facility

freq
row percent

AWaRe classification	Butaro	Rwinkwavu	Kirehe	Total
Access	116 25.4%	110 24.1%	230 50.4%	456 100%
Watch	61 32.3%	50 26.5%	78 41.3%	189 100%
Total	177 27.4%	160 24.8%	308 47.8%	645 100.0

h. Frequently prescribed antibiotics class per AWaRe class (N^a=313)

Antibiotic class	**Access**	**Watch**	**(%)**
Penicillin	123		39.3
Third-generation cephalosporins		81	25.9
Aminoglycosides	53		16.9
Imidazole	32		10.2
Fluoroquinolones		13	4.2
Beta-lactam/beta-lactamase-inhibitor	3		0.96
Macrolides		3	0.96

Sulfonamide-trimethoprim-combinations	2		0.6
Tetracyclines	2		0.6
Nitrofuran-derivatives	1		0.3
Total	**216**	**97**	

i. AWaRe class distribution (unique patient)

AWaRe classification	freq	percent (%)	cum (%)
Access	216	69.01	69.01
Watch	97	30.99	100.0

Table 4: Provider characteristics and prescribing scenarios (rationale and practice)
N=51 Providers

Variables	**n**	**%**
Hospital		
Butaro	23	45.1
Rwinkwavu	15	29.4
Kirehe	13	25.5
Age		
< 30	36	70.6
31-40	9	17.7
41-50	5	9.8
51-60	1	1.9
Gender		
Male	46	90.2
Medical School		
A University from Burundi	2	3.92
A University from Congo	4	7.8
University of Rwanda	43	84.3
Mbarara University	1	1.9
A University in the US	1	1.9
Level of medical training		
Medical school	44	86.3

Residency/Master's level	7	13.7
Experience in medical practice		
<1 yr	30	58.8
1-5 yrs	15	29.4
6-10 yrs	2	3.9
11-15 yrs	4	7.8
Specialization		
General practitioner	40	78.4
Pediatrics	3	5.9
Internal Medicine	5	9.8
OB/GYN	1	1.0
Surgery	1	1.9
Other - MPH	1	1.9
Primary Ward (Unit)		
Maternity/OB/GYN	18	35.3
Internal Medicine	11	21.6
Emergency Medicine	2	3.9
Pediatrics	8	15.7
Neonatology	4	7.8
Surgery/OR	5	9.8
Oncology	2	3.9
Clinical services/Admin	1	1.9
Prescription of antibiotics without any ordering of laboratory results		
Never	16	31.3
Rarely	20	39.2
Sometimes	15	29.4
Prescription of antibiotics before placement of laboratory results		
Never	3	5.9
Rarely	23	45.1

Sometimes	25	49.0
Prescription of antibiotics upon placement of laboratory results		
Never	1	2.0
Rarely	3	5.9
Sometimes	36	70.6
Always	11	21.6
Prescription of antibiotics after receiving laboratory results		
Rarely	2	3.9
Sometimes	36	70.6
Always	13	25.5
In which situation(s) in which you prescribe an antibiotic before getting the patient's laboratory results?		
Based on common infection presentation and assessment: signs and symptoms	46	90.2
Preoperative administration	38	74.5
Laboratory results take time to come [will optimize/adjust treatment if wrong]	16	31.4
Other ▫ Neutropenic fever ▫ No change in status from first-line antibiotics ▫ Emergency: Sepsis ▫ Generalized peritonitis ▫ Broad spectrum coverage ▫ Premature rupture of membranes (PROM)	6	11.8
[For Surgery-Related care] When do you prescribe antibiotics?		
Pre-operatively only	1	2.0
Both before and after surgery	41	80.4
Missing	9	17.6
[For Surgery-Related care] If antibiotics are prescribed before and after surgery, the patient starts them when: (N=41)		
1 hour before the procedure	18	43.9
Immediately before the procedure in emergence	14	34.1
30 min before the procedure	8	19.5
15 min before the procedure	1	2.4

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