



EFFECT OF ANTIBIOTIC STEWARDSHIP PROGRAMS ON ANTIBIOTIC CONSUMPTION IN AMHARA REGION, NORTHWEST ETHIOPIA

Asrat Agalu Abejew

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Department of Social and Administrative Pharmacy
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A Ph.D. thesis submitted to department of Social and Administrative Pharmacy, School of Pharmacy, Addis Ababa University on the effect of antibiotics stewardship programs on antibiotic consumption in Amhara Region, Northwest Ethiopia in partial fulfillment for the Ph.D. Degree in Social and Administrative Pharmacy.

By: Asrat Agalu Abejew (BPharm, MSc.)

Research Supervisors:

1. Professor Teferi Gedif
2. Gizachew Yismaw (BSc. MSc., Ph.D.)

STATEMENT OF DECLARATION

I, Asrat Agalu Abejew, hereby affirm that this thesis entitled “**Effect of Antibiotic Stewardship Programs on Antibiotic Consumption in Amhara Region, Northwest Ethiopia**” is my original work. Contributions made by others to this body of work have been duly acknowledged and properly referenced. This research has not been submitted previously for any degree or examination at this or any other university. We, the supervisors, attest that this dissertation has been completed under our guidance and is the original work of the student. We, the examiners, have examined the student and hereby confirm that this thesis meets the requirements for the award of the degree and is worthy of acceptance.

Name of the principal investigator	Signature	Date
1. Asrat Agalu Abejew	_____	_____

Name of supervisors	Signature	Date
1. Professor Teferi Gedif	_____	_____
2. Dr. Gizachew Yismaw	_____	_____

Name of Examiners	Signature	Date
1. Professor Bisrat Hailemeskel	_____	_____
2. Professor Damen Hailemariam	_____	_____

Department Chair

LIST OF publications and manuscripts

The published papers and manuscripts currently under review are listed here after.

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5. Abejew A.A, Wubetu G.Y., Fenta T.G. A Six Years Trend Analysis of Antimicrobial Resistance among Bacterial Isolates in Amhara Region, Northwest Ethiopia. BioMed Research International. 2025. <https://doi.org/10.1155/bmri/7676973>
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TABLE OF CONTENTS

Content	page
STATEMENT OF DECLARATION.....	III
LIST OF publications and manuscripts.....	IV
ACKNOWLEDGMENTS	V
TABLE OF CONTENTS.....	VI
ABSTRACT	IX
ABBREVIATIONS AND ACRONYMS.....	XII
LIST OF TABLES	XIV
LIST OF FIGURES	XV
CHAPTER ONE: INTRODUCTION	1
1.1. Background information	1
1.2. Statement of the Problems	2
1.3. Structure of the Dissertation	4
1.4. Literature Review	5
1.4.1. Overview of ASPs	5
1.4.2. Effectiveness of the ASP	6
1.4.3. Factors affecting effectiveness of ASPs	8
1.5. Theoretical Framework	9
1.6. Conceptual Framework	12
1.7. Scope of the Study	14
1.8. Significance of the Study	37
CHAPTER TWO: OBJECTIVES OF THE STUDY AND RESEARCH QUESTIONS	38
2.1. The General Objective	38
2.2. Specific Objectives	38
2.3. Research Questions	39
CHAPTER THREE: RESEARCH METHODOLOGY.....	40
3.1. Philosophical Foundation: Ontological, Epistemological and Axiological Considerations	40
3.2. Methods.....	42
3.2.1. Study settings and period	42
3.2.2. Study Design	43

3.2.3. Study Population	43
3.2.3.1. Source Population	43
3.2.3.2. Study Population	43
3.2.4. Sample size determination	44
3.2.5. Theoretical Framework for Structural equation modeling	45
3.2.6. Data collection instruments	45
3.2.7. Data collection process	46
3.2.8. Outcome assessment	46
3.2.9. Study Variables	47
3.2.9.1. Dependent variables	47
3.2.9.2. Independent variables	48
3.2.10. Data quality control	48
3.2.11. Data processing and analysis	48
3.2.12. Dissemination of study findings	51
3.2.13. Ethical consideration	51
3.2.14. Operational Definitions and Definitions of Terms	51
CHAPTER FOUR: KEY FINDINGS AND DISCUSSION	53
4.1. Key findings	53
4.1.1. Morbidity and Mortality from Bacterial infections	53
4.1.2. Antibiotic consumption at EPSS	55
4.1.3. Antibiotic consumption in hospitals	56
4.1.4. Trends in AMR	58
4.1.5. Antibiotic prescribing behavior of physicians	61
4.1.6. Situational analysis of ASP implementation in hospitals	65
4.2. Discussion	72
4.3. Strength and Limitations of the Study	84
CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS	85
5.1. Conclusions	85
5.2. Recommendations	86
5.3. Directions for further research	87
References	88

List of manuscripts articles and manuscripts.....	109
Manuscript I	110
Manuscript II	125
Manuscript III.....	137
Manuscript IV.....	154
Manuscript V	167
Manuscript VI.....	179
Annexes.....	211
Annex I: Consent Forms	211
Annex II: Situational analysis of Hospital’s readiness for AMS implementation	211
Annex III. Knowledge and attitude survey	221

ABSTRACT

Background: In developing countries like Ethiopia, infectious diseases are common, and antibiotic resistance poses a serious threat to public health. Inappropriate antibiotic use and consumption are the leading causes for resistance. Antibiotic stewardship programs are proven to optimize antibiotic use and reduce resistance and healthcare costs. Since 2018, the Ethiopian Ministry of Health has been working to institutionalize stewardship programs across hospitals in the country. Despite evidence from a specialized hospital in Addis Ababa and the availability of national guidelines, multicenter studies haven't been conducted in Ethiopia. This study aimed to determine the current status and effect of stewardship programs on antibiotic consumption and will suggest practical strategies to improve antibiotic use in the hospitals.

Objective: To assess the effect of antibiotic stewardship programs on antibiotic consumption in public hospitals in Amhara Region, Northwest Ethiopia.

Methods: A multicenter cross-sectional study was conducted across five hospitals in 2022. Data were collected using questionnaires and review tools, hospital records, and regional databases. Antibiotic consumption data was analyzed using DDD per 1,000 inhabitants per day (DIDs), and infections were classified in to syndromes. Perceived prescriptions for outpatient visits, and upper respiratory tract infections (URTIs) were used to assess prescribing behaviors of physicians. Data were analyzed in SPSS v21 using descriptive statistics, linear and polynomial regressions, chi-square, ANOVA, and SEM, with significance at $P < 0.05$.

Results: A total of 39,666 cases (20.1%) and 2,763 deaths (21.2%) were attributed to bacterial infections during the 5 years period in five hospitals. Bacterial infections showed an increased trend but is predicted to decline ($R^2 = 0.99$), while mortality, though initially declining, was projected to rise ($R^2 = 0.95$). Sepsis/septic shock and pulmonary infections were the leading causes, accounting for 29.9% and 25.8% for infections, and 45.2% and 21.3% for mortality, respectively.

According to EPSS data, a total of 30.3 DIDs of antibiotics were consumed over a six-year period. Antibiotic consumption declined by 87.4%, dropping from 6.9 DIDs in 2016/17 to 0.9 DIDs in 2021/22. The trend in antibiotic consumption has been decreasing as a function of $y = -0.5911x^2 + 2376.6x - 2E+06$ ($R^2 = 0.86$). About 23.4 (77.1%) DIDs of the total antibiotics consumed belonged to Access category, while oral formulations accounted for 29.2 DIDs (96.2%) of overall antibiotic

consumption. Seven antibiotics, accounting for 62.7% of the \$7,281,680.9 expenditure, made up the DU90%. The most common antibiotics were amoxicillin, doxycycline and ciprofloxacin.

On the other hand, antibiotic consumption over three years in hospitals accounted for 296.16 DID, and has been decreasing by 11.3% from 2020 to 2022 ($R^2 = 1$) which was also decreasing in hospitals with active stewardship programs ($R^2 = 1$) compared with increased consumption in the one which attempted to implement but interrupted ($R^2 = 1$). Watch-category antibiotics comprised 50.8% of use, while oral formulations accounted for 64.6%. Eleven antibiotics (DU90%) accounted for 59.2% of \$1,100,101.5 expenditure, with ceftriaxone, sulfamethoxazole-trimethoprim, cephalexin, and amoxicillin being the most consumed.

Based on secondary data from APHI, from 25,143 specimens tested for culture and susceptibility, in 16,825 (66.9%) bacteria were isolated. Of these isolates, 12,528 (74.5%) were gram-negative, and 4,297 (25.5%) were gram-positive bacteria. The common gram-negative bacteria isolates were *K. pneumoniae* 3,783 (30.2%) and *E. coli* 3,199 (25.5%), while coagulase negative staphylococcus 1,765 (40.1%) and *S. aureus* 1,293 (30.1%) were the most common gram-positive bacteria. The prevalence of antibiotic resistance was 2,738 (59.9%). Of these gram-negative bacteria accounted for 1807 (66.0%), and 931 (34.0%) for gram-positive bacteria. Among the resistant gram-negative isolates, *K. pneumoniae* 743 (80.2%), *E. cloacae* 196 (74.8%) and *A. baumannii* 213 (66.6%) were highly resistant. From gram-positive bacteria, coagulase negative staphylococcus 406 (58.0%), *Streptococcus* species 34 (50.0%), and *S. aureus* 196 (37.0%) showed the highest resistance. About 571 (20.9%) of bacteria were resistant at least two antibiotics (range 2–10). The trend of antimicrobial resistance has been rising and then decreasing over the years, following the function $y = -5.3247x^2 + 46.768x - 36.069$ ($R^2 = 0.94$).

Based on a survey of 185 physicians in outpatient departments, approximately 54.8% (60.1 ± 53.5) of weekly patient visits would encounter antibiotic prescriptions. About 49.5% of patients with URIs would likely receive antibiotics, with 96.2% of physicians prescribing to at least one case (mean 5.9 ± 2.2) from 10 encounters. Although 65.4% of participants exhibited good prescribing knowledge, which significantly predicted their subjective norms and perceived behavioral control ($P = 0.000$), their prescribing behavior not significantly influenced by their intentions to prescribe or reduce usage ($P > 0.05$).

Similarly, among 181 healthcare professionals surveyed in inpatient wards (58.6% physicians, 41.4% pharmacists), over 89% identified resistance as a serious national and global issue. Easy access (85.6%) and inappropriate use (75.7%) were cited as key contributors. Nearly half of reported antibiotic uses were prescribed without lab results or susceptibility data. Most agreed that antibiotic stewardship programs could reduce hospital stays (75.7%) and improve care (73.5%). Recommended strategies included education (83.4%), institutional guidelines (79.0%), and audit-feedback mechanisms (78.5%). There was significant difference on the perception of health professionals on stewardship programs in hospitals attempted to implement the program compared with those which didn't. Overall, the program implementation is rated poor, with four hospitals were ready for strengthening or implementation.

Conclusions: Bacterial infections remain a significant cause of morbidity and mortality in hospitals, with morbidity on the rise and mortality rates declining. Antibiotic consumption at the Ethiopian Pharmaceutical Supply Service remained low and showed a consistent downward trend over time. Despite this, physicians reported a high perceived rate of antibiotic prescribing, often citing limited control over prescribing decisions. In contrast, antibiotic consumption within hospitals was high with decreasing trend over the three years period. Antimicrobial resistance identified by the regional laboratory was widespread and increasing, despite a downward-opening trend indicated by a quadratic time analysis. The implementation of antibiotic stewardship programs in the hospitals had positive effect in reducing antibiotic consumption and high levels of awareness and positive attitudes among staff related to attempts to implement the program although its status of implementation was poor. Given the availability of relevant infrastructure, strengthening existing stewardship programs and implementing new ones in hospitals is currently feasible. Overall, the findings underline the need for context-specific interventions and improved infection prevention and control strategies to reduce the burden of bacterial infections and the excessive use of antibiotics in hospital settings.

Key Words: *antibiotic consumption, AMR, ASP, Core elements of ASP, infectious diseases, morbidity, mortality, readiness to implement ASP, SEM, status of ASP, Trend analysis*

ABBREVIATIONS AND ACRONYMS

AMR	Antimicrobial resistance
APHI	Amhara public health institute
ASP	Antibiotic stewardship program
AWaRe	Access, Watch and Reserve
BCW	Behavior changes wheel
CDC	U.S. Centers for Disease Control and Prevention
CD	Coefficient of determination
CdI	Clostridium <i>difficile</i> infection
CEO	Chief Executive Officer
CFI	Comparative fit index
CNS	Central nervous system
DDD	Defined daily dose
DIDs	Defined daily dose per 1000 inhabitants per day
DMCSH	Debre Markos Comprehensive Specialized Hospital
DOT	Days of therapy
DTC	Drug and therapeutics committee
DU90%	Drug utilization 90%
EMR	Electronic medical records
EPSS	Ethiopian Pharmaceutical Supply Service
FHCSH	Felege Hiwot Comprehensive Specialized Hospital
FSGH	Finote Selam General Hospital
FRP	Formulary restriction and preauthorization
GP	General Practitioner
HAI	Healthcare-acquired infection
HIMS	Health information management system
ICD	International classification of disease
ID	Infectious disease
IPC	Infections prevention and control
IGH	Injibara General Hospital
JUMC	Jimma University Medical Center

LMICs	Low- and Middle-income Countries
LOS	Length of Stay
MDR	Multi-drug-resistant
MRSA	Methicillin-resistant <i>S. aureus</i>
MTPB	Modified theory of planned behavior
OR	Operation room
OPD	Outpatient department
PAF	Prospective audit with intervention and feedback
PBC	Perceived behavioral control
PD	Patient days
PDSA	Plan do study act
FRP	Formulary restriction and Pre-prescription Authorization
RMSEA	Root mean square error of approximation
SRMR	Standardized root mean squared residual
TASH	Tikur Ambesa Specialized Hospital
TGSH	Tibebe Ghion Specialized Hospital
TPB	Theory of planned behavior
TLI	Tucker Lewis index
SEM	Structural Equation Modeling
SN	Subjective norm
SXT	Sulfamethoxazole / Trimethoprim
URTI	Upper respiratory Tract Infections
USA	United States of America
WHO	World Health Organization

LIST OF TABLES

Table 1: A summary of the research questions, methodology, rationale, and methods	50
Table 2: The most common infectious syndromes (July 2017 to June 2022), in hospitals in Northwest Ethiopia, (N = 39,666).	54
Table 3: Characteristics of physician respondents in OPDs in hospital, 2022, (N=185)	62
Table 4: The model goodness of fit indexes for antibiotic prescribing behaviors of Physicians at OPDs, 2022 (N=185).....	63
Table 5: Effects of direct and indirect of intention to prescribe antibiotics on antibiotic prescribing behavior in hospitals in 2022, (N=181).	64
Table 6: Socio-demographic characteristics of health professionals in the hospitals, in 2022, (N=181) ...	65
Table 7: Beliefs on factors contributing to antibiotic resistance among health professionals in hospitals, 2022, (N=181)	67
Table 8: Believe on antibiotics prescription/dispensing practices among health professionals in hospitals, 2022, (N=181)	68
Table 9: Perception on implementation of ASP among health professionals in hospitals, 2022, (N=181)	69

LIST OF FIGURES

Figure 1: Actors and actions within the ASP, Dyar O.J. et al. [71].....	10
Figure 2: Schematic overview of the expected timeline of the impact of a subset of ASP different aspects, Dik J-W.H., et al [128]	11
Figure 3: The conceptual framework adopted based on the literature	13
Figure 4: The structural components of an activity [133].....	40
Figure 5: Theory of planned behavior [141].....	45
Figure 6. Trends in morbidity and mortality (July 2017- June 2022) from bacterial infections, in hospitals in Northwest Ethiopia.	54
Figure 7: Trends of antibiotic consumption in EPSS Bahir Dar Branch during 6 years period, July 2016- June 2022	55
Figure 8: Consumption of systemic antibiotics (July 2019 – June 2022), at EPSS and in the hospitals, in Northwest Ethiopia	56
Figure 9: Trends of antibiotic in EPSS Bahir Dar Branch during 6 years period, July 2016- June 2022...	57
Figure 10: Use of systemic antibiotics (July 2019 – June 2022), in the hospitals, in Northwest Ethiopia .	57
Figure 11: Use of systemic antibiotics (July 2019 – June 2022), at EPSS and in the hospitals, in Northwest Ethiopia	58
Figure 12: Overall prevalence of AMR (2016-2021), APHI, Amhara Region, Ethiopia	60
Figure 13: Trends in AMR (2016-2021), APHI, Amhara Region, Ethiopia.....	60
Figure 14: : Belief on scope of AMR among health professionals in hospitals, 2022, (N=181).....	67
Figure 15: Belief on potential intervention to combat AMR among health professionals in hospitals, 2022, (N=181):.....	70

CHAPTER ONE: INTRODUCTION

1.1. Background information

The discovery of antibiotics is one of modern medicine's greatest achievements, saving millions of lives and revolutionizing healthcare [1, 2]. This success has led to a marked decline in infectious disease mortality [1–4], though bacterial infections continue to cause substantial global morbidity and mortality [5–11]. Global antibiotic consumption has steadily increased, especially in Low-and-Middle income countries) LMICs [12], with public hospitals, particularly medical and pediatric wards, being major contributors [13–17]. However, an estimated 30–50% of hospital antibiotic prescriptions remain unnecessary or inappropriate, especially in these wards [12, 18–20].

The misuse and overuse of antibiotics have significantly diminished effectiveness of antibiotics [2, 21, 22], fueling antimicrobial resistance (AMR), treatment failures, and complications such as *Clostridium difficile* infections (CdIs) [1, 4, 23]. This contributes to rising healthcare costs, higher mortality, and limited treatment options [24]. Globally, bacterial infections are responsible for approximately 7.7 million deaths, including 1.86 million in Africa, of which 1.05 million are linked to AMR [8–11]. Sub-Saharan Africa carries the highest AMR-related mortality rate at 27.3 per 100,000 populations [5]. In Ethiopia, bacterial infections—including healthcare-associated infections (HAIs) are major causes of death [10, 25–31], with around 21,200 deaths directly attributed to AMR and 85,300 deaths associated with AMR-related infections [32].

Despite this burden, Ethiopia faces significant gaps in implementing antibiotic stewardship programs (ASPs) and infection prevention and control (IPC) measures [33]. Globally, the rise of antibiotic-resistant pathogens is driven largely by overuse, misuse, prolonged and prophylactic use of antibiotics [2, 21], compounded by patient expectations, diagnostic delays, prescriber knowledge gaps, and financial barriers [24, 34–36]. The COVID-19 pandemic has further aggravated these issues [37]. As antibiotic effectiveness declines, healthcare systems worldwide face mounting risks [1, 2, 38], emphasizing the urgent need for coordinated action to preserve antibiotic efficacy and safeguard public health [24, 38].

In Ethiopia, the AMR challenge reflects global trends [20]. Although AMR has been identified as a national priority [39] and national ASP guidelines exist since 2018 [3], official ASP implementation remains largely absent [40]. A few studies report widespread antibiotic misuse and overuse [41], but comprehensive ASPs have yet to be adopted nationwide. To date, only Tikur Anbessa Specialized

Hospital (TASH) has piloted ASP implementation [17, 41], with limited evidence available from hospitals in northwest Ethiopia except attempts to implement. Therefore, this study aims to assess the status and effect of ASPs on antibiotic consumption in public hospitals in Amhara Region in northwest Ethiopia.

1.2. Statement of the Problems

Studies in various hospital wards using diverse methods have reported the prevalence of infectious diseases, antibiotic consumption patterns, and AMR [5–11], highlighting the need for infection prevention, optimized antibiotic use, improved microbiological capacity, and broader vaccine utilization [6, 24].

Bacterial infections remain major causes of hospitalization and mortality worldwide [8, 9, 21]. In 2019, AMR contributed to 4.95 million deaths, including 1.5 million from lower respiratory tract infections (LRTIs) [5]. Globally, LRTIs, diarrheal diseases, tuberculosis, and meningitis are leading causes of infection-related deaths, especially in children [7]. Regional data reflect this burden: in Sweden, pneumonia, endocarditis, and sepsis/bacteremia were leading causes of 30-day mortality [8]; in Nepal, bacterial infections accounted for 86% of deaths, mainly pneumonia, sepsis, and meningitis [9]. In Africa, bacterial infections caused 1.86 million deaths, with LRTIs, tuberculosis, bloodstream infections, and intra-abdominal infections responsible for 75% of these fatalities [11, 31].

In Ethiopia, infectious diseases contribute to 50% of deaths [10, 26], with neonatal bacterial infections accounting for up to 95.8% of deaths [25]. Common bacterial infectious syndromes include LRTIs, bloodstream infections, intra-abdominal infections, meningitis, and urinary tract infections [26, 32]. The HAIs affect 17% of hospitalized patients, with surgical site infections, urinary tract infections, bloodstream infections, and respiratory infections being most common [28]. Compliance to IPC remains low at 52.2% [33], and limited diagnostics contribute to misdiagnosis and inappropriate antibiotic use [24].

Inappropriate antibiotic use drives AMR [4, 24]. Over-the-counter antibiotic access worsens the problem in many countries [21]. Monitoring antibiotic use is essential to contain resistance [34]. Between 2000 and 2015, global antibiotic consumption rose 65% (21.1 to 34.8 billion defined daily doses (DDDs)), with projections suggesting a 200% increase by 2030 [12]. Three-quarters of this increase occurred in Brazil, Russia, India, China and South Africa [38], and COVID-19 may have further accelerated global antibiotic use [35]. In LMICs, antibiotic consumption rose 114%, while

high-income countries saw a 4% decline [12]. In Sub-Saharan Africa, 95% of animal health professionals prescribe antibiotics without testing, and many owners' self-treat animals with limited knowledge [43]. Public and private healthcare sectors differ in antibiotic availability, limiting treatment options [42].

Hospital antibiotic use remains high: in the United states of America (USA), usage nearly tripled between 2012–2016 [13]; in Sweden, one-third of inpatients receive antibiotics, with a 9% rise in consumption [44]; pediatric use reaches 35% in the USA, 70% in China [14, 18]; and 78.2% of Nigerian inpatients receive antibiotics [15]. Broad-spectrum agents like fluoroquinolones, cephalosporins, piperacillin/tazobactam, and carbapenems dominate prescriptions [38, 44], with global inpatient antibiotic use reaching 89.3% in some hospitals [45]. In Ethiopia, community antibiotic use increased from 11.02 DID (2016) to 12.83 DID (2020) [46]. Inpatient prescribing rates reach 73.7%, and 86.4% in pediatric wards [16, 47]. Approximately 49.2% of antibiotics are used inappropriately [20], often due to prolonged treatment, microorganism-drug mismatches, unnecessary prophylaxis, and empiric broad-spectrum therapy [14, 17, 19]. Many prescriptions involve WHO Watch and Reserve category antibiotics [19]. Polypharmacy, prescriber perceptions, and financial incentives also drive overuse [16, 48, 49].

The emergence of multidrug-resistant (MDR) bacteria complicates treatment further. In Ethiopia, MDR prevalence averages 59.7%, with MDR *E. coli* (68.1%) and *S. aureus* (59.2%) highly MDR [20] where Methicillin resistant *S. aureus* (MRSA) shows full resistance to multiple antibiotics [52], and total *S. aureus* resistance reaches 97% [53]. Gram-negative resistance reaches 87.2% [54], with 80% Extended-spectrum beta-lactamase producers at Felege Hiwot Hospital [55]. MDR pathogens challenge empirical therapy, emphasizing the urgent need for ASPs [56, 57]. AMR leads to higher mortality, longer hospital stays, and significant economic losses [34, 58]. Without action, AMR deaths could reach 10 million annually by 2050, costing the global economy up to \$100 trillion [24]. Multiple factors contribute to inappropriate antibiotic use: limited knowledge, diagnostics, healthcare organization, and self-medication [12, 42, 48, 49]. Up to 50% of hospital antibiotic use may be unnecessary [48]. Physicians often lack motivation to change prescribing habits and are influenced by attitudes, norms, and external pressures [36, 37, 49]. ASPs are recommended to improve prescribing and reduce AMR [59].

In LMICs, including Ethiopia, one million children die annually from treatable infections [38]. Ethiopia developed a national AMR strategy (2015–2020) aligned with World health organization's (WHO's) global action plan [60, 61] and an ASP guide for hospitals, though implementation remains limited [3]. Overall, WHO recommends 60% of prescriptions should come from Access group antibiotics [65] which warrants local clinical guidelines, ASP indicators, and restrictions on Watch and Reserve antibiotics as key strategies [66–68]. However, comprehensive ASP implementation in Ethiopia remains limited, except for a project at TASH [17, 41] and attempts to implement in some hospitals. This study aims to assess the status and effect of ASP on antibiotic consumption in public hospitals in Amhara region in northwest Ethiopia.

1.3. Structure of the Dissertation

This paper is organized into five sections based on the standard protocols of Addis Ababa University. The first section provides a general introduction to infectious diseases epidemiology, antibiotic consumption and use, AMR, ASP, and the statement of the problem. The statement of problem showed gaps in antibiotic consumption and use, AMR, and their consequences with possible solutions. Following the statement of problem overview of ASPs and their strategies as potential solutions were discussed to address the issues of AMR by reducing the indiscriminate use of antibiotics. Finally, a literature review, theoretical framework and the rationale for the study are presented and conceptual framework was drawn to contextualize the overall study. The second section describes general and specific objectives, and questions the study aims to answer.

Following objectives, the third section describes the research methodology focusing on philosophical foundations, methods and materials of the study. This section addresses all possible strategies and approaches utilized to meet the study's objectives. It describes philosophical foundations of the study, and methods. In the methods part the study area, study design, target population, sampling methods, sample size, data collection materials, and processes were described. Additionally, it outlines the methods for data quality control and analysis, operational definitions and definition of terms and then concludes with ethical considerations. The fourth section presents the key findings of the study and discusses them, while also acknowledging the strengths and limitations of the study. Lastly, the fifth section outlines the study's conclusion, draws recommendations and suggested future directions. Finally, references list for the main document, and published and unpublished manuscripts are

provided following the references in sequential manner. At last annexed documents are presented at the end of the document.

1.4. Literature Review

ASP is crucial to preserve antibiotic effectiveness and reduce morbidity and mortality. Inappropriate antibiotic use drives AMR, leading to treatment failures. Hospitals should adopt prospective audit and feedback (PAF) and formulary restriction and pre-authorization (FRP) strategies. Studies using various methods have demonstrated the effectiveness of ASPs [4, 59, 70, 96–98]. This section reviews on history of ASP implementation and its evidence of effectiveness and factors affecting implementation in different countries.

1.4.1. Overview of ASPs

Antibiotics must be prescribed when indicated. According to the WHO's Access, Watch, and Reserve (AWaRe) classification, last-resort antibiotics (Reserve group) should be reserved for patients who truly need them [2]. ASP ensures effective antibiotics remain available by promoting appropriate use across all healthcare settings, guided by local epidemiology, colonization status, prior antibiotic use, healthcare exposure, infection source, and infection severity [2, 3, 70-72].

Over the past two decades, ASP has become a global priority, with organizations implementing interventions to optimize antibiotic use, particularly in secondary care settings [73]. The Infectious Disease Society of America defines ASPs as programs that ensure patients receive the most effective, least toxic, and least costly antibiotics for the necessary duration [74]. Similarly, the British Society for Antimicrobial Chemotherapy emphasizes optimal selection, dosage, and duration to achieve the best clinical outcome with minimal toxicity and resistance impact [75]. In 2019, the United States based center for disease control and prevention (CDC) emphasized optimizing prescribing, improving infection treatment, and minimizing adverse events such as CdIs [2].

Effective ASP implementation requires strong governance, clear structures, and context-specific strategies [2-4, 76, 77]. The CDC's seven core elements serve as a framework, using structural and process measures to assess capacity, implementation, and progress. Process indicators aligned with specific ASP interventions are recommended to track improvements in antibiotic use [2, 3, 76, 77]. Success also depends on local context, implementation approach, and stakeholder engagement to modify prescribing behaviors [78]. Core ASP strategies include PAF, FRP, with supplemental

elements such as education, guidelines, order forms; de-escalation, dose optimization, and IV-to-oral switch [1-4, 76]. Both FRP and PAF reduce antibiotic use; however, PAF has a greater impact on reducing days of therapy (DOT) and length of therapy [63]. PAF-based ASPs also achieve significant reductions in antibiotic consumption among hospitalized patients [78-82]. Combining PAF and FRP is recommended, but in resource-limited settings like Ethiopia, PAF is especially preferred [2-4, 17, 63, 76, 77].

To implement PAIF effectively, local adaptation is essential to overcome challenges in communication, patient identification, and resource development [4, 59, 83, 84]. A multidisciplinary ASP team—ideally including infectious disease physicians, clinical pharmacists with infectious disease (ID) training, microbiologists, hospital epidemiologists, infection control professionals, nurses, and information systems specialists—is recommended [2-4, 17, 70, 85]. Either a physician or a clinical pharmacist can lead the team, depending on availability [79-86]. The ASP committee's role is to optimize antibiotic use while promoting behavioral change to improve care quality, minimize unnecessary antibiotic exposure, and reduce healthcare costs [87]. ASP teams often collaborate closely with IPC teams, with overlapping membership and leadership, particularly in LMICs where team composition is shaped by local context [87-90].

The primary goal of ASPs is to optimize antibiotic use, improve clinical outcomes, and promote sustainable prescribing behavior among physicians. Secondary goals include reducing healthcare costs and minimizing antibiotic-induced collateral damage [2-4, 75]. Evaluation should include process metrics such as DDDs per 1,000 patient-days, DOT, and cost per DDD, as well as outcome measures such as resistance trends, readmission rates, and adherence to ASP recommendations [2, 70, 91-93]. However, no clear consensus exists on microbiological outcomes and stakeholder perspectives—including physicians, pharmacists, administrators, and Drug and therapeutics committee (DTC) members—are essential for successful ASP implementation [93-95]. Overall, ASPs are critical for improving patient outcomes, reducing adverse events and costs, and preventing AMR. The engagement of all healthcare providers and a thorough understanding of outcome metrics are essential for their success.

1.4.2. Effectiveness of the ASP

A. Effectiveness of ASPs

A systematic review and meta-analysis in Asia found that ASP implementation shortened antibiotic therapy duration, reduced overall antibiotic consumption by 9.7%, carbapenem use by 10.6%, and antibiotic costs by 9.7% to 58.1%. Resistance rates of CdI, MRSA, carbapenem-resistant *Pseudomonas* spp., *Acinetobacter* spp., and MDR also declined [98]. In China, a segmented regression analysis across 65 hospitals showed ASP reduced inpatient antibiotic prescribing by 2.3% per month, consumption by 2.2 DDD/100 bed-days, prescription rates from 62.9% to 35.3%, and costs by \$7 monthly; hospital stay costs fell 53%, and very-restricted antibiotic costs dropped 87% [99].

In India, a pre-post quasi-experimental study using audit and feedback improved appropriate antibiotic use from 66.8% to 86.8%, reduced consumption from 4.4% to 3.9%, length of stay from 17.3 to 14.1 days, and HAI risk by 43% [100]. However, barriers such as limited clinical pharmacists, physician resistance, and incomplete electronic medical records (EMRs) were reported [101]. In Japan, post-prescription review reduced carbapenem DOT from 5.5 to 2.8 days/100 patient days (PDs), cutting costs by \$150,000 [102]. Another Japanese study reported reductions in prolonged antibiotic use (from 5.2% to 2.9%) and MRSA prevalence (from 47.6% to 39.5%), though overall antibiotic consumption remained stable [103]. In Thailand, a pediatric study found decreased vancomycin and colistin use post-ASP, while LOS remained at 7 days overall but declined from 27 to 24 days for patients on selected antibiotics [79]. In Switzerland, guideline dissemination and multidisciplinary quality circles reduced antibiotic consumption from 45.6 to 35.5 DDD/1000 beds/day in 65% of long-term care facilities; 63% of use was in the Core-Access group and 27% in Watch group [104].

In Ethiopia, at TASH, audit-feedback intervention reduced DOT during implementation (754 vs. 1549/1000 PDs post-intervention), shortened treatment duration (8.7 vs. 12.8 days), length of stay (LOS) (19.8 vs. 24.1 days), and lowered mortality (6.9% vs. 14.7%) [17]. Despite high physician acceptance, lack of institutional support and lab capacity were challenges; however, national ASP initiatives and the AMR crisis present opportunities [44].

Globally, AMR may reduce gross domestic product by \$3.4–6.1 trillion annually by 2050 due to workforce and livestock losses [59]. Given limited healthcare resources and gaps in ASP benefit evidence, robust evaluations of ASP cost-effectiveness are essential [105,106]. A Spanish decision model showed ASPs in critical care reduced antibiotic use short-term, generating a €71,738 net benefit; long-term costs reached €107,569, with €7,342 per MDR infection avoided and €9,788 per life-year gained [107]. In the U.S., ASPs cut antibiotic costs from 14.4% to 9.8% annually, saving \$1.7 million

and reducing DDDs by 9.7% [108]. A review of 16 studies showed antibiotic costs dropped by \$448.3/100 PDs (25%), consumption declined by 16%, mortality decreased by 3.3%, and HAIs by 7.7%, though revenue impacts varied [109].

1.4.3. Factors affecting effectiveness of ASPs

In Korean hospitals, ASP compliance was 70.4%, with low adherence attributed to ignorance (56.3%), prescriber stubbornness (25.0%), and lack of interest (18.7%) [110]. In Japan, adherence to prospective audit and feedback (PAF) was 78%, with lower adherence linked to liver disease, diabetes, and multiple PAF advisories; non-adherence negatively affected antibiotic duration and infection-related outcomes [111]. Integrating practice visits, needs assessments, peer feedback, and audits enhances engagement in ASP, while private discussions, education, discouraging repeated misuse, and organizing conferences can improve compliance [111,112].

A North American survey among ASP clinicians for pediatric oncology identified barriers including limited data resources, clinician time, ASP authority, communication gaps, expertise in immunocompromised care, and prioritization of other populations. Oncology clinicians were more concerned about rare adverse events than long-term antibiotic risks, often lacked confidence in ASP input, preferred autonomy, and were unconcerned about antibiotic costs [113]. In Australia, barriers included a culture of independence, limited feedback, personal relationships, geographic isolation, poor benchmarking, and resource limitations, absence of guidelines, knowledge gaps, workload pressures, perceived patient expectations, and fear of patient dissatisfaction [114,115].

Prescriber knowledge, attitudes, and practices play a key role in AMR prevention [116-123]. Antibiotic prescribing is influenced by both prescribers' intrinsic factors and external systemic factors [123]. In India, while physicians demonstrated good knowledge (77.3%) and attitudes (87.3%), practice scores were lower (67.6%); 7.4% of informal providers prescribed antibiotics for common colds [117]. In Brazil, 99% recognized AMR as serious, 86.7% acknowledged overprescription, but only 2.9% prioritized antibiotic control [121]. In Delphi, 90% of physicians supported hospital antibiotic policies, 78.7% felt confident in their prescribing, 86.2% believed policies reduced AMR, and 72.5% practiced de-escalation. However, 16.2% didn't consult seniors for stronger antibiotics [124].

Structural equation modeling (SEM) of physicians' prescribing behaviors in hospitals indicated that subjective Norm (SN), particularly patient pressure, is the strongest predictor of indiscriminate antibiotic prescribing behaviors. However, both attitude and perceived behavioral control perceived

behavioral control (PBC) also play significant roles in determining antibiotic prescribing behavior [37]. Another SEM-based study found that higher knowledge among physicians was linked to more favorable attitudes and intentions regarding ASPs. Enhanced understanding helped reduce fear, and ignorance, indirectly shaping prescribing intentions through diminished ignorance-related attitudes. Although improved knowledge was associated with more rational antibiotic use attitudes, it did not directly influence prescribing behaviors. Additionally, high levels of perceived pressure from patients were associated with less favorable attitudes toward appropriate antibiotic use and contributed to increase in prescribing [123].

1.5. Theoretical Framework

ASPs have been conceptualized in various ways, including as a set of coordinated interventions, a program, a philosophy, and an ethic [71]. ASP interventions better be implemented using a stepwise approach that builds on existing structures and reporting, maximizes teamwork, and encourages champions and clinical staff, including prescribers, to participate. Integrating with existing continuous quality improvement models, such as the Plan-Do-Study-Act (PDSA) cycle, to engage clinical staff in ASP team efforts may bear better effects [2]. Effective ASP must bring together various "actors" (individuals, organizations, governments) and activities to facilitate the cyclical collection, analysis, and feedback of data on antibiotic consumption, resistance surveillance of microorganisms, and data on the quality of antibiotic use. This data is essential for assessing the effectiveness of ASP strategies. As indicated in the figure 1, ASPs focus on changing prescriber behavior to promote better antibiotic prescribing and use. Therefore, ASP interventions should be designed with the prescriber at the center [71].

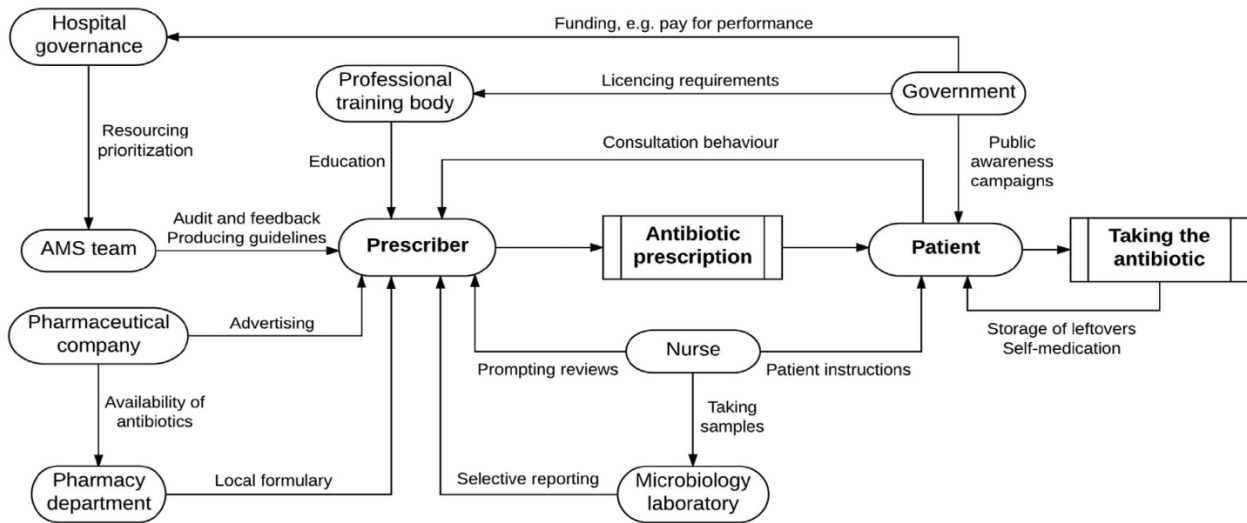


Figure 1: Actors and actions within the ASP, Dyar O.J. et al. [71]

The objectives of the ASP, along with how they are achieved and measured based on the strategies, must be agreed upon by all key stakeholders and communicated clearly. One effective method for achieving this is to produce a driver diagram, which is a logic chart with three or more levels. It should include the goal or vision, the high-level factors needed to achieve the goal (referred to as "primary drivers"), and specific objectives and activities designed to influence these factors. A driver diagram helps an ASP team explore factors that may hinder the achievement of a specific overall goal, illustrates how these factors are connected, serves as a communication tool for explaining a change strategy, and provides the basis for a measurement framework [125]. Using a driver diagram is a valuable approach for determining which interventions to include in the ASP program. It organizes information on proposed activities, ensuring that the relationships between the aims of the improvement project and the changes to be tested and implemented are clear [76].

When assessing the impact of a stewardship intervention, it is essential to consider all intended and potential unintended effects [126]. AMR containment is one of the highest priorities in public health, and ASPs are among the most important strategies to achieve this goal [127]. By changing the prescribing behavior of physicians, ASPs can improve patient care by increasing the appropriateness of all types of antibiotic use, including prophylactic, empirical, and directed therapy. The short-term effects of ASP interventions include changes in knowledge, attitudes, and beliefs about antibiotics and improving patient care, while long-term effects manifest as improvements in outcomes related to resistance and cost savings [128].

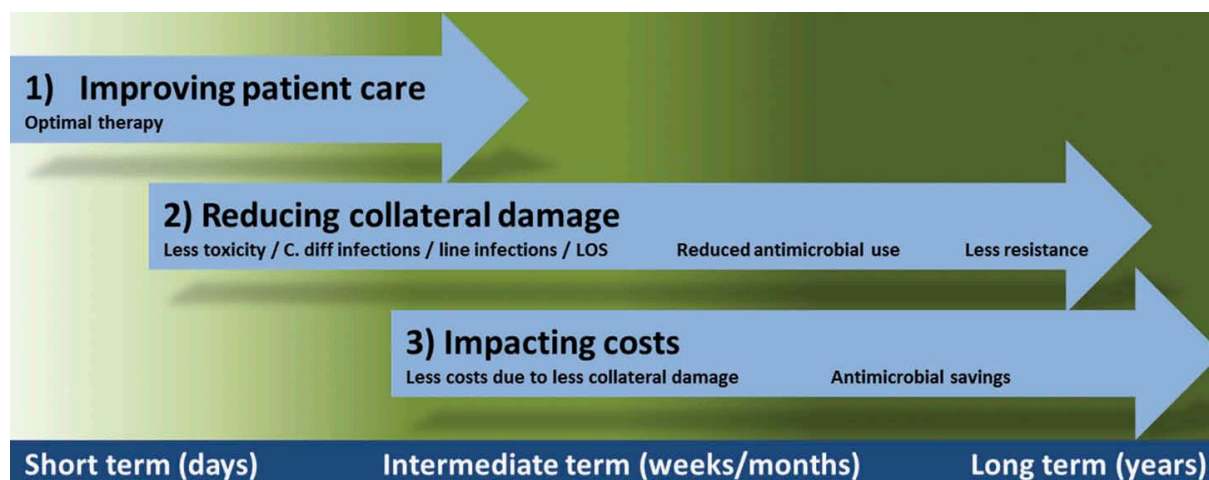


Figure 2: Schematic overview of the expected timeline of the impact of a subset of ASP different aspects, Dik J-W.H., et al [128]

The Behavior Change Wheel model (BCW), designed for characterizing and developing behavior change interventions, has been customized and validated as a framework for use in ASPs for better outcomes [129]. According to the BCW, once problem is identified and contextualized, interventions, and policies can be implemented to change behavior based on interactions within and between layers. The Capability, opportunity and motivation model will be utilized to understand behaviors and the impact of behavior change on antibiotic consumption [130].

Optimizing antibiotic use and reducing AMR is a global priority [1, 2, 4], with ASPs being key to this effort. Achieving evidence-based prescribing requires behavioral changes guided by effective strategies. However, prescribing is affected by limited diagnostics, absence of guidelines, difficulty monitoring patient progress, poor rural intensive care, patient demand for quick relief, expectations from past prescriptions, and fear of losing patients to competitors [42, 131]. Factors at individual, interpersonal, organizational, and policy levels also influence prescribing [132]. Overall ASPs have proven effective globally in reducing inappropriate antibiotic use, lowering healthcare costs, and combating AMR. While studies from well-resourced settings demonstrate significant improvements in antibiotic prescribing patterns and clinical outcomes, evidence from low-income countries like Ethiopia remains limited. The few available studies, including one at TASH, show ASPs can reduce antibiotic use, but face implementation challenges including weak health infrastructure, limited diagnostic capacity, and staffing shortages. These systemic constraints, combined with persistent inappropriate prescribing despite healthcare providers' knowledge, highlight the complex barriers to effective stewardship in resource-limited settings.

The persistence of irrational antibiotic use points to deeper behavioral and institutional factors that undermine stewardship efforts. Prescriber autonomy, patient demands, lack of feedback mechanisms, and poor interdisciplinary collaboration often outweigh clinical guidelines and knowledge. These challenges call for tailored, context-specific stewardship models that address both structural limitations and the human factors influencing prescribing behaviors. Developing sustainable ASPs and evaluating the existing ones will require solutions that account for local health system realities. Such approaches must balance immediate clinical needs with long-term antimicrobial preservation goals in resource-constrained environments. This study is therefore needed to address the existing gaps in ASP implementation and determine the effectiveness of the attempts already on place. It also helped to customize a conceptual framework to determine the outcomes of ASPs based on the aforementioned literature reviews and theoretical frameworks.

1.6. Conceptual Framework

The conceptual framework (Figure 3), based on the theory of planned behavior (TPB), integrates individual and systemic factors influencing antibiotic prescribing and ASPs. At the individual level, physicians' knowledge shapes attitudes, perceived control, and norms, which affect their intent to prescribe antibiotics. Positive attitudes, supportive norms, and confidence promote rational prescribing. However, intention may not always lead to action, as prescribing is also influenced by patient factors like illness severity and socio-demographics.

The framework also incorporates hospital-level factors affecting prescribing and ASP implementation, such as resource availability (antibiotics, diagnostics), leadership, expertise, monitoring systems, education, and institutional guidelines (IPC, DTC functionality). These factors enable or limit evidence-based decisions and ASP sustainability. Patient factors further shape prescribing by influencing clinical urgency and judgment.

External factors, including national policies, government support, partnerships, and networks (e.g., stakeholders, labs, accreditation bodies), create the broader environment for ASP effectiveness. Additionally, healthcare professionals' awareness, experience, attitudes, team dynamics, and adherence to ASPs directly impact program success and patient outcomes. Altogether, this framework captures the complex, multi-level factors that shape prescribing behavior and ASP effectiveness, aiming to optimize antibiotic use, reduce AMR, and improve care quality.

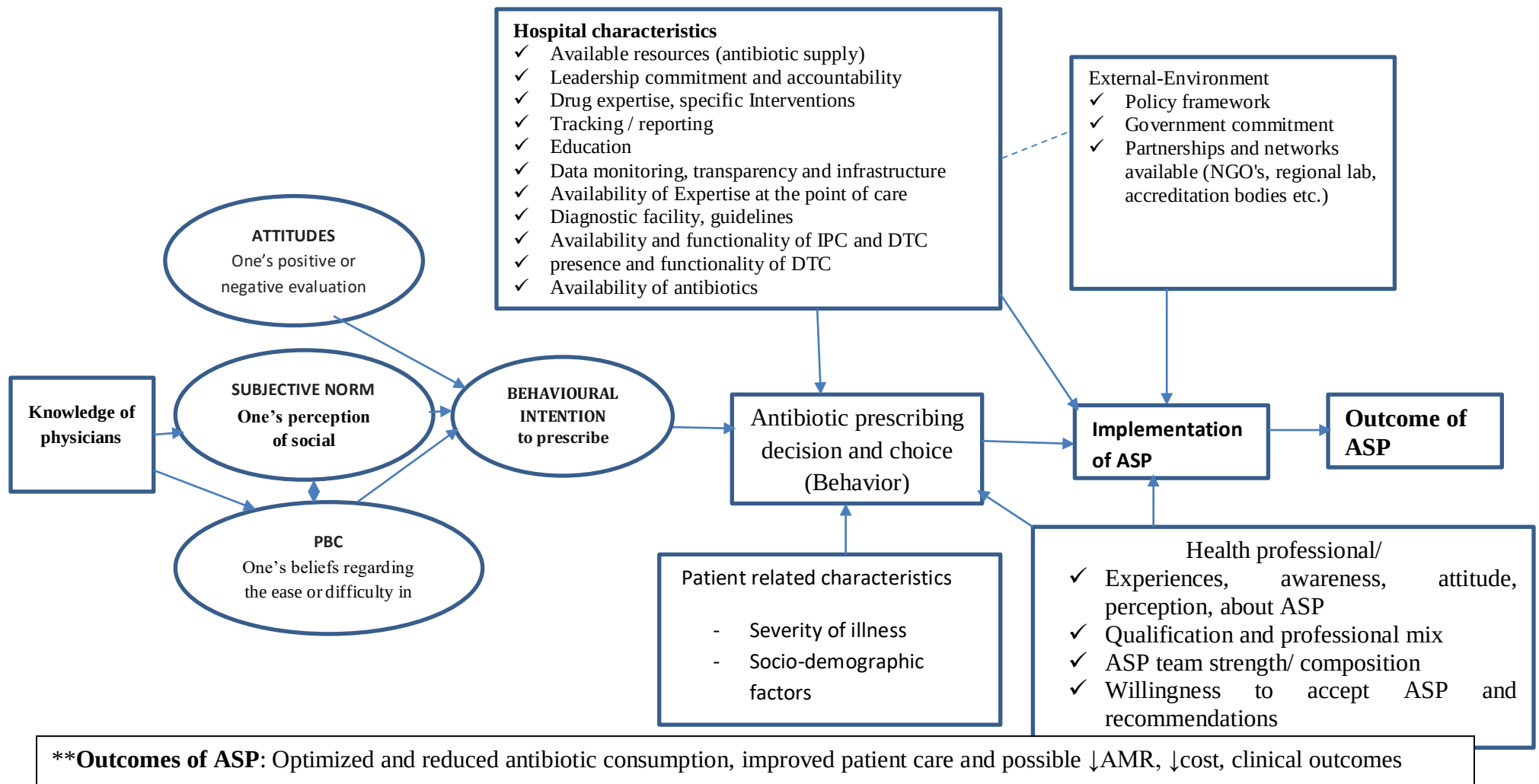


Figure 3: The conceptual framework adopted based on the literature

1.7. Scope of the Study

This study collected data on epidemiology, antibiotic consumption, prescribing behaviors of physicians, the current status of ASPs, the challenges and opportunities in implementing ASPs in hospitals. In addition, antibiotic consumption data were collected from the EPSS, and the AMR data from the APhi were included to see the trends of antibiotic consumption and AMR in the area.

The study also assessed the status of ASPs in these hospitals and their current readiness to implement such programs. A readiness assessment survey evaluating healthcare professionals' perceptions of AMR, antibiotic prescription practices, ASPs, and potential strategies to control AMR was conducted. In addition, a survey was performed to determine the relationship between knowledge, attitudes, SN, and PBC regarding antibiotic prescribing, which was linked to the intention to prescribe antibiotics as a latent indicator of prescribing behavior among (GPs) and resident physicians practicing in the outpatient departments of hospitals. Since there were no available data on antibiotic prescriptions by the physicians, it was not possible to link the intention to prescribe antibiotics. Thus, the study primarily focused on gathering data on status of ASPs in hospitals and identification of gaps for further improvement and implementation.

1.8. Significance of the Study

In Ethiopia, data on antibiotic consumption and AMR remain lacking, despite infections being common and the leading cause of mortality. The usual approach to managing infectious diseases is largely based on empirical therapy, which is significantly influenced by drug promoters and the experiences of physicians. There is no organized monitoring process for antibiotic consumption in hospitals, nor are there established treatment guidelines or health facility-based formularies. Determining the existing practices regarding antibiotic consumption and the capacity of hospitals, along with implementing facility-specific ASPs based on available resources, is critical. In this context, the study will have significant value for the general public, and more specifically, for patients and the hospital community.

Thus, the rationale for this study is to identify gaps in antibiotic use and fill them by raising awareness among healthcare professionals and hospitals about mindful antibiotic prescribing. The study aims to produce evidence for action in hospitals, assist the healthcare system in understanding affordability, and inform decision-making regarding the use of these interventions. Additionally, it seeks to identify challenges specific to the study area concerning ASPs and devise appropriate solutions. Overall, the findings will benefit hospital managers, patients, healthcare professionals, local health leaders and decision-makers, and non-governmental organizations.

CHAPTER TWO: OBJECTIVES OF THE STUDY AND RESEARCH QUESTIONS

2.1. The General Objective

- To assess the current status and effect of antibiotic stewardship programs on antibiotic consumption in public hospitals in Amhara Region, Northwest Ethiopia, 2025.

2.2. Specific Objectives

The specific objectives of the study were:

- To determine trends in morbidity and mortality from bacterial infections in hospitals
- To determine trends in antibiotic consumption at EPSS over six years period
- To determine effect of ASP on antibiotic consumption in the hospitals over three years period
- To determine relationship between antibiotic use and AMR
- To determine trends in AMR at APMI over 6 years period
- To model determinants for antibiotic prescribing behaviors in outpatient departments among physicians using an SEM
- To assess the status of ASP implementation in the hospitals

2.3. Research Questions

It is hypothesized that the introduction of an ASP leads to improved appropriate antibiotic utilization, reduced antibiotic consumption, and lower costs of antibiotics. Similarly, it is hypothesized that knowledge has direct and indirect effect on the intentions to prescribe and reduce antibiotics. In this context, the study will address the following questions:

1. What is the readiness of hospitals to implement ASP?
 - ➔ What is the current trend in morbidity and mortality from bacterial infections?
 - ➔ What is the current status of ASP in hospitals?
 - ➔ What is the awareness level and attitude of health professionals about ASP?
 - ➔ Are the hospitals ready to implement ASP?
2. What is trend of antibiotic consumption and AMR in the study areas?
 - ➔ What is the trend in antibiotic consumption and AMR?
 - ➔ Is there difference in antibiotic consumption in hospitals with active ASP and those without?
3. What are the factors that affect drug prescribing behaviors?
 - ➔ Is there a relationship between knowledge and attitude, SN, and PBC?
 - ➔ Is there a relationship between Attitude, SN and PBC and intention of antibiotic prescribing?
 - ➔ Is there a relationship between intentions of antibiotic prescribing with perceived behavior to prescribe antibiotics?
4. What are challenges and opportunities to implement ASP in the hospitals?

CHAPTER THREE: RESEARCH METHODOLOGY

The research methodology is viewed as the theory behind the organization of an activity, involving an active interaction between humans and their external environment [133]. Research philosophy refers to a system of assumptions and beliefs regarding the development of knowledge [134], framing activity as a comprehensive aspect of human life; thus, a human being is defined as an active being [133]. The philosophical assumptions that researchers bring to a study serve as the foundation for the types of research strategies used (e.g., quantitative or qualitative) and the specific methods employed to implement these strategies (e.g., quantitative versus qualitative data collection) [135].

The methodology of scientific research serves as a bridge and occupies an intermediate position in the following hierarchy: the philosophy of science, the methodology of scientific research, research design, and research techniques [133]. Incorporating elements from various disciplines, such as philosophy, psychology, systems analysis, or systems engineering, can facilitate the selection of the general structure of activity [133], as presented in Figure 4. Thus, describing the philosophical foundation of the research is important and is outlined in the next pages.

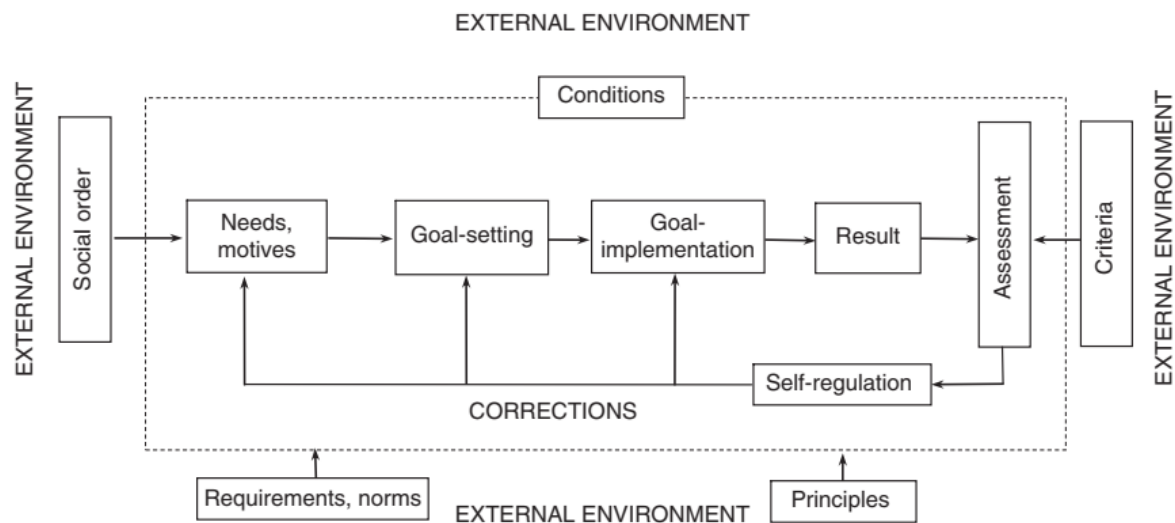


Figure 4: The structural components of an activity [133]

3.1. Philosophical Foundation: Ontological, Epistemological and Axiological Considerations

Our beliefs and assumptions about what is important affect all of us in our decisions. These include assumptions about human knowledge (epistemological assumptions), the realities we encounter in our research (ontological assumptions), and the extent to which our values influence the research process (axiological assumptions) [134]. A credible research philosophy comprises a well-thought-out and

consistent set of assumptions that underpin methodological choices, research strategies, data collection techniques, and analysis procedures [135].

Epistemology concerns assumptions about knowledge and knowing, including what constitutes acceptable, valid, and legitimate knowledge, as well as how we can communicate knowledge to others [134]. It represents a philosophical belief system regarding how research proceeds and what counts as knowledge [135]. Ontology refers to assumptions about the nature of reality, with researchers' ontological assumptions shaping how they perceive and study their research subjects [134]. It serves as a philosophical belief system about the nature of the social world (e.g., whether it is patterned and predictable or constantly re-created by humans) [136]. Axiology, on the other hand, pertains to the role of values and ethics within the research process [134]. Together, these elements form a paradigm, a worldview, or a framework through which knowledge is filtered, constituting a foundational perspective that guides the research process [136].

In general, a researcher's ontological and epistemological views shape the paradigm and axiology. Accordingly, paradigms and axiology can be broadly organized into four categories [137]. These are relevant to pharmacy practice research and can be described as follows:

- **Positivism:** The belief in one "true" reality that can be perfectly apprehended.
- **Post-positivism (or realism):** The belief that reality, while objective, is only imperfectly apprehendable, expressed only as a statistical probability.
- **Interpretivism (or constructivism):** The belief that worldviews cannot be removed from research, and therefore researchers must acknowledge, describe, and fully consider their roles.
- **Pragmatism:** The belief that reality is constructed and cannot be separated from its socio-historical context and power imbalances.

The development and evaluation of ontologies to guide appropriate antibiotic prescribing is common in healthcare. Quantitative studies typically employ positivism and post-positivism, whereas qualitative studies and mixed methods research utilize interpretivism and pragmatism, respectively [137]. One of effective methods to better understand stewardship and antibiotic prescribing, as well as the challenges to good prescribing practices, is to directly engage with prescribers through qualitative interviews [37, 58, 112, 123]. Qualitative research aims to explore and understand the social world, while quantitative research uses numerical data to formulate facts and uncover patterns about the natural world. Mixed or

semi-mixed methods should be established to integrate these two research approaches, enabling both breadth and depth of understanding, as well as justification of a rationale for mixing quantitative and qualitative research approaches complement and corroborate each other [135].

In cognizant that reality exists independent of our beliefs, and acquisition of knowledge is independent of morals or values, the current study employs positivism paradigm. The study used systematic review, analysis of routinely collected and quantitative and semi-structured interviews as research methods. Overall structured and semi-structured questionnaires were used to assess current antibiotic use practices, status of ASP and readiness for ASPs in hospitals, and for SEM on antibiotic prescribing behavior of physicians in the hospitals.

3.2. Methods

3.2.1. Study settings and period

The study was conducted from April 2022 to January 2024 in public hospitals across four zones in the former Gojjam area, including Bahir Dar city. The study included Tibebe Ghion Specialized Hospital (TGSH), Debre Markos Comprehensive Specialized Hospital (DMCSH), Felege Hiwot Comprehensive Specialized Hospital (FHCSH), Finote Selam General Hospital (FSGH), and Injibara General Hospital (IGH). These five facilities, selected based on regional security conditions, are part of the 81 hospitals located in the Amhara National Regional State [138] and were selected based on the security situation in the region. Additionally, EPSS and APHI were included to assess the local magnitude of antibiotic consumption and AMR. EPSS is the main public supply agency responsible for providing pharmaceuticals, laboratory reagents, medical equipment, and supplies, including antibiotics, to the region [139]. APHI, established to consolidate various work processes within the regional health bureau and laboratory centers, is the only institute responsible for coordinating AMR surveillance in the area. APHI aims to improve health services by integrating newer technologies and expanding their use based on available records [140].

Although Ethiopia tried to implement since 2018, Amhara regional health bureau started to implement ASPs since January 2020. The hospitals deliver comprehensive care through outpatient departments, inpatient wards, and ICUs. Although efforts have been made to assign clinical pharmacists, clinical pharmacy services remain only partially integrated into patient care. There are no computerized physician order entry systems, EMRs, or unit-dose dispensing systems currently in use. As of 2021, the hospitals collectively had 1,718 beds and reported 13,896 admissions annually. Data on hospital

readiness for ASP implementation and for the retrospective analysis was collected between July and December 2022. The admission and mortality trend analysis for bacterial infections spans five years (2018–2022), AMR trend data covers 2016–2021, and antibiotic consumption data were obtained from EPSS (2017–2022) and hospital records from 2020–2022, respectively.

3.2.2. Study Design

This study employed a multicenter cross-sectional study design with quantitative methodologies, utilizing primary and secondary data. Retrospective data on the burden of infectious diseases, antibiotic consumption and use, and AMR were collected using cross-sectional data collection methods. Additionally, review of relationship between antibiotic consumption and resistance was conducted. A cross-sectional survey was conducted to assess prescribing behavior of physicians, hospitals' readiness to implement ASP, as well as the perceptions of healthcare professionals regarding AMR, possible causes, ASP and potential solutions.

3.2.3. Study Population

3.2.3.1. Source Population

The source population for this study included all patients admitted to inpatient wards across the hospitals. Key personnel and healthcare professionals were also included as part of the readiness study. Additionally, laboratory logbooks, health information management system (HIMS) data, and Bin cards were used as secondary data sources for antibiotic consumption, use and AMR in APHI, hospitals, and EPSS. For SEM study, both GPs and residents working in outpatient departments (OPDs) and involved in antibiotic prescribing in the hospitals served as the source population.

3.2.3.2. Study Population

For the readiness study, physicians and pharmacists involved in patient care, as well as hospital managers (CEO, medical director, head of human resources, head of the laboratory, ASP leader, and heads of the pharmacy department) were included. For the SEM study, physicians (GPs and residents) serving in OPD were included. Six years of antibiotic consumption data from EPSS and six years of AMR data from APHI were analyzed. Additionally, three years of antibiotic use data from hospitals, based on Bin cards, as well as data on infectious diseases from the HIMS, were incorporated into the study.

3.2.4. Sample size determination

The retrospective data on infectious diseases epidemiology, antibiotic consumption and use, and AMR, included all available records. The SEM study and assessment of health professionals' perception about ASP was determined based on formula for finite population:

$$n = \frac{Z^2 \cdot N \cdot P(1 - P)}{(d^2 \cdot (N - 1) + Z^2 \cdot P(1 - P))}$$

Where:

- **n** is the sample size
- **X²** is the table value of the chi-square for 1 degree of freedom at the desired confidence level ($1.96^2 = 3.84$)
- **N** is the total population, which was determined based on the estimated number of professionals available in the hospitals for inpatient and outpatient department (OPD) services (half for inpatient services and half for outpatient services for each study)
- **P** is the population proportion
- **d** is the degree of accuracy, expressed as a proportion (0.05).

According to Gebretekla et al. [41], physicians are perceived to prescribe antibiotics to about 25% of their patients. Therefore, a prevalence of 25% was used to calculate the sample size for this study. The sample size (n) was calculated as follows:

$$\begin{aligned} &= (1.96^2 \cdot 1.96) \cdot 487 \cdot 0.25(1-0.25) / ((0.05^2 \cdot 0.05) \cdot (487-1) + (1.96^2 \cdot 1.96) \cdot 0.25(1-0.25)) \\ &= 182 \end{aligned}$$

Thus, the required sample size (**n**) was approximately 182. To account for potential non-response, 10% was added, bringing the total sample size for the readiness assessment and SEM study to 200. Samples were proportionally allocated for each hospitals and wards.

3.2.5. Theoretical Framework for Structural equation modeling

Attitudes, SNs, and PBC are related to a specific set of salient behavioral, normative, and control beliefs about antibiotic prescribing. PBC, along with behavioral intention, can be used directly to predict behavioral outcomes. Attitudes are defined as the degree to which a prescriber favors the use of antibiotics in outpatient encounters, while SN and PBC measure the perceived social pressure regarding antibiotic prescriptions and how easy a prescriber feels in making rational decisions about antibiotic prescriptions, respectively. Behavioral intention serves as an intermediate measure of the degree to which a prescriber is willing to prescribe antibiotics [141]. Thus, the modified theory of planned behavior (MTPB) based on theory of TPB (Figure 5) was used and linked knowledge to attitudes, SN, and PBC, ultimately connecting to antibiotic consumption, intentions to prescribe antibiotics, and behaviors influencing antibiotic prescribing [36, 37].

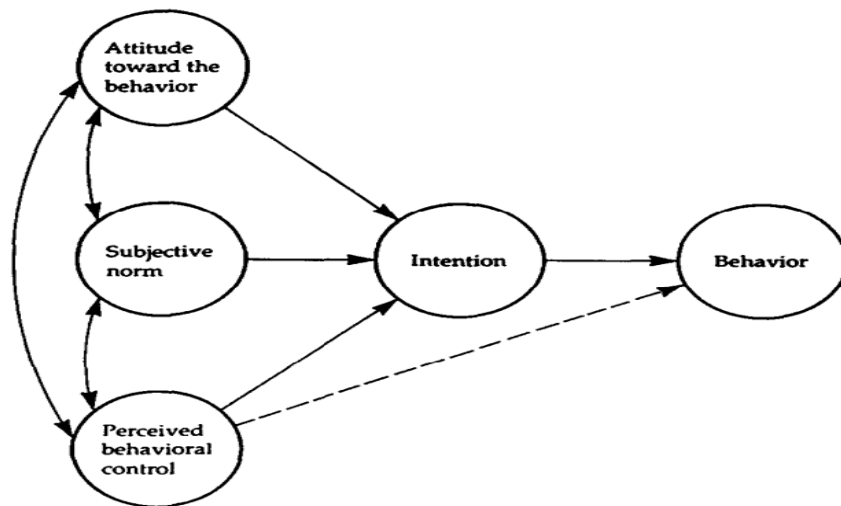


Figure 5: Theory of planned behavior [141]

3.2.6. Data collection instruments

The data collection tools were developed in alignment with the study objectives. The capacity and readiness of health facilities were assessed based on the core elements of hospital ASP [72]. Additionally, SEM for knowledge, attitudes, and behaviors regarding antibiotic prescribing, as developed by Liu et al. and Pan et al. [36, 37], was adopted. Customized [2, 17, 41] data collection

checklists and formats were designed to gather data on the status of ASPs and to extract retrospective data.

The questionnaire included items on experiences with antibiotic use, perceptions of AMR, causes of AMR, barriers to compliance with infection control precautions, strategies for preventing AMR, and sources of information about antibiotics. It was based on a multidimensional construct measured using a 5-point Likert scales, ranging from 1 = strongly disagree to 5 = strongly agree for both awareness and the SEM study. Overall, structured and semi-structured self-administered questionnaires, along with data abstraction checklists, were utilized to collect data from health professionals, hospitals, and records regarding antibiotic consumption, use, costs, AMR, and bacterial infections.

3.2.7. Data collection process

The data collection tools were developed to achieve the objectives of the study. Data was collected by health professionals, preferably pharmacists, after an orientation session. A self-administered, structured questionnaire was distributed to all health professionals and collected once completed. For the SEM study, only physicians who had been practicing for at least one year after graduation participated and filled the self-administered questionnaire. For the hospital readiness analysis, an interview-based approach was employed alongside a document review for basic information. Multiple individuals (e.g., medical directors, CEOs, human resource directors, and pharmacy directors) were approached to secure sufficient information. However, for collecting data on the core elements of hospital ASPs, a single respondent (either the medical director, leader of ASP or secretary) filled out the form.

Retrospective data from EPSS, APHI, and hospitals on antibiotic consumption, use, AMR and infectious diseases, were extracted from available databases and sorted. Overall, the data collection process followed a series of steps, from tool development to the actual data collection. Finally, antibiotics were classified based on the WHO AWaRe classification, admission and mortality from bacterial infections were identified and categorized into syndromes, and the outcomes for each data set (e.g., aggregate or Likert scale) were determined and analyzed to meet the study objectives.

3.2.8. Outcome assessment

The outcomes for antibiotic consumption were determined based on the literature [17, 125-128, 142, 143]. Antibiotic consumption was extracted and categorized according to the Anatomic and therapeutic

classification system and expressed in DDD, following WHO's recommendations [144]. Bacterial infections were identified among all causes of admission using the HIMS coding and classified based on international classification of disease (ICD-10) [145], standard textbooks [146, 147] and literature [5, 6]. Physicians were consulted for input on infectious disease classification. Accordingly, the disease burden associated with and attributable to morbidity and mortality for 15 major infectious syndromes (pulmonary tract infections, bloodstream infections, diarrheal diseases, tuberculosis, bacterial infections of the skin and subcutaneous systems, peritoneal and intra-abdominal infections, meningitis and other central nervous system (CNS) infections, endocarditis and other cardiac infections; infections of bones, joints, and related organs, typhoid and invasive Salmonella infections, urinary tract infections, pyelonephritis, and cystitis, sexually transmitted infections, surgical site infections, and other zoonotic bacterial infections), and bacterial infections of unspecified syndromes were classified.

The DDD metric focuses on population-based parameters and assumes that patients and hospitals are homogeneous entities. In this study, DDD per 1,000 inhabitants per days (DIDs), and DDD per admissions per day (DIDs) based on catchment population and annual admissions respectively were used as the primary outcome measures of antibiotic consumption at EPSS and use in hospitals, respectively. Trend analysis and descriptive statistics were used to represent the prevalence of AMR in APHI, as well as the prevalence and trends in bacterial-related mortality and admission in hospitals. In addition, drugs accounted for 90% of antibiotic consumption (DU90%) and Cost/DDD were also used.

Antibiotic consumption and use were calculated annually in aggregate for each antibiotic, each antibiotic class, and for all antibiotics combined. Additionally, aggregated costs per DDD were used as a cost metric for antibiotic consumption. Similarly, AMR was calculated as the percentage of resistant organisms tested for each microorganism annually, with trends analyzed for specific antibiotics and overall resistance. Morbidity and mortality from bacterial infections were also calculated based on annual admissions for trend analysis.

3.2.9. Study Variables

3.2.9.1. Dependent variables

- Admission and mortality from bacterial infections
- Trends in antibiotic consumption
- Trends in antibiotic use
- Trends in AMR

- Antibiotic prescribing behavior
- Beliefs of health professionals
- Effect of ASP
- Status of the ASP

3.2.9.2. Independent variables

- Socio-demographic variables (age, sex, service year, Experience, etc.)
- Attitude, SN, and PBC
- Knowledge
- Type and level of hospitals
- Implementation status of ASP
- Time

3.2.10. Data quality control

To ensure data quality, the data collectors received orientation and guidance from the principal investigator. The collected data was reviewed and checked for completeness and consistency before processing. The study design, data collection, analysis, interpretation, and report writing were not influenced by any external parties and were solely determined by the research team.

3.2.11. Data processing and analysis

Before analyzing, the data was coded and entered into SPSS version 21, then cleaned and analyzed. Stata/SE 14.0 was used for SEM. SEM assumes that the data follow a multivariate normal distribution (multivariate normality), relationships between variables are assumed to be linear and Errors (residuals) should not be correlated unless specified (independence of errors).

Descriptive analysis was conducted for all studies to summarize the basic findings. Linear and polynomial trend analyses were applied to assess infectious disease and mortality, antibiotic consumption and use, and AMR. Additionally, regression analysis, chi-square (χ^2) tests, and ANOVA were used to compute and compare variables. Univariable and multivariable regressions were used to explore potential relationships between variables. The maximum likelihood technique was employed to estimate parameters in the SEM of prescribing behavior. Statistical significance was determined at $p < 0.05$. Model fit was assessed using standard fit indices, with recommended thresholds such as $P > \chi^2$ test ($P > 0.05$), standardized root mean squared residual (SRMR) < 0.09 , root mean square error of

approximation (RMSEA) < 0.08 , Tucker-Lewis index (TLI) > 0.90 , comparative fit index (CFI) > 0.90 , and coefficient of determination (CD) ≥ 0.7 . Costs of antibiotics were reported as both total and average values. The processed data was compiled, organized, and presented using tables and figures, depending on the type of data.

Table 1: A summary of the research questions, methodology, rationale, and methods

S. No	Research questions	Methodology	Rationale	Methods	Analysis methods
1	What is the trend of morbidity and mortality from bacterial infection in hospitals?	Quantitative	To determine the baseline antibiotic consumption and AMR in the hospitals	Retrospective review based on data abstraction formats	Descriptive statistics, ANOVA and trend analysis
2	What is the level of readiness of hospitals to implement ASP?	Quantitative	To assess the current situation of hospitals	Self-administered cross-sectional survey based on a semi-structured questionnaire	Descriptive statistics, X^2 tests
3	What is the trend in antibiotic consumption, and AMR?	Quantitative	To determine the baseline antibiotic consumption and AMR	Retrospective review based on data abstraction formats	Descriptive statistics, ANOVA, trend analysis
4	What is the effect of the knowledge and attitudes on physicians antibiotic prescribing behavior in hospitals?	Quantitative	To measure the effect of the knowledge and attitudes of physicians on antibiotic prescribing behavior	Self-administered cross-sectional survey based on a semi-structured questionnaire	Structural equation modeling (SEM)

3.2.12. Dissemination of study findings

The results of the study will be disseminated to the concerned stakeholders and authorities responsible for addressing the identified gaps. Additionally, the publication of the findings in peer-reviewed journals, as well as presentations at seminars, journal clubs, and conferences, were considered. Interventions based on the identified gaps will be considered in the future.

3.2.13. Ethical consideration

Ethical approval for the study was obtained from the Ethical Review Board of Addis Ababa University, College of Health Sciences, and the School of Pharmacy. During data collection, all hospital and patient-related information was kept strictly confidential. Participants were asked to sign a consent form attached to the questionnaire. The collected information was used exclusively for research purposes and remained confidential. To further ensure confidentiality, participants' identities were anonymized throughout the study

3.2.14. Operational Definitions and Definitions of Terms

- **Antibiogram:** An antibiogram is an overall profile of the antibiotic susceptibility testing results of a specific microorganism to a battery of antibiotic drugs.
- **Antibiotics:** Antibiotics are a drugs used in the treatment and prevention of bacterial infections.
- **Antimicrobial resistance:** the ability of microorganisms to resist the effects of an antibiotic to which they were once sensitive
- **Antibiotic stewardship Program:** Used to refer only antibacterial drugs excluding anti-parasitic, antiviral, and antifungal drugs.
- **Attitude:** The degree to which a participant has a positive or negative evaluation of indiscriminate antibiotic use.
- **Behavioral intentions intention to prescribe:** estimate the degree to which a prescriber is willing to prescribe antibiotics.
- **Behavior:** self-reported antibiotic prescribing behavior.
- **Clinical outcomes:** These are the medical events that occur during management (e.g., Safety, and efficacy endpoints).

- **De-escalation:** Antibiotic de-escalation is defined as changing the empiric antibiotic regimen to a culture-directed single agent with a narrower spectrum than the original empiric regimen upon identification of the causative organisms.
- **Dose Optimization:** It involves “optimization of antibiotic dosing based on patient characteristics (e.g., weight, renal/liver function), causative organism, site of infection (e.g., central nervous system, blood), and pharmacokinetic and pharmacodynamic characteristics of the drug (e.g., concentration or time-dependent activity).
- **DOT:** denotes the number of days that a patient is on each antibiotic, regardless of dose, based on the underlying assumption that antibiotic dosing is appropriate. DOT is the sum of days of therapy for each antibiotic within a given day the patient received any antibiotic.
- **Empiric therapy:** treating symptoms or signs of infection.
- **Formulary restriction:** this is a method of limiting access to some selected medication prescribed by specific practitioners. Hence, prescriptions for selected medicines require preapproval by responsible body before dispensing.
- **Hospital associated infectious:** A hospital-acquired infection, also known as a nosocomial infection, is an infection that is acquired in a hospital or other healthcare facility or any infection developed after 3 days of admission to the health facility.
- **Knowledge:** participants understanding and awareness regarding indiscriminate antibiotic use and AMR.
- **Length of therapy:** The actual length of the antibiotic treatment period for a patient, irrespective of how many antibiotics were prescribed per day.
- **Morbidity:** Morbidity in this study shall mean admissions due to bacterial infections
- **Pediatrics:** in this study was used to denote population groups' ≤ 15 years old.
- **Perceived Behavioral Control:** a participant's beliefs regarding the ease or difficulty of making a rational decision on antibiotic prescriptions
- **Prophylaxis:** preventing infections when patients are asymptomatic or when the antibiotics were used for the perioperative phase.
- **Subjective norm:** participant's belief about whether significant others would approve or disapprove of an indiscriminate use of antibiotic.

CHAPTER FOUR: KEY FINDINGS AND DISCUSSION

4.1. Key findings

Introduction

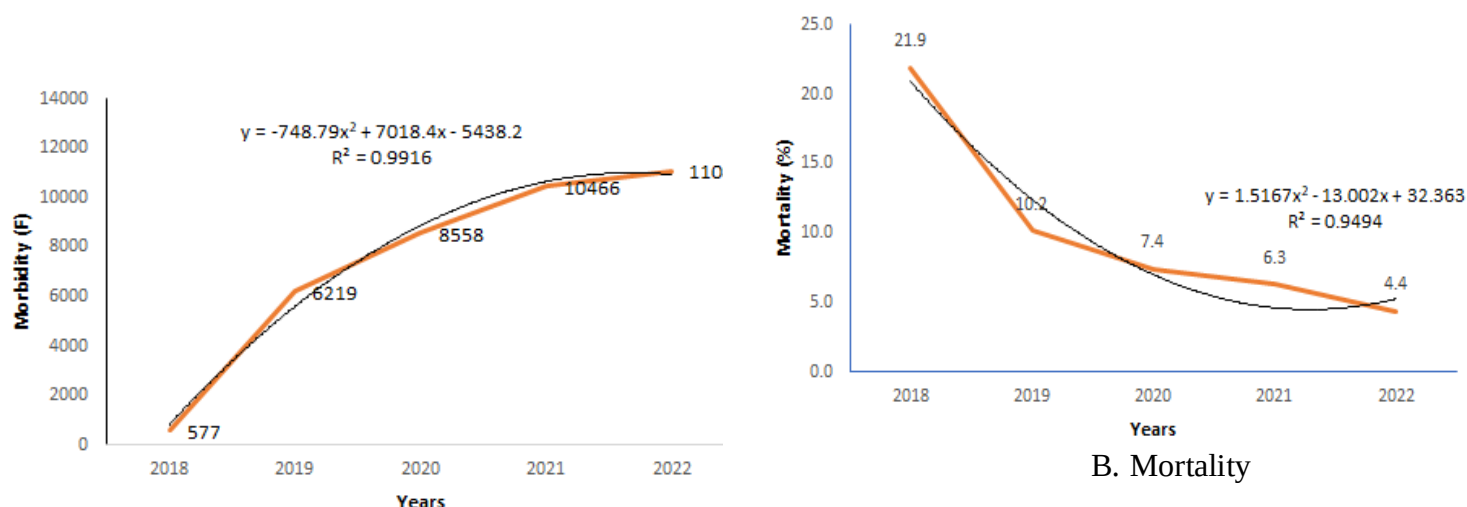
The study assesses the status and effect of ASP on antibiotic consumption in hospitals, antibiotic prescribing behaviors, and trends in and mortality from bacterial infections in hospitals in Amhara region, in northwest Ethiopia. To gain a clear understanding of AMR and antibiotic consumption within the catchment population of the hospitals, AMR data from APHI and antibiotic consumption from EPSS are particularly focused on, as these two institutions serve as the primary regional facilities for antibiotic sensitivity testing and antibiotic distribution, respectively. This chapter presents the characteristics of study participants and the key findings of the assessment. Except for review article, the main findings of the study were summarized, followed by a general result description, discussion of key findings, and suggestions for future research. Additionally, it discussed the strengths and limitations of the study, drew conclusions, and made recommendations. The detailed description of results is available at the list of manuscripts and papers part (I-VI).

4.1.1. Morbidity and Mortality from Bacterial infections

Over the past 5 years, there were approximately 197,576 hospital admissions and 13,051 (6.7%) mortalities, of which 39,666 (20.1%) admissions were due to bacterial-related infections. Among these, 23,154 (58.4%) were male, and 13,875 (35.0%) were children under 1 year old, followed by 9,322 (23.5%) aged 30-64 years, and 7,591 (19.1%) aged 15-29 years.

The prevalence of morbidity and mortality from bacterial infections accounted for 39,666 (20.1%) of all hospital admissions and 2,763 (21.2%) of all-cause mortalities in the hospitals, respectively. The majority of the infections were from FHCSH, 15337 (38.7%), and from IGH, 8851 (22.0%), followed by 7923 (20%) from TGSH, and 6970 (17.6%) from FSGH. Where, the majority of mortalities were from FHCSH, 1644 (59.5%), and DMCSH, 585 (21.2%), followed by 212 (7.7%), 158 (5.7%), and 164 (6%) from TGSH, FSGH, and IGH, respectively.

Overall, bacterial infections in hospitals increased from 33.5% in 2018/19 to 37.5% in 2021/22 following a second degree polynomial equation as a function of $y = -748.79x^2 + 7018.4x - 5438.2$ ($R^2 = 0.9916$) (Figure 6A). On the other hand, the prevalence of mortality among bacterial infections was 7.0% and decreasing from time to time. The mortality rate declined from 21.9% in 2017/18 to 4.4% in 2021/22, as a function of $y = 1.5167x^2 - 13.002x + 32.363$ ($R^2 = 0.9494$) (Figure 6B).



A. Morbidity

Figure 6. Trends in morbidity and mortality (July 2017- June 2022) from bacterial infections, in hospitals in Northwest Ethiopia.

Sepsis or septic shock 11,845 (29.9%), pulmonary tract infections 10,236 (25.8%), and intra-abdominal infections and abscesses 6,257 (15.8%), were the most common bacterial infectious syndromes (Table 2). The most frequent specific bacterial infections were sepsis, with 11,121 cases (28.0%), and pneumonia, with 9,882 cases (24.9%), followed by appendicitis, with 4,202 cases (10.6%), and meningitis, with 2,916 cases (7.4%).

Table 2. The most common infectious syndromes (July 2017 to June 2022), in hospitals in Northwest Ethiopia, (N = 39,666).

Bacterial Infectious Syndromes	Frequency (%)
Sepsis/septic shock	11,845 (29.9)
Pulmonary tract infection	10,236 (25.8)
Intra-abdominal infections and abscess	6257 (15.8)
CNS infections	3275 (8.3)
Infections of skin, muscles, and soft tissues	1713 (4.3)
Endocarditis and other cardiac infections	1430 (3.6)
Eye, ear, nose, throat, or mouth infection	1235 (3.1)
Tuberculosis	1214 (3.1)
Infections of bones, joints, and related organs	767 (1.9)
Genitourinary tract infections	687 (1.7)
Surgical site infections	631 (1.6)
Sexually transmitted diseases	238 (0.6)
Zoonotic bacterial infections	95 (0.24)
Typhoid/Salmonella typhi infections	80 (0.2)
Other bacterial infections not specified	1250 (3.2)
Total	39,666 (100)

CNS: central nervous system infections

About 1,248 (45.2%) mortalities were due to bloodstream infections, followed by pulmonary tract infections 589 (21.3%), CNS infections 417 (15.1%), tuberculosis 194 (7.0%), and intra-abdominal infections and abscesses 109 (3.9%), among others. The most common causes of mortality from bacterial infections were sepsis 908 (32.9%), pneumonia 576 (20.8%), and septic shock 340 (12.3%). Linear regression analysis, revealed significantly associated with patient age and gender (p-values of 0.0001 and 0.011, respectively) with number of bacterial related morbidity, where 1-year-old children and females being at higher risk for bacterial infections. However, only age (p-value = 0.000) was significantly associated with mortality, with children younger than 1 year being at higher risk of mortality from bacterial infections (Manuscript I).

4.1.2. Antibiotic consumption at EPSS

Based on data from EPSS, total antibiotic consumption over the six-year period from 2016/17 to 2021/22 was 30.3 DIDs, averaging 5.3 DIDs annually. During this time, overall antibiotic consumption decreased by 87.4% (from 6.9 in 2016/17 to 0.9 DIDs in 2021/22) following a second degree polynomial equation as a function of $y = -0.5911x^2 + 2376.6x - 2E+06$ ($R^2 = 0.8634$), (Figure 7).

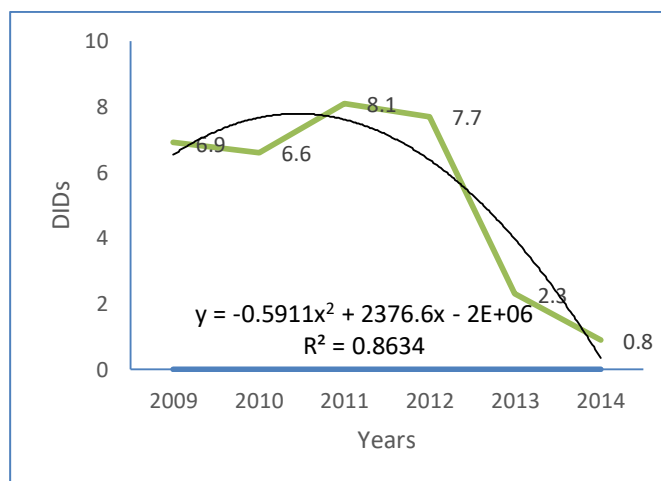


Figure 7: Trends of antibiotic consumption at EPSS Bahir Dar Branch during 6 years period (July 2016- June 2022)

At EPSS, the most frequently used antibiotic classes were beta-lactams and penicillins (J01C), with a consumption of 14.9 DIDs, followed by tetracyclines (J01A) 5.3 DIDs, and quinolones (J01M) 4.1 DIDs. According to the WHO AWaRe classification, antibiotics categorized under Access accounted for 23.4 DIDs (77.1%) of the total consumption at EPSS, while those in the

Watch category comprised 6.9 DIDs (22.9%). The trend in antibiotic consumption across all categories was decreasing over years (Figure 8).

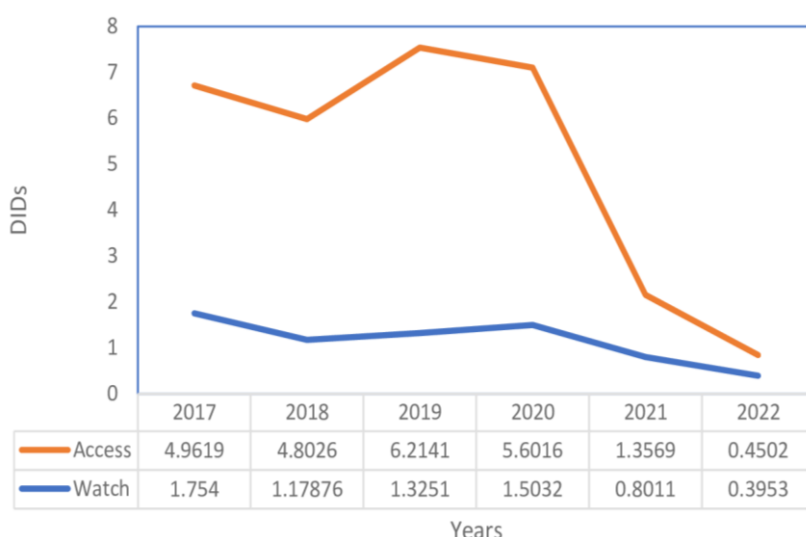


Figure 8: Consumption of systemic antibiotics (July 2019 – June 2022), at EPSS and in the hospitals, in Northwest Ethiopia

At EPSS, seven antibiotics made up the DU90%, with amoxicillin (10.1 DIDs), doxycycline (5.3 DIDs), ciprofloxacin (3.4 DIDs), and cloxacillin (3.1 DIDs) being the most commonly consumed. The total expenditure on antibiotics was approximately \$7,281,680.91 (385,200,920 Ethiopian birr), with 74.4% of the costs attributed to Access category antibiotics and 62.7% to purchase DU90%. The total cost per total DDD of antibiotics was 3 birr (Article II).

4.1.3. Antibiotic consumption in hospitals

Antibiotic consumption in hospitals was 296.2 DIDs (average 98.7 DIDs per year). In hospital antibiotic consumption over a three-year period (2019/20 to 2021/22) showed an 11.4% reduction, falling from 96.2 to 85.2 DIDs, following $y = -23.95x^2 + 90.382x + 29.72$ ($R^2 = 1$) (see Figure 9). The consumption patterns varied among hospitals which do have active ASP and those which interrupted the committees signifying the positive effect of ASP on antibiotic consumption (Figure 10).

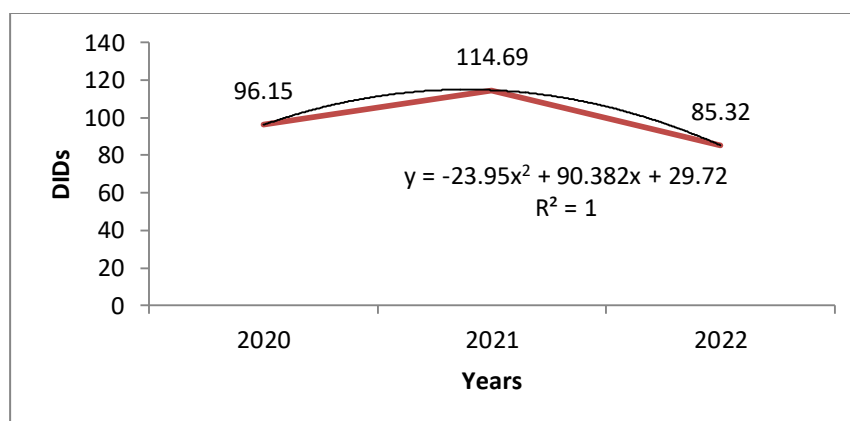


Figure 9: Trends of antibiotic consumption in during 3 years period, 2020- 2022

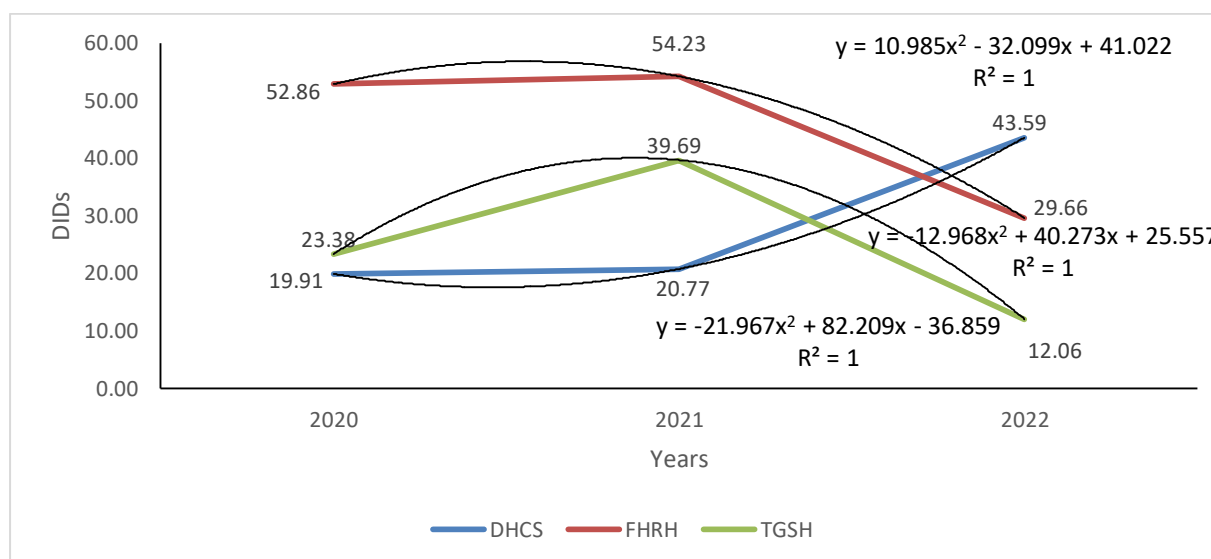


Figure 10: consumption of systemic antibiotics (July 2019 – June 2022), in the hospitals, in Northwest Ethiopia

The most frequently consumed antibiotic class in hospitals was beta-lactam antibacterials (J01D), accounting for 135.1 DID's (45.6%). This was followed by beta-lactam antibacterials, penicillins (J01C) 56.8 DID's (18.5%), and sulfonamides and trimethoprim (J01E) 40.5 DID's (13.7%). According to the WHO AWaRe classification, 145.3 DID's (49.1%) of antibiotics consumed in hospitals belonged to the Access category, 150.7 DID's (51.6%) were in the Watch category, and 0.49 DID's (0.2%) fell under the Reserve category. While the consumption of Watch antibiotics showed a downward trend, the consumption of Access category antibiotics was increasing (see Figure 11).

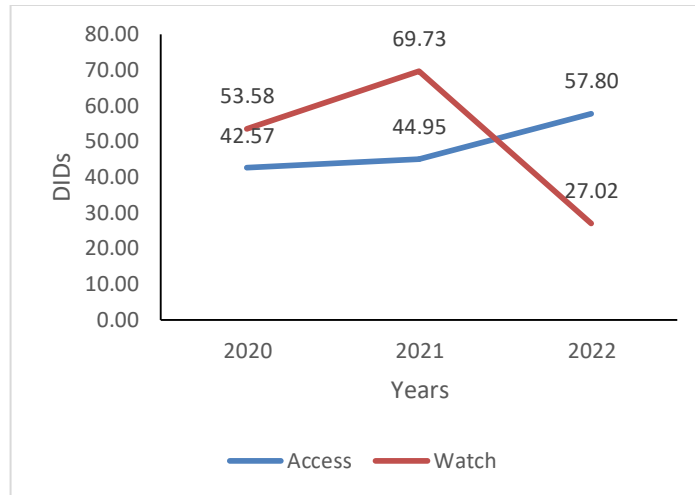


Figure 11: Consumption of systemic antibiotics (2021 – 2022), in the hospitals, in Northwest Ethiopia

In hospitals, ceftriaxone, TXS, cephalixin, amoxicillin, amoxicillin-clavulanate, cefuroxime, ciprofloxacin, doxycycline, cloxacillin, azithromycin, and metronidazole consumption constituted the DU90% in increasing order of frequency. Overall, the cost expenditure for antibiotics consumed in hospitals was \$1,100,101.48 (60,054,539.9 Ethiopian birr). The cost expenditure accounted for 60.0% of the total for Watch antibiotics, 40.0% for DU90% and 65.2% for parenteral antibiotics (35% consumed) in hospitals; the cost of antibiotics consumed was 6 birr per DDD in hospitals (Manuscript III).

4.1.4. Trends in AMR

Between 2016 and 2021, a total of 25,143 bacterial isolates were obtained from the APMI recorded based on AMR testing. Most of the samples were collected from male patients (13,376; 53.2%) and children under the age of 15 (11,985; 47.6%). Blood (11,785; 46.9%) and urine (6,354; 25.3%) were the most commonly collected specimen types (see Table 5).

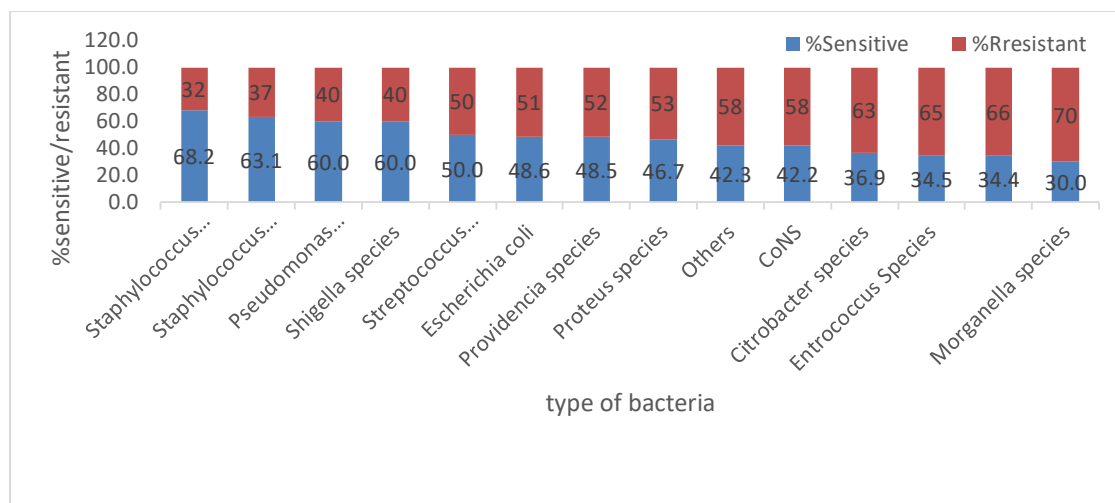
Table 5: Distribution of samples by different variables (2016-2021), APMI, Amhara Region, Ethiopia (N=25143):

Variables		Frequency (%)
Sex	Male	13376 (53.2)
	Female	11767 (46.8)
Age	<15 years	11985 (47.6)
	15-64 years	11205 (44.6)
	>=65 years	1347 (5.4)
	Not recorded	606 (2.4)
Facility	Public facility	19194 (76.3)

	Private facility	4867 (19.4)
	Not known	1083 (4.3)
	Total	25143 (100)
Residence	Bahir Dar city	23719 (98.6)
	Awi Zone	176 (0.7)
	South Gondar Zone	111 (0.5)
	West Gojjam Zone	50 (0.2)
	Gondar City	4 (0.02)
	Not specified	1083 (4.3)
	Total	25143(100)
Source of sample	Blood	11785(46.87%)
	Urine	6354(25.27%)
	Swabs	1993(7.9%)
	Stool	1620(6.4)
	Discharges	436(1.7)
	Body effusions	401 (1.6)
	Sputum	200(0.8%)

Among the bacterial isolates, gram-negative organisms were predominant, accounting for 74.5% (12,528) of the total. The most frequently identified species included *Klebsiella pneumoniae* (30.2%), *Escherichia coli* (25.5%), *Acinetobacter baumannii* (11.5%), *Enterobacter* species (10.6%), and *Pseudomonas aeruginosa* (7.1%). In contrast, gram-positive bacteria made up 25.5% (4,297) of the isolates, with coagulase-negative *Staphylococcus* species (40.1%), *Staphylococcus aureus* (30.1%), and *Enterococcus* species (18.9%) being the most frequently detected.

At APHI, the overall AMR was 2,738 cases, representing 59.9% of all bacterial isolates. Of these, gram-negative bacteria accounted for 1,807 (66.0%), while gram-positive bacteria made up 931 (34.0%). Resistance was observed in 2,083 (64.6%) of the gram-negative isolates and 931 (54.0%) of the gram-positive ones. The leading gram-negative organisms contributing to resistance included *Klebsiella pneumoniae* (743 cases; 80.2%), *Enterobacter cloacae* (196 cases; 74.8%), *Morganella* species (14 cases; 70%), *Acinetobacter baumannii* (213 cases; 66.6%), and *Escherichia coli* (431 cases; 51.0%). Among gram-positive bacteria, the most resistant species were CoNS with 406 cases (58.0%), *Streptococcus* species with 34 cases (50.0%), and *Staphylococcus aureus* with 196 cases (37.0%) (Figure 12).



*Others: *Salmonella choleraesuis*, *Bacillus*, *Moraxella catarrhalis*, unidentified

Figure 12: Overall prevalence of AMR (2016-2021), APHI, Amhara Region, Ethiopia

The prevalence of AMR showed a sharp rise from 0 cases among 81 samples tested in 2016 to 6,579 cases (64.8%) by 2019. However, there was a slight decrease in 2021, with 2,339 cases (56.9%). The trend of AMR over time followed a quadratic pattern, forming a downward-opening parabola. The peak of this curve was approximately at year 4.4 with a resistance rate of 66.9%. The relationship was best described by the quadratic equation $y = -5.3247x^2 + 46.768x - 36.069$, with a strong goodness of fit ($R^2 = 0.94$) (Figure 13).

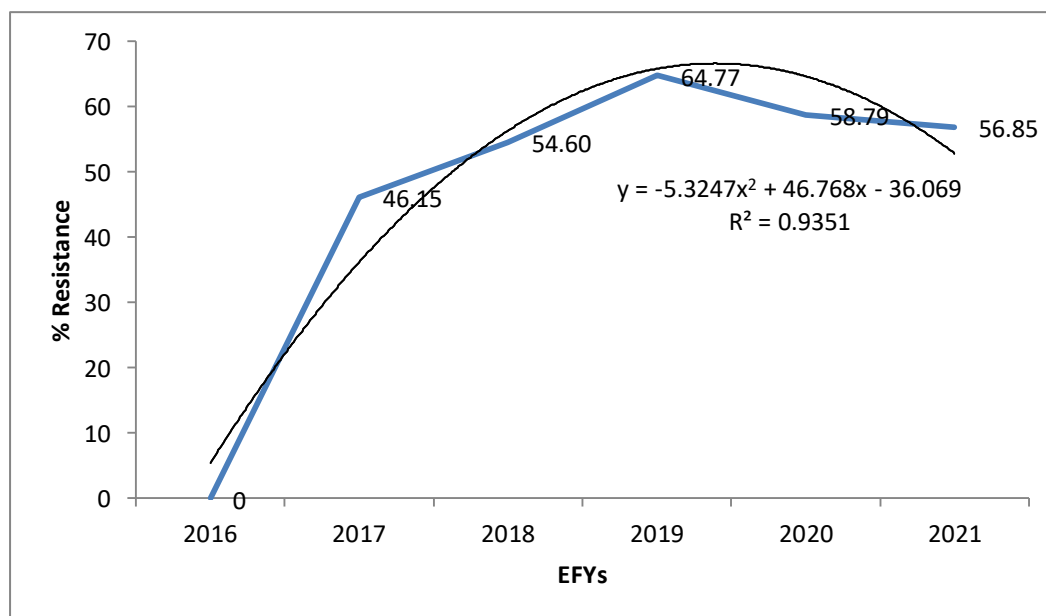


Figure 13: Trends in AMR (2016-2021), APHI, Amhara Region, Ethiopia

A. baumannii resistance to ceftriaxone was 31 (100%), followed by SXT 37(97.4%), tobramycin 25 (96.2%), tetracycline 18 (94.8%), ciprofloxacin 30 (90.9%), gentamicin 28 (82.4%); *CoNS* resistance was ciprofloxacin 58 (89.2%), clindamycin 30 (100%), SXT 88 (100%), erythromycin 84 (100%), gentamicin 34 (100%), oxacillin 24 (100%), and tetracycline 50 (96.2%); *Enterobacter spp.* to ampicillin 14 (100%), amoxicillin-clavulanate 33 (9.7%), ceftriaxone 31 (100%), ciprofloxacin 29 (100%), SXT, 40 (100%), gentamicin 236 (79.4%), tetracycline 16 (100%), tobramycin 22 (95.7%); *E. coli* to ampicillin 29 (100%), amoxicillin-clavulanate 49 (92.5%), ceftriaxone 39 (92.9%), ciprofloxacin 64 (100%), SXT 79 (100%), tetracycline 41 (100%) and tobramycin 33 (97.1%); *K. pneumonia* resistance to ceftriaxone 95 (100%), ciprofloxacin 91 (100%), ampicillin 38 (100%), and amoxicillin-clavulanate 73 (92.4%) ; SXT 125 (100%), tetracycline 53 (96.4%), gentamicin 115 (95%), and tobramycin 82 (91.1%); *S. aureus* to erythromycin 41 (100%), SXT 39 (100%), gentamicin 20 (100%), and tetracycline 29 (93.5%). MDR bacteria accounted for 571 (20.9%) total resistant strains.

MDR bacterial isolates constituted 571 cases (20.9%), with 378 (18.1%) from gram-negative and 193 (20.9%) from gram-positive bacteria. The most frequently identified MDR organisms included *coagulase-negative Staphylococci* 98 (50.0%), *Klebsiella pneumoniae* 133 (35.2%), *Staphylococcus aureus* 46 (23.6%), *Escherichia coli* 86 (22.8%), *Enterococcus* species 27 (14.2%), *Acinetobacter baumannii* 39 (10.3%), and *Enterobacter cloacae* 37 (9.8%). Resistance patterns across most antibiotics remained relatively consistent over the years. However, there was a steady increase in resistance among key pathogens, including ampicillin-resistant *E. coli*, augmentin-resistant *Acinetobacter*, ceftazidime-resistant *E. coli*, ceftriaxone-resistant *Klebsiella*, and ciprofloxacin-resistant *Klebsiella*. Furthermore, multivariate binary logistic regression analysis revealed significant associations between antibiotic resistance and patient age ($p = 0.004$), gender ($p = 0.002$), and type of healthcare facility ($p < 0.001$) (article IV).

4.1.5. Antibiotic prescribing behavior of physicians

Out of 200 questionnaires distributed to physicians at the OPD, 185 (92.5%) were returned. Among the respondents, 153 (82.7%) were male, with an average age of 30.3 ± 3.9 years. Notably, 49 (80.5%) of the physicians had served less than 5 years in their current position. The mean knowledge score among physicians was 4.9 ± 1.6 (Table 3).

Table 3: Characteristics of physician respondents in OPDs in hospital, 2022, (N=185)

Variables		Frequency (%)
Sex	Male	153(82.7)
	Female	32 (17.3)
Age	<=30	116 (62.7)
	>30	69 (37.3)
Professional title	GPs	93 (50.2)
	Residents	92 ((49.8)
Facility	FHRH	43 (23.2)
	TGSH	87 (47.0)
	DMRH	31(16.8)
	IGH	24 (13)
Practice area	Medical	36 (19.5)
	Surgery	40 (21.6)
	Pediatrics	48 (25.9)
	Gyne/obs	55 (29.9)
	Others	6 (3.2)
Service in the current hospital	<5 years	172 (93)
	>=5 years	13 (7)
Overall service in current position	<5 years	149 (80.5)
	>=5 years	36 (19.5)
Training on antibiotic use	No	159 (85.9)
	Yes	26 (14.1)
Average number of patients seen per week		97.5±79.7
Average number of patients received antibiotics per week		54.8% of total seen 60.1±53.5

Among the participating physicians, 121 (65.4%) demonstrated a good level of knowledge (those who answered ≥ 5 out of 11)—while 64 (34.6%) showed poor knowledge. The average score for attitude-related items was 2.3 ± 0.4 . Concerning subjective norms and perceived behavioral control related to antibiotic prescribing, the mean scores were 4.27 ± 0.76 and 4.0 ± 1.1 , respectively. Regarding intentions, the average score for reducing antibiotic use was 2.4 ± 0.9 , while the intention to prescribe antibiotics had a mean score of 2.5 ± 0.8 . In terms of perceived prescribing behavior, it was estimated that 54.8% of patients seen in OPDs (average 60.1 ± 53.5 patients per week) received at least one antibiotic. About 178 physicians (96.2%) reported prescribing antibiotics to at least one out of every 10 such patients diagnosed with URTIs, with an average of 5.9 ± 2.2 patients per physician. Overall, antibiotics were perceived to be prescribed to 916 patients, accounting for 49.5% of total cases.

The coefficient of determination (R^2) indicated that 94.6% of the variance in antibiotic prescribing behavior was accounted for by the exogenous variables in the model. The MTPB model showed a

good fit to the data, evidenced by a log likelihood value of -6951.79, a RMSEA of 0.049 (below the 0.08 threshold), and SRMR of 0.07 (well under 0.9). Additionally, the CFI was 0.91 and the TLI was 0.901, both exceeding the acceptable cutoff of 0.90. The model was saturated, with a chi-square value of 445.17 across 587 degrees of freedom, and a corresponding p-value less than 0.001 (see Table 4).

Table 4: The model goodness of fit indexes for antibiotic prescribing behaviors of Physicians at OPDs, 2022 (N=185)

Fit statistics		Value	Description	Standard
Likelihood ratio				
	χ^2_{ms} (314)	445.17	Model versus saturated	—
	$P > \chi^2$	0.0001		—
	χ^2_{bs} (348)	1878.87	Baseline versus saturated	—
	$P > \chi^2$	0.0001		—
Information criteria				
	AIC	14075.59	Akaike information criterion	
	BIC	14352.54	Bayesian information criterion	
Population error				
	RMSEA	0.049	Root mean squared error of approximation	0.08
	90% CI	0.038-0.058		—
	Pclose	0.581	Probability of RMSEA ≤ 0.05	—
Size of residuals				
	SRMR	0.071	Standardized root mean squared residual	<0.09
	CD	0.946	Coefficient of determination	—
Baseline comparison				
	CFI	0.910	comparative fit index	≥ 0.90
	TLI	0.901	Tucker-Lewis index	≥ 0.90

The SEM confirmed the theoretical framework for physicians' antibiotic prescribing behaviors, albeit with some modifications. The MTPB model indicated that only physicians' knowledge was associated with PBC and SN, with a significant negative covariance between SN and PBC ($P = 0.000$). Neither attitude, SN, nor PBC was found to be associated with the intention to prescribe or reduce antibiotics ($P \geq 0.05$). Furthermore, perceived antibiotic prescriptions in OPDs and for URTIs did not correlate with the intention to prescribe or reduce antibiotics ($P \geq 0.05$).

The SEM analysis supported the proposed theoretical framework of physicians' antibiotic prescribing behaviors, although some adjustments were necessary. According to the MTPB model, physicians'

knowledge was the only factor significantly linked to PBC and SN, with a notable negative correlation between SN and PBC ($P = 0.000$). However, attitudes, SN, and PBC did not show any significant relationship with the intention to either prescribe or reduce antibiotic use ($P \geq 0.05$). Additionally, the perceived antibiotic prescribing practices in OPDs and for URTIs were not significantly associated with intentions to prescribe or reduce antibiotics ($P \geq 0.05$).

Physicians' age ($P = 0.004$) and professional level ($P = 0.023$) significantly predicted their perceived antibiotic prescribing for URTIs. Additionally, age ($P = 0.001$), sex ($P = 0.031$), and professional level ($P = 0.018$) were significant predictors of perceived antibiotic prescribing during weekly OPD visits. Physicians' knowledge had a direct positive effect on both SN ($P = 0.000$) and PBC ($P = 0.000$). However, no indirect associations were found between perceived prescribing behaviors and knowledge, attitude, SN, or PBC (see Table 5) (Article VI).

Table 5: Effects of direct and indirect of intention to prescribe antibiotics on antibiotic prescribing behavior in hospitals in 2022, (N=181).

Factors		Effects of covariates on each other		
		B	SE	P value
Subjective norms				
	Knowledge	1.5	0.49	<.001
Perceived behavioural control				
	Knowledge	-2.2	0.43	<.001
Intention to reduce antibiotic prescriptions				
	Attitude	0.07	0.20	.42
	Subjective norms	0.10	0.20	.45
	Perceived behavioural control	0.14	0.21	.53
Intention to prescribe antibiotics				
	Attitude	0.01	0.89	.91
	Subjective norms	-0.05	0.93	.83
	Perceived behavioural control	-0.42	0.89	.79
Proportion of patients from 10 who were estimated to be prescribed antibiotics for a URTI^a				
	Facility	3.09	1.84	.09
	Age	1.59	0.37	.004
	Sex	5.19	4.09	.20
	Work area	0.17	1.56	.91
	Professional level	8.34	3.24	.03
	Length of employment in the current hospital	0.36	1.64	.83
	Overall length of	-0.31	1.31	.81

	employment in the current position			
	Training	3.68	4.28	.39
	ITRABx ^b	1.58	2.69	.54
	ITPABx ^c	Constrained	Constrained	Constrained
Proportion of weekly visits during which physicians estimated they would prescribe antibiotics				
	Facility	1.19	2.31	.61
	Age	1.11	0.46	.001
	Sex	10.64	5.16	.03
	Work area	-2.83	1.97	.15
	Professional level	5.77	4.08	.02
	Length of employment in the current hospital	1.97	2.07	.34
	Overall length of employment in the current position	-1.03	1.65	.53
	Training	-8.13	5.39	.13
	ITRABx	2.36	3.38	.39
	ITPABx	0.65	0.78	.41

^aURTI: upper respiratory tract infection; ^bITRABx: intention to reduce antibiotics; ^cITPABx: intention to prescribe antibiotics.

4.1.6. Situational analysis of ASP implementation in hospitals

Among the 200 questionnaires distributed to determine the perceptions of health professionals on AMR, antibiotic use, and ASP, 181 (90.5%) returned the questionnaire. About 106 (58.6%) were physicians, and 41.4% were pharmacists. About 122 (75.8%) of professionals were more than 29 years old (32 ± 4.3), and 124 (77.0%) were male (Table 6).

Out of 200 questionnaires distributed to assess health professionals' perceptions of AMR, antibiotic use, and ASP, 181 (90.5%) were returned. Among the respondents, 106 (58.6%) were physicians, while 41.4% were pharmacists. The majority of professionals, 122 (75.8%), were older than 29 years, with a mean age of 32 ± 4.3 years. About, 124 (77.0%) of the respondents were male (Table 6).

Table 6: Socio-demographic characteristics of health professionals in the hospitals, in 2022, (N=181)

Variables	Frequency (%)
Age in years	18-29
	46 (25.4)
	30-64
	135 (74.6)
	Total
	181 (100)
Sex	Male
	138 (76.2)

	Female	43 (23.8)
	Total	181 (100)
Facility	FHRH	46 (25.4)
	TGSH	68 (37.6)
	DMCSH	31 (17.1)
	IGH	16 (8.8)
	FSGH	20 (11)
	Total	181 (100)
Work area	Medicine	29 (16)
	Surgery	29 (16)
	Pediatrics	28 (15.5)
	Gyne/obs	20 (11)
	Pharmacy	75 (41.4)
	Total	181 (100)
Position/profession	Physician	106 (58.6)
	Pharmacy	75 (41.4)
	Total	181 (100)
Work experience in the current hospital	Overall	3.7±2.3
	<5 years	137 (75.7)
	≥5 years	44 (24.3)
	Total	181 (100)
Work experience in the current position	Overall	4.5±4.1
	<5 years	123 (68)
	≥5 years	58 (32)
	Total	181 (100)
Average number patients treated/dispensed per week	34997	254±198
Average number patients treated or dispensed with at least one antibiotic per week among visits	23415(66.9%)	204±135

When assessing health professionals' views on AMR, 163 (90.1%) recognized AMR as a major issue in Ethiopia, and 161 (89.0%) acknowledged its global significance. In contrast, only 53 (29.3%) and 52 (28.7%) agreed that more than 30% of MRSA cases and gram-negative infections, respectively, in their hospital exhibit high drug resistance. Additionally, 128 (70.7%) considered AMR a serious concern within their hospital, and 109 (60.2%) reported that AMR affects their everyday clinical practice (Figure 14).

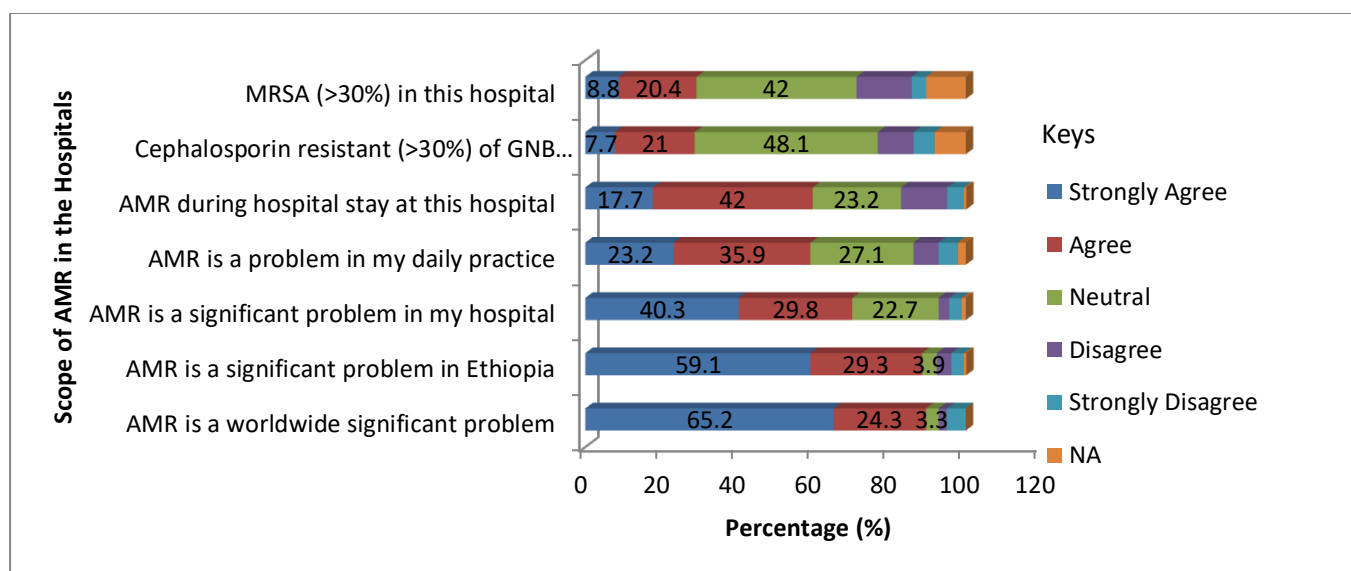


Figure 14: Belief on scope of AMR among health professionals in hospitals, 2022, (N=181)

Regarding factors contributing to AMR, 155 (85.6%) of health professionals agreed that easy access to antibiotics plays a major role, and 137 (75.7%) identified inappropriate antibiotic use as a significant contributor. Additionally, 119 (65.7%) believed that insufficient diagnostic testing in their hospital leads to antibiotic overuse. About 126 (69.6%) felt that patient cost considerations influence their antibiotic selection, while 111 (61.3%) reported that antibiotic availability, rather than local antibiogram data or the underlying cause of infection, often guides their choice of antibiotics (Table 7).

Table 7: Beliefs on factors contributing to antibiotic resistance among health professionals in hospitals, 2022, (N=181)

Statements	Frequency (%) of responses on each statement					
	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	NA
Beliefs on factors contributing to antibiotic resistance in the hospitals						
Improper antibiotic use is a key driver of resistance in this hospital.	76(42)	61(33.7)	29(16)	10(5.5)	4(2.2)	1(0.6)
Easy, prescription-free access to antibiotics drives resistance in Ethiopia.	112(61.9)	43(23.8)	10(5.5)	6(3.3)	9(5)	1(0.6)
Broad-spectrum antibiotic use is linked to resistance in this hospital.	50(27.6)	54(29.8)	46(25.4)	13(7.2)	16(8.8)	2(1.1)
The hospital performs adequate surveillance for drug-resistant organisms.	5(2.8)	14(7.7)	31(17.1)	60(33.1)	67(37)	4(2.2)
Lack of diagnostic tests leads to antibiotic overuse.	63(34.8)	56(30.9)	30(16.6)	19(10.5)	11(6.1)	2(2.2)
Staff receive proper education on antibiotic use and resistance.	12(6.6)	11(6.1)	33(18.2)	62(34.3)	61(33.7)	2(2.2)
Some antibiotics may be low quality and ineffective.	10(5.5)	17(9.4)	50(27.6)	60(33.1)	41(22.7)	3(1.7)

Irregular antibiotic supply causes therapy interruptions, increasing resistance.	28(15.5)	62(34.3)	50(27.6)	27(14.9)	13(7.2)	1(0.6)
Poor clinical follow-up during treatment contributes to resistance.	38(21)	67(37)	40(22.1)	26(14.4)	8(4.4)	2(1.1)
Patient demands lead to antibiotic overuse.	20(11)	48(26.5)	58(32)	33(18.2)	20(11)	2(1.1)
Poor infection control spreads resistance.	30(16.6)	75(41.4)	39(21.5)	27(14.9)	9(5)	1(0.6)
Hand hygiene compliance is acceptable.	23(12.7)	41(22.7)	48(26.5)	44(24.3)	25(13.8)	
Cleaning protocols for rooms and equipment after resistant cases are followed.	11(6.1)	27(14.9)	49(27.1)	51(28.2)	39(21.5)	4(2.2)

NA: not applicable

Regarding antibiotic prescribing and dispensing practices, 57.5% of health professionals reported routinely switching intravenous antibiotics to oral forms after about three days. However, 55.8% often prescribe broad-spectrum antibiotics empirically due to delayed microbiology lab results. Additionally, 44.8% of physicians do not regularly consider local antibiotic susceptibility patterns, 47.5% do not routinely review lab results when prescribing, and 46.4% believe lab results are not communicated promptly (Table 8).

Table 8: Believe on antibiotics prescription/dispensing practices among health professionals in hospitals, 2022, (N=181)

Statements	Frequency (%) of responses on each statement					
	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	NA
Antibiotics prescription/dispensing practices						
Antibiotic choice often influenced by availability, not local antibiograms or infection cause.	39(21.5)	72(39.8)	33(18.2)	18(9.9)	18(9.9)	1(0.6)
Patient costs affect antibiotic selection.	41(22.7)	83(45.9)	26(14.4)	12(6.6)	17(9.4)	2(1.1)
Microbiology results are timely communicated.	9(5)	32(17.7)	43(23.8)	41(22.7)	43(23.8)	13(7.2)
Regularly consider susceptibility patterns when prescribing.	5(2.8)	39(21.5)	46(25.4)	44(24.3)	37(20.4)	10(5.5)
Step down IV to oral antibiotics when appropriate after 3 days.	33(18.2)	71(39.2)	38(21)	28(15.5)	11(6.1)	0
Switch broad- to narrow-spectrum antibiotics when appropriate after 3 days.	24(13.3)	44(24.3)	50(27.6)	40(22.1)	22(12.2)	1(0.6)
Restrictions may limit quality of care.	19(10.5)	60(33.1)	38(21)	42(23.2)	22(12.2)	0
Empirically prescribe broad-spectrum antibiotics due to suspected resistance or delayed lab results.	12(6.6)	44(24.3)	43(23.8)	49(27.1)	28(15.5)	5(2.8)
Routinely check microbiology results to guide treatment.	46(25.4)	55(30.4)	18(9.9)	39(21.5)	17(9.4)	6(3.3)
In the past week, prescribed broad-spectrum antibiotics >3 days for varying patient percentages (<10%, 10–50%, >50%).	10(5.5)	40(22.1)	35(19.3)	47(26)	39(21.5)	10(5.5)

Antibiotic choice often influenced by availability, not local antibiograms or infection cause.	13(7.2)	38(21)	50(27.6)	44(24.3)	26(14.4)	10(5.5)
Patient costs affect antibiotic selection.	14(7.7)	38(21)	47(26)	45(24.9)	24(13.2)	13(7.2)
Microbiology results are timely communicated.	16(8.8)	36(19.9)	43(23.8)	47(26)	26(14.4)	13(7.2)

More than half (51.4%) of health professionals hold a positive view of ASP in hospitals. Around 73.5% agree that ASP helps reduce hospital stay length and costs and improves patient care quality. However, only 16.0% see ASPs as a barrier to good care, and 22.2% think that only prescribing doctors need to understand ASPs (Table 9).

Table 9: Perception on implementation of ASP among health professionals in hospitals, 2022, (N=181)

Statements	Frequency (%) of responses on each statement					
	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	NA
Perception on Implementation of ASP						
ASPs (ASP) improve quality of patient care	70(38.7)	63(34.8)	29(16)	2(1.1)	7(3.9)	10(5.5)
ASP reduces overall antibiotic consumption and can result in cost savings	61(33.7)	68(37.6)	31(17.1)	10(5.5)	5(2.8)	6(3.3)
ASP reduces duration of hospital stay and associated costs	52(28.7)	85(47)	19(10.5)	13(7.2)	7(3.9)	5(2.8)
ASP reduce the problem of antibiotic resistance	61(33.7)	65(35.9)	29(16)	13(7.2)	7(3.9)	6(3.3)
ASP has impact on an institution's nosocomial infection rates	39(21.5)	79(43.6)	41(22.7)	9(5)	6(3.3)	7(3.9)
This hospital has the capacity to establish and implement an effective ASP	35(19.3)	58(32)	47(26)	24(13.3)	11(6.1)	6(3.3)
My individual efforts in antibiotic stewardship can significantly impact this hospital's antibiotic resistance problem	37(20.4)	68(37.6)	46(25.4)	19(10.5)	7(3.9)	4(2.2)
I would like to receive more feedback on my antibiotic selection	37(20.4)	84(46.4)	31(17.1)	20(11)	4(2.2)	5(2.8)
ASPs can be an obstacle to good patient care	12(6.6)	17(9.4)	38(21)	60(33.1)	51(28.2)	3(1.7)
ASPs override prescribers' decision autonomy	10(5.5)	27(14.9)	57(31.5)	56(30.9)	27(14.9)	4(2.2)
I do not have enough time to further invest into ASP	7(3.9)	23(12.7)	50(27.6)	66(36.5)	29(16)	6(3.3)
Infectious diseases experts that can provide guidance in antibiotic selection and prescription are available in this hospital	21(11.6)	27(14.9)	39(21.5)	54(29.8)	36(19.9)	4(2.2)
Additional staff education on antibiotic prescribing and use is needed in this hospital	64(35.4)	59(32.6)	26(14.4)	19(10.5)	12(6.6)	1(0.6)
Prescribing physicians are the only professionals who need to understand antibiotic stewardship	20(11)	19(10.5)	15(8.3)	54(29.8)	72(39.8)	1(0.6)
Pharmacists with sufficient training to provide guidance on antibiotics (ex. Antibiotic switches, IV to PO step-down, renal dose adjustments) are available in this hospital	17(9.4)	36(19.9)	36(19.9)	39(21.5)	47(26)	6(3.3)
Implementation of electronic medical recording (e.g., receiving results electronically) can improve effect of ASP	42(23.2)	78(43.1)	45(24.9)	7(3.9)	7(3.9)	2(1.1)

NA: not applicable

Regarding potential interventions to combat AMR in hospitals, a majority of health professionals identified several effective strategies. Specifically, 151 (83.4%) supported education on antibiotic therapy for medical and pharmacy staff; 143 (79.0%) endorsed developing new institutional guidelines for empiric antibiotic use; 142 (78.5%) favored implementing prospective audits and feedback; and 137 (75.7%) agreed on the active involvement of the hospital IPC team as well as access to institution-specific antibiograms for treating teams. Additionally, about 108 (59.7%) and 107 (59.2%) believed that antibiotic restriction and antibiotic cycling are effective ASP strategies (Figure 15).

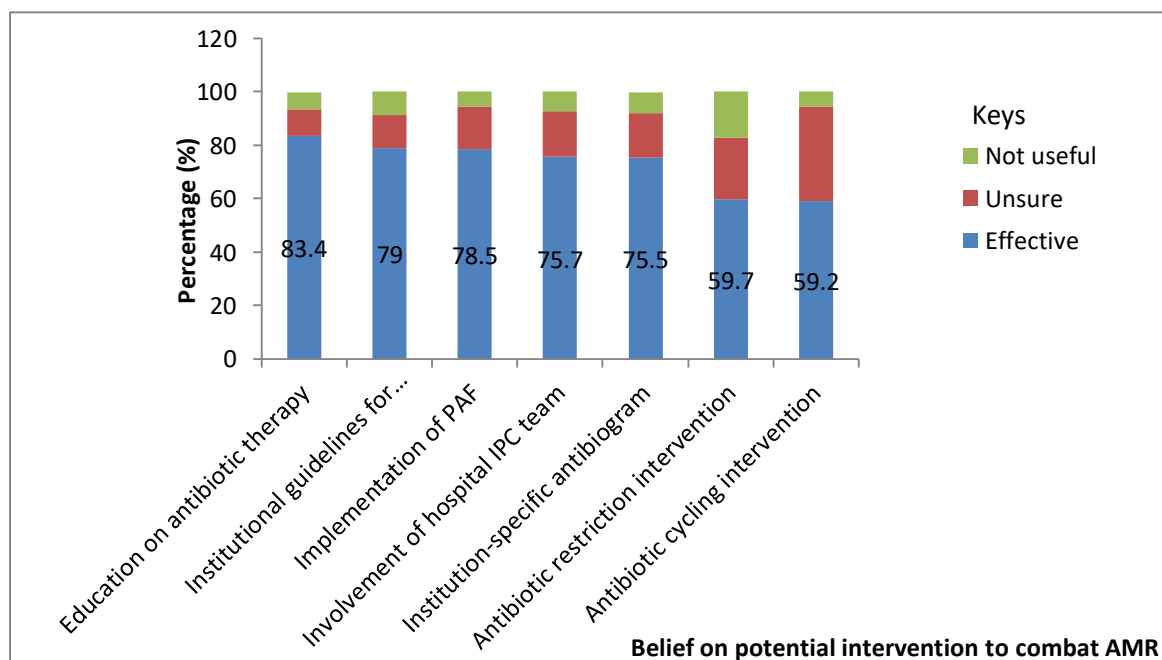


Figure 15 Belief on potential intervention to combat AMR among health professionals in hospitals, 2022, (N=181):

The overall differences in agreement levels between physicians and pharmacists are detailed in **table 7 in article VII**. Additionally, there was a noticeable variation in agreement among health professionals working in hospitals that had initiated ASPs compared to those that had not. Professionals in hospitals with ASP efforts showed greater agreement on statements such as “AMR is a significant problem worldwide” ($P = 0.013$), “Inappropriate antibiotic use is a major cause of antibiotic resistance in this hospital” ($P = 0.034$), and “Easy access to antibiotics without a prescription in Ethiopia contributes to antibiotic resistance” ($P = 0.003$). In contrast, those working in hospitals without ASP implementation more strongly agreed with the views that “The lack of adequate diagnostic testing leads to antibiotic overuse” ($P = 0.035$) and “My antibiotic choices are often influenced by drug availability” ($P = 0.012$).

Among the five hospitals assessed, three had initiated ASP activities, with FHCSH and TGSH maintaining active ASP committees during the data collection period. Although the programs had not yet met all the core requirements for full ASP implementation, multidisciplinary teams were in place at both FHCSH and TGSH. These teams included representatives from physicians, pharmacists, infection prevention units, quality assurance, microbiology, nursing, and IT departments—though TGSH's team did not include IT staff and lacked epidemiologists. In both hospitals, the ASP committees were chaired by internists, with clinical pharmacists serving as secretaries. Overall, four of the five hospitals expressed a commitment to either enhancing current ASPs or initiating new ones. Proposed focus areas for ASP activities included internal medicine wards, intensive care unit, recovery rooms, pediatric units, and operating rooms at FHCSH and IGH—areas commonly associated with frequent prescribing of reserve antibiotics.

Across all hospitals, there was no established system for formally reviewing the appropriateness of antibiotic use within 48–72 hours of initiation. Instead, assessments were typically limited to routine morning sessions and daily ward rounds. Only two hospitals (DMCSH and FHCSH) had antibiograms available; however, there were no structured efforts to track AMR trends. At FHCSH, antibiograms were updated quarterly but lacked formal clinical review and interpretation. TGSH had made initial efforts to conduct culture and sensitivity testing, but due to persistent supply shortages, antibiograms had not yet been generated. The absence of adequate laboratory infrastructure for performing culture and sensitivity testing remained a significant challenge across all sites. Moreover, apart from isolated evaluations of vancomycin use (at DMCSH and FHCSH), ceftriaxone use (at FHCSH and TGSH), and attempts to adapt the WHO AWaRe classification (at DMCSH and FHCSH), none of the hospitals had a comprehensive system to monitor antibiotic use patterns.

The evaluation of ASP implementation at FHRH and TGSH revealed that only limited progress had been made toward meeting the seven core elements recommended for ASPs. Of these, the two hospitals had made the most progress in ensuring accountability and including drug experts within the ASP team. However, other essential components showed minimal achievement: leadership engagement was observed in only 4 out of 16 indicators, implementation of actions to enhance antibiotic use scored 8 out of 22, tracking activities scored 8 out of 18, reporting was 2 out of 6, and education-related efforts were just 1 out of 6. Notably, neither hospital had instituted a formal system for conducting prospective audits or providing feedback focused on specific infections or antibiotic

classes. Additionally, there was no structured mechanism in place to improve antibiotic use or monitor antibiotic consumption and resistance trends, as detailed in Article VII.

4.2. Discussion

Infectious diseases pose a significant threat to both national and global security, and their epidemiology has changed markedly over the years [148,149]. Estimating trends in and mortality from bacterial infections facilitates communication among stakeholders and raises awareness, encouraging healthcare professionals and policymakers to support efforts to combat AMR [150]. Therefore, integrating the assessment of infectious disease epidemiology (a key approach to understanding AMR and curbing the spread of infectious diseases) with antibiotic consumption, which is a major driver of AMR, is a crucial strategy for containing AMR. This is essential to controlling both prevalent and emerging infectious diseases globally [151, 152]. Given the strong relationship between antibiotic consumption and resistance [5, 153, 154], the key findings on admissions and mortality from bacterial infections, antibiotic consumption, trends in AMR, antibiotic prescribing behavior and the situational analysis and readiness of hospitals' to implement ASPs are discussed in sequence hereafter.

The current study revealed that bacterial infections accounted for 39,666 (20.1%) of all hospital admissions. This is comparable to a study in Norway, which reported that 22% of hospital admissions were due to bacterial infections [8], and a study in Uganda, where approximately 28% of admissions were for infectious diseases, the majority of which were bacterial in origin [155]. In contrast, a prevalence of 8.9% was reported for bacterial infections among febrile infants during COVID-19 in 97 hospitals in the USA and Canada [156], which is lower than the findings of the current study. However, the prevalence of bacterial infections can be much higher (28%) among patients in intensive care units [157], and immunocompromised patients, as seen in global studies on cirrhosis patients, where the prevalence reached 57% [158].

Sepsis/septic shock (11,845 (29.9%)), pulmonary tract infections (10,236 (25.8%)), intra-abdominal infections and abscesses (6,257 (15.8%)), and CNS infections (3,275 (8.3%)) were the most common bacterial infectious syndromes in the hospitals. A study in Norway reported pneumonia (35.4%), urinary tract infections (30.6%), sepsis (18.8%), and intra-abdominal infections (7.8%) as the top four bacterial infectious syndromes in hospitals [8]. According to a global report on bacterial infections, pulmonary tract infections, bloodstream infections, and peritoneal/intra-abdominal infections were the three most common infectious disease syndromes [6]. A study in Nepal reported that 86% of deaths

were attributable to bacterial infections, with 47.3% caused by pneumonia, followed by sepsis (44.6%) and meningitis (34.1%) [9].

In the current study, bacterial infections were responsible for 2,763 (21.2%) of overall mortalities, with bloodstream infections accounting for 1,248 (45.2%), pulmonary tract infections for 589 (21.3%), and CNS infections for 417 (15.1%). These findings are similar to those of the Nepalese study, where pneumonia (49.3%), sepsis (46.5%), and meningitis (4.2%) were common causes of mortality [9]. The difference in ranking may be attributed to variations in population dynamics such as age, population density, immunity levels, and demographic trends, etc. In southern Ethiopia, communicable diseases accounted for 49.2% of total mortalities, with tuberculosis alone responsible for 16.8% of total deaths [10]. It was indicated that respiratory tract infections, bloodstream infections, and peritoneal/intra-abdominal infections accounted for more than 75% of the estimated 7.7 million bacterial-related deaths globally in 2019, of which 1.3 million were attributed to AMR bacteria [5].

Overall, trends in bacterial infections increased by 437.8% (from 8,556 cases in 2018 to 11,082 cases in 2022). This contrasts with a study in China, which reported stable incidence rates of infectious diseases from 2010 to 2019 [159], and a 33.5% increase in Brazil from 2012 to 2016 [160]. The current study revealed a 26.3% decrease in mortality, from 687 deaths in 2018 to 506 deaths in 2022. This decline is almost identical to the 20.6% decrease observed in Brazil from 2012 to 2016, but differs from reports in China, which showed a 66.7% decrease from 2008 to 2017 [161] and an 8.76% increase from 2010 to 2019 [159]. The differences in trends for both mortality and morbidity from bacterial infections may be attributed to variations in diagnostic techniques available, availability of effective antibiotics, vaccination and other infection control and prevention measures, as well as population demographic differences, and technological advancements [162]. The WHO has reported a lack of effective treatments for an increasing number of infections, such as urinary tract infections, tuberculosis, and sepsis, in many parts of the world due to resistance [154], which helps explain the differences in infection and mortality rates across regions.

The current study reported varying levels of antibiotic consumption, with EPSS-based data showing 30.3 DIDs (an average of 5.3 DIDs per year). According to the WHO, from 2015 to 2018, antibiotic consumption ranged from 4.4 to 64.4 DIDs across countries, indicating overuse in some countries and limited access in others, which may be due to limited availability of these life-saving medicines [154]. These findings were in line with the current study reports. It was also lower compared to other studies

in Ethiopia, which reported 58.41 DIDds (average 11.8 DIDds) from 2016 to 2020, and 15.4 DIDds from 2017 to 2019 [46, 163], as well as 241.4 DIDds in Tanzania from 2017 to 2019 [164]. But it was higher than the 19 DIDds reported in Sierra Leone from 2017 to 2019 [165], and antibiotic consumption in African countries from 2015 to 2018, which ranged from 4.4 DIDds in Burundi to 27.3 DIDds in Tanzania [154]. The differences may be attributed to underreporting to the WHO, leading to limited data coverage. The low consumption of antibiotics at EPSS, which could be due to insufficient supply, may cause for a lack of access to essential antibiotics, which can in turn fuel AMR.

Recent studies reported an 87.4% decrease in antibiotic consumption at EPSS (from 6.9 to 0.9 DIDds). The decrease in consumption at EPSS is consistent with a study in Ethiopia from 2017-2019, which reported an 87.2% reduction from baseline [163]. A study in Southeastern Europe noted a 33.8% decline in antibiotic consumption from 2011 to 2019 [166], while a study in Tanzania reported a 29.3% reduction from 2017 to 2019 [164], which are lower than the current findings from EPSS. However, these results differ from the 16.4% increase in antibiotic consumption in Ethiopia from 2016 to 2020 [146], as well as from global antibiotic consumption trends, which saw a 39% rise between 2000 and 2015 (from 11.3 to 15.7 DIDds), and a 46% increase from 2000 to 2018 [5, 167]. In Tanzania, antibiotic consumption increased by 610.8% between 2010 and 2016 [168], which is extremely higher than current studies. Global antibiotic sales were also reported to be positively correlated with the number of COVID-19 cases [169], resulting in increased consumption of antibiotics. The variations in trends may be attributed to differences in drug supply and the impact of COVID-19.

Classifying antibiotics into Access antibiotics, Watch antibiotics, and Reserve antibiotics is crucial to identifying the most consumed antibiotics [151, 170]. This study revealed 23.4 DIDds (77.1%) of antibiotic consumptions from Access category, and 6.9 DIDds (22.9%) from Watch category. This is in line with national antimicrobial consumption data from the Ethiopian Food and Drug Authority (EFDA), which reported that 67.9% of antibiotics came from the WHO Access category [163], and also in line with WHO's 60% recommendation [5, 170]. In Ghana, Access antibiotics accounted for 63.3%, and Watch antibiotics for 36.7% of total antibiotic consumption [162]. Similarly, a Southeastern European country reported 74.3% consumption of Access category antibiotics and 25.7% Watch antibiotics [166], both consistent with WHO's 60% recommendation [170]. In Tanzania, consumption of Access antibiotics accounted for over 90% of consumption, which is higher than in the current study [164]. The low consumption of Watch antibiotics in this study may be attributed to increased supply of Access antibiotics to primary health care facilities. Although there are significant

variations in the use of AWaRe antibiotics across countries, their classification serves as a useful metric for assessing the appropriateness of antibiotic use [171].

The consumption of Access antibiotics at EPSS decreased by 72.7% (from 5 to 0.5 DIDs) between 2017 and 2022, while Watch antibiotics decreased by 54.3% (from 1.8 to 0.4 DIDs). However, this trend contrasts with a report in Southeastern European country, which reported only an 18.2% decrease in Access antibiotics but a 33.3% increase in Watch antibiotics [166]. Similarly, in Ghana, from 2016 to 2021, the consumption of Access antibiotics decreased by 14.4%, while the consumption of Watch antibiotics increased by 68.3% [172]. Although the figures differ, the downward trend in Access antibiotics at EPSS is similar to the trend observed in Ghana.

According to the WHO's report on antibiotic subgroups from 2015 to 2018, penicillins (J01C), and sulfonamides and trimethoprim (J01E) were the most commonly consumed antibiotics in Burkina Faso and Côte d'Ivoire, while penicillins (J01C) and tetracyclines were the top consumed antibiotics in Tanzania [154]. The current report at EPSS, revealed beta-lactam antibiotics, penicillins (J01C) (14.9 DIDs) and tetracyclines (J01A) (5.3 DIDs), as the most commonly consumed, which is similar to the report in Tanzania [154]. A national EPSS-based study [46] uncovered the most common antibiotic classes as beta-lactam antibiotics, penicillins (J01C), tetracyclines (J01A), and quinolones (J01M), which is similar to the current findings at EPSS.

The DU90% is an inexpensive, flexible, and simple method for assessing the quality of drug prescribing in routine healthcare. It has been proven useful in studying antibiotic use patterns in hospitals by assessing the overall quality of prescribing, and it serves as a basis for more disease- or patient-specific analyses. A higher DU90% indicates increased levels of low-priority prescribing and associated costs, signaling the need for greater use of formularies to enhance prescribing quality and reduce costs [173-176]. This method can also provide comparative data among different facilities and institutions [173]. Accordingly, the current study revealed the consumption of seven antibiotics constituting DU90% at EPSS, only seven antibiotics. Another study based on national hub identified nine antibiotics as making up DU90% [44], which is greater than the current findings at EPSS. Another consumption study based on Ethiopian food and drug administration (EFDA) also revealed the ten most commonly consumed antibiotics [163], which is higher than current study. These variations, including differences from the current reports, could be attributed to differences in infectious diseases and national priorities. In general, there is significant intra- and interregional variation in antibiotic

consumption [154]. Overall, antibiotics worth approximately \$7,281,680.91 were consumed at EPSS over six years. A study in Ghana over six years reported an expenditure of \$2,365,241.00 on antibiotics [172], which is much lower than the current report from EPSS.

In similar way, antibiotic use in hospitals revealed that 296.2 DIDs (an average of 98.7 DIDs) of antibiotics were used during the three years period. According to the WHO, from 2015 to 2018, antibiotic use ranged from 4.4 to 64.4 DIDs across countries, indicating overuse in some countries and limited access in others, which may be due to limited availability of these life-saving medicines [154]. These findings differ from the current report. Hospital-based antibiotic consumption was higher compared to other studies in Ethiopia, which reported 58.41 DIDs (average 11.8 DIDs) from 2016 to 2020, and 15.4 DIDs from 2017 to 2019 [46, 163], as well as 241.4 DIDs in Tanzania from 2017 to 2019 [164], 19 DIDs reported in Sierra Leone from 2017 to 2019 [165], and antibiotic consumption in African countries from 2015 to 2018, which ranged from 4.4 DIDs in Burundi to 27.3 DIDs in Tanzania [154]. The differences may be attributed to underreporting to the WHO, leading to limited data coverage. The high use of antibiotics in hospitals suggests overuse, which can contribute to rising rates of AMR.

Recent studies reported an 11.4% (from 96.2 to 85.2 DIDs) decrease in antibiotic use in hospitals. The decrease in use is consistent with a study in Ethiopia from 2017-2019, which reported an 87.2% reduction from baseline [163], although the magnitude is different. A study in Southeastern Europe noted a 33.8% decline in antibiotic consumption from 2011 to 2019 [166], while a study in Tanzania reported a 29.3% reduction from 2017 to 2019 [164], which are also higher than the current findings in hospitals. However, these results differ from the 16.4% increase in antibiotic consumption in Ethiopia from 2016 to 2020 [146], as well as from global antibiotic consumption trends, which saw a 39% rise between 2000 and 2015 (from 11.3 to 15.7 DIDs), and a 46% increase from 2000 to 2018 [5, 167]. In Tanzania, antibiotic consumption increased by 610.8% between 2010 and 2016 [168], which is extremely higher than current studies. Global antibiotic sales were also reported to be positively correlated with the number of COVID-19 cases [169], resulting in increased consumption of antibiotics. The variations in trends may be attributed to differences in drug supply and the impact of COVID-19.

Classifying antibiotics into Access antibiotics, Watch antibiotics, and Reserve antibiotics is crucial to identifying the most consumed antibiotics [151, 170]. This study revealed 145.3 DIDs (49.1%) of used

antibiotics from Access category antibiotics, while 150.7 DID (51.6%) were Watch category antibiotics. The use of Access antibiotics is lower than national antimicrobial consumption data based on EFDA, which reported that 67.9% consumption from Access category [163]. It was also lower compared with consumption of Access antibiotics accounted for 63.3% in Ghana [162] and 90% in Tanzania [164]. Although WHO recommends 60% from Access category [170] globally, the use of Access and Watch antibiotics varies from 7.8% in China to 61.2% in Slovenia, and from 23.0% in Finland to 77.3% in Iran, respectively [171]. Overall, high use of Watch antibiotics in this study may be attributed to increased ceftriaxone use.

The use of Access antibiotics in the hospitals increased by 35.8% but there was a 49.6% decrease in Watch category antibiotics. However, this trend contrasts with a report in Southeastern European country, which reported an 18.2% decrease in Access antibiotics and a 33.3% increase in Watch antibiotics [166]. Similarly, in Ghana, from 2016 to 2021, the consumption of Access antibiotics decreased by 14.4%, while the consumption of Watch antibiotics increased by 68.3% [172]. According to the WHO's report on antibiotic subgroups from 2015 to 2018, penicillins (J01C), and sulfonamides and trimethoprim (J01E) were the most commonly consumed antibiotics in Burkina Faso and Côte d'Ivoire, while penicillins (J01C) and tetracyclines were the top consumed antibiotics in Tanzania [154]. The current study revealed the most commonly used antibiotics from beta-lactam antibacterials (J01D), 135.1 DIDs (45.6%), beta-lactam antibiotics, penicillins (J01C), 56.87 DIDs (18.5%), and sulfonamides and trimethoprim (J01E), 40.45 DIDs (13.7%), which is different from the WHO's report [154]. A national EPSS-based study uncovered the most common antibiotic classes as beta-lactam antibiotics, penicillins (J01C), tetracyclines (J01A), and quinolones (J01M) [46], which are different from current this study. The difference may be attributed use of ceftriaxone and other cephalosporins use to manage severe infections in hospitals.

A higher DU90% indicates increased levels of low-priority prescribing and associated costs, signaling the need for greater use of formularies to enhance prescribing quality and reduce costs [173-176]. The current study revealed the use of eleven antibiotics constituting DU90% in the hospitals which is higher than seven antibiotics accounted for DU90% in regional public supply hub [189]. A study based on EPSS and EFDA data identified nine antibiotics [44] and ten antibiotics [163] respectively, as making up DU90%, which is lower than the current findings in the hospitals. In Tanzania, the three most commonly consumed antibiotics were doxycycline, amoxicillin, and SXT [164], while in Ghana, they were amoxicillin-clavulanate, cefuroxime, and SXT [172]. In general, there is significant intra-

and interregional variation in antibiotic consumption [154]. The current study reported contrasted findings from the reports in Tanzania and Ghana, may be due to high use of Ceftriaxone in the current study.

In the hospitals, although antibiotic prescribing was not under control of physicians, physicians perceived a high level of antibiotic prescribing (54.8%) for outpatient visits in a week, and about 178 (96.2%) of physicians estimated to prescribe antibiotics at least for one patient among 10 patients with URTIS; thus, 916 (49.5%) patients with URTIs would be prescribed antibiotics. This was high compared with antibiotic prescriptions for 33–36% of monthly outpatient patient encounters in Ghana [177], but lower than 62.6% of antibiotic prescribing for URTIs in India [178], 69.80% in Pakistan [179], and 79.1% [180] in Ethiopia. This supports the deviation of antibiotic prescribing indicators in the African region from the WHO reference targets (30%) [181].

The MTPB model revealed that knowledge of physicians was associated with PBC and SN ($P = 0.000$) but not with attitude ($P > 0.05$) which was against a report from China that revealed that high knowledge is positively associated with attitudes towards rational use of antibiotics [36, 123,] and behavioral intention for containing antibiotic prescriptions [36]. Attitude, SN, and PBC in the current study were not associated with the intention to prescribe or reduce antibiotic prescribing. This was against another study in China which reported a favorable attitude toward higher intention to prescribe antibiotics and a lower intention to reduce antibiotic use [182]. In the current study, knowledge doesn't have an indirect effect on intention to prescribe antibiotics, which is against a report in China that reported indirect effects of knowledge on intentions to prescribe antibiotics and low knowledge on intentions to prescribe antibiotics for URTIs [36].

Overall, Antibiotic prescribing is a complex process and is influenced by many physician-related factors, patient-related factors, and healthcare system-related factors resulting in the variability of antibiotic prescriptions [183-187]. This requires continues training and professional updates to improve the knowledge, attitude, and practice of physicians by familiarizing them with national guidelines on the use of antibiotics and local Anti-biograms, in addition to changing personal paradigms related to the physicians' decision-making [188]. Thus, determining the behavior of physicians will contribute to generating new and more effective strategies for improving antibiotic prescribing and allaying global concern about antibiotic resistance.

Overall, increased use of antibiotics can lead to the emergence and spread of AMR, which is a major threat to global health and human development, affecting our ability to treat a wide range of infections [154]. AMR results in high rates of illness and mortality, especially in LMICs, where access to diagnostics is limited and the prescription and use of antimicrobials are poorly regulated [190]. The use and misuse of antibiotics are key drivers for the emergence of AMR, and this issue has been further exacerbated by the COVID-19 pandemic [191]. One of the aims of ASPs is to monitor antimicrobial consumption, as increased consumption is associated with increased AMR [92]. With this in mind, the current study determined trends in antibiotic consumption and AMR in the catchment areas. Thus, the under-consumption and over-use of antibiotics at EPSS and hospitals, respectively, could have contributed to increase in AMR, which will be discussed in the following paragraphs.

In the current study based on APHI data, the most common sources for bacterial isolation were blood (11,785; 46.87%), urine (6,354; 25.3%), and swabs (1,993; 7.9%). This is consistent with a systematic review conducted in WHO African regions, which identified bloodstream (82.0%), urinary tract (10.0%), gastroenteric (6%), and genital swabs (2.0%) as the most common sample sources [191]. A retrospective analysis from a referral hospital in Southern Ethiopia similarly reported urine (36.2%), pus (27.4%), and blood (18.9%) as the predominant sample sources [192]. At Jimma University Medical Center (JUMC), among patients with nosocomial infections, urine (55.0%), wound swabs/pus (24.2%), blood (15%), and sputum (5.8%) were the most common sources [193]. In contrast, Wolaita Sodo Hospital reported discharges (47.2%), body fluids (21.5%), urine (18.6%), and stool (12.2%) as frequently collected specimens [194]. A national systematic review in Ethiopia also identified urine (28%), discharges (27.0%), and blood (21.0%) as the leading sample types [195]. These variations may be attributed to differences in infection types and institutional practices concerning culture and sensitivity testing.

In this study, bacterial growth was observed in 16,825 (66.9%) of the total samples. Among the positive cultures, gram-negative bacteria were predominant, comprising 12,528 (74.5%) of the isolates. The most frequently identified gram-negative organisms included *Klebsiella pneumoniae* (3,783; 30.2%), *Escherichia coli* (3,199; 25.5%), and *Acinetobacter baumannii* (1,444; 11.5%). Gram-positive bacteria accounted for 4,297 (25.5%) of the isolates, with coagulase-negative staphylococci (CoNS) being the most common (1,765; 40.1%), followed by *Staphylococcus aureus* (1,293; 30.1%) and *Enterococcus* species (870; 18.9%). The overall culture positivity rate was higher than those reported at JUMC (61.5%) [194], tertiary hospitals in Sierra Leone (45%) [174], Wolaita Sodo Hospital (40%)

[182], and the pooled prevalence in an Ethiopian systematic review (29.1%) [20]. Notably, while gram-negative bacteria dominated in the current study, the majority of isolates at Wolaita Sodo Hospital were gram-positive (69.6%) [194], highlighting a key contrast. Regarding commonly isolated pathogens, *S. aureus*, *E. coli*, and *Pseudomonas aeruginosa* were most frequent in Wolaita Sodo Hospital [193]. Similarly, in JUMC and Sierra Leone, frequent isolates included *E. coli*, *K. pneumoniae*, *Pseudomonas* spp., and *S. aureus* [192, 196]. A study from Nepal also reported *Klebsiella* species (42.2%), *Proteus* species (13.6%), and *S. aureus* (16.2%) as dominant isolates [9]. These discrepancies compared to the current findings—where *K. pneumoniae*, *E. coli*, CoNS, *A. baumannii*, and *S. aureus* were most prevalent—may reflect differences in infection types, patient populations, and clinical settings influencing the types and frequencies of bacterial isolates [190].

The current study confirmed a high prevalence of AMR, with 2,738 (59.9%) of the isolates exhibiting resistance. Of these, gram-negative bacteria constituted 1,807 (66.0%) and gram-positive bacteria 931 (34.0%). This overall resistance rate is consistent with findings from a 2019 systematic review in Ethiopia, which reported a 59.7% prevalence of multidrug-resistant bacteria [20]. However, it is notably higher than the 38.4% pooled prevalence reported in a systematic review examining the association between AMR and antibiotic consumption [153]. A study conducted at JUMC, similarly reported that 79.4% of resistant isolates were gram-negative, while 19.6% were gram-positive [192]. At FHCSH, gram-negative bacteria made up 70.3% of resistant isolates, and gram-positive bacteria 29.7%, a pattern that aligns closely with the current findings [55]. Despite differences in exact percentages, gram-negative bacteria consistently show higher resistance rates, as also observed in Southern Ethiopia, where they accounted for 435 (62.8%) of resistant cases [192]. Globally, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* remain the top bacterial pathogens associated with mortality [5, 6].

AMR is a growing global threat, particularly in LMICs, where 40–60% of infections are resistant—significantly higher than the 17% reported in OECD countries [152, 170]. In LMICs, AMR has shown a steady increase over recent decades [197]. Consistently, the current study reported a rise in AMR from 0.2% in 2016 to 29.9% in 2021, despite a slight decline from 33.7% in 2019 to 25.7% in 2020. In contrast, OECD countries showed only a 2% increase in resistance over a decade (from 18% in 2009 to 20% in 2019) across 12 antibiotic-pathogen combinations [198]. Globally, third-generation cephalosporin-resistant *K. pneumoniae*, fluoroquinolone- and cephalosporin-resistant *E. coli*, and

MRSA are leading AMR threats [199]. These pathogens—particularly *E. coli*, *K. pneumoniae*, and *S. aureus*—contribute to the majority of AMR-related deaths, complicating the treatment of bloodstream infections, meningitis, and surgical site infections [198]. In line with global data, the current study found high resistance rates: *A. baumannii* (82.4–100%) to multiple antibiotics; CoNS (89.2–100%) to ciprofloxacin, tetracycline, clindamycin, and others; *Enterobacter* spp. (95.5–100%); *E. coli* (92.5–100%); *K. pneumoniae* (92.4–100%); and *S. aureus* (93.5–100%) to several commonly used antibiotics. These findings reinforce global reports highlighting significant variation in resistance patterns across countries, bacteria, and antibiotic classes [199].

This study identified 571 (20.9%) MDR bacterial isolates among resistant strains—lower than pooled estimates from Ethiopian systematic reviews, which reported 59.7% and 70.5% MDR prevalence [20, 188], including 72.1% in hospital-acquired and 69.8% in community-acquired infections [200]. However, the result aligns with findings from Nepal (26.8%) [9] and with 80.0% MDR gram-negatives reported at one hospital in the study area [55]. Among gram-negative MDR isolates (378; 18.1%), the most frequent were *K. pneumoniae* (133; 35.2%), *E. coli* (86; 22.8%), *A. baumannii* (39; 10.3%), and *Enterobacter cloacae* (37; 9.8%). For gram-positives (195; 20.9%), CoNS (98; 50%), *S. aureus* (46; 23.6%), and *Enterococcus* spp. (27; 14.2%) were predominant. In Nepal, *Klebsiella* (50%) and *Acinetobacter* (30.8%) were the leading MDR gram-negative pathogens, higher than in this study [9]. Globally, the rise of MDR, extensively drug-resistant, and pan-drug-resistant gram-negative bacteria is a growing public health concern [21]. The burden of AMR-related infections has been comparable to that of influenza and tuberculosis, increasing steadily between 2007 and 2015 [201].

Despite AMR being a critical public health threat, significant gaps antibiotic use in hospitals [21]. Assessing hospital ASP implementation, along with identifying challenges and opportunities, remains essential [41, 202-205]. In the current study, health professionals believe that AMR is a significant problem in Ethiopia 163 (90.1%), worldwide 161 (89.0%), and hospitals (70.7%). According to a report from another hospital in Ethiopia, AMR is a problem in Ethiopia (94.6%), worldwide (91.7%), and in the hospitals (85.6%) [41], which is almost similar to the current report but different from a report from among physicians in Ghana, which reported perceived AMR as a global problem (30.1%), a national problem (18.5%), and a problem in their hospital (8.1%) [206]. This supports the fact that AMR is a major global public health concern with serious consequences in LMICs, due to the widespread, and inappropriate use of antibiotics along with inadequate management of pharmaceutical waste [189]. In this study, health professional believe that inappropriate consumption of antibiotics is a

major cause of AMR 137 (75.7%) where easy access to antibiotics without a prescription in Ethiopia contributes to AMR 155 (85.6%), and prescription of broad-spectrum antibiotics is directly linked to AMR 104 (57.5%). This is in agreement with another study at TASH in Ethiopia [41]. Unlike the current study, in Ghana, overuse of antibiotics, self-medication, and uncompleted antibiotic therapy were perceived common causes for AMR [206]. Unless management of infections is optimized and reduce adverse events associated with antibiotic use [207], the problem of AMR will be vicious [208].

Regarding Core elements of ASP, implementation, in the current study, only three hospitals (3 out of 5) attempted to establish ASPs which are core elements of leadership (4 out of 16), action on implementing ASP and improving antibiotic consumption (8 out of 22), tracking (8 out of 18), reporting (2 out of 6), and education (1 out of 6). Although ASPs can be implemented in a variety of contextual ways that are feasible for hospitals, the implementation of the CDC's seven (7) core elements of hospital ASPs will serve as guidance to assist hospitals in starting and expanding ASPs to reduce AMR and CdIs by improving antibiotic prescribing and antibiotic use [72]. Partners across the country are using the implementation of core elements to guide partners in supporting antibiotic stewardship efforts in hospital settings [77]. To optimize the treatment of infections and reduce adverse events associated with antibiotic use enhancing IPC, controlling source control, prescribing antibiotics when they are truly needed, prescribing appropriate antibiotics with adequate dosages, reassessing treatment when culture results are available, using the shortest duration of antibiotics based on evidence, educating staff, supporting surveillance of AMR and HAIs, monitoring antibiotic consumption, and supporting an interdisciplinary approach as core elements of ASP [207]. In fact, implementation of core elements of ASPs in resource limited settings is poor [208].

The hospitals didn't implement a specific strategy and set metrics to evaluate the ASPs except for attempts to evaluate vancomycin use, ceftriaxone use, and customizing antibiotic AWaRe classifications. Different strategies, such as prescriber education, formulary restriction, prior approval, streamlining, antibiotic cycling, and computer-assisted programs, have been proposed to improve antibiotic use [66, 208]. Effective hospital-based ASPs should implement at least one core active strategy: of prospective audit with intervention and feedback or formulary restriction and preauthorization with or without supplementary strategies such as education, guidelines, and clinical pathways; antimicrobial cycling; antimicrobial order forms; combination therapy; streamlining or de-escalation of therapy; dose optimization; and parenteral to oral conversion [4]. The ASP team composition in the current study in line with the recommendations [4, 208], which consist of

physicians, pharmacists, infection prevention, quality assurance, microbiologists, nurses, and/or epidemiologists or information technology professionals in two hospitals that do have active teams at the time of data collection.

The health professionals in the current study believed that ASP improves the quality of patient care 133 (73.5%), reduces overall antibiotic consumption and can result in cost savings 129 (71.3%), reduces the duration of hospital stays and associated costs 137 (75.7%), and reduces the problem of AMR 126 (69.6%). This is an opportunity to implement ASP in hospitals for antibiotic prescription and AMR bacteria [72, 77, 184]. Regarding ASP strategies, health professionals believed that education on antibiotic therapy to medical and pharmacy staff 151 (83.4%), developing new institutional guidelines for empiric antibiotic use 143 (79.0%), implementation of prospective audit and feedback 142 (78.5%), active involvement of hospital IPC team 137 (75.7%), and access to institution-specific antibiogram to treating teams 137 (75.5%) were effective potential interventions to combat AMR in hospitals. Education, which is known to be a supplementary element of comprehensive efforts for improving antibiotic use in hospitals [4, 184], was rated number one to improve antibiotic prescription and AMR bacteria. In fact, the implementation of prospective audits and feedback which is the core strategy for ASPs [4] was believed to be the third strategy in the current study. This might be related to the knowledge gap on the types of strategies for ASPs. Implementation of ASP or relying on the PDSA model to improve the efficiency as well as the likelihood of success of the ASP in the LMICs is recommended [208].

In general, antibiotic prescribing is a complex process and is influenced by many factors [177, 188, 207, 208]. This requires continues training and professional updates to improve the knowledge, attitude, and practice of physicians by familiarizing them with national guidelines on the use of antibiotics and local Anti-biograms, in addition to changing personal paradigms related to the physicians' decision-making [188, 209]. Furthermore, prevention of AMR requires integrated and coordinated multi-sectorial approach encompassing ASP, IPC, surveillance and monitoring, research and innovation, and public awareness and education [210]. Enhancing IPC systems within health facilities, elevating ASP practices, augmenting the capacity for laboratory surveillance of AMR, accessing to essential health services, timely and accurate diagnosis of infectious diseases, appropriate quality-assured treatments and fostering a One Health approach to AMR surveillance that bridges the human and animal health sectors in achieving the Sustainable Development Goals are critical to overcome barriers faced by people and health systems in addressing AMR [211- 213]. ASPs are cost-

effective, reduce AMR, improve clinical and patient outcomes, alter prescribing behavior of physicians without compromising short-term outcomes, and reduce HAIs and associated societal costs [66, 69, 211]. Inclusion of capacity building interventions, improved diagnosis, surveillance and management of AMR pathogens across human and animal health are critical components of ASPs to contain AMR [212-215]. ASP is needed to limit the emergence of AMR, prolong the effectiveness of currently available antibiotics, reduced costs and improve patient outcomes by promoting responsible use of antibiotics [66, 69]. Despite the challenges, implementing contextualized ASP interventions based on available resources is highly recommended [186, 209].

4.3. Strength and Limitations of the Study

The strength of this study lies in its comprehensive approach to examining multiple aspects of antibiotic consumption, from distribution data to hospital-level consumption. It also investigated antibiotic prescription behaviors, along with the current status of ASPs in hospitals and their readiness for ASP implementation. Additionally, the study assessed the core elements of ASPs in hospitals that have attempted implementation.

The study utilized retrospective data collection on bacterial infections, antibiotic consumption, and AMR, which may have certain limitations. Due to financial constraints and lack of funding, the actual implementation of ASPs was not possible. As a result, the research focus shifted from examining the effect of ASPs on antibiotic consumption to evaluating the current status of ASPs. Furthermore, insufficient AMR data in health facilities, coupled with a lack of funds to access existing AMR data, made it impossible to determine the relationship between antibiotic consumption and resistance. To compensate for this, AMR data from the APhi and antibiotic consumption data from the EPSS were used as area-specific indicators of AMR and antibiotic consumption, respectively. A small sample size may have limited the study's ability to establish a relationship between attitudes, SN, and PBC with the intention to prescribe or reduce antibiotic use. This, in turn, was not directly associated with perceived antibiotic prescribing behavior. Additionally, physicians' reluctance and busy schedules in completing questionnaires, internet disruptions, and security issues posed further challenges to the study.

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1. Conclusions

The current study provides critical insights into the burden of bacterial infections, antibiotic consumption and patterns, and AMR in hospitals and public pharmaceutical supply and public institute settings. Bacterial infections contribute significantly to hospital admissions and mortalities, with sepsis, pulmonary infections, and CNS infections being the most prevalent causes. Although overall mortality from bacterial infections has declined, the infection trend has sharply increased, indicating growing infection rates despite reduced fatality. The analysis of antibiotic consumption reveals divergent trends between the EPSS and hospitals. While EPSS reported under-consumption of antibiotics—likely due to supply constraints—hospitals demonstrated high and potentially inappropriate consumption, particularly of Watch category antibiotics, such as ceftriaxone. This overuse in hospitals may be a key driver of AMR in the region. Although a modest decline in antibiotic consumption at both EPSS and hospital levels were seen, the consumption of Watch category antibiotics remains high in the hospitals, surpassing WHO recommendations.

The study also revealed high antibiotics prescribing practice which was not under the volitional control of physicians. The predominant use of cephalosporins in hospital settings also suggests a narrow prescribing pattern that could contribute to resistance. DU90% analysis further indicated more focused supply at EPSS and a variety of antibiotics accounting for the majority of consumption in the hospitals, underlining the need for more balanced and evidence-based use and prescribing practices. Overall, the implementation of antibiotic stewardship programs in the hospitals had positive effect in reducing antibiotic consumption and increasing levels of awareness and positive attitudes among staff related in hospitals attempts to implement the program although its status of implementation was poor. The study underlines the urgent need for strengthening and implementation of ASPs, improved antibiotic supply management, and regulation of hospital antibiotic prescribing practices. Addressing both underuse and overuse of antibiotics is essential to curbing AMR and improving outcomes related to infectious diseases.

5.2. Recommendations

The findings of this study will help address gaps in antibiotic consumption, AMR, and the implementation of ASPs. They can also assist policymakers and healthcare administrators in making informed decisions regarding the implementation and regulation of ASPs. Future studies should focus on collecting patient specific antibiotic use data before the implementation of specific ASP interventions in hospitals. Successful ASPs should incorporate all elements of effective quality improvement programs, including antimicrobial use impact measurement, prescribing audit, and ongoing monitoring of both the processes and outcomes of AMR, in order to provide regular feedback to prescribers.

While this study has identified a potentially feasible set of recommendations to improve antibiotic prescribing and facilitate ASP implementation, further efforts are needed to ensure that these recommendations are operationalized and their impacts evaluated. Based on the findings, the following recommendations are made:

- Develop and implement robust IPC strategies to reduce the growing burden of illness and mortality from bacterial infections
- Devise strategies to align antibiotic distribution and supply systems with the actual needs and consumption patterns of health facilities.
- Establish processes for obtaining expert advice on antibiotic prescribing and allocate resources to support appropriate antimicrobial use.
- Incorporate AMR and ASP topics into pre-service education and ongoing professional development programs for healthcare workers.
- Ensure sufficient funding and budget allocations to allow health facilities to implement ASPs in line with national and international standards.
- Strengthen staff competencies, promote the use of local data for decision-making, and integrate ASP-related activities into routine hospital operations.
- Recognize that reducing inappropriate antibiotic prescribing requires more than knowledge—it demands a systemic, behavior-focused approach to transforming prescribing practices.
- Strong control practice on antibiotic use regulation is highly recommended to prevent unnecessary use and self-medications.

5.3. Directions for further research

The implementation of ASPs alongside IPC strategies is essential for preventing and mitigating the emergence and spread of AMR. This is achieved by optimizing antimicrobial prescribing and treatment—ensuring appropriate selection, dosage, route of administration, and duration. However, challenges such as inefficient supply chains frequently lead to antimicrobial shortages, promoting inappropriate antibiotic use and exacerbating AMR. Decisions regarding antibiotic use require a careful balance between optimizing individual patient outcomes and protecting the public in from AMR. Political and distributive injustices at the population level also influence facility-level decisions and contribute to disparities in antibiotic access and use. Addressing these systemic factors is crucial for designing equitable and effective interventions.

Although AMR is an inevitable consequence of antibiotic use, the rate of resistance development is largely dependent on how and to what extent antibiotics are used. Reducing the overuse and misuse of antibiotics—recognized as the primary drivers of AMR—should be a research priority. This includes exploring the use and resistance potential of new and existing antibiotics, as well as strategies to extend the effectiveness of current treatments. Although not the primary focus of the current study, observations of ASP implementation across health facilities revealed policy gaps that undermine progress in curbing AMR. To reverse this trend, national policies on antibiotic use and ASPs must be strengthened and uniformly enforced.

Furthermore, the combination of low antibiotic consumption from public suppliers and a high burden of infection and AMR underlines the urgent need to better integrate ASPs with:

- Supply chain management
- Infection prevention and control
- Point-of-care diagnostic techniques for bacterial infection identification

Future research should prioritize the development of efficient and secure antimicrobial supply chains that ensure antibiotics are accessible, affordable, and consistently available for treating common infections.

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List of manuscripts articles and manuscripts

Manuscript I

Trends in Morbidity and Mortality from Bacterial Infections in Hospitals in Northwest Ethiopia

Asrat Agalu Abejew^{1,2,*}, Gizachew Yismaw Wubetu³ and Teferi Gedif Fenta¹

¹Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

²School of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia

³Amhara Public Health Institute, Bahir Dar, Ethiopia

*Correspondence: asruphar@gmail.com; Tel.: +251- (0)91-715-6682

Abstract

Background: Morbidity and mortality from bacterial infections are significant components of the burden of disease in Ethiopia. This study aimed to determine the trends in morbidity and mortality from bacterial infections in five hospitals in Northwest Ethiopia from 2018 to 2022.

Methods: A cross-sectional study was conducted based on disease registries in health management information system (HMIS) from July 2017 to June 2022. Bacterial infections were extracted in August 2022, descriptive statistics and trend analysis, and ANOVA was used to compare morbidity and mortality in hospitals with age and sex were computed using linear regression at a p value < 0.05 .

Results: There were 39,666 (20.1%) morbidities and 2763 (21.2%) mortalities due to bacterial infections. Morbidity from bacterial infections increased as a function of $y = -748.79x^2 + 7018.4x - 5438.2$ ($R^2 = 0.9916$), but mortality decreased as a function of $y = 1.5167x^2 - 13.002x + 32.363$ ($R^2 = 0.9494$). Sepsis/septic shock (11,845 (29.9%) for morbidity and 1248 (45.2%) for mortality, and pulmonary tract infections 10,236 (25.8%) for morbidity and 589 (21.3%) for mortality were the most common. Sepsis and pneumonia were the most common causes for morbidity and mortality, with 11,121 (28.0%) and 908 (32.9%), 9882 (24.9%) and 576 (20.8%), respectively. The age of the patients was the sole risk factor for morbidity and mortality, where children < 1 -year-old, 13875 (35.0%) were at risk of admission due to bacterial infections compared 5-14 years old and ≥ 65 years old, with high mean difference (mean difference = 18.5 [95%CI: 14.35- 22.66]) and (mean difference = 18.771 [95% CI: 14.3-23.2]), respectively; at risk of dying 912 (33.0%) compared with 5-14 years and 1 - 4 years with (mean difference = 3.0 [95%CI: 1.72-4.32]) and (mean difference = 2.97 [95%CI: 1.62-4.33]), respectively.

Conclusion: Bacterial infections remain a major public health concern in Northwest Ethiopia, accounting for significant proportions of both morbidity and mortality. Over the five-year period, morbidity showed an increasing trend, while mortality declined. Sepsis and pneumonia were the leading causes of both morbidity and mortality. Age was identified as the only significant risk factor associated with these outcomes. These findings underscore the need for age-targeted interventions and enhanced infection prevention and control strategies to reduce the burden of bacterial infections in healthcare settings.

Keywords: infectious diseases; morbidity; mortality; burden; inpatient wards; HMIS

Introduction

Infectious diseases are the major sources of morbidity and mortality and serious health issues [1–3]. Although they are present everywhere [3], bacterial diseases are the most common causes of morbidity and mortality, in low- and middle-income countries (LMICs) [2,3]. Approximately 56.2% of all infection-related deaths and 13.6% of all deaths worldwide are caused by bacterial illnesses [4]. Antibiotic-resistant (AMR) bacteria pose a severe danger to global health [4] and cause millions of deaths [5]. The magnitude of infection from resistant bacteria increased significantly between 2016 and 2020 [6], and projected to be the cause of approximately 10 million annual fatalities, with a USD 100 trillion economic loss by 2050 with a greater impact in LMICs [7]. Bacterial infections in Ethiopia contributed up to 95.8% of all neonatal illnesses from 2018 to 2019 [8], and reports from 2010 to 2012 showed that they were the cause of death for more than 25% of all-cause mortalities in the inpatient wards in a referral hospital [9].

Bacterial infections are the second leading cause of death worldwide [4]. The number of cases and case fatalities linked to a particular infection has been used to gauge how infectious diseases affect population health [10]. If the morbidity and mortality associated with bacterial infections are determined stakeholders will easily communicate and raise awareness to tackle the major sources of health loss from infectious diseases, by increasing healthcare professionals' and policymakers' adherence to containment techniques and supporting initiatives [4,10]. In cognizant of this, the International Classification of Diseases 10 (ICD-10) [11], which could be tailored to distinct syndromes [4,12] in different areas, was created by the World Health Organization (WHO). The high rate of AMR warrants the need for regular epidemiological surveillance and implementation infection control measures and antimicrobial stewardship program [13].

Bacterial infections are common causes of in-hospital admissions, resulting in 7.7 million deaths globally among which 1.86 million were in Africa [2, 14–16]. Sub-Saharan Africa had the largest burden, with an average of 230 deaths per 100,000 people [4, 17]. Lower respiratory tract infections are the greatest cause of mortality in Sub-Saharan Africa [18]. In Africa, 1.05 million deaths were associated with AMR [16], where in Sub-Saharan Africa, the mortality rate from AMR bacteria was 27.3 per 100,000 [5]. The most frequent causes

of morbidity [12] and mortality [4] were attributed to *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [4,12,13].

Bacterial infections, including healthcare-associated infections (HAIs), are prevalent and major causes of death in Ethiopia [8, 14, 18-23]. In Ethiopia, there were 21,200 deaths attributable to AMR and 85,300 deaths associated with AMR [24], which included cases from *K. pneumoniae* (15,800), *S. pneumoniae* (15,000), *E. coli* (13,100), *S. aureus* (10,200), and *Group B Streptococcus* (4,700) [25]. On the other hand, infection prevention practice and ASP implementation in Ethiopia are either very poor or lacking [13,25].

Despite reported trends alarming increase in AMR [26, 27], and high prevalence of specific bacterial disease syndromes, comprehensive analysis of bacterial infections in Ethiopia is still lacking [21,28,29]. Without changes evidence on infectious disease patterns, clinical or public health practice may suffer from inappropriate on expenditure, introduce unexpected externalities, and put an additional load on the healthcare system, impacting performance [10]. It is crucial to determine the burden of illnesses from infectious disease on healthcare services and the implement of evidence based antimicrobial stewardship programs integrated with infection prevention and control practices which are very poor in Ethiopia [13,25]. Thus, the purpose of this study is to determine the trends in morbidity and mortality from bacterial infections in the inpatient wards of five hospitals in Northwest Ethiopia.

Methods

Study Area and Period

A retrospective cross-sectional study was conducted in August 2022 in five hospitals in Northwest Ethiopia. The hospitals were Tibebe Ghion Specialized Hospital (TGSH), Felege Hiwot Comprehensive Specialized Hospital (FHSCH), Finote Selam General Hospital (FSGH), Injibara General Hospital (IGH), and Debre Markos Comprehensive Specialized Hospital (DMSCH), with the last only providing mortality data. These hospitals are among the 81 hospitals in the Amhara National Regional State [30]. The hospitals provide integrated services to patients in their outpatient departments, emergency triage assessment and treatment departments, inpatient departments, and neonatal intensive care units. Since we used the Ethiopian fiscal year, it should be understood that 2010=2017/18, 2011=2018/19, 2012=2019/20, 2013=2020/21, and 2014=2021/22, and for the sake of convenience, we used the next year in the figures, i.e., 2018-2022.

Study Participants

The study covered all bacterial infections among patients who were admitted to inpatient wards in the hospitals between July 2017 and 30 June 2022. Those data that did not identify inpatient admissions and outpatient visits were excluded from the study. The study included data for FHSCH that were available from July 2017 to June 2022; however, data were available for three hospitals (TGSH, FSGH, and IGH) from July 2018 to June 2022 but for DMSCH, although data were available from July 2017 to June 2022, neither inpatient nor outpatient status was determined. As a result, only mortality data from July 2017 to June 2022 were included from DMSCH. Bacterial infections were identified among all causes of admission using the HMIS coding and ICD-10 [11]. Thus, the study included infections that were specifically identified as being bacterial and those known to be mostly bacterial. Finally, morbidity and mortality were identified and categorized into syndromes based on standard textbooks [1,31] and the literature [4,5]. Additionally, senior physicians who specialized in internal medicine and pediatrics were consulted.

Data Collection Process

The data were obtained from hospitals based data registered in the health management information system (HMIS) records from July 2017 to 30 June 2022 as part of a larger inquiry for antimicrobial stewardship program (ASP) implementation. In 2017, data from only one hospital were included, but during the last three years, data were included from all hospitals (one hospital started service in 2018–2019). HMIS data from each hospital were collected in Excel format and combined in one template prepared for extraction process. The template was prepared based on the ICD-10 and includes, facility, year, demographic characteristics of patients, disease category, name of infection, and outcomes (morbidity and mortality), among others. Then, infectious disease were sorted and extracted from compiled HMIS data from all hospitals. Although accuracy of diagnosis and the cause for death was not evaluated, the disease burden associated with and attributable to morbidity and mortality for 15 major infectious syndromes (pulmonary tract infections, bloodstream infections, diarrheal diseases, tuberculosis, bacterial infections of the skin and subcutaneous systems, peritoneal and intra-abdominal infections, meningitis and other central nervous system (CNS) infections, endocarditis and other cardiac infections; infections of bones, joints, and related organs, typhoid and invasive *Salmonella* infections, urinary tract infections, pyelonephritis, and cystitis, sexually transmitted infections, surgical site infections, and other zoonotic bacterial infections), and bacterial infections of unspecified syndromes were classified.

Data Analysis and Presentation

The Excel data were imported to SPSS version 20 and then cleared and analyzed. Descriptive statistics such as frequency and percent were computed. In addition, trend analysis, ANOVA, and linear regression tests were used to determine the association between morbidity and mortality and demographic variables at a p value of 0.05. Total admissions and mortality were used to calculate the prevalence of morbidity and mortality from bacterial infections.

Ethical Consideration

Before the study, ethical approval was obtained from the ethical review board of Addis Ababa University, the College of Health Sciences (protocol code: ERB/SOP/472/14/2022), and the School of Pharmacy (protocol code: 106/22/SoP). A support letter to the hospitals was obtained from the Amhara Public Health Institute (APHI). Since these were secondary data, informed consent was not obtained. All data obtained were kept confidential and used only for research purposes. Thus, ethical issues were considered in order not to disclose data to persons outside the research team.

Results

All inpatient admissions and mortalities from bacterial infections were included in the study except for one hospital from which only mortality was included. During the last five years, there were approximately 197,576 admissions and 13,051 (6.7%) mortalities. Overall, the all-cause admission trend in the hospitals increased and projected to decline as a function of $y = -3442.4x^2 + 34452x - 25975$ ($R^2 = 0.99$).

Sociodemographic Characteristics of Patients with Bacterial Infections

The majority of the patients were male (23,154 (58.4%)), and 16,512 (41.6%) were females. The majority were children < 1 year old, 13,875 (35%), followed by 30–64 years old, 9322 (23.5%), and 15–29 years old, 7591 (19.1%). The majority of the infections were from FHSCH, 15337 (38.7%), and from IGH, 8851 (22.0%), whereas the majority of mortalities were from FHSCH, 1644 (59.5%), and DMSCH, 585 (21.2%) (Table 1).

Table 1: Socio-demographic characteristics and distribution of bacterial infections (July 2017-June 2022) in hospitals in Northwest Ethiopia

Variables		Frequency (%)
Sex of patients	Female	16512 (41.6)
	Male	23154 (58.4)
	Total	39666 (100)
Age of patients	< 1 year	13875 (35)
	1 - 4 years	3797 (9.6)
	5 - 14 years	2812 (7.1)
	15 - 29 years	7591 (19.1)

	30 - 64 years	9322 (23.5)
	>=65 years	2269 (5.7)
	Total	39666 (100)
Distribution in years	2018	689 (1.7)
	2019	6975 (17.6)
	2020	9245 (23.3)
	2021	11169 (28.2)
	2022	11588 (29.2)
	Total	39666 (100)
Distribution of total morbidity in hospitals	DMCSH	585 (1.5)
	FHRH	15337 (38.7)
	FSGH	6970 (17.6)
	IGH	8849 (23.5)
	TGSH	7923 (19.7)
	Total	39666 (100)
Distribution of Distribution of total mortality in hospitals	DMCSH	585 (21.2)
	FHRH	1644 (59.5)
	FSGH	158 (5.7)
	IGH	164 (5.9)
	TGSH	212 (7.7)
	total	2763 (100)

Trends in Morbidity from Bacterial Infections

Morbidity from bacterial infections increased from 33.5% in 2018/19 to 37.5% in 2021/22. The prevalence of morbidity from bacterial infections accounted for 39,666 (20.1%) cases from which 11082 (27.99%) and 10466 (26.4%) were in 2022 and 2021, respectively. During the last 5 years, bacterial infections increased linearly as a function of $y = -748.79x^2 + 7018.4x - 5438.2$ ($R^2 = 0.9916$) (Figure 1). The trend is also similar in specific hospitals (figure 2).

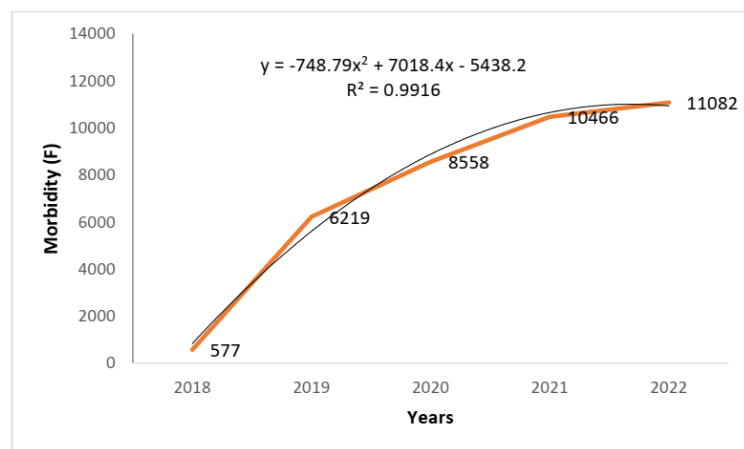


Figure 1. General trend in morbidity from bacterial infections (July 2017-June 2022) in hospitals in North-west Ethiopia (N=39,666).

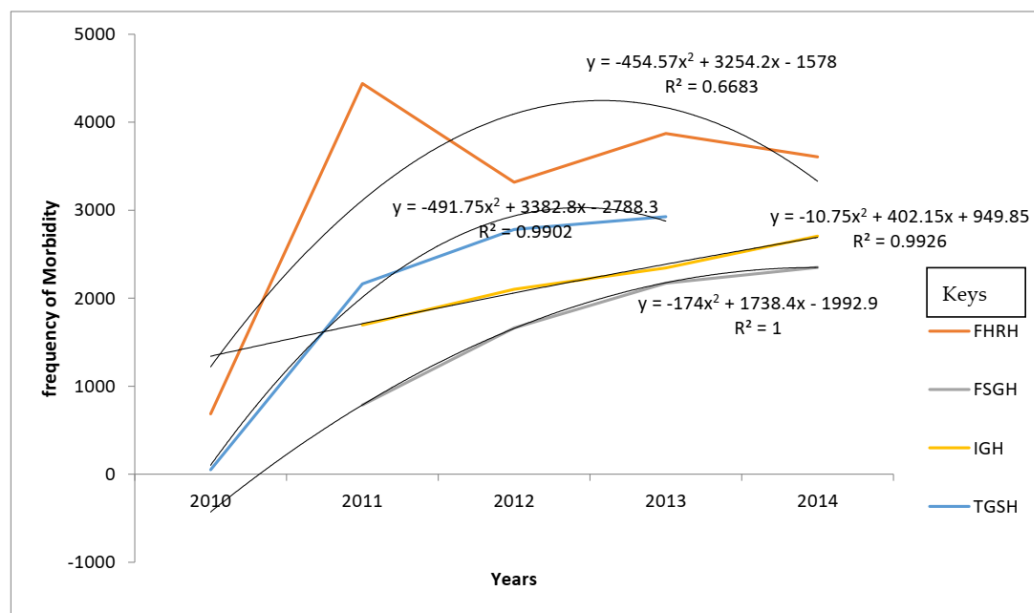


Figure 2. Trends in morbidity from bacterial infections (July 2017-June 2022) in each hospitals in Northwest Ethiopia (N=39,666).

The most common syndromes of bacterial infections were sepsis or septic shock, 11,845 (29.9%), and pulmonary tract infections, 10,236 (25.8%), followed by intra-abdominal infections and abscesses, 6257 (15.8%). Zoonotic bacterial infections, 95 (0.24%), and typhoid fever/Salmonella typhi infections, 80 (0.2%), were the least common (Table 2).

Table 2. The most common infectious syndromes (July 2017 to June 2022) in hospitals in Northwest Ethiopia (N = 39,666).

Bacterial Infection Syndromes	Frequency (%)
Sepsis/septic shock	11,845 (29.9)
Pulmonary tract infection	10,236 (25.8)
Intra-abdominal infections and abscess	6257 (15.8)
CNS infections	3275 (8.3)
Infections of skin, muscles, and soft tissues	1713 (4.3)
Endocarditis and other cardiac infections	1430 (3.6)
Eye, ear, nose, throat, or mouth infection	1235 (3.1)
Tuberculosis	1214 (3.1)
Infections of bones, joints, and related organs	767 (1.9)
Genitourinary tract infections	687 (1.7)
Surgical site infections	631 (1.6)
Sexually transmitted diseases	238 (0.6)
Zoonotic bacterial infections	95 (0.24)
Typhoid/Salmonella typhi infections	80 (0.2)
Other bacterial infections not specified	1250 (3.2)
Total	39,666 (100)

CNS: central nervous system infections

The most common specific bacterial infections were sepsis, 11,121 (28.0%), and pneumonia, 9882 (24.9%), followed by appendicitis, 4202 (10.6%). Urinary tract infections, 453 (1.1%), tetany/tetanus, 399 (1.0%), furuncle and carbuncle, 323 (0.8%), pyelonephritis, 288 (0.7%), and pyoderma gangrenosum, 219 (0.6%), were the least common (Figure 3).

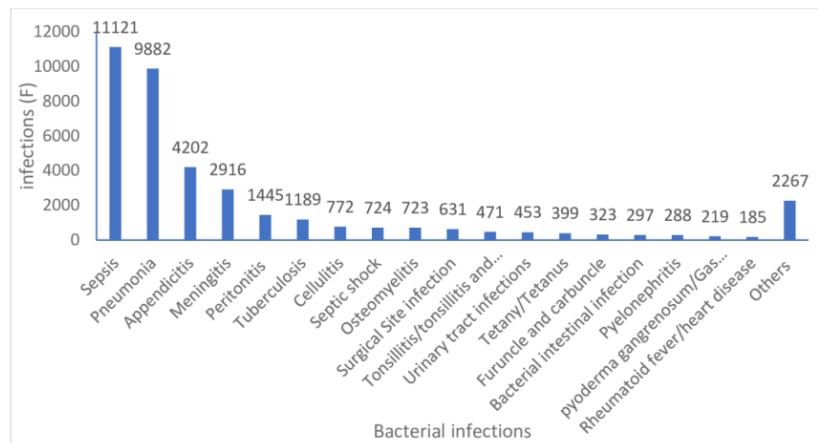


Figure 3. The most common bacterial infections (July 2017-June 2022) were in hospitals in Northwest Ethiopia (N=39,666). Others: abscesses, syphilis, orchitis and epididymitis, typhoid fever, cystitis, enteritis, impetigo, STIs, endocarditis, gonorrhea, anthrax, shigellosis, Lyme disease, chlamydial infection, botulism, co-infections and unspecified infections.

Trends in Mortality from Bacterial Infections in the Hospitals

The overall prevalence of mortality was 2763 (21.2%). The prevalence of mortality among bacterial infections was 7.0%. In 2017/18, it was 162 (21.9%); in 2018/19, it was 706 (10.2%); in 2019/20, it was 687 (7.4%); in 2020/21, it was 702 (6.3%); and in 2021/22, it was 506 (4.4%). Although the number of mortalities linearly increased as a function of $y = 167.05x$ ($R^2 = 0.9011$), the rate of mortality decreased from 21.9% in 2017/18 to 4.4% in 2021/22, with an overall rate of mortality that decreased linearly as a function of $y = 1.5167x^2 - 13.002x + 32.363$ ($R^2 = 0.9494$) (Figure 4). Approximately 1248 (45.2%) of the mortalities were due to bloodstream infections, followed by pulmonary tract infections (589 (21.3%)) and CNS infections (417 (15.1%)) (Table 3).

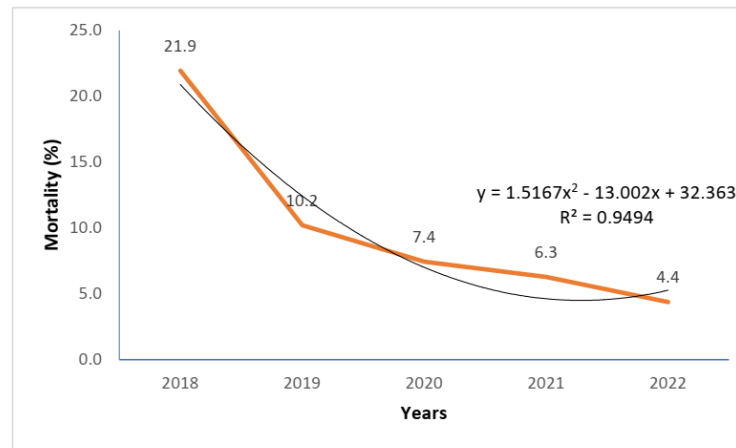


Figure 4. Trends in mortality from bacterial infections (July 2017 - June 2022) in hospitals in Northwest Ethiopia (N=2673).

Table 3. The most common infectious syndromes that resulted in mortality (July 2017 to June 2022) in hospitals in Northwest Ethiopia (N = 2763).

Syndrome of Infections	Frequency (%)
Sepsis/septic shock	1248 (45.2)
Pulmonary tract infection	589 (21.3)
CNS infections	417 (15.1)
Tuberculosis	194 (7.0)
Intra-abdominal infections and abscess	109 (3.9)
Other bacterial infections	79 (2.8)
Eye, ear, nose, throat, or mouth infection	50 (1.8)
Infections of skin, muscles, and soft tissues	28 (1.0)
Endocarditis and other cardiac infections	19 (0.69)
Infections of bones, joints, and related organs	18 (0.65)
Others *	12 (0.4)

Others*: Zoonotic, typhoid/Salmonella, UTI

Nine types of infections contributed to 2452 (91.1%) of the total mortalities. The most common causes of mortality from bacterial infections were sepsis, 908 (32.9%), and pneumonia, 576 (20.8%), followed by septic shock, 340 (12.3%). Botulism, 1 (0.04%), furuncle and carbuncle, 1 (0.04%), pyelonephritis, 1 (0.04%), relapsing fever/spirochetal, 1 (0.04%), shigellosis, 1 (0.04%), and typhus fever, 1 (0.04%), were the least common (Figure 5).

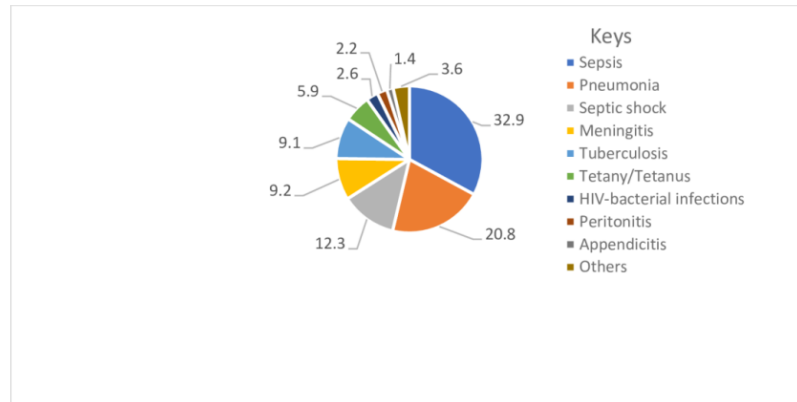


Figure 5. The most common bacterial infections that resulted in death (July 2017 to June 2022) in hospitals in Northwest Ethiopia (N=2763). **Others:** Different abscess, cellulitis, infective endocarditis, botulism, shigellosis, typhoid fever, relapsing fever, urinary tract infections, cancrum oris, pyoderma gangrenosum/gas gangrene, myocarditis, rheumatoid fever/heart disease, pyelonephritis, co-infections and unspecified bacterial infections.

Predictors of Mortality and Morbidity from Bacterial Infections

ANOVA with a single factor was used to compare morbidity and mortality, and the association was calculated using linear regression. In the linear regression, only patient age and sex (p values of 0.000 and 0.011, respectively) were significantly associated with morbidity. But only age was found to show significant difference in multivariable comparison, children less than 1-year-old 13875 (35.0%) were at risk of admission due to bacterial infections compared with all age groups, with high mean difference (mean difference= 18.5 [95%CI: 14.4- 22.7]) and (mean difference = 18.8 [95% CI: 14.3-23.2]) being for 5-14 years old and ≥ 65 years old, respectively. However, only age (p value = 0.000) was found to be significantly associated with mortality. Being a child younger than 1 year 912 (33.0%) was at risk of dying than other age groups where it was more likely than 5-14 years and 1 - 4 years (mean difference = 3.0 [95%CI: 1.7-4.3]) and (mean difference = 2.97 [95%CI: 1.6-4.3]), respectively (Tables S1 and S2 are annexed as supplementary). Multiple comparisons of morbidity and mortality did not show a significant difference among facilities.

Discussion

Infections continue to cause a substantial health burden in healthcare settings [32]. Most of the health burden is attributable to a small number of infectious agents, for which many effective interventions have already been identified. Bacterial infections are predominant in immunocompromised patients, resulting in high mortality and complications [33,34]. Neonatal bacterial infections are a major cause of death in LIMCs and a risk factor for the emergence of AMR, and dissemination is exacerbated by poor antibiotic control and precarious living conditions [8,35,36]. Determining common infections that are a high burden to healthcare is of paramount importance because it guides public health policy, planning, and research [32]. Disease burden estimates will provide credible information to decision-makers on the need for targeted interventions and the potential health and economic impact of interventions [37]. In line with this, the current study determined the burden of morbidity and mortality from bacterial infections in the inpatient wards of healthcare facilities. The prevalence of morbidity and mortality was 39,666 (20.1%) and 2763 (21.2%), where morbidity increased from 33.5% in 2018 to 37.5% in 2022 but mortality decreased from 162 (21.9%) in 2018 to 506 (4.4%) in 2022. Sepsis/septic shock 11,845 (29.9%), pulmonary tract infection 10,236 (25.8%) and intra-abdominal infections and abscess 6257 (15.8%) were the most common causes for morbidity, whereas sepsis/septic shock 1248 (45.2%), pulmonary tract infection 589 (21.3%) CNS infections 417 (15.1%) to mortality. The specific diseases were also in line with the syndromes.

In this study, bacterial infections accounted for 39,666 (20.1%). The prevalence of bacterial infections was high compared with 1.2% of admission records reported with at least one blood culture-positive result for bacteria in nine public hospitals in Thailand between 2004 and 2010 [38]. It was low compared with 43% in Australia and 60% in Asia and the Middle East among patients with suspected or proven bacterial infections [39]. In Germany, bacterial infections among cirrhotic patients accounted for 33.9% of total admissions [40]. The differences may be attributed to differences in geographic area, diagnostic approaches, types of patients, and the methods used for the study. Africa, including Ethiopia, is known to be a region with the highest significant infectious disease burden and the weakest public health infrastructure among all regions in the world.

On the other hand, in this study admission due to bacterial infections increased from 33.5% in 2018 to 37.5% in 2022. The trend was different from a study conducted in Portugal, which reported a successive decrease over three years and an overt increase in bacterial infections at the end, from -3.8% in 2012 to 75.7% in 2016 [12]. The increased trend in admissions due to bacterial infections might be due to the emergence and spread of drug-resistant bacteria, as evidenced by the fact that 54.3% of emerging infections globally are due to resistant bacteria [41]. The evolution of resistant bacteria continues to challenge healthcare to devise new ways to circumvent the problem by developing countermeasures against deliberately engineered microbes [42]. Although infectious diseases have relatively decreased due to reduced handshaking and the use of hand rubs

and sanitizers during the COVID-19 era, due to poverty, global warming, lack of access to safe drinking water, environmental degradation, lack of sanitation, and habitat destruction, infectious diseases are still on the rise.

Deaths associated with 33 bacteria were ranked as the second-leading cause of death globally in 2019 [4]. In this study, from all mortalities in the hospitals, the prevalence of mortality from bacterial infections was 2763 (21.2%). It was lower when compared with an analysis of the causes of mortality in India, which revealed that in 86% of patient deaths; at least one bacterial agent was identified [2], and in-hospital mortality due to bacterial infections in Ethiopia, which reported 26% mortalities among all inpatient mortalities in the hospital [9]. However, it was relatively higher than the global death rate from bacterial infections, which comprises 13.6% of all deaths [4]. A study among cirrhotic patients revealed that the prevalence of mortality from bacterial causes accounted for approximately 24% of overall in-hospital mortality [43]. The difference might be that the current study uses clinical syndromes recorded in the databases, whereas the former study uses bacterial-specific and laboratory-confirmed infections among patients at risk of infection. In the current study, the overall prevalence of mortality among bacterial infections was 7%. It was comparable to the overall mortality rate of 6.8% in Portugal over 5 years [12]. However, studies in India revealed a 13.1% to 86% overall mortality rate among multidrug-resistant bacterial infections in hospitals [2,44].

Pulmonary tract infections, bloodstream infections, and peritoneal and intra-abdominal infections are the three most common bacterial infections reported globally [4]. In the current study, sepsis/septic shock (11,845, 29.9%), pulmonary tract infection (10,236, 25.8%), and intra-abdominal infections and abscesses (6257, 15.8%) were the three most common bacterial infectious syndromes. In Israel, the prevalence of bloodstream infections was higher (25.6%) [45], although the value was lower than the 29.9% of sepsis/septic shock in the current study. Except for urinary tract infections, it was in line with a study in Ontario, which revealed pneumonia, septicemia, and urinary tract infections to be the top three infectious diseases, accounting for 74% of the total infections [32]. However, in Portugal, the major morbidities from bacterial infections were respiratory tract infections (34.0%), genitourinary tract infections (34.0%), gastrointestinal infections (4.0%), soft tissue infections (4.0%), bloodstream infections (3.0%), bone and joint infections (0.7%), and central nervous system infections (0.3%) [12], which is comparable with the current study except for some cases. The high disease burden of genitourinary tract infections in Portugal and Ontario may be due to differences in population demography.

In the current study, three infectious disease syndromes accounted for 81.6% of all bacterial mortalities: sepsis or septic shock, 1248 (45.2%); pulmonary tract infections, 589 (21.3%); and CNS infections, 417 (15.1%). This was similar with a reported three infectious disease syndromes responsible for more than 75% of the estimated 7.7 million bacteria-related deaths globally in 2019. These were lower respiratory infections (4.00 million deaths), bloodstream infections (2.91 million deaths), and peritoneal and intra-abdominal infections, were [4]. It was also similar in pattern to that reported in the Dessie referral hospital, where pulmonary tract

infections (37.9%), sepsis/shock (29.4%), and CNS infections (14%) were the three common causes of mortality from bacterial infections [9]. In addition to CNS infections, it was also similar to a global report [4]. The difference in the magnitude and pattern of infectious syndromes might be attributed to the difference in the pattern of morbidity, which is usually different across geographic regions.

In the current study, sepsis (11,121, 28.0%), pneumonia (9882, 24.9%), and appendicitis (4202, 10.6%) were the three most common bacterial infections. Bloodstream infections, including sepsis, are the most common causes of morbidity and mortality [4,28,46–48]. The burden of lower respiratory infections is enormous, leading to morbidity and mortality around the world [4,17,49]. Although the current study did not determine the specific causative agent, 78.9% of deaths from lower respiratory infections were attributed to *S. pneumoniae*, 30.4% of peritoneal and intra-abdominal infections were associated with *E. coli*, and 25.1% of bloodstream infections were due to *S. aureus* [4]. A pooled prevalence from bloodstream infections in Ethiopia identified 15.5% of gram-positive and 10.48% of gram-negative bacterial isolates [28]. In India, *S. aureus* (14.7%) and *K. pneumoniae* (26.6%) are two pathogens identified in bloodstream infections with high rates of resistance to first-line treatment options for neonates and children [47], and these could result in approximately 21.2% of neonatal deaths in Sub-Saharan Africa [47]. Mortality from bacterial infections is approximately six times higher among MDR pathogens [48].

The age of the patient was significantly associated with morbidity and mortality from bacterial infections, where it was high among children younger than 1 year. This was in line with a study in Europe, which reported the highest burden of bacterial infections due to resistant strains in infants (children under one year of age), resulting in an average of 180 disability-adjusted life years (DALYs) per 100,000 people [6]. The percentage of all global deaths related to sepsis in 2017 peaked in early childhood, declined through early adulthood, and then rose among older adults [50]. The bacteria known to be common causes of mortality were *S. aureus* in individuals older than 15 years (940,000 deaths), *Salmonella typhi* in children aged 5–14 years (49,000 deaths), *S. pneumoniae* among young children postneonatal to age 4 years (225,000 deaths), and *K. pneumoniae* in neonates (124,000 deaths) [4]. Similar to the current study, there were no differences between males and females regarding death from bacterial infections [4].

Bacterial infections are a significant cause of health loss globally [4], showing direct implications for health policymakers, clinicians, and researchers, including health care services. Implementing context-tailored, integrated intervention programs and packages to improve antibiotic use and reduce AMR and burden of healthcare-associated bacterial infections, especially in LMICs, requires a contextual understanding of the existing situation [51, 52]. The current study might be used to guide empirical antibiotic use in Ethiopian healthcare systems with “organizational, technical, behavioral, and process factors that need further attention to improve the quality and use of routine health information system data” [53]. In addition estimating morbidity and mortality will serve as the basis for implementation of ASPs [54].

An ASP is an organizational or system-wide healthcare strategy designed to promote, improve, monitor, and evaluate the rational use of antimicrobials to preserve their future effectiveness, along with the promotion and protection of public health by implementing evidence-based interventions [55,56]. Since AMR is a significant and urgent threat to global public health and is responsible for increased morbidity and mortality, resulting in a high economic burden [56], the current study may have its own input on the need to have effective ASPs and improve point-of-care diagnostic techniques to easily detect bacterial infections in healthcare facilities to reduce bacterial-infection-related morbidity and mortality in hospitals. This study was conducted to determine the prevalence of bacterial infections to serve as a baseline for the implementation of ASPs in hospitals.

Despite limitations due to retrospective data and diagnostic inconsistencies, the study provides critical baseline information to guide public health planning and the implementation of targeted programs to reduce the burden of bacterial infections and combat antimicrobial resistance (AMR) in healthcare facilities. The strengths of this study may include, but are not limited to, a comprehensive analysis of infectious diseases and their trends over a 5-year period. It also tried to standardize the infectious disease syndromes, which could be an opportunity for those who are interested in syndrome-based project implementation in hospitals.

Although the study tried to characterize bacterial infections based on the available information through retrospective analysis, it might face its own limitations. Lack of sufficient variables to determine association and the fact that it did not check the correctness of the diagnosis; it did not provide detailed information on clinical presentation, antibiotic treatment, and/or the final cause of death. The exclusion of unspecified infections may also underestimate the prevalence of bacterial infections. The study did not conduct analyses on seasonal variations during the year since the records were on a yearly basis. Being retrospective study, there was no chance to check diagnosis and evaluating causes for death. The clinical service for infectious diseases in all health facilities in the region is mostly carried out based mainly on clinical diagnosis and complete blood count (CBC) results which couldn't show the real prevalence of the infectious disease since it will over exaggerate or under rate.

In conclusion, this study revealed that bacterial infections pose a substantial and sustained burden in the hospitals. Over the five-year period, there was a notable increase in hospital admissions due to bacterial infections, rising from 33.5% to 37.5%, although mortality slightly declined. Sepsis/septic shock, pulmonary tract infections, and intra-abdominal infections were the leading contributors to morbidity and mortality. Infants under one year were highly affected, highlighting a vulnerable population group. The high prevalence and impact of bacterial infections emphasize the urgent need for robust, evidence-based interventions such as Antimicrobial Stewardship Programs, improved diagnostic capabilities, and enhanced infection prevention strategies. Furthermore, regional differences in morbidity and mortality patterns reflect the importance of context-specific policy and clinical interventions.

Author contribution: A.A.A. was involved in the conception, study design, execution, and acquisition of data, analysis and interpretation, and writing and review of the manuscript. T.G.F. was involved in the conception, study design, supervision, and writing and review of the manuscript. G.Y. was involved in the study design, supervision, and writing and review of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Addis Ababa University, the College of Health Sciences (protocol code: 106/22/SoP and date of approval: December 23, 2022), and the School of Pharmacy (protocol code: ERB/SOP/472/14/2022 and date of approval: November 18, 2022).

Informed Consent Statement: Not applicable

Data Availability Statement: All data are included in the study. If specific data are needed, they will be available upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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RESEARCH ARTICLE

A six years trend analysis of systemic antibiotic consumption in Northwest Ethiopia

Asrat Agalu Abejew^{1,2*}, Gizachew Yismaw Wubetu³, Teferi Gedif Fenta¹

1 Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia, **2** Department of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia, **3** Amhara Public Health Institute, Bahir Dar, Ethiopia

* asruphar@gmail.com

Abstract



Background

Consumption of antibiotics, a major global threat to public health, is perhaps the key driver of antibiotic resistance. Monitoring antibiotic consumption is crucial to tackling antimicrobial resistance. This study assessed antibiotic consumption trends during the last six years in the Bahir Dar branch of the Ethiopian pharmaceutical supply agency (EPSA), Northwest Ethiopia, in 2022.

Methods

Retrospective data were collected in August 2022 based on antibiotic distribution data from the Bahir Dar Branch of EPSA from July 2016 to June 2022. Data were analyzed according to the Anatomic Therapeutic Classification (ATC) developed by the World Health Organization (WHO). We measured antibiotic consumption using a defined daily dose per 1000 inhabitants per day (DIDs) based on the Agency's catchment population. Descriptive statistics and trend analyses were conducted.

Results

About 30.34 DIDs of antibiotics were consumed during the six years. The consumption of antibiotics decreased by 87.4%, from 6.9 DIDs in 2016/17 to 0.9 DIDs in 2021/22. Based on the WHO AWARe classification, 23.39 DIDs (77.1%) of the consumed antibiotics were from the Access category. Consumption of Access category antibiotics was decreased by 72.7% (from 5 to 0.5 DIDs) but Watch antibiotics decreased by 54.3% (from 1.8 to 0.4 DIDs). Oral antibiotics accounted for 29.19 DIDs (96.2%) of all consumed systemic antibiotics. The average cost expenditure per DDD for all antibiotics was 54.1 birr/DDD (0.4–482.3 birr/DDD). Only seven antibiotics accounted for DU90% and the cost expenditure per DDD for the DU90% antibiotics ranged from 0.4/DDD for Doxycycline to 232.8 birr/DDD for Piperacillin/tazobactam. Overall, during the last six years, the most commonly used antibiotic was Amoxicillin (10.1 DIDs), followed by Doxycycline (5.3 DIDs) and Ciprofloxacin (3.4 DIDs).

OPEN ACCESS

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Conclusion

In this study, we found that antibiotic usage was low and continuously declining over time. Minimizing unnecessary antibiotic usage is one possible approach to reduced AMR. However, a shortage of access to important medicines can compromise the quality of treatment and patient outcomes. A prospective study is needed to evaluate the balance of patient outcomes and reduce AMR by optimizing the community consumption of systemic antibiotics.

Introduction

Consumption of antimicrobials is perhaps the key driver of antibiotic resistance (AMR), a major global threat to public health [1, 2]. The rise in the consumption of last-resort antibiotics is a serious public health concern [2, 3]. Global antibiotic consumption increased by 36% between 2000 and 2010 [2], by 46% between 2000 and 2018 [3], and from 2000 to 2015, global per-capita consumption of watch antibiotics increased by 90.9% [4]. The WHO Access, Watch, and Reserve (AWaRe) antibiotic classification was developed to measure and drive improvements in antibiotic stewardship efforts on global, regional, and national levels [2–4]. This calls for periodic antibiotic consumption evaluation as an important component of AMR prevention and reduction strategies [2, 5, 6]. For this purpose, the WHO developed annually updated guidelines on the Anatomical Therapeutic Chemical (ATC) classification system and Defined Daily Dose (DDD) as a measuring unit for monitoring antibiotic consumption using a standardized population-based metric and research [7].

Low- and middle-income countries (LMICs) are face two challenges: inappropriate antibiotic therapy, lack of access to effective antibiotics, unregulated dispensing, manufacturing of antibiotics with a lack of money to pay for appropriate, high-quality antibiotics, and high rates of AMR and multidrug-resistant bacteria [3, 8, 9]. From 2000 to 2015, the consumption of Watch antibiotics increased by 165.0% in [4]. In LMICs, antibiotic consumption in Sub-Saharan Africa is very low [3] and varies across countries, in Tanzania it was 154.51 DIDs from 2010–2016 [10] and 241.41 DIDs from 2017 to 2019 [11], 58.41 DIDs in Ethiopia from 2016 to 2020 [12], 104,791,827 DDD in Uganda from 2017 to 2019 [13], and 19 DIDs in Sierra Leone from 2017 to 2019 [14]. Overall, antibiotic expenditures are increasing in public healthcare institutions [15]. If appropriate intervention is not in place, AMR will have health and social consequences, resulting in increased morbidity and mortality, healthcare costs, and a negative impact on economic growth [16].

In Ethiopia, data on antibiotic consumption using standard measures like DIDs is limited [12, 17, 18], particularly in the study area. On the other hand, the consumption of antibiotics in outpatient departments was reported to be high [17], and in inpatient wards, three out of four patients were prescribed antibiotics [18]. National community-based consumption of systemic antibiotics increased by 16.4% (from 11.02 DID to 12.83 DID) from 2016 to 2020 [12]. Determining antibiotic consumption using a standardized population-based metric, such as DIDs calculated based on import and sales data, and classifying them based on WHO AWaRe can serve as a proxy indicator for antibiotic use at the patient level [7, 19]. This allows the audit of patterns of antibiotic utilization and the identification of problem areas to devise appropriate interventions [7]. Thus, this study was conducted to determine antibiotic consumption using DIDs for six years in Northwest Ethiopia.

Methods

Study area and period

An institution-based cross-sectional study was conducted from the EPSA Bahir Dar Branch registers in August 2022 based on drugs distributed from 2016 to June 2022. EPSA is a legal entity established under the Federal Government to assure an uninterrupted supply of pharmaceuticals to the public at an affordable price. The EPSA has 19 branches grouped into seven clusters. EPSA Bahir Dar Branch, located in Bahir Dar City, is one of these Branches serving as outposts to distribute pharmaceuticals, chemical reagents, medical supplies, and equipment to the localities [20]. It serves more than 9 million people in two regions (Amhara National Regional State and Benishangul Gumuz National Regional State) clustered in six Zones (South Gondar, East Gojjam, West Gojjam, Awi Administrative and Metekel Zones, and Bahir Dar City Administration) and 67 woredas. It supplies both public and private health facilities (38 hospitals and 355 health centers) [21]. Since we have used the Ethiopian fiscal year, it should be understood that 2009 = 2016/17, 2010 = 2017/18, 2011 = 2018/19, 2012 = 2019/20, 2013 = 2020/21, 2014 = 2021/22 and for the sake of convenience, we used the next year in the figures, i.e., 2017–2022 is used in the figures.

Data collection process

The study included all systemic antibiotics procured and distributed and the associated cost expenditure in each year (July 2016 to June 2022) in the EPSA Bahir Dar Branch. The dosage form, strength, the unit of measurement (packs, boxes (number of tablets or capsules), vials, ampoules, MIU, Unit dose, etc.), amount delivered, unit cost and total cost were documented in the registry.

Outcome measures

Based on the registry, AMC too was used to assign DDDs for each antibiotic based on WHO's 2019 Anatomical Therapeutic Chemical Classification System (ATC/DDD) and AWaRe classification [7, 19]. It was then standardized into DIDs based on the catchment population [21]. In addition, the number of drugs accounted for 90% of antibiotic consumption (DU90%), and the costs for the DU90% antibiotics and all antibiotics were also calculated as cost per DDD (birr/DDD) was calculated. The DDD/1000 inhabitants/day (DID) was calculated based on the following formula:

$$\frac{\text{DDD}}{1000 \text{ inhabitants} \times \text{day}} = \frac{\text{Amount of drug sold in one year (mg)}}{\text{DDD (mg)} \times 365 \text{ days} \times \# \text{ of inhabitants}} \times 1000 \text{ inhabitants}$$

Data analysis

Data were cleared, and DDDs and DIDs were calculated for each antibiotic distributed over six years. DDD and DID were calculated separately for antibiotics marketed in fixed-dose combinations (Trimethoprim and Sulfamethoxazole). For antibiotics combined with β -Lactamase inhibitors, only the amount of antibiotics was calculated. In addition, based on the DDD, DU90% and cost per unit were calculated. Descriptive statistics and trend analyses were performed. Finally, the results are presented in the tables and figures.

Operational definitions and definition of terms

- **AWaRe antibiotic classification:** The Access, Watch, and Reserve (AWaRe) classification is a useful tool developed by the WHO to reduce antimicrobial resistance and ensure access to

key antibiotics by balancing appropriate access to antibiotics and stewardship use. Access antibiotics indicate the antibiotics of choice for each of the 25 most common infections, which should be available at all times, affordable, and quality-assured. Watch antibiotics include most of the highest-priority, critically important antibiotics for human medicine and veterinary use, which are recommended only for specific, limited indications, whereas reserve antibiotics are those that should only be used as a last resort when all other antibiotics have failed.

- **Defined Daily Dose (DDD):** The assumed average maintenance dose per day for a drug used for its main indication in adults.
- **Defined Daily Doses (DDDs) per 1000 inhabitant days per year (DIDs):** To standardize the metrics of measurement, the DID was used to measure distributed antibiotics from EPSA, which was calculated as $DDDs \times 1000 \text{ days} / (\text{catchment population} \times 365 \text{ days})$.
- **The drug utilization 90% (DU90%):** Is an inexpensive, flexible, and simple method for assessing the quality of drug prescribing in routine health care for drugs accounting for 90% of the volume of the prescribed drugs after ranking the drugs used by volume of DDD
- **Cost expenditure for antibiotics:** Shall mean the money spent on purchasing antibiotics.

Ethical consideration

Ethical Approval was obtained from the ethical review board of Addis Ababa University, the College of Health Sciences, and the School of Pharmacy. A letter of Support for the EPSA was obtained from the Amhara Public Health Institute (APHI). As these were secondary data, informed consent was not obtained. All the information provided was kept confidential and was used only for research purposes.

Results

Overall trend and consumption of antibiotics

During the last six years (2016/17 to 2021/22), the Bahir Dar Branch of EPSA distributed a total of 99,682,410 DDDs, or 30.34 DIDs (average 5.33 DIDs in year) of antibiotics to various health facilities and sectors under study.

From 2016/17 to 2021/22, the overall antibiotic consumption decreased by 87.4% (from 6.9 to 0.9 DIDs). The trend analysis revealed that the overall antibiotic consumption decreased linearly as a function of $y = -1.2371x + 2493.9$ ($R^2 = 0.5806$), and will decrease by 58.1% in each year (Fig 1).

Antibiotic consumption and trends in different districts/zones

The majority, 7.8 (25.9%) DIDs, were distributed to East Gojjam Zone, followed by West Gojjam Zone, 7.55 (24.9%), and South Gondar Zone, 6.21 (20.5%) (Table 1).

Trends in consumption by antibiotic class

The consumption trend in each category is almost similar. However, for some classes of antibiotics, it was relatively high in 2017/18 and 2018/19. The most commonly consumed classes of antibiotics were beta-lactam antibiotics, and penicillins (J01C), with 14.9 DIDs, followed by tetracyclines (J01A) and quinolones (J01M), which had 5.3 DIDs and 4.1 DIDs, respectively. Aminoglycosides (J01G) were the least consumed antibiotics, with 0.2 DIDs (Table 2).

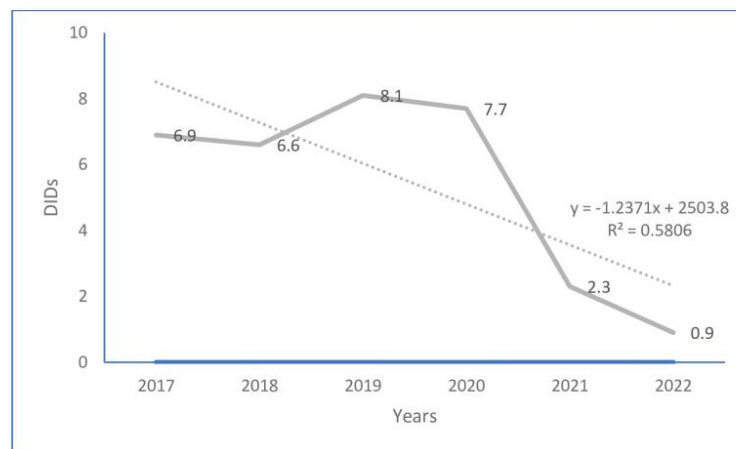


Fig 1. Trends of antibiotic consumption (July 2016– June 2022), Bahir Dar Branch of EPSA, Ethiopia.

<https://doi.org/10.1371/journal.pone.0290391.g001>

Consumption of antibiotics based on WHO AWaRe classification

Based on the WHO AWaRe classification, 23.39 DIDs (77.1%) of consumed antibiotics were from the Access category, and 6.95 DIDs (22.9%) were from the Watch category. Between 2016/17 and 2021/22, consumption of Access antibiotics decreased by 72.7% (from 5 to 0.5 DIDs) compared with Watch antibiotics, which decreased by 54.3% (from 1.8 to 0.4 DIDs) (Fig 2).

Consumption of specific antibiotics

Oral antibiotics accounted for 29.19 of total DIDs (96.2%), and parenteral antibiotics accounted for 1.15 DIDs (3.8%). Only seven antibiotics (Amoxicillin, Doxycycline, Ciprofloxacin, Cloxacillin, Metronidazole, Ampicillin, and Piperacillin/tazobactam) accounted for DU90%. Overall, during the last six years, Amoxicillin (10.1 DIDs) was the most commonly consumed antibiotic, followed by Doxycycline (5.3 DIDs), Ciprofloxacin (3.4 DIDs), and Cloxacillin (3.06 DIDs). Compared with baseline consumption, Azithromycin, Ceftazidime, and

Table 1. Distribution of antibiotics in Zones and facilities (July 2016–June 2022), Bahir Dar Brach of EPSA, Ethiopia.

Zones	Distribution to	DIDs in each year						Total
		2016/17	2017/18	2018/19	2019/20	2020/21	2021/22	
	East Gojjam Zone	1.73	1.52	1.87	1.95	0.63	0.14	7.85
	West Gojjam Zone	1.76	1.65	1.94	1.70	0.41	0.10	7.55
	South Gondar Zone	1.48	1.19	1.52	1.46	0.43	0.13	6.21
	Awi administrative Zone	0.93	1.03	1.20	1.11	0.37	0.36	5.00
	Bahir Dar City administration	0.69	0.56	0.61	0.56	0.27	0.10	2.79
	Others *	0.12	0.04	0.39	0.33	0.05	0.01	0.94
	Total	6.7	6.0	7.5	7.1	2.2	0.8	30.3

Others*: Central Gondar Zone, West Gondar Zone, Waghimra Administrative Zone, Other Hubs, Metekel Zone

<https://doi.org/10.1371/journal.pone.0290391.t001>

Table 2. Class of antibiotics consumed (July 2016 –June 2022), Bahir Dar Branch of EPSA, Ethiopia.

Class of antibiotics	Year						Total
	2016/17	2017/18	2018/19	2019/20	2020/21	2021/22	
Beta-lactam antibiotics, penicillins (J01C)	2.918	3.463	3.911	3.098	1.165	0.311	14.866
Tetracyclines (J01A)	1.272	0.558	1.354	2.085	0.076		5.344
Quinolones (J01M)	0.721	0.721	0.842	1.190	0.387	0.209	4.070
Other antimicrobials (J01X)	0.608	0.492	0.808	0.194	0.030	0.137	2.269
Macrolides, lincosamides (J01F)	0.266	0.292	0.357	0.085	0.248	0.072	1.320
Sulfonamides & trimethoprim (J01E)	0.723	0.080	0.030	0.154	0.009	0.071	1.067
Other beta-lactams (J01D)	0.105	0.193	0.205	0.165	0.239	0.046	0.952
Amphenicols (J01B)	0.080	0.091	0.004	0.056			0.232
Aminoglycosides (J01G)	0.024	0.092	0.028	0.078	0.004		0.225
Total	6.716	5.981	7.539	7.105	2.158	0.845	30.34

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Vancomycin were slightly increased, but for others, it either decreased or remained constant (Table 3).

Cost expenditure for antibiotics

The overall cost expenditure for purchasing antibiotics was \$7,281,680.907 (385, 200, 920 Ethiopian Birr), which increased from 29.85% in 2016/17 to 32.31% in 2017/18, then decreased to 26.53% in 2018/19, 17.5% in 2019/20, and 13.4% in 2020/21. The percentage cost expenditure on antibiotics based on the total cost expenditure for drugs and the actual cost expenditure for antibiotics decreased linearly from time to time as a function of $y = -0.0295x + 0.3399$ ($R^2 = 0.5725$) and $y = -8E+06x + 9E+07$ ($R^2 = 0.3305$) as shown in Fig 3A and 3B, respectively (Fig 3).

About 74.4% of the total expenditures for purchasing antibiotics were used for purchasing Access antibiotics, and only 25.6% were for purchasing Watch antibiotics. From 2016/17 to

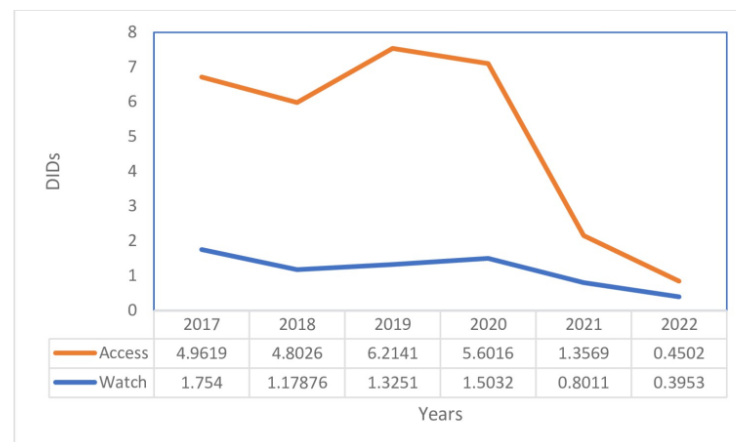


Fig 2. Trends of antibiotic consumption based on WHO AWaRe classification (July 2016– June 2022), Bahir Dar Branch of EPSA, Ethiopia.

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Table 3. Consumption of each antibiotic (July 2016 –June 2022), Bahir Dar Branch of EPSC, Ethiopia.

Antibiotics	DID in each year						Total
	2016/17	2017/18	2018/19	2019/20	2020/21	2021/22	
Amoxicillin	1.9947	2.3467	3.0016	1.9268	0.6914	0.1216	10.0827
Amoxicillin /clavulanic	0.0746	0.0705	0.1034	0.0698	0.2262	0.0228	0.5673
Ampicillin	0.3166	0.4576	0.2717	0.0592	0.0099	0.0065	1.1214
Ampicillin/sulbactam	0.0000	0.0000	0.0000	0.0001	0.0001	0.0000	0.0003
Azithromycin	0.0001	0.0023	0.1369	0.0000	0.0526	0.0668	0.2587
Cefepime	0.0000	0.0000	0.0000	0.0001	0.0304	0.0000	0.0306
Cefixime	0.0000	0.0001	0.0000	0.0002	0.0007	0.0000	0.0011
Cefotaxime	0.0000		0.0020	0.0000	0.0140	0.0000	0.0160
Ceftazidime	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0003
Ceftriaxone	0.0008	0.0010	0.0002	0.0019	0.0037	0.0019	0.0094
Cefuroxime	0.0432	0.0862	0.0909	0.0719	0.1034	0.0401	0.4356
Cephalexin		0.0001					0.0001
Cefazoline	0.0606	0.1051	0.1115	0.0907	0.0863	0.0044	0.4586
Chloramphenicol	0.0796	0.0914	0.0044	0.0563		0.0000	0.2317
Ciprofloxacin	0.5722	0.6378	0.6868	0.9798	0.3243	0.1996	3.4006
Clarithromycin	0.1538	0.2813	0.0649	0.0643	0.1953	0.0030	0.7628
Clindamycin	0.0006	0.0019	0.0010	0.0029		0.0000	0.0063
Cloxacillin	0.5282	0.5797	0.5249	1.0364	0.2270	0.1603	3.0564
Doxycycline	1.2670	0.5175	1.3500	2.0849	0.0758	0.0000	5.2953
Erythromycin	0.1118	0.0062	0.1543	0.0178	0.0000	0.0021	0.2922
Gentamicin	0.0235	0.0918	0.0276	0.0776	0.0043	0.0000	0.2248
Meropenem	0.0000	0.00006				0.0000	0.0000
Metronidazole	0.6066	0.4913	0.8029	0.1908	0.0248	0.1343	2.2506
Norfloxacin	0.1491	0.0830	0.1550	0.2104	0.0628	0.0091	0.6695
Penicillin G	0.0038	0.0086	0.0099	0.0054	0.0101	0.0000	0.0378
Piperacillin/Tazobactam	0.7230	0.0802	0.0303	0.1542	0.0091	0.0707	1.0674
SXT	0.0049	0.0400	0.0041			0.0000	0.0491
Tetracycline	0.0012	0.0004	0.0011	0.0007	0.0010	0.0003	0.0045
Vancomycin	0.0000	0.0005	0.0038	0.0026	0.0047	0.0020	0.0136
Total	6.7161	5.9806	7.5390	7.1050	2.1580	0.8455	30.3442

SXT: Sulfamethoxazole- trimethoprim

<https://doi.org/10.1371/journal.pone.0290391.t003>

2021/22, the total expenditure for purchasing antibiotics decreased by 64%. Similarly, the cost expenditure for Access and Watch antibiotics decreased by 72.3% and 33.6%, respectively. Of the total antibiotic cost expenditures, 26.4% were used to purchase Amoxicillin, followed by Cloxacillin (13.6%), Metronidazole (10.5%), Ceftriaxone (9.6%), and Amoxicillin/clavulanic (6.1%). Only about 62.7% of the expenditure was used to purchase DU90% antibiotics.

The average expenditure per DDD for all antibiotics was 54.1 birr/DDD (0.4–482.3 birr/DDD). The highest cost expenditure per DDD was for Cefotaxime (91.1), Ceftazidime (120.8), Cefepime (133.5), Vancomycin (160.4), Meropenem (214.0), Piperacillin/tazobactam (232.8), and Ampicillin/sulbactam (482.3) in increasing order. The cost per DDD for the DU90% antibiotics was Amoxicillin (2.8 birr/DDD), Doxycycline (0.4/DDD), Ciprofloxacin (1.6 birr/DDD), Cloxacillin (4.8 birr/DDD), Metronidazole (2.9 birr/DDD), Ampicillin (4.9 birr/DDD), and Piperacillin/tazobactam (232.8 birr/DDD). The trend and overall cost expenditure per DDD are presented in (Table 4).

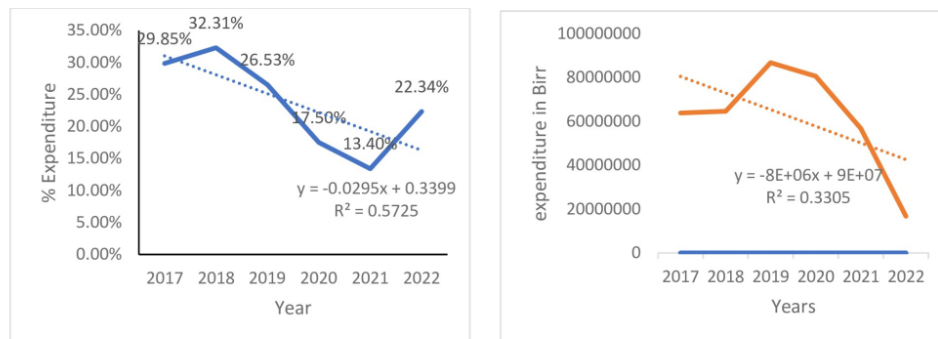


Fig 3. Trends in antibiotic expenditure (July 2016– June 2022), Bahir Dar Branch of EPSA, Ethiopia. A. Percent expenditure for antibiotics, B. Actual expenditure for antibiotics.

<https://doi.org/10.1371/journal.pone.0290391.g003>

Discussion

This study attempted to quantify antibiotic consumption based on available data from the Bahir Dar Branch of EPSA, Northwestern Ethiopia, from July 2016 to June 2022. In general, the overall consumption of antibiotics was 30.34 DIDs, which decreased by 87.4% (from 6.9 to 0.9 DIDs) from July 2016 to June 2022. From 30.34 DIDs, 14.9 DIDs accounted for beta-lactam antibiotics, and penicillins (J01C), and 23.39 DIDs were for Access antibiotics. The overall consumption of antibiotics decreased by 87.4%, and consumption of Access antibiotics decreased by 72.7%. About 29.19 DIDs (96.2%) of systemic antibiotics were administered orally. The total cost expenditure for antibiotics accounted for \$7,281,680.907, of which 74.4% was used for purchasing access antibiotics.

Antibiotic consumption is a major driver of AMR [2]. Variations in AMR across different countries are attributable to the difference in volume and pattern of antibiotic consumption [2, 22, 23]. In this study, total antibiotic consumption from July 2016 to June 2022 was 30.34 DIDs. This is low than the national consumption of antibiotics from 2016 to 2020 in Ethiopia, which was 58.95 DIDs [12], and it was extremely low compared with a study in Tanzania, which reported consumption of 242.41 (80.80 ± 39.35) of antibiotics from 2017 to 2019 [13]. Compared with the estimated global antibiotic consumption rate of 14.3 DIDs from 2000 to 2018 [3] and the total consumption of antibiotics in Sierra Leone from 2017 to 2019, which was 19 DIDs [14], the consumption of antibiotics in the current study was high. The current study's low level of antibiotic consumption might be linked to budget shifts to save lives due to increased internal displacements in the region due to instabilities and inflated global market dynamics due to the COVID-19 pandemic. However, the decline in the consumption of antibiotics from government sources could have resulted in an alternative source of antibiotic supply, which could affect affordability in the community, probably fueling the emergence and spread of AMR.

The current study reported an 87.4% (from 6.9 to 0.9 DIDs) decrease in antibiotic consumption from July 2016 to June 2022. This was in contrast to national consumption from 2016 to 2020, which increased by 16.4% (from 11.02 DID to 12.83) [12], a global report, which increased by 46% (92–1005 DIDs) from 2000 to 2018 [3], a Tanzanian study, which increased

Table 4. Trends in cost expenditure per DDD of antibiotics (July 2016–June 2022), Bahir Dar Branch of EPSA, Ethiopia.

Antibiotic	Cost expenditure /DDD						Total
	2016/17	2017/18	2018/19	2019/20	2020/21	2021/22	
Amoxicillin	2.7	2.6	2.9	3.0	2.9	3.3	2.8
Amoxicillin /clavulanic	12.9	9.2	8.7	15.6	12.0	7.7	11.4
Ampicillin	3.8	3.2	6.2	11.8	33.7	21.9	4.9
Ampicillin/sulbactam	280.1	232.4	1062.1	498.4	510.3		482.3
Azithromycin	19.3	3.3	2.5		8.0	2.0	3.5
Cefazoline		81.1		81.1	0.1		0.5
Cefepime		124.4	108.4	108.4	144.7		133.5
Cefixime			19.2	19.8	6.8		8.4
Cefotaxime	64.2	68.5	95.2	73.1	128.0	0.0	91.1
Ceftazidime	225.8	88.2	117.4	92.9	140.7	83.1	120.8
Ceftriaxone	23.6	17.3	27.5	22.3	25.0	24.1	23.4
Cefuroxime		33.7					33.7
Cephalexin	6.2	6.0	9.6	8.3	11.8	14.3	8.6
Chloramphenicol	11.1	5.2	33.3	22.3			10.2
Ciprofloxacin	1.7	1.5	1.1	1.6	2.0	2.3	1.6
Clarithromycin	3.9	3.8	6.0	4.3	5.7		4.5
Clindamycin	15.8	12.2	23.4	18.1			16.9
Cloxacillin	3.2	3.1	6.1	4.8	9.7	5.4	4.8
Doxycycline	0.4	0.4	0.4	0.3	0.4		0.4
Erythromycin	5.6	8.4	4.8	12.4		12.2	5.8
Gentamicin	6.2	5.0	1.3	5.1	0.7		4.6
Meropenem		210.8	252.5				214.0
Metronidazole	1.4	2.5	2.5	5.0	11.9	36.2	2.9
Norfloxacin	1.7	1.5	1.7	1.7	1.9		1.7
Penicillin G	42.8	21.2	26.1	29.8	27.1		27.3
Piperacillin/Tazobactam		232.8					232.8
Sulphathiazole	3.6	5.0	13.3	5.6	31.0	2.8	4.4
Tetracycline	4.0	1.2	1.3				1.5
Trimethoprim	2.5	5.0	8.7	5.6	33.5	13.1	3.9
Vancomycin	157.0	135.3	147.5	171.3	176.7	143.2	160.4
Total	899.5	1324.8	1989.7	1222.6	1324.6	371.6	1622.6

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by 610.8% (6.78–48.19 DIDs) from 2010 to 2016 [10], and an Indian study reported 22% increase in antibiotic consumption from 2008 to 2012 [24]. Similar to our finding, a decrease in the consumption of antibiotics reported in a recent study in Tanzania, declined by 29.33% (136.41 to 54.98 DIDs) from 2017 to 2019 [11], and in another recent study from India, and then decline by 3.6% between 2011–2019 [25]. The decline was 3.6% between 2011 and 2019 [25]. The highest decrease in antibiotic consumption in the current study from 2019/20 might be directly related to the COVID-19 pandemic, as was evident in the global antimicrobial consumption level decrease of 18.7% worldwide from April to August 2020 compared with the previous year, 2019 [26]. The political instabilities in the country that could have shifted attention and health priority to survival issues, resulting in a reduced supply of antibiotics. The difference in trends in consumption [27–29] in the current study may be attributed to the decrease in cost expenditure for antibiotics and inflation in the cost of antibiotics, indicating that the possible reason for the decrease in antibiotic consumption is related to the decrease in expenditure, as well as inflation in drug cost and currency.

This study accounted for 14.9 DIDs out of 30.3 DIDs for β -lactam antibiotics and penicillins (J01C). This is similar to national antibiotic consumption in Ethiopia [12]. Similar results have been reported in Bhutan, where the penicillin group of beta-lactam antibacterials (J01C) was the most commonly used subgroup [30]. This was due to the overwhelming use of Amoxicillin and other penicillins in healthcare facilities because they are the antibiotics of choice for many indications in inpatient and outpatient settings. The WHO recommends that the consumption of access antibiotics should make up at least 60% of national consumption [19], justifying the overwhelming use of penicillin groups in the current study.

In the current study, the consumption of access antibiotics was 77.1%, and watch antibiotics accounted for 22.9%. Although consumption of access antibiotics was in agreement with WHO's minimum 60% recommendation [20], the value is high compared with a study in Sierra Leone [14] and China [27], which reported 65% and 42% of antibiotic consumption in the Access category, respectively. However, the consumption of Watch antibiotics (31%), was relatively higher in Sierra Leone [14] than in the current study. The current study, similar to Sierra Leone's case [14], didn't report the consumption of reserve antibiotics. The difference might be due to differences in government policy and accessibility of antibiotics.

Similar to the overall trend in antibiotic consumption, in the current study, the consumption of Access antibiotics decreased by 72.7% (from 5 to 0.5 DIDs), and the consumption of Watch antibiotics decreased by 54.3% (from 1.8 to 0.4 DIDs). This was in contrast to the WHO's assessment from 2000 to 2015, which showed consumption of Watch antibiotics increased by 90.9% (from 3.3 to 6.3 DIDs) and 26.2% (from 8.4 to 10.6 DIDs) in Access antibiotics [4]. In India, the consumption of Access antibiotics decreased by only 13.1% [24], which is lower than that in the current study.

The current study revealed 29.19 DIDs (96.2%) for consumption of oral antibiotics and 1.15 DIDs (3.8%) of parenteral antibiotics. This is in agreement with a study in Sierra Leone, which showed 98.4% oral antibiotic consumption and 1.6% parenteral antibiotics consumption [14]. The consumption of oral antibiotic was higher in the current study than in China, which reported less than 70% oral antibiotic consumption and 31%–36% of parenteral total antibiotic consumption [27]. In Uganda, the oral route of administration accounted for 59% and the parenteral route accounted for 41% [13], which was also different from the current study.

Using the current exchange rate of (52.9 as of 25/11/2022), the current study's total antibiotic expenditure was \$7,281,680.907 (385,200,920 Ethiopian Birr). This was lower than the \$56.0 billion expenditure on purchasing antibiotics over the six-year (between 2010 and 2015) in healthcare settings in the United States [31]. It was also low compared with the overall antibiotic expenditure in public healthcare institutions in Shandong Province in China from 2012 to 2016, which accounted for \$717 million, a 56% increase from the baseline [15]; in the current study, the total expenditure for purchasing antibiotics decreased by 64%. In the current study, 74.4% of the total antibiotic expenditure was used to purchase access antibiotics, and only 25.6% was for purchasing antibiotics in the Watch category, which was contrary to another study in China, which showed 55.57% expenditure on the Watch group and 9.91% for Access group antibiotics [29].

DU90% is an inexpensive, flexible, and simple method for assessing the quality of antibiotic prescribing in routine healthcare [32]. Studies on antibiotic consumption using the DU90% methodology has also been conducted at community level [33]. In the current study, only seven antibiotics (Amoxicillin, Doxycycline, Ciprofloxacin, Cloxacillin, Metronidazole, Ampicillin, and Piperacillin/tazobactam) constituted the DU90%. This is different from national antibiotic consumption, which reported that nine antibiotics (Amoxicillin, Doxycycline, Ciprofloxacin, Cloxacillin, Metronidazole, Trimethoprim, Sulfamethoxazole, Ampicillin, and

Norfloxacin) constituted DU90% of the whole consumption [12]. However, the cost expenditure of the seven antibiotics in the current study accounted for only 62.7% of the cost used to purchase DU90% of drugs. This was different from the 80.8% total cost expenditure for DU90% antibiotics compared with the 19.2% for the remaining 10% [32]. The highest cost per DDD was among antibiotics in the 10%. A substantial amount of money can be saved without compromising the quality of care by using recommended and commonly utilized antibiotics [34].

Determining antibiotic consumption based on procurement or sales data serves as an overall proxy indicator for actual exposure in the community [35]. Although reducing unnecessary antibiotics, improving access, implementing and measuring stewardship programs, and tracking and using data are possible advanced solutions to tackle AMR [36], the positive impact of antibiotics on health is frequently threatened by increasing levels of antimicrobial resistance (AMR) and hampered by a lack of access to essential antibiotics [3]. A continuously reduced supply of antibiotics may have many implications for healthcare facilities in the catchment area. According to Namomsa G., among the community-based health insurance (CBHI) users, only 60% of the members reported getting prescribed medicines after being prescribed for treatment. The absence of antibiotics in health facilities is an implication for poor service provision, resulting in a reduced enrollment rate for CBHI [37]. Addressing lack of access and inappropriate antibiotic use is crucial for tackling the growing threat of antimicrobial resistance and ensuring fair and equitable access to essential medicines for all [3]. The aftereffects of decreased antibiotic supply have multiple far-reaching negative consequences, ranging from a lack of availability in public health facilities resulting in suboptimal or broad-spectrum antibiotic use or necessitating the use of reserve antibiotics to treat common infections to increased healthcare costs, and eventually, a rise in the number of drug-resistant infections. Thus, identifying the reasons for shortages of antibiotic supply and proposing solutions to address the issue is the first step in the complex process of changing antibiotic supply-related problems.

The strength of the current study is documenting the community-based annual consumption of systemic antibiotics in the regional hub EPSA over six years using standard methodology and applying DID to estimate the general population's exposure to antibiotics in the catchment area. It also analyzes the trend in antibiotic consumption and expenditure, including the total budget allocated for antibiotics. Nevertheless, there might be limitations arising from the organizational structure of the agency and the nature of secondary data. It will not necessarily show the captured seasonal variations in the community-based consumption of antibiotics in the area. It didn't conduct validation of antibiotic distribution and, thus, will not show actual patient-level use of antibiotics in the area by simply collecting available resources on drug distribution and extracting antibiotics from them. It also didn't take into account the possibility of unrecorded drugs in the Hub.

In conclusion, antibiotic consumption was very low in Northwest Ethiopia. Antibiotic consumption, percent allocation from total expenditures to antibiotic procurement, and actual expenditure for antibiotic procurement decreased linearly during the last six years. Consumption of Access category and oral antibiotics was very good, although Access antibiotics decreased from time to time in line with total antibiotic consumption. Seven antibiotics constituted DU90%, and less than 2/3 of the cost was used on DU90% antibiotics. Since EPSA is the sole public supplier in the area, the finding directly implies a reduced supply of antibiotics at the institutional level which could in turn affect the quality of care and patient stratification specifically patients on CBHI may suffer a lot from lack of antibiotics. Antibiotic resistance is a multifactorial problem resulting from multisectoral failures to use antibiotics and enforce stewardship measures appropriately. This calls for a prospective mixed-methods study to

understand the spiral of antibiotic usage and resistance which might help to assure a continuous supply of key antibiotics while optimizing the use and reducing unnecessary prescribing practices that fuel AMR.

Supporting information

S1 Data. Raw data on antibiotics.
(XLSX)

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Author Contributions

Conceptualization: Asrat Agalu Abejew, Teferi Gedif Fenta.

Data curation: Asrat Agalu Abejew.

Formal analysis: Asrat Agalu Abejew.

Methodology: Asrat Agalu Abejew.

Software: Asrat Agalu Abejew.

Supervision: Gizachew Yismaw Wubetu, Teferi Gedif Fenta.

Writing – original draft: Asrat Agalu Abejew.

Writing – review & editing: Asrat Agalu Abejew, Gizachew Yismaw Wubetu, Teferi Gedif Fenta.

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Manuscript III

Hospital level Use of Systemic Antibiotics in Specialized Hospitals from 2020 to 2022: analysis of Pharmaceutical procurement data

Asrat Agalu Abejew^{1, 2*}, Gizachew Yismaw Wubetu³, Teferi Gedif Fenta¹

Addresses:

¹Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

²Department of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia

³Amhara Public Health Institute, Bahir Dar, Ethiopia

***Correspondence:** asruphar@gmail.com; +251917156682

Abstract

Background: Consumption of antibiotics is a key driver of antibiotic resistance (AMR) and is a major global threat to public health. This study assessed antibiotic consumption in the referral hospitals in Northwest Ethiopia in 2022.

Methods: Retrospective data were collected in August 2022 based on antibiotic procurement data in the referral hospitals from July 2019 to June 2022. The data were collected and analyzed based on the Anatomic Therapeutic Classification (ATC) developed by the World Health Organization (WHO). Antibiotic consumption was measured using a defined daily dose per 1000 inhabitants per day (DIDs). Finally, descriptive statistics and trend analyses were conducted.

Results: 296.16 DIDs of antibiotics were consumed during the three years. The overall consumption of antibiotics decreased linearly as a function of $y = -23.95x^2 + 90.382x + 29.72$ ($R^2 = 1$) and decreased by 11.3% (from 96.15 in 2020 to 85.32 DIDs in 2022). Based on the WHO AWaRe classification, 150.34 DIDs (50.8%) of the consumed antibiotics were from the Watch category, and 145.32 DIDs (41.1%) were from the Access category. The consumption of Access antibiotics increased by 35.8%, but Watch antibiotics decreased by 49.6%. Oral antibiotics accounted for 191.41 DIDs (64.6%), and eleven antibiotics constituted drug utilization 90% (DU90%). The consumption of ceftriaxone accounted for 84.29 DIDs, sulfamethoxazole-trimethoprim (35.64 DIDs), cephalexin (31.21 DIDs), and amoxicillin (26.10

DIDs). The cost expenditure for parenteral antibiotics was 65.2%, 59.98% for Watch antibiotics, and 59.2% for DU90% antibiotics.

Conclusion: Antibiotic consumption in hospitals is high, and slightly decreased. AMR is a multifactorial problem resulting from multi-sectorial failures to appropriately use antibiotics, and enforce stewardship measures. A prospective patient-level study is needed to evaluate patient outcomes and optimize the consumption of antibiotics.

Keywords: *antibiotics, consumption, expenditure, specialized Hospitals, Northwest Ethiopia*

Introduction

Antibiotic resistance (AMR) is a serious threat to public health [1] where the major drivers for the emergence and spread of antibiotic-resistant bacteria (AMR) are attributed to antibiotic consumption [2–5]. The variation in antibiotic resistance pattern across different countries is attributable to difference in volumes and patterns for antibiotic consumption [2]. Despite spatial disparities in the rates of antibiotic consumption globally, antibiotic consumption is increasing from time to time [2, 6]. In response to the rising global threat of AMR, a global action plan (GAP) on AMR was developed and adopted by many countries, among the objectives of the GAP was to optimize the use of antibiotics [7]. Monitoring hospital antibiotic consumption is becoming an important step toward improving antibiotic consumption in order to combat AMR [8, 9]. To facilitate the surveillance process, world health organization (WHO) developed annually updated guidelines on the Anatomical Therapeutic Chemical (ATC) classification system, and Defined Daily Dose (DDD) as a metric of measure for antibiotic consumption [8, 10], and Access, Watch, and Reserve (AWaRe) antibiotic classification [11]. Currently, periodic antibiotic consumption evaluation is an important component of AMR prevention, and reduction strategies [2, 6, 7] to optimizing antibiotic prescribing and minimize AMR through tracking antibiotic consumption patterns across countries [12].

Globally, antibiotic consumption increased by 36% from 2000-2010, 76% of which was in Brazil, Russia, India, China, and South Africa [2], and by 46% from 2000-2018, among which the highest consumption was reported from Eastern Europe and Central Asia [6]. From 200 to 2015, global antibiotic consumption was increased by 65%, the majority of which were driven by consumption in low-and middle income countries (LMICs) [12], and from 2000 to 2018 an increase was estimated to be 46% where lowest levels were in sub-Saharan Africa and the

highest was in Europe and Asia [6]. Similarly, consumption of Watch antibiotics increased by 90.9% from 2000 to 2015 at the global level while in LMICs, it was as high as 165% [13]. Overall, global antibiotic consumption is rising from time to time despite variations in consumption across countries.

In Africa, about 27.6 to 83.5% of hospitalized patients received antibiotics, with the highest consumption in West Africa (51.4–83.5%) followed by North Africa (79.1%), East Africa (27.6–73.7%), and South Africa (33.6–49.7%) [14]. In Sub-Saharan Africa, the consumption of antibiotics was reported to be the lowest compared with developed countries [6] and ranges from 19 DIDs in Sierra Leone from 2017 to 2019 [15] to 241.41 DIDs in Tanzania from 2017 to 2019 [16]. In Ethiopia, the national average antibiotic consumption was 15.36 DIDs from 2017 to 2019, with an 87.7% decrease rate (from 37.03 to 4.30 DIDs) [17], but it was 58.41 DIDs (average 11.78 DIDs) and increased by 16.4% (11.02 to 12.83 DIDs) from 2016 to 2020 [18]. But a recent analysis of regional antibiotic consumption based on distribution data from public supplier revealed 30.34 DIDs (average 5.33 DIDs), with an 87.4% (from 6.9 to 0.9) decrease rate from 2016 to 2022 [19]. In the hospital setting total antibiotic consumption in adult outpatient departments in teaching hospitals in Ethiopia was also very low which was 5.31 DDD per 100 outpatients per day [20].

Despite attempts to determine antibiotic consumption based on distribution and import data [17–19], hospital-level antibiotic consumption data is lacking in Ethiopia specifically in the study area. On the other hand, trends in bacterial infections and AMR in the study area were increasing from time to time [21, 22]. The strong correlation between AMR and antibiotic consumption [2–5, 23] warrants determining antibiotic consumption as a proxy indicator for AMR and is one of the potential strategies to tackle the growing threat of AMR [2]. Thus, this study was aimed to determine antibiotic consumption in the hospitals in Northwest Ethiopia.

Methods

Study area and period

A cross-sectional study was conducted in Debre Markos Comprehensive Specialized hospital (DMCSH), Felege Hiwot Comprehensive Specialized Hospital (FHCSH), and Tibebe Ghion Specialized Hospital (TGSH) in August 2022 based on retrospective antibiotic consumption data from July 2019 to June 2022. The hospitals are among referral Hospitals in the Amhara National Regional State [24], which serve more than 9 million people referred from regional hospitals,

and health centers in Northwest Ethiopia. The annual hospital visits from July 2019 to June 2022 (Inpatient and outpatient): TGSH (42464, 74201, 95858), FHCSH (87835, 96332, 111672), and DMCSH (110216, 104647, 105755), and the prevalence of bacterial infections in the hospitals accounted for 20% of total admissions [21]. Since September 2019, there has been an attempt to implement antibiotic stewardship programs (ASPs) in the hospitals in the region in collaboration with the Medicines, Technologies, and Pharmaceutical Services (MTaPS), although it was neither fully functional nor standardized. Antibiotic consumption in the hospitals in the region is mainly based on empiric therapy. Since we have used the Ethiopian fiscal year, it should be understood that 2012 = 2019/20, 2013 = 2020/21, 2014 = 2021/2022, and for the sake of convenience, we used the next year in the figures, i.e., 2020-2022.

Data collection process

The study included all systemic antibiotics procured and associated cost expenditures from July 2019 to June 2022 in the hospitals. Aggregate antibiotic consumption based on available records in the hospitals was used for analysis. Accordingly, general item records (FHCSH), BIN card (TGSH), and ABC analysis (DMCSH) were used as sources of antibiotic consumption data. Antibiotics were extracted and sorted based on the year, and each antibiotic's dosage form, strength, unit of measurement (packs, boxes (number of tablets or capsules), vials, ampoules, MIU, Unit dose (UD), etc.), amount procured, unit cost, and total cost were documented in the registry were used.

Outcome measures

Defined Daily Doses (DDD) were calculated for each antibiotic based on WHO's 2019 Anatomical Therapeutic Chemical Classification System (ATC/DDD) [25], and guidelines [8–11] for general use. It was standardized into DDDs per 1000 inhabitant days per year DIDs based on annual hospital visits for each hospital. In addition, the number of drugs accounting for 75%, and 90% of total antibiotic consumption (DU75% and DU90%), and the costs for the DU75% and DU90% antibiotics, and all antibiotics were also calculated as cost per DDD (USD/DDD). The DDD/1000 visits/day (DID) was calculated based on the following formula:

$$\frac{\text{DDD}}{1000 \text{ inhabitants} \times \text{day}} = \frac{\text{Amount of drug sold in one year (mg)}}{\text{DDD (mg)} \times 365 \text{ days} \times \# \text{ of inhabitants}} \times 1000 \text{ inhabitants}$$

Data Analysis

Data were cleared; DDDs and DIDs were calculated for antibiotics procured during the three years. DDD and DID were calculated separately for antibiotics marketed in fixed-dose combinations (e.g., Trimethoprim and Sulfamethoxazole (SXT)), but for antibiotics combined with beta-lactamase inhibitors, only the amount of active antibiotic was calculated. Based on the DDD, DU90%, and cost per unit, descriptive statistics and trend analyses using linear regression were computed using Excel. Finally, the results were presented in the table and figures.

Operational Definitions and definitions of terms

- **AWaRe antibiotic classification:** Access, Watch, and Reserve (AWaRe) classification is a useful tool developed by WHO to reduce AMR and ensure access to key antibiotics by balancing appropriate access to antibiotics and stewardship use. Access to antibiotics indicates the antibiotic of choice for each of the 25 most common infections, which should be available at all times, affordable, and quality-assured. Watch antibiotics include most of the highest-priority, critically important antibiotics for human medicine and veterinary use, which are recommended only for specific, limited indications, whereas Reserve antibiotics are those antibiotics that should only be used as a last resort when all other antibiotics have failed.
- **Cost expenditure for antibiotics:** shall mean money spent on purchasing antibiotics.
- **Defined Daily Dose (DDD):** The assumed average maintenance dose per day for a drug used for its main indication in adults.
- **Defined Daily Doses (DDD) per 1000 inhabitant days per year (DIDs):** To standardize the metrics of measurement, Defined Daily Doses (DDDs) per 1000 hospital visits per day were used to take into account the outpatient visits too. DID was used to measure antibiotic supply in the hospitals based on the store data, which was calculated as $DDDs * 1000 \text{ days} / (\text{annual hospital visits} * 365 \text{ days})$. DID can be interpreted as follows: in a representative sample of 1000 hospital visits, DDDs of the drug are utilized on average on any given day of the year analyzed.
- **Inhabitants:** Here, shall mean Annual hospital visits.
- **Drug utilization 90% (DU90%):** is an inexpensive, flexible, and simple method for assessing the quality of drug prescribing in routine health care for drugs accounting for 90% of the volume of the prescribed drugs after ranking the drugs used by volume of DDD.

Ethical consideration

Ethical approval was obtained from Addis Ababa University, the College of Health Sciences (protocol code: ERB/SOP/472/14/2022), and the School of Pharmacy (protocol code: 106/22/SoP). Before the study, ethical approval was obtained from the ethical review board of Addis Ababa University, College of Health Sciences. A support letter to the hospitals was obtained from the Amhara Public Health Institute (APHI). Since these were secondary data, informed consent was not obtained. All information obtained was kept confidential and used only for research purposes.

Results

During the three years, 9857569.79 DDD or 296.16 DIDs of antibiotics were consumed in the hospitals. The average yearly consumption rate was 98.72 DIDs where it was 28.1 DID in DMCSH, 45.58 in FHCSH, and 25.05 in TGSH.

Overall trends in antibiotic consumption

The overall consumption of antibiotics decreased by 11.4% (from 96.15 DIDs in 2020 to 85.23 DIDs in 2022) although it was increased by 15.1% (from 96.15 DIDs in 2020 to 110.67 DIDs 2021) and then decreased by 22.99% (from 110.67 DIDs 2021 to 85.23 DIDs in 2022). The overall trend in the consumption of antibiotics in the three hospitals decreased following a second degree polynomial equation as a function of $y = -23.95x^2 + 90.382x + 29.72$ ($R^2 = 1$) (Fig. 1).

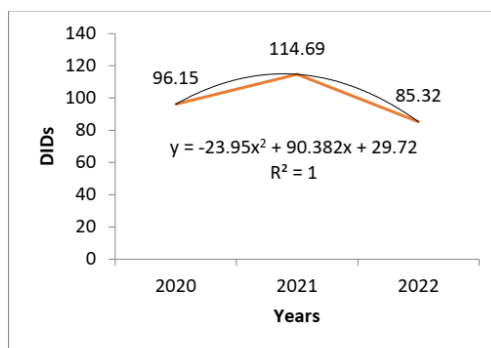


Fig. 1: Trends in Consumption of systemic antibiotics (July 2019 – June 2022), in the hospitals, in Northwest Ethiopia

Trend in antibiotic consumption in the hospitals

The trend in antibiotic consumption decreased by 43.9% in FHCSH, and 48.4% in TGSH as functions of $y = -12.968x^2 + 40.273x + 25.557$ ($R^2 = 1$) and $y = -21.967x^2 + 82.209x - 36.859$ ($R^2 = 1$), respectively, but in DMCSH it increased by 119% as functions of $y = 10.985x^2 - 32.099x + 41.022$ ($R^2 = 1$) ($R^2 = 0.7771$) (Fig. 2).

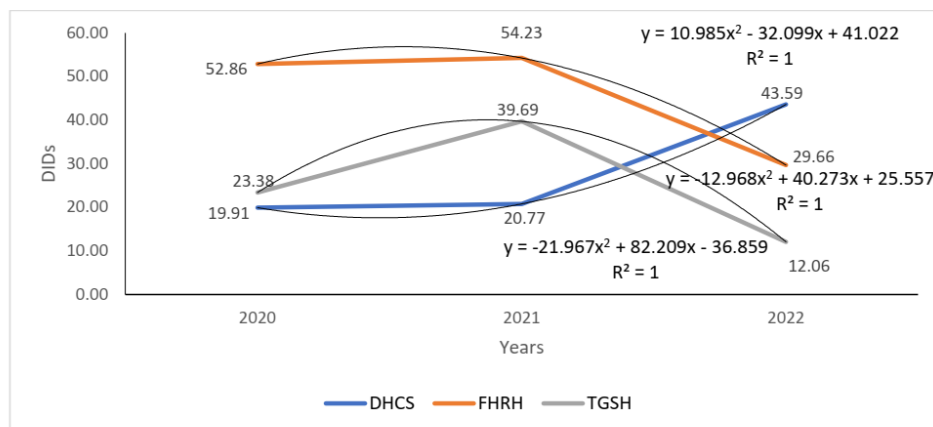


Fig. 2: Consumption of systemic antibiotics (July 2019 – June 2022), in the hospitals, in Northwest Ethiopia

Trends in antibiotic consumption based on class of antibiotics

The most commonly consumed classes of antibiotics were other beta-lactam antibacterials (J01D) with 135.12 DIDs (45.6%), followed by beta-lactam antibacterials, penicillins (J01C), and sulfonamides and trimethoprim (J01E), which were 56.87 (18.5%), and 40.45 (13.7%), respectively. Amphenicols (J01B) were the least consumed antibiotics, with 0.02 (0.01%) DIDs (Table 1).

Table 1: Consumption of antibiotics based on antibiotic class (July 2019 – June 2022), in the hospitals, in Northwest Ethiopia

Class of antibiotics	Facilities			
	DHCS	FHRH	TGSH	Total
Other beta-lactam antibacterials (J01D)	9.374	98.597	27.147	135.12
Beta-lactam antibacterials, penicillins (J01C)	27.959	7.722	19.192	54.87
Sulfonamides and trimethoprim (J01E)	9.478	19.998	10.970	40.45
Quinolone antibacterials(J01M)	14.078	4.623	6.119	24.82
Macrolides, and lincosamides (J01F)	5.332	2.539	7.193	15.06

Other antibacterials (J01X)	7.941	3.119	3.546	14.61
Tetracyclines (J01A)	9.934		0.924	10.86
Aminoglycoside (J01G)	0.155	0.153	0.044	0.35
Amphenicols (J01B)	0.017	0.001		0.02
Total	84.268	136.752	75.135	296.16

Consumption of antibiotics based on WHO AWaRe classification

Based on the WHO AWaRe classification, 145.32 DIDs (49.1%) of consumed antibiotics were from the Access category (40.65% in FHCSH, 35.09% in DMCSH and 24.26% in TGSH), 150.74 DIDs (51.6%) were from the Watch category (51.67% in FHCSH, 26.53% in TGSH and 21.81% in DMCSH), and 0.49 DIDs (0.2%) were from the Reserve category (all at DMCSH). Overall, between 2020 and 2022, consumption of Access antibiotics increased by 35.8% (from 42.57 to 57.80 DIDs), but consumption of Watch antibiotics decreased by 49.6% (from 53.58 to 27.02) (Fig. 3).

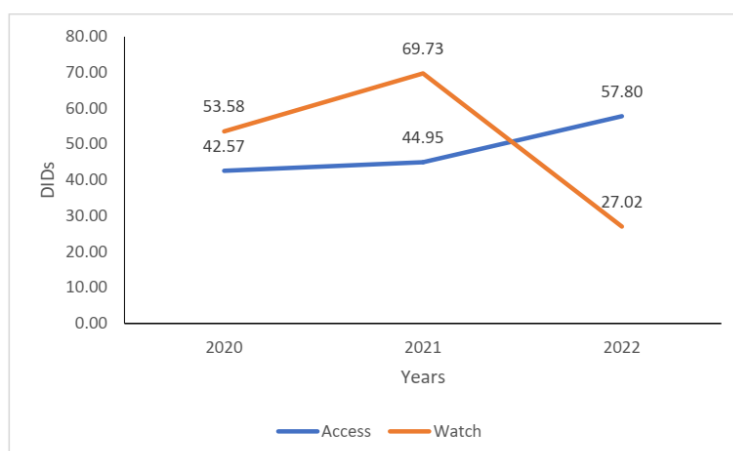


Fig. 3: Trends in antibiotic consumption based on WHO AWaRe classification (July 2019 - June 2022), in the hospitals, Northwest Ethiopia

Consumption of specific antibiotics

The consumption of oral antibiotics accounted for 191.41 DIDs (64.6%) and parenteral antibiotics for 104.74 DIDs (35.4%). Seven antibiotics constituted DU75%, and 11 antibiotics, namely ceftriaxone, SXT, cephalixin, amoxicillin, amoxicillin/clavulanic acid, cefuroxime, ciprofloxacin, doxycycline, cloxacillin, azithromycin, and metronidazole, constituted DU90% in increasing order of frequency. Consumption of ceftriaxone accounted for 84.29 DIDs of the total

antibiotic consumption in the hospitals, followed by SXT (35.64 DIDs), cephalexin (31.21 DIDs), amoxicillin (26.10 DIDs), amoxicillin/clavulanic acid (18.84 DIDs), cefuroxime (17.37 DIDs), and ciprofloxacin (17.34 DIDs) (Table 2).

Table 2: Consumption of specific antibiotics (July 2019 – June 2022), in the hospitals, Northwest Ethiopia

Antibiotics	Facility			
	DHCS	FHRH	TGSH	Total
Ceftriaxone	6.98	52.37	24.93	84.29
SXT	9.48	20.00	6.17	35.64
Cephalexin	1.71	28.37	1.13	31.21
Amoxicillin	15.42	2.83	7.85	26.10
Amoxicillin/clavulanic acid	3.45	2.31	13.09	18.84
Cefuroxime		17.35	0.02	17.37
Ciprofloxacin	7.57	4.27	5.50	17.34
Doxycycline	9.93		0.92	10.86
Cloxacillin	6.67	2.05	1.88	10.60
Azithromycin	4.25	1.49	3.14	8.88
Metronidazole	1.70	2.77	2.98	7.45
Vancomycin	5.71	0.35	0.56	6.63
Clarithromycin	1.00	0.96	3.92	5.87
Levofloxacin	5.68	0.09		5.77
Penicillin G	2.40	0.08	0.21	2.70
Norfloxacin	0.83	0.18	0.61	1.62
Ampicillin	0.03	0.45	0.96	1.43
Ceftazidime	0.15	0.16	0.54	0.84
Cefixime		0.25	0.32	0.57
Meropenem	0.53		0.00	0.53
Linezolid	0.49			0.49
Gentamicin	0.16	0.15	0.04	0.35
Erythromycin	0.09	0.08	0.13	0.30
Cefepime	0.01	0.04	0.18	0.23
Moxifloxacin		0.09		0.09
Cephazolin		0.05	0.01	0.06
Nitrofurantoin	0.03			0.03
Chloramphenicol	0.02	0.00		0.02
Clindamycin		0.01	0.01	0.02
Cefotaxime			0.01	0.01
Cephazolin			0.01	0.01
Total	84.27	136.75	75.13	296.16

* SXT: Sulfamethoxazole/Trimethoprim

Cost Expenditure for Antibiotics

Using the current exchange rate of 54.59 birr for a dollar as of July 20, 2023), the overall cost expenditure for antibiotic purchasing was USD 1,100,101.48 (60,054,539.90 Ethiopian Birr). The cost for parenteral antibiotics was USD 716794.5 (65.2%), and for oral antibiotics, it was USD 383307 (34.8%). The cost expenditure accounted for USD 659865.08 (59.98%) of Watch antibiotics, USD 439635.28 (39.96%), and the rest (0.05%) for Reserve category antibiotics. About USD 651776.29 (59.2%) of the total expenditure is accounted for the purchase of DU90% antibiotics, but 90% of the cost goes to the purchase of ceftriaxone (27.6%), vancomycin (14.7%), cephalexin (11.1%), metronidazole (8.5%), ceftazidime (5.7%), amoxicillin/clavulanic acid (4.7%), SXT (4.1%), ciprofloxacin (3.1%), cloxacillin (3.0%), ampicillin (3.0%), ampicillin (2.7%), and cefepime (2.6%). The average cost of antibiotics was USD 105.12 per DDD. The highest cost per DDD was accounted for ampicillin (USD17.57), nitrofurantoin (USD17.14), penicillin G (USD7.43), meropenem (USD6.82), and cefepime (USD5.35) (Table 3).

Table 3: Average cost expenditure (USD) per DDD (July 2019 - June 2022), in the hospitals, Northwest Ethiopia

Antibiotic	Average cost per DDD
Ampicillin	17.57
Nitrofurantoin	17.14
Penicillin G	7.43
Meropenem	6.82
Cefepime	5.35
Vancomycin	2.65
Ceftazidime	2.54
Cefotaxime	2.34
Grand Total	2.09
Cephazolin	2.02
Cephalexin	1.27
Cephazolin	1.11
Gentamicin	0.91
Clindamycin	0.51
Ceftriaxone	0.49
Metronidazole	0.46
SXT	0.42
Azithromycin	0.38
Ciprofloxacin	0.36
Cefixime	0.35

Amoxicillin/Clavulanic acid	0.30
Chloramphenicol	0.21
Norfloxacin	0.17
Moxifloxacin	0.17
Cloxacillin	0.14
Clarithromycin	0.09
Levofloxacin	0.09
Erythromycin	0.08
Amoxicillin	0.06
Cefuroxime	0.05
Linezolid	0.02
Doxycycline	0.01

*SXT: Sulfamethoxazole/Trimethoprim

Difference in antibiotic consumption

There is significant difference in antibiotic consumption in the hospitals ($P=0.000$) which high in FHCSH and TGSH compared with DMCSH (Table 4).

Table 4: Difference in antibiotic consumption (July 2019 - June 2022), in the hospitals, Northwest Ethiopia

Multiple Comparison of antibiotic in hospitals using Bonferroni						
(I) facility	(J) facility	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
FHRH	TGSH	-.1262776	.0862499	.430	-.332981	.080426
	DHCS	.3750051*	.0533394	.000	.247173	.502837
TGSH	FHRH	.1262776	.0862499	.430	-.080426	.332981
	DHCS	.5012826*	.0761814	.000	.318709	.683857
DHCS	FHRH	-.3750051*	.0533394	.000	-.502837	-.247173
	TGSH	-.5012826*	.0761814	.000	-.683857	-.318709

Discussion

Determining antibiotic consumption is critical in informing the need for, and evaluating ASPs at the hospital, regional, and national levels so as to combat AMR [26]. This study attempted to quantify antibiotic consumption based on available data from the three referral Hospitals in Northwestern Ethiopia from July 2019 to June 2022. In general, the overall consumption of antibiotics was 296.16 DIDs (average yearly consumption of 98.72 DIDs), which decreased by 11.3% from 96.15 DIDs in 2020 to 85.32 DIDs in 2022. The most commonly consumed classes

of antibiotics were other beta-lactam antibacterials (J01D), 135.12 DIDs (45.6%), and beta-lactam antibacterials, penicillins (J01C), 56.87 (18.5%). About 150.34 DIDs (50.8%) of the consumed antibiotics were from the Watch category, and 191.41 DIDs (64.6%) were orally administered. The consumption of Access category antibiotics increased by 35.8% (from 42.56 to 57.80 DIDs), but Watch category antibiotics decreased by 49.6% (from 53.58 to 27.02). Seven antibiotics constituted DU75%, and 11 antibiotics constituted DU90%. The consumption of ceftriaxone accounted for 84.29 DIDs, followed by SXT (35.64 DIDs), cephalixin (31.21 DIDs), and amoxicillin (26.10 DIDs). Total expenditure for antibiotic purchasing was USD 1,100,101.48, among which 59.98% accounted for Watch antibiotics, 59.2% for DU90% antibiotics, and 65.2% for parenteral antibiotics. The average cost expenditure for antibiotics was USD105.12 per DDD.

The current study revealed 296.16 DIDs (Average 98.71 DIDs) of systemic antibiotic consumption in the hospitals from July 2019 to June 2022. This was high compared with 14.3 DIDs between 2000 to 2018 in global level [6], 15.36 DIDs in Ethiopia at national level from 2017 to 2019 based on antibiotics registered at Ethiopian food and drug authority (EFDA) [17], 30.34 DIDs (average of 5.33 DIDs) from 2016 to 2022 in regional EPSA [19], and 58.95 DIDs from 2016 to 2020 in Ethiopia based on main branch of Ethiopian pharmaceutical supply agency (EPSA) [18]. It was still high compared with the 7.03 DIDs of antibiotic consumption rate from 2016 through 2021 in a secondary healthcare facility based on pharmacy issue data in Ghana [26], and 53.1 DIDs in adult outpatient departments in medical center of a teaching hospital in Ethiopia (JMC) [20]. The difference in consumption may reflect difference in prevalence of infectious disease and service provision in the inpatient verses outpatient departments and with hospital level aggregate verses pharmacy issue data.

The current study reported an 11.3% decrease in antibiotic consumption, from 96.15 DIDs in 2020 to 85.32 DIDs in 2022 which was almost similar to the global antibiotic consumption decreased by 18.7% from 2019 to 2020 [27], and three studies in public hospitals in China which reported decrease in antibiotic consumption by 29.4% (from 16.07 in 2012 to 11.35 in 2017) [28], 18.8% (from 12.94 in 2018 to 10.51 DIDs in 2020) [29], and 9% (from 14.48 DID in 2012 to 13.09 DID in 2020 [30]. Although decrease in trend of antibiotic consumption in the community in Ethiopia based on regional branch of Ethiopian pharmaceutical supply agency (EPSA) was similar, rate of decrease in the current study was low compared with 87.4%

decrease (from 6.7 in 2016 to 0.8 DIDs in 2022) in regional EPSA [19], and the national consumption in Ethiopia which reported 87.2% decrease (from 37.03 in 2017 to 4.75 DIDs in 2019) in antibiotic consumption based on antibiotics registered at EFDA [17]. It was still different from another study in Ethiopia which reported 16.4% increase (from 11.02 in 2016 to 12.83 DIDs in 2020) in main EPSA Branch [18], and progressively increased global consumption trends from 36% increase in between 2000 and 2010 [2] to 39% (11.3–15.7 DIDs) between 2010 and 2015 [12] and 46% from 2000 to 2018 [6]. A study in Ghana in a secondary healthcare facility reported a lack of difference in antibiotic consumption between 2016 and 2021 [26]. Although the global antibiotic consumption was projected to increase by 200% in 2030 [12], slight decrease in consumption in the current study might be attributed to a reduced supply of antibiotics from regional EPSA [19].

The current study 135.12 DIDs (45.6%) consumption of antibiotics accounted for other beta-lactam antibacterials (J01D). This was similar to antibiotic consumption reports based on hospitalized patients' at Jimma University Medical Center, which reported 42.8% consumption of cephalosporines [31], although another study in outpatient settings reported major consumption of tetracycline antibiotics in JMC in Ethiopia [20]. But this was against the 39% consumption of penicillins from all class of antibiotics at global level [12], and antibiotic consumption in Ethiopia based on regional EPSA [19] and main EPSA branch [18], which reported 49.2% and 39% consumption of beta-lactam antibiotics, penicillins (J01C), respectively. The difference is also noted in studies in Bhutan, where the penicillin group of beta-lactam antibacterials (J01C) were the most commonly consumed antibiotic groups [32]. The difference might be attributed due to the overwhelming consumption of ceftriaxone and other cephalosporins in the hospitals probably because it is considered the first-line treatment options for common infections as evidenced based on the report of sepsis (28.0%), pneumonia (24.9%), and appendicitis (10.6%) in the study area [21].

The current study revealed only 145.32 DIDs (49.1%) of Access category antibiotic consumption, which was against WHO's recommendation which states at least 60% of antibiotic consumption should be in access category [11]. It was also low compared to 77.1% [19], 67.87% [17], and 63.3% [26] consumption of antibiotics from Access category in regional branch of EPSA in Ethiopia, national level consumption based on EFDA in Ethiopia and in secondary health facilities in Ghana. The report from current study was similar to a report from the

outpatient departments in JMC in Ethiopia, which reported 49.31% consumption of Access category antibiotics [20], but it was high compared with another study in JMC which 34% consumption of "Access" group antibiotic consumption among hospitalized [31]. The current study reported 0.49 DIDs (0.2%) consumption of Reserve group antibiotics, which was against other studies [17-20] that didn't report from the category, but it was lower than 8.4% of antibiotics consumption in "Reserve" group among hospitalized patients in JMC [31], although it was not reported from outpatient consumption based on another study at JMC [20]. High consumption of Watch category antibiotics could be due to the use of specific antibiotics, classified within the Watch group, to respond to the high prevalence rates of specific pathogens.

In the current study, the consumption of Access category antibiotics increased by 35.8.7% (from 42.57 in 2020 to 57.80 DIDs in 2022), but the consumption of Watch antibiotics decreased by 49.6% (from 53.58 in 2020 to 27.02 DIDs in 2022). This was different from the reported consumption of access category antibiotics at regional EPSA which reported decrease by 72.7% (from 5 in 2017 to 0.5 DIDs in 2022), although the consumption of Watch antibiotics was similarly decreased by 54.3% (from 1.8 in 2017 to 0.4 DIDs in 2022) [19]. The national antibiotic consumption from 2017 to 2019 was also decreased by 91.5% for Access and 75.6% for watch category antibiotics [17]. In contrast to the current study, the WHO assessment from 2000 to 2015 reported increased consumption of Watch category antibiotics by 90.9% (from 3.3 to 6.3 DIDs) and 26.2% (from 8.4 to 10.6 DIDs) in access category antibiotics [13]. A progressive increase in the consumption of Access category antibiotics was reported between 2018 and 2020 in China [29]. Increased trend in consumption of Access category antibiotics may be related to the focus on relatively low-cost antibiotics due to decreased supply from public supplier, and the increased cost of antibiotics from private suppliers as evidenced from global market.

The current study revealed 191.41 DIDs (64.6%) for consumption of oral antibiotics and 104.74 DIDs (35.4%) for parenteral antibiotics. This was almost similar to the consumption of oral antibiotics in healthcare institutions in China, which reported less than 70% oral antibiotic consumption [29]. But it was low compared with 96.2% consumption of oral antibiotics and 3.8% for parenteral antibiotics in regional EPSA in Ethiopia [19], and another national study in Ethiopia which reported 98.6% of oral antibiotic consumptions [17]. Point prevalence survey of

antibiotic use in hospitals in Uganda reported 11% of orally administered and 88% administered parenteral antibiotics [33], although analysis of central store supplies to inpatient care health facilities in Uganda reported parenteral route of administration accounted for 59.9% and oral route 40.1% [34], which is different from the current study. The need to treat high prevalence rates of bacterial infections in inpatient wards might have contributed to the higher use of parenteral antibiotics such as ceftriaxone compared with oral antibiotics. Overuse of parenteral antibiotics needs to be closely monitored.

DU90% is an inexpensive, flexible, and simple method for assessing the quality of antibiotic prescriptions in routine healthcare [35]. Studies on antibiotic consumption using the DU90% methodology have also been applied at the community level [36]. In the current study, 11 antibiotics (ceftriaxone, SXT, cephalixin, amoxicillin, amoxicillin/clavulanic acid, cefuroxime, ciprofloxacin, doxycycline, cloxacillin, azithromycin, and metronidazole) constituted DU90%. The trend analysis in regional EPSA in Ethiopia revealed seven antibiotics (amoxicillin, doxycycline, ciprofloxacin, cloxacillin, metronidazole, ampicillin, and piperacillin/tazobactam) constituting DU90% [19], and the national antibiotic consumption in Ethiopia reported nine antibiotics (amoxicillin, doxycycline, ciprofloxacin, cloxacillin, metronidazole, SXT, ampicillin, and norfloxacin) constituting DU90% [13]. The difference might be attributed in selection of common access category antibiotics in the public suppliers and concern to cover common infectious disease syndromes in hospitals.

In this study, the consumption of ceftriaxone (28.5%), SXT (12%), cephalixin (10.5%), and amoxicillin (8.8%) was most common. A point prevalence survey of antibiotic use across 13 Hospitals reported use of ceftriaxone (37%), metronidazole (27%), and gentamicin (7%) [33], but Metronidazole (17.5%), amoxicillin-clavulanic acid (13.4%), ceftriaxone (12.1%), and cefuroxime (10.0%) were the most commonly consumed antibiotics in a tertiary healthcare facility in Ghana [26]. The difference in magnitude, type, and number of drugs from DU90% at the national and regional levels may indicate the presence of alternative private supplies to the hospitals. Sepsis/septic shock (29.9%), pulmonary tract infections (25.8%), intra-abdominal infections and abscesses (15.8%), and meningitis and other CNS infections (8.3%) were the most common bacterial infectious syndromes in the study area [21], which justifies the most commonly, used antibiotics in the current study.

In the current study, the total expenditure for antibiotics was USD 1,100,101.48. This was lower than the USD56.0 billion spent on antibiotics between 2010 and 2015 in healthcare settings in the United States [35]. The study revealed that the cost of parenteral antibiotics accounted for 65.2%, 59.98% of Watch Category antibiotics, and 59.2% of DU90% antibiotics. A substantial amount of money can be saved without compromising the quality of care by using recommended and commonly utilized antibiotics [36].

Determining antibiotic consumption based on procurement or sales data serves as an overall proxy indicator for actual patient level exposure of antibiotics in the hospitals [37]. The high antibiotic consumption in the hospitals may directly implicate a high prevalence of bacterial infections in the hospitals accounted for 20.1% of total admissions [21] and high prevalence (59.9%) of AMR in the area [22] although there was decreased supply from public drug supplier was reported to be low justifying alternative supply from private suppliers [19]. Reducing AMR which is complex process involving multiple factors beyond antibiotics [38] might need reducing unnecessary antibiotic consumption while improving access to antibiotics, implementing and monitoring of ASPs, and tracking and using data as possible advanced solutions to tackle AMR [39]. Implementing multidisciplinary ASPs in healthcare facilities is strongly recommended to reduce inappropriate antibiotic use and AMR [40]. Thus, implementation of context-specific, locally tailored ASPs is highly recommended in the hospitals.

The strength of this study is that it documented hospital-level consumption of systemic antibiotics in Ethiopia over a three years period which could be for the first time, using WHO-recommended standard methodology and applying a standardized measurement system (DID) to estimate the exposure of the patients visiting hospital to antibiotics in the hospitals. But, being secondary procurement data, there may be limitations since wouldn't clearly delineate antibiotics used in inpatients and outpatients. It will not necessarily show actual patient use in the hospitals, which depends on the prescribing behavior of physicians. We used the available data in the hospitals and didn't conduct validation for antibiotic consumption. Thus, it will not show actual patient-level use of antibiotics in hospitals than simply collecting available resources on drug procurement and extracting antibiotics from them. It also didn't take into account the possibility of unrecorded drugs in the hospitals, and seasonal variation in antibiotic consumption.

In conclusion, antibiotic consumption is very high in the hospitals, and decreased. Although the consumption of Access category antibiotics is increasing from time to time, the consumption is very low which could lead to lack of essential antibiotics. Consumption of oral antibiotics was low, and eleven antibiotics constituted DU90%. About 60% of the cost was used for DU90% antibiotics. Attention has to be paid to minimizing consumption of the Watch category and parenteral antibiotics. AMR is a multifactorial problem resulting from multi-sectorial failures in antibiotics use, and enforce stewardship measures appropriately. This calls for a prospective mixed-methods study to understand the spiral of antibiotic usage and AMR. Optimizing use and reducing unnecessary consumptions that fuel AMR is crucial.

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Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Transparency declarations: All Authors declare that there is no conflict of interest

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Review Article

Relationship between Antibiotic Consumption and Resistance: A Systematic Review

Asrat Agalu Abejew^{1,2}, Gizachew Yismaw Wubetu,³ and Teferi Gedif Fenta¹

¹Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

²Department of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia

³Amhara Public Health Institute, Bahir Dar, Ethiopia

Correspondence should be addressed to Asrat Agalu Abejew; asratagl@yahoo.com

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Background. Unreserved use of antibiotics exerted selective pressure on susceptible bacteria, resulting in the survival of resistant strains. Despite this, the relationship between antibiotic resistance (ABR) and antibiotic consumption (ABC) is rarely studied. This systematic review aims to review the relationship between ABC and ABR from 2016 to 2022. **Methods.** Articles published over 7 years (2016–2022) were searched from December 23 to 31, 2022. The search strategy was developed by using keywords for ABC and ABR. From 3367 articles, 58 eligible articles were included in the final review. **Results.** The pooled ABC was 948017.9 DPDs and 4108.6 DIDs where over 70% of antibiotics were from the Watch and Reserve category based on the WHO AWaRe classification. The average pooled prevalence of ABR was 38.4%. *Enterococcus faecium* (59.4%), *A. baumannii* (52.6%), and *P. aeruginosa* (48.6%) were the most common antibiotic-resistant bacteria. Cephalosporins (76.8%), penicillin (58.3%), and aminoglycosides (52%) were commonly involved antibiotics in ABR. The positive correlation between ABR and consumption accounted for 311 (81%). The correlation between ABR *P. aeruginosa* and ABC accounted for 87 (22.7%), followed by 78 (20.3%) and 77 (20.1%) for ABR *E. coli* and *K. pneumoniae* with ABCs, respectively. Consumption of carbapenems and fluoroquinolones was most commonly correlated with resistance rates of *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and *A. baumannii*. **Conclusion.** There is a positive correlation between ABC and the rate of ABR. The review also revealed a cross-resistance between the consumption of different antibiotics and ABR. Optimizing antibiotic therapy and reducing unnecessary ABC will prevent the emergence and spread of ABR. Thus, advocating the implementation of stewardship programs plays a pivotal role in containing ABR.

1. Introduction

The discovery of antibiotics is the most significant achievement in the twentieth century [1]. It changed medical practice and significantly decreased morbidity and mortality associated with bacterial infections. In recent years, the emergence and spread of antibiotic-resistant pathogens on the one hand and decreased invention of new antibiotics on the other hand challenged healthcare [2, 3]. High rates of resistance against frequently used antibiotics to treat infections have been observed worldwide, resulting in running out of effective antibiotics to treat common infections [4]. Due to this, access to antibiotics remains a critical issue

globally [3, 5]. According to the Centers for Disease Control and Prevention (CDC), there were 2,868,700 infections due to resistant pathogens and 35,900 deaths from antibiotic-resistant bacterial infections each year [6].

ABR is a natural phenomenon augmented by human actions such as the inappropriate use of antibiotics [7]. Increased utilization of antibiotics results in an increased frequency of inappropriate antibiotic use [8]. Given the association between antibiotic use and the selection of resistant pathogens, inappropriate use of antibiotics is often used as a surrogate marker for the avoidable ABR [9]. Thus, the increase in bacterial resistance is contributed by selection pressure on antibiotics as a result of use, overuse, and misuse

[10–12], and total consumption of antibiotics is the critical factor in selecting resistance [11]. There were individual studies that confirmed the correlation between ABC and ABR patterns [13–17]. Antibiotic stewardship programs (ASPs) are usually aimed at reducing overall ABC, and thus, preventing and reversing resistance [1, 11]. Thus, it is recommended to monitor antibiotic prescribing to improve the quality of antibiotic use and to reduce ABR [18]. Thus, this review aims to determine the relationship between ABC and rates of ABR based on articles published globally from 2016 to 2022.

2. Methodology

2.1. Study and Data Collection. Eligible articles were identified by the search strategy developed by using keywords for antibiotic resistance and ABC. Mainly the PubMed (Medline) database was used to search for eligible articles. Additional articles were identified by searching from Google Scholar. Searches were performed for 7 years, and it was performed from December 23 to 31, 2022. Search terms used included a combination of keywords like “drug resistance,” “antimicrobial resistance,” “bacterial resistance,” “antibiotic resistance,” “antibiotic use,” “ABC,” “antimicrobial use,” and “antimicrobial consumption.” Articles were initially reviewed based on title and abstracts, and then, the whole document was read to select eligible articles for review. Articles that had determined the correlation between ABR and ABC using correlation coefficients and association at a P value of 0.05 were included in the review. Thus, articles relating to nonhuman infections, previous systematic reviews, commentaries, editorial letters, and available only in the abstracts were excluded from the review (Figure 1).

For the sake of discussion, the correlation coefficients were classified as very strong (0.9–1), strong (0.7–0.89), moderate (0.4–0.69), weak (0.1–0.39), and negligible (<0.1) [19]. Finally, the results were compiled and described. The defined daily dose (DDD)/100(0) patient days (DPDs) and DDD/1000 inhabitant days per year (DIDs) were used to report ABCs.

3. Results

3.1. General Description of Articles Included in the Review. Overall, 58 articles [20–77] published globally from 2016 to 2022 were included in the systematic review. The summary of articles included, including the correlation between bacterial resistance and ABC, is summarized and annexed in Annex 1.

The majority of the articles 13 (22.3%) were published in China [21, 25–28, 42, 60, 62–64, 68, 72, 77], 4 (6.9%) Europe [48, 49, 74, 75], 4 (6.9%) South Korea [31, 54, 61, 65], 4 (6.9%) Serbia [34, 36, 39, 52], 3 (5.2%) Japan [20, 30, 40], 2 (3.4%) Italy [22, 33], 2 (3.4%) Thailand [35, 57], 2 (3.4%) France [46, 56], 2 (3.4%) Spain [43, 59], 2 (3.4%) Slovenia [47, 71], 2 (3.4%) Switzerland [45, 70], and the rest were in different countries [23, 29, 32, 37, 38, 41, 44, 50, 51, 53, 55, 58, 66, 67, 69, 73, 76, 77]. The majority of the articles 11 (23.4%) were published in 2017 [22, 33, 36, 44, 47, 48, 52, 56, 59, 64, 67],

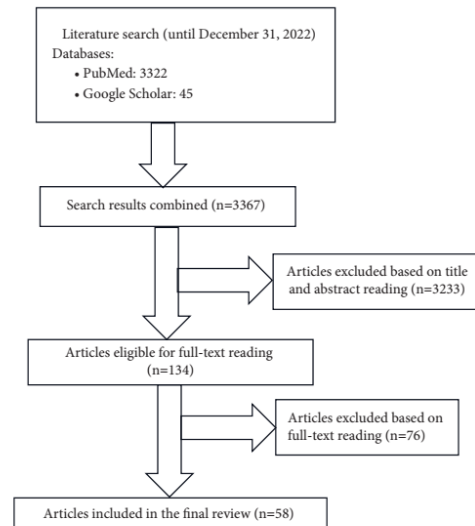


FIGURE 1: Flowchart for selection of articles for systematic review.

2018 [20, 23, 26, 35, 45, 46, 53, 54, 61, 63, 65], 2019 [21, 25, 30, 31, 40, 42, 43, 50, 51, 55, 62], 2021 [24, 29, 32, 38, 43, 60, 69–71, 75, 76], and each 5 (8.6%) in 2016 [34, 37, 41, 57, 58] and 2022 [68, 72–74, 77], but only 4 were published in 2020 [27, 38, 39, 49]. Almost all 53 (91.4%) of the articles were based on retrospective data, and the rest (8.6%) were prospective observational studies.

3.2. Antibiotic consumption. ABC was measured by different metrics. The unit of measure for ABC was not uniform for all articles. The units of ABC were standardized to 1000 patient days (DPDs) [21–23, 25, 30, 31, 35, 37, 40, 41, 44, 46, 49–52, 55–61, 64–68, 77] and 100 patient days (DPDs) [20, 26–29, 32–34, 36, 38, 39, 42, 43, 45, 53, 69, 70, 73, 76], but in addition, DIDs [30, 40, 47, 48, 56, 59, 65, 66, 68, 71, 72, 74, 75], grams [24], and average/percentage trend [54, 62] were used to measure ABC. Accordingly, about 948017.9 DPDs (904622.9 standardized per 1000 patient days and 4339.5 per 100 patient days) and 4108.6 DIDs were reported, but about 173616.9 and 99800 were reported in average consumption and in grams, respectively. More than 70% of antibiotics were consumed in the Watch and Reserve categories based on the WHO AWaRe classification. Due to a lack of uniform measurement and recording of antibiotics among the articles, overall ABC was not summarized (Table 1).

3.3. Prevalence of Antibiotic Resistance. ABR was reported as a percentage (rate, trend, or prevalence) in all articles except three, which reported the incidence density of ABR [22, 52, 63, 68]. The average pooled prevalence of antibiotic-resistant bacteria was 38.4%, with *Enterococcus faecium* (59.4%), *A. baumannii* (52.6%), *P. aeruginosa* (48.5%), coagulase-negative *Staphylococcus* (43.7%), *Enterobacter*

TABLE 1: Pooled antibiotic consumption by different metrics of measurement, 2016–2022 (N = 58).

Antibiotics	Metrics			
	Average	DDD/100 patient days	DDD/1000 patient days	DDD/1000 inhabitant days Grams
Amikacin		6.0	22094.2	20.9 3300
Aminoglycosides	155.2	12.4	797.6	
Aminopenicillins				944.0
Aminopenicillins and enzyme inhibitors				682.3
Amoxicillin		1.5	110.9	
Amoxicillin/ampicillin		2.7		
Amoxicillin/clavulanate		104.4	258.0	
Amphenicols			5.2	
Ampicillin			21.4	
Ampicillin/sulbactam		3.0	61.3	
Aminoglycosides		3.8		
Antipseudomonal			68.9	
Benzylpenicillin			2.2	
Biapenem		154.6	7.1	
Carbapenems	548.2	190.9	888.0	2.2
Cefazolin		2		
Cefepime		8.6	8382.6	6.1
Cefixime			72.0	
Cefotaxime			2156.2	0.1
Cefoxitin				0.0
Cefpodoxime			38.0	
Ceftazidime		3.5	70434.2	2.9
Ceftazidime/cefepime		3.2		
Ceftriaxone		136.3	128296.9	
Cefuroxime		5.0	42.1	2500
Cephalosporins	53411.4	256.1	14660.7	658.8
Cepharmycin			2200.0	0.1
Ciprofloxacin		136.6	275875.2	26.7 3000
Clarithromycin			10.7	
Clindamycin		6.3	53.4	1000
Cloxacillin/cefazolin			85.2	
Colistin		7.1	883.3	
Daptomycin			6.24	
Doripenem			2.53	
Doripenem		72.5		
Ertapenem		4.1	79.8	
Erythromycin			0.8	
Flucloxacillin		5		
Fluoroquinolones	28630.6	58.7	7554.0	632.1
Fosfomycin			5.4	0.0
Gentamicin		81.4	81311.8	42.7
Glycopeptides	298.3	11.1	118.6	
Imipenem		225.7	57558.2	
Imipenem/cilastatin			99.2	2.6
Levofloxacin		100.1	573.4	7.1
Lincosamides			44.5	
Linezolid	21504.6	365.9	5.3	
Macrolides		2.2	9552.3	102.55
Meropenem		607.3	50276.5	6.3 4800
Metronidazole		102.5	85.8	
Monobactams			4.4	
Moxifloxacin		1.91	153.3	
Nitrofurantoin			0.0	1.32 6000
Norfloxacin		0.8	66.5	
Ofloxacin			141.5	
Oxacephems			30.0	
Oxacillin		2	13.4	6000
Oxazolidinone			7.5	
Panipenem		30.5		
Penicillin		54.9	308.5	12.5

TABLE 1: Continued.

Antibiotics	Metrics				
	Average	DDD/100 patient days	DDD/1000 patient days	DDD/1000 inhabitant days	Grams
Piperacillin/tazobactam	69068.6	77.2	8614.4	22.3	65000
Polymyxin			2.9		
Rifampicin			84.2		
Sodium fusidate			0.3		
Sulfonamides			30.0		
Teicoplanin		1.6	38.9		
Tetracyclines			53.5	890.2	
Tigecycline		8.5	27.0		
Tobramycin			4.7		
Trimethoprim/sulfamethoxazole		1.7	156049.4	0.2	2200
Vancomycin		214.4	97.0		6000
Others		1265.7	4109.8	44.8	0
Total	173616.9	4339.5	904622.9	4108.6	99800

(46.1%), and *P. mirabilis* (48.5%) being the most common resistant bacteria. Cephalosporins (76.8%), penicillin (58.3%), aminoglycosides (52%), fluoroquinolones (48.3%), tetracyclines (48.6%), and carbapenems (30%) were resistant in a different way for each bacterium (Table 2).

3.4. Distribution of Antibiotic Consumption and Resistant Bacteria. The overall systematic review of 58 articles revealed a positive association between bacterial resistance and ABC, both in community and hospital settings. Except for some antibiotics, either increased consumption was associated with increased resistance, or decreased consumption was associated with decreased resistance. The analysis revealed that about 311 (81%) of the correlations between ABC and the ABR rate were directly related to ABC, but 73 (19%) were negatively correlated, indicating the protective nature of ABC for the development of resistance. *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and *A. baumannii* were the bacteria for which a relationship between ABC and the resistance rate or pattern was commonly studied. About 73 (83.9%), 63 (81.8%), 68 (87.2%), and 53 (85.5%) antibiotics were positively correlated with the resistance rates of *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and *A. baumannii*, respectively (Table 3).

3.5. Relationship between ABC and ABR. Here, the relationship between ABC and ABR is described for each bacterium based on the correlation coefficient reported by articles [20–78]. However, it has to be noted that all studies did not provide detailed information and similar reports.

There was a very strong correlation between the consumption of meropenem and the incidence of carbapenem-resistant *P. aeruginosa* [44] and meropenem-resistant *P. aeruginosa* [69], penicillin with the incidence of combined-resistant *P. aeruginosa* [44], imipenem [57], and ertapenem [69] with imipenem resistance *P. aeruginosa* [57, 69]. There was also a very strong correlation between amikacin consumption and the resistance rate of *P. aeruginosa* to amikacin [24] and between piperacillin/tazobactam and piperacillin/tazobactam-resistant *P. aeruginosa*

[69]. Similarly, there was a strong correlation between imipenem and meropenem and the rate of carbapenem-resistant *P. aeruginosa* [34], carbapenems with the rate of imipenem-resistant [44], meropenem-resistant [44], carbapenem-resistant [44], and ceftazidime-resistant [77] *P. aeruginosa*. There was also a very strong correlation between ciprofloxacin consumption and the resistance rate of *P. aeruginosa* [42].

A strong correlation was observed between the consumption of aminoglycosides and the rate of *P. aeruginosa* resistance to amikacin and gentamicin, gentamicin with the rate of aminoglycoside-resistant *P. aeruginosa* [34], and levofloxacin with the resistance rate of *P. aeruginosa* to levofloxacin [42]. A moderate correlation was found between the consumption of extended-spectrum antibiotics and cephalosporin with resistant *P. aeruginosa* [37], piperacillin/tazobactam with the incidence of combined-resistant *P. aeruginosa*, and amikacin with aminoglycoside-resistant *P. aeruginosa* [34]. Moderate correlations were found between the consumption of carbapenem and the rate of carbapenem-resistant *P. aeruginosa* [37, 57], carbapenem with imipenem and meropenem-resistant *P. aeruginosa* [30], and amikacin, gentamicin, and levofloxacin with resistant *P. aeruginosa* to respective antibiotics [72].

Some studies reported a decreased resistance rate of *P. aeruginosa* from the consumption of carbapenems. There was a very strong negative correlation between consumption of carbapenem and resistance rates in *P. aeruginosa* [20, 57], a strong negative correlation between carbapenem and the rate of imipenem resistance in *P. aeruginosa* [25], and a moderate negative correlation between carbapenem and the rate of carbapenem-resistant *P. aeruginosa* [37], and amikacin was very strongly correlated with decreased rates of multidrug-resistant (MDR) *P. aeruginosa* [57].

There was also cross-resistance between ABC and resistance to another antibiotic, which was also common. There was a very strong correlation between consumption of ceftazidime and meropenem-resistant *P. aeruginosa* [69]. There is a very strong correlation between the consumption of carbapenems and the incidence density of *P. aeruginosa* resistance to third-generation cephalosporins and aminoglycosides [22] and aminoglycosides with the rate of imipenem resistance in *P. aeruginosa* [25]. There was a very

Antibiotics	<i>A. baumannii</i>	CON <i>slapfeyceci</i>	<i>E. coli</i>	<i>Enterobacter</i>	<i>Enterobacter</i> <i>cloacae</i>	<i>Enterobacter</i> <i>faecium</i>	<i>Enterobacter</i> <i>jeikei</i>	<i>Enterobacteriaceae</i>	<i>H. influenza</i>	<i>H. pylori</i>	<i>K. pneumoniae</i>	<i>N. meningitidis</i>	<i>P. aeruginosa</i>	<i>P. mirabilis</i>	<i>S. aureus</i>	<i>S. pneumoniae</i>
3GC			24.4	17.8		60					37.5		17.7			40.6
Amikacin	43.3	3	34.5								63.0		45.1			59.6
Amphotericin B	60.8				64.0											32.4
Antipseudomonals				5.3	24.5											24.5
Antipseudomonals																
Anisoxillin		62.0								0.2					46.0	36.1
Anisoxillin/clavulanic acid		39.0							20.0		19.8				24.6	24.6
Ampicillin	26.6	83.4			20.8	97.7			84.0		26.4			9.21	67.4	67.4
Ampicillin/sulbactam		57.5									52.1				40.7	
Aztreonam		22.1		20.4							36.0				26.2	
Benzylpenicillin															1.0	
Carbapenems	55.5	8.6	74.1								23.4		33.3	53.8	1.0	33.6
Cefaclor															55.5	
Cefepime	56.7	62.3		18.2					55.5		69.7				27.7	27.7
Cefepime/sulbactam		8.8									16.4		22.0			
Cefotaxime	100.0											11.0				59.0
Cefotaxime		27.3									20.0		100.0		35.1	46.8
Cefoxitin		0.6									10.3				10.3	10.3
Ceftazidime	66.4	17.0													47.6	
Ceftazidime/cefepime	95.2	25.3		24.8							29.5		100.0		25.7	47.6
Ceftazidime	62.8	41.3		20.8	25.4						32.5		25.3		32.3	32.3
Ceftazidime		87.4									37.6		22.9		59.1	59.1
Chloramphenicol		87.4									19.5		91.4		38.2	45.6
Ciprofloxacin	56.2	57.8	36.3	1.0	5.1	86.0			3.9		68	0	0	48.5	0	19.7
Clarithromycin															0	0
Clindamycin															6.0	5.0
Clindamycin															6.0	5.0
Colistin																
Doripenem	3.8															
Ertapenem	24.4			18												
Erythromycin																
Fluoroquinolones	71.7	18.2	39.5		26.7						42.7		38.8		48.3	48.3
Fosfomycin		1			16.0						27.9				14.5	14.5
Fosfomycin		14									80				47	47
Gentamicin	40.4	50.7	22.5	4.5		59.1					19.1		21.6	29.2	28.3	27.6
Glycopeptides															33.0	33.0
Imipenem	51.4	0.6		8.3							19.9		27.7		27.2	27.2
Imipenem/cilastatin															13	13
Levofloxacin	21.2	46.2		1.2		70.0			15.8		13.5		30.3	17.9	0.3	26.9
Linzolid	11.9															

TABLE 3: Distribution of correlation between ABC and antibiotic-resistant bacteria, 2016–2022 (N = 58).

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)										
		Positive and negative correlation between ABC and rate of resistance		<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>N. gonorrhoeae</i>	<i>A. baumannii</i>	<i>E. cloacae</i>	MRSA	Others (11)	
Overall correlation between ABC and rate of resistance												
Carbapenem	Carbapenem	87	77	78	8	62	17	26	29			
	Levofloxacin	6(2)	8(1)	3		11	3	1	1			
	Imipenem	4(1)		0/1		2			0			
	Ceftazidime	1	0/1						0			
	Amikacin						1		0			
	Fluoroquinolone	1	1						0			
	3GC		1	1					0			
Monobactam	Meropenem	2							0			
	Ciprofloxacin			0/1					0			
	Monobactam											
Meropenem	Carbapenems					1	2					
	Meropenem	3				1		1	0			
	Piperacillin/tazobactam								1			
Cefepime/Cefotaxime	Carbapenems	2							0			
	Cefepime/Cefotaxime	1		2(1)		2			1			
	Imipenem	1(1)	1			1			0			
Imipenem	Meropenem	1	1									
	Piperacillin/tazobactam	1										
	Carbapenems	1							0			
Imipenem/cilastatin	Imipenem/cilastatin	1	1	1				0/1	0			
	Piperacillin/tazobactam	4	1	2		2	0/1	0/1	3			
	Imipenem		1									
Piperacillin/tazobactam	Meropenem		1			1						
	Aminoglycoside		1						0			
	Linezolid											
Fluoroquinolone	Linezolid								1			
	Fluoroquinolone	3	3(1)	5	1	1			3			
	Trimethoprim/sulfamethoxazole		1						0			
	Levofloxacin			3		2			1			
	Imipenem	1				0/1			0			
	Ceftazidime		2						0			
	Amikacin						1		0			
Levofloxacin	Carbapenem		0/1	1(1)					1			
	Ciprofloxacin	2(2)	3(1)	3(1)	1	3	0/1	1(2)	3			
	3GC		1	2					0			
	Levofloxacin											
Levofloxacin	Levofloxacin	2		1		1		1	0			
	Fluoroquinolone	1	1	1					0			
	Carbapenem		1						0			

TABLE 3: Continued.

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)						
		<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>N. gonorrhoeae</i>	<i>A. baumannii</i>	MRSA	Others (11)
Ciprofloxacin	Ciprofloxacin	2(1)	2	3	1 (1)			1
	Carbapenem		0/1					0
	Meropenem					1		
	Imipenem					1		
Norfloxacin	Piperacillin/tazobactam							
	Fluoroquinolone			1				0
Ofloxacin	Norfloxacin		0/1	1				0
	Carbapenem							0
Beta-lactam/beta-lactamase inhibitor	Ofloxacin		0/1	0/1				0
	Carbapenem							0
	Beta-lactam/beta-lactamase inhibitor		1	2				0
	Carbapenem			1		4	2(1)	0
Beta-lactam/beta-lactamase inhibitor	Levofloxacin		2					0
	Imipenem	2				1		0
	Piperacillin/tazobactam	0/1						0
	Ceftazidime	4						0
Amoxicillin/clavulanate	Piperacillin/tazobactam							0
	Amoxicillin/clavulanate	1	1(1)	2			1(2)	2
	3GC		1					0
	Cephalosporin							0
Cephalosporin	Amoxicillin/clavulanate	1	7(1)	7	1	1	2	0
	Trimethoprim/sulfamethoxazole			1				0
	Levofloxacin		1	1		1		0
	3GC		1	2				0
Aminoglycosides	Ciprofloxacin				1			0
	Carbapenem		1			3		0
	Piperacillin/tazobactam	2	0/1					0
	Cefotaxime			2				0
Aminoglycosides	Cefepime	0/1	2	2(1)				0
	Ceftazidime		0/1					0
	Aminoglycosides	1						0
	3GC		1(1)	1(1)		2(2)	0/1	0
Aminoglycosides	Ciprofloxacin			1(1)				0
	Imipenem	1			1	1		0
	Ceftazidime		1					0
	Amikacin	2					1	0
Macrolides	Gentamicin	2						0
	Carbapenems	1						0
	Macrolides							0
	Cefixime				1			2
Macrolides	Ciprofloxacin				1			0
	Clarithromycin				1			2

TABLE 3: Continued.

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)					
		<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>N. gonorrhoeae</i>	<i>A. baumannii</i>	Others (11)
Tigecycline	Tigecycline						
	Piperacillin/azobactam	0/1				1	0
Amikacin	Amikacin	3(2)			0/1		0
	Aminoglycosides	1					0
	Imipenem	1 (1)			0/1		0
	Meropenem				0/1		0
Gentamicin	Gentamicin	1	1(1)	1	1		1
	Aminoglycosides	1					0
Fosfomycin	Fosfomycin			1	1		0
Oxacephems	Oxacephems				1		0
	Levofloxacin			1			0
	Imipenem	2			0/1		0
	Ceftazidime		1				0
Sulfonamides	Sulfonamides		2	2		1	0
	Imipenem	1					0
	Ceftazidime		1				0
All antibiotics	All antibiotics		1	1		1	2
	Fluoroquinolone		1	1		1	0
	Levofloxacin			1			0
	3GC		1	1			0
	Carbapenem		1	1			0
	Cloxacillin						0
	Macrolides					1	1
	β -Lactam antibiotics		1				0
	3GC		2	1			0
	Carbapenem	1	1				0
Cloxacillin	Cloxacillin					1	0
Tetracycline	Tetracycline						0
	Fluoroquinolone			1			0
	Nalidixic acid			1			0
	Carbapenem				1		0

TABLE 3: Continued.

ABC	Resistant antibiotic	Bacterial resistance to antibiotic in question (±)							
		<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>N. gonorrhoeae</i>	<i>A. baumannii</i>	<i>E. cloacae</i>	MRSA	Others (11)
Ceftazidime	Ceftazidime	1				1			
	Imipenem								
	Meropenem	1				1			
Glycopeptides	Glycopeptides	1					1	0/2	1
	Amikacin			0/1		0/1	0/1	0	0
	Gentamicin							1(1)	3
	Carbapenem		1			1			
	Piperacillin/tazobactam	1						1	0
	Extended-spectrum cephalosporin			1					
	Amikacin	1		1		1		1	1
Others	Oxacillin							1	0
				1				2 (1)	0

3GC: third-generation cephalosporins.

strong cross-correlation between consumption of amikacin and rates of imipenem resistance strains of *P. aeruginosa* and MDR strains of *P. aeruginosa* [57] and aminoglycosides with rates of *P. aeruginosa* resistance to tazobactam-piperacillin [39].

A strong cross-correlation was recorded between consumption of all beta-lactam antibiotics and the rate of carbapenem-resistant *P. aeruginosa* [34], penicillin with the resistance density of carbapenem-resistant *P. aeruginosa* [53], beta-lactam/beta-lactamase inhibitor combinations, oxacephems, sulfonamides, and quinolones with the rate of imipenem resistance in *P. aeruginosa* [25], and carbapenems with the rate of ceftazidime-resistant *P. aeruginosa* [77]. But moderate cross-resistance was observed between quinolone consumption and resistance density of carbapenem-resistant *P. aeruginosa* [53] and all beta-lactam antibiotics with rate carbapenem-resistant *P. aeruginosa* [34], carbapenems and glycopeptides with aminoglycosides-resistant *P. aeruginosa* [68], cephalosporin/beta-lactamase inhibitor and penicillin/beta-lactamase inhibitor combinations with ceftazidime-resistant *P. aeruginosa* [77], and penicillin/beta-lactamase inhibitor combinations, fluoroquinolones, imidazole, colistin, and tigecycline consumption with piperacillin-tazobactam-resistant *P. aeruginosa* [39].

Similar to *P. aeruginosa*, there were records on the relationship between the rate of antibiotic-resistant *A. baumannii* and ABC. Consumption of carbapenems was very strongly correlated with imipenem resistance in *A. baumannii* [25] and with carbapenem resistance in *A. baumannii* [60, 68]. Consumption of carbapenems was strongly correlated with the rate of carbapenem-resistant *A. baumannii* [33, 37, 52, 77] and carbapenems and imipenem with imipenem-resistant *A. baumannii* [55, 61], but meropenem was moderately correlated with the rate of meropenem-resistant *A. baumannii* [32].

Likewise, consumption of cefepime was very strongly correlated with cefepime-resistant *A. baumannii* [33] and tigecycline with the incidence density of *Acinetobacter* [52]. The consumption of piperacillin/tazobactam and extended-spectrum cephalosporins was strongly correlated with piperacillin/tazobactam-resistant and extended-spectrum cephalosporin-resistant *A. baumannii* retrospectively [37]. There was also a strong correlation between the consumption of fluoroquinolones and ciprofloxacin-resistant *A. baumannii* [62]. A moderate correlation was found between the consumption of cefepime and ciprofloxacin with cefepime and ciprofloxacin-resistant *A. baumannii*, respectively [32], gentamicin with gentamicin-resistant *A. baumannii* [58], and fosfomycin with the rate of fosfomycin resistance in *A. baumannii* [55]. However, there were strong negative correlations between the consumption of aminoglycosides and an incidence density of aminoglycoside-resistant *Acinetobacter* spp. [52] and a moderate negative correlation between ciprofloxacin and ciprofloxacin-resistant *A. baumannii* [37].

Cross-resistance was also reported for different antibiotics and resistant *A. baumannii*. There was a very strong correlation between consumption of ceftazidime and both imipenem and meropenem-resistant *A. baumannii* [69], cephalosporin/beta-lactamase inhibitor combinations

[60, 77], and tetracyclines [60] with carbapenem-resistant *A. baumannii*. There was a strong correlation between consumption of cephalosporins, cephalosporin/beta-lactamase inhibitor combinations, and other beta-lactam/beta-lactamase inhibitor combinations with carbapenem-resistant *A. baumannii* [77], but a moderate correlation was evident between cephalosporin carbapenem-resistant *A. baumannii* [77] and glycopeptide with carbapenem-resistant *A. baumannii* [68], and monobactams were moderately correlated with rates of carbapenem-resistant *A. baumannii* [77], but amikacin was very strongly and negatively correlated with rates of MDR strain *A. baumannii*, rates of imipenem-resistant strain *A. baumannii*, and rates of resistant meropenem strain *A. baumannii* [57]. A negative strong cross-correlation was also reported between the consumption of glycopeptides and amikacin-resistant *A. baumannii* [62] and aminoglycosides, quinolones, and oxacephems with imipenem-resistant *A. baumannii* [25], whereas ciprofloxacin was strongly and negatively correlated with both imipenem and meropenem-resistant *A. baumannii* [69].

Similarly, there was a very strong correlation between the consumption of imipenem/cilastatin and the resistance rate of *K. pneumoniae* to imipenem/cilastatin and fluoroquinolones with the prevalence of ciprofloxacin-resistant *K. pneumoniae* [43], but there were very strong negative correlations between imipenem and imipenem- and meropenem-resistant *K. pneumoniae* [69]. There was a strong correlation between the consumption of carbapenems and carbapenem-resistant *K. pneumoniae* [77] and extended-spectrum cephalosporins with extended-spectrum cephalosporin-resistant *K. pneumoniae* [69]. Colistin resistance was strongly correlated with the consumption of colistin [39]. Consumption of carbapenems was moderately correlated with doripenem-resistant, ertapenem-resistant, and meropenem-resistant *K. pneumoniae* [39] and carbapenem-resistant *K. pneumoniae* [44]. Consumption of cephalosporins was also moderately correlated with the rate of cephalosporin-resistant *K. pneumoniae* [44] and fluoroquinolones with ciprofloxacin-resistant *K. pneumoniae* [61].

A very strong cross-correlation was observed between the consumption of piperacillin/tazobactam and aminoglycoside-resistant *K. pneumoniae* [22], meropenem-resistant and imipenem-resistant *K. pneumoniae* [69], fluoroquinolones with trimethoprim/sulfamethoxazole-resistant *K. pneumoniae* [22], and the beta-lactam/beta-lactamase inhibitor combinations with carbapenem-resistant *K. pneumoniae* [22]. Consumption of sulfonamides was also very strongly correlated with the rate of ceftazidime-resistant *K. pneumoniae* and ceftazidime with quinolone-resistant *K. pneumoniae* [25]. There was a strong correlation between colistin-resistant *K. pneumoniae* and imidazoles, carbapenems, and colistin [39], doripenem-resistant *K. pneumoniae* with the consumption of imidazoles, ertapenem-resistant *K. pneumoniae* with glycopeptides, and meropenem-resistant *K. pneumoniae* with glycopeptides [39], and ceftriaxone was moderately correlated with the rate of carbapenem-resistant *K. pneumoniae* [35] and carbapenems with *K. pneumoniae* resistant to third-generation cephalosporin [63]. A moderate cross-correlation was observed

between the consumption of glycopeptides and carbapenem-resistant *K. pneumoniae* [68].

A very strong negative cross-resistance was found between consumption of beta-lactam/beta-lactamase inhibitor combinations with fluoroquinolone-resistant *K. pneumoniae* [22], between doripenem-resistant *K. pneumoniae* and first- and second-generation cephalosporins, and aminoglycosides [39]. There was a strong negative correlation between the consumption of ciprofloxacin, ofloxacin, and norfloxacin with carbapenem-resistant *K. pneumoniae* [35]; colistin-resistant *K. pneumoniae* with first- and second-generation cephalosporins and penicillin/beta-lactamase inhibitor; between doripenem-resistant *K. pneumoniae* and third- and fourth-generation cephalosporin and glycopeptides; between ertapenem-resistant *K. pneumoniae* and first- and second-generation cephalosporins; and between meropenem-resistant *K. pneumoniae* and penicillin/beta-lactamase inhibitor combinations, fluoroquinolone, and tigecycline [39]. A strong correlation was also found between carbapenem and rates of ceftazidime resistance in *K. pneumoniae* [25], fourth-generation cephalosporins, and fluoroquinolone within cefepime-resistant and ciprofloxacin-resistant *K. pneumoniae* [62].

Antibiotic-resistant *E. coli* was also correlated with the consumption of several antibiotics. There was a very strong correlation between ciprofloxacin consumption with fluoroquinolone-resistant *E. coli* [65], and a strong correlation was found between fluoroquinolone and fluoroquinolone-resistant *E. coli* [48, 65], fluoroquinolones with the resistance rate of *E. coli* to levofloxacin and resistance rate of *E. coli* to ciprofloxacin [42], and ciprofloxacin with ciprofloxacin-resistant *E. coli* [37], but there was a strong negative correlation between fluoroquinolone and ciprofloxacin-resistant *E. coli* [62]. There was also a very strong correlation between cefotaxime and cefotaxime-resistant *E. coli* and a strong correlation between cefoxitin and cefoxitin-resistant *E. coli* [65], gentamicin with resistant *E. coli* [33], extended-spectrum cephalosporin with resistant *E. coli* [37], and imipenem/cilastatin with imipenem/cilastatin-resistant *E. coli* [62].

There was a very strong cross-correlation between third- and fourth-generation cephalosporin use and *E. coli* resistance rates to cefotaxime and cephamycin use with *E. coli* resistance rates to cefoxitin [65]. A strong cross-correlation was found between carbapenems and third-generation cephalosporin-resistant *E. coli* [61] and beta-lactam/beta-lactamase inhibitor combinations with resistance density of third-generation cephalosporin-resistant *E. coli* [62], but fourth-generation cephalosporins were negatively correlated with cefepime-resistant *E. coli*, glycopeptides with amikacin-resistant *E. coli* [62], aminoglycosides [35, 61], and ofloxacin with carbapenem-resistant *E. coli* [35].

Antibiotic-resistant *N. gonorrhoeae* was reported in two studies [23, 49]. Consumption of ceftriaxone was strongly correlated with resistant *N. gonorrhoeae*, but consumption of ciprofloxacin was moderately correlated [23]. Macrolide consumption and cefixime resistance in *N. gonorrhoeae* and consumption of cephalosporin, macrolide, and quinolone were strongly correlated with ciprofloxacin resistance in

N. gonorrhoeae [49]. Consumption of quinolones and cefotaxime was positively associated with ciprofloxacin-resistant and cefotaxime-resistant *N. gonorrhoeae*, respectively [74].

Consumption of aminoglycosides, quinolones, and carbapenem was strongly correlated with amikacin-resistant *E. cloacae* [25]. But carbapenem-resistant *E. cloacae* showed significant, very strong negative correlations with the usage of penicillin/beta-lactamase inhibitor I combinations, beta-lactam/beta-lactamase inhibitor combinations, meropenem, and carbapenems, but a very strong positive correlation was shown with total cephalosporin use [60]. Consumption of piperacillin/tazobactam was very strongly correlated with resistant *C. difficile*, but it was very strongly but negatively correlated with vancomycin [31] and ESBL-positive *Enterobacteriaceae* rates [33]. A positive association was also reported from the consumption of macrolides and clarithromycin-resistant *H. pylori* [50, 75] and consumption of quinolones with levofloxacin-resistant *H. pylori* [75].

Consumption of meropenem was very strongly correlated with piperacillin/tazobactam-resistant *Enterobacter* spp. [69] and meropenem and ciprofloxacin with piperacillin/tazobactam-resistant *Enterobacter* spp. [69], and piperacillin/tazobactam and resistant *C. difficile* [31] and strong correlation between carbapenems with carbapenem-resistant *E. cloacae* [77], aminoglycoside and quinolone with amikacin-resistant *E. cloacae* [25], and fluoroquinolone and MDR *H. influenzae* and *Shigella* spp. [41], but the moderate correlation was shown between macrolide and macrolide-resistant *T. pallidum* [51], carbapenem and carbapenem-resistant *Enterobacteriales* [70], and carbapenems, monobactams, cephalosporin/beta-lactamase inhibitor, and penicillin/beta-lactamase inhibitor with carbapenem-resistant *E. cloacae* [77]. A very strong negative correlation was reported between the consumption of vancomycin and resistant *C. difficile* [31] and piperacillin/tazobactam and third- and fourth-generation cephalosporin-resistant *P. mirabilis* [22]; a strong negative relationship was observed between piperacillin/tazobactam and piperacillin/tazobactam-resistant *Proteus* spp. and ESBL-positive *Enterobacteriaceae* [33].

A very strong correlation was observed between the consumption of beta-lactams or beta-lactam/beta-lactamase inhibitors and methicillin-resistant *S. aureus* [22] and clindamycin with oxacillin-resistant *S. aureus* [69]. There was a strong correlation between the consumption of extended-spectrum cephalosporin [70] and cloxacillin [48] and methicillin-resistant *S. aureus* [48, 70], and third-generation cephalosporins, carbapenems, glycopeptides, and monobactams were also moderately correlated with MRSA [63]; monobactams and sulphonamides were also moderately correlated with MRSA [64]. A very strong correlation was between the consumption of linezolid [38] and vancomycin [69] with vancomycin-resistant *E. faecium* [38, 69]. A moderate correlation was shown between glycopeptides and glycopeptide-resistant *E. faecalis/faecium* [70], penicillin with penicillin resistance in *S. pneumoniae* [71], and extended-spectrum penicillin and penicillin/beta-lactamase inhibitor combinations with the resistance of *S. pneumoniae* to respective antibiotics [71].

There was a very strong negative correlation between the consumption of fluoroquinolone with ciprofloxacin-resistant *E. faecalis* [62] and third-generation cephalosporins and Hlr-gentamicin-resistant *E. faecalis* [22] and strong negative correlation between the consumption of fluoroquinolone and ciprofloxacin-resistant *S. aureus*, glycopeptides, and gentamicin-resistant *S. aureus*, glycopeptides, and gentamicin-resistant CoN *Staphylococcus*; glycopeptides with amikacin-resistant *E. faecium* and gentamicin-resistant *E. faecalis* [62] and piperacillin/tazobactam and vancomycin with oxacillin-resistant *S. aureus* [33]. A moderate correlation was shown between the consumption of gentamicin and gentamicin-resistant *E. faecalis* [48] and fluoroquinolone with ciprofloxacin-resistant CoN *Staphylococcus* [62]. The consumption of amoxicillin/clavulanate and oxacillin resistance in *S. aureus* [33] and imipenem/cilastatin and imipenem/cilastatin-resistant MRSA were very strongly and negatively correlated [42]. Consumption of glycopeptides and aminoglycosides was negatively correlated with MRSA [64].

4. Discussion

ABR is identified as one of the top threats to public health and challenges progress in health care, food production, and life expectancy [6, 78]. Due to overuse and misuse of antibiotics, bacteria have become increasingly resistant to various antibiotics [1]. A recent point prevalence survey at the global level reported about 136 million per year hospital-associated infections resistant to antibiotics caused by high-priority pathogens (*E. coli*, *Acinetobacter* spp., *Klebsiella* spp., *S. aureus*, *Enterobacter* spp., and *Pseudomonas* spp.) [79]. The current review revealed 38.4% of the average pooled prevalence of antibiotic resistance to bacteria, with *E. faecium* (59.4%), *A. baumannii* (52.6%), *P. aeruginosa* (48.5%), coagulase-negative *Staphylococcus* (43.7%), *Enterobacter* (46.1%), and *P. mirabilis* (48.5%). This complements the global concerns on the ABR [1, 6, 78, 79]. The burden of the ESKAPE and antibiotic resistance pattern calls for surveillance of antibiotic resistance targeting these pathogens by incorporating them into the infection control policy [80, 81]. It requires preventing infections as priority, slowing the development of ABR through better antibiotic use, and stopping the spread of ABR when it develops [78].

According to a recent report from a global point prevalence survey, high use of antibiotics (62.0%) and prolonged surgical antibiotic prophylaxis (60.9%) were the most common problems [82]. Thus, overuse and inappropriate use of antibiotics are recognized as a significant driver of the emergence of resistant strains of bacteria as the increased exposure to antibiotics encourages the development of ABR [83–85]. Increased ABC of broad-spectrum and last-resort antibiotics is a serious concern for public health [84–86]. Inappropriate consumption of antibiotics has also been shown to contribute to the occurrence of MDR organisms [86]. The current review [20–78] has clearly shown the relationship between ABC and ABR. It revealed more than 70% consumption of antibiotics from the Watch and Reserve categories based on the WHO AWaRe

classification, among which consumption of carbapenems and fluoroquinolones were the most frequently involved in ABR including cross-resistance with consumption of other antibiotics. This was in line with a recent report from the global level which concluded, “a large proportion of prescriptions for key Watch antibiotics were issued for indications other than those for which they were included in the Essential Medicine List” [82]. Thus, a direct epidemiological relationship between ABC and the emergence and dissemination of resistant bacterial strains needs to be worked on for further understanding.

Biofilm-forming pathogens such as *P. aeruginosa*, *A. baumannii*, *C. jejuni*, *C. difficile*, *C. perfringens*, *E. faecalis*, *K. pneumoniae*, *P. mirabilis*, *B. cepacia*, *P. pseudomallei*, *H. influenzae*, *E. coli*, *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *S. pyogenes*, *Salmonella* spp., *L. monocytogenes*, *S. agalactiae*, and *V. cholerae* are very difficult to treat with conventional antibiotics due to their greater resistance profile [87, 88]. The CDC and WHO classified most of these microorganisms as threats to healthcare [6, 78] and call for close monitoring of resistance patterns for highly susceptible antibiotics [6, 78]. WHO classified carbapenem- and third-generation cephalosporin-resistant *P. aeruginosa*, *A. baumannii*, *Enterobacteriaceae*, *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp. as critical threats (top priority) to health care and vancomycin-resistant *E. faecium*, methicillin-resistant and vancomycin-intermediate and resistant *S. aureus*, clarithromycin-resistant *H. pylori*, fluoroquinolone-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonella* spp., and third-generation cephalosporin-resistant fluoroquinolone-resistant *N. gonorrhoeae* as a high priority [78]. The direct relationship between ABCs as evidenced from the current review [20–78] indicates a need for developing new therapeutic strategies that can be effective against common infections in addition to optimizing the use of available antibiotics.

Similarly, the CDC classified carbapenem-resistant *Acinetobacter*, *C. difficile*, carbapenem-resistant *Enterobacteriaceae*, and drug-resistant *N. gonorrhoeae* as urgent threats and drug-resistant *Campylobacter*, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, vancomycin-resistant *Enterococci*, MDR *P. aeruginosa*, drug-resistant nontyphoidal *Salmonella*, drug-resistant *Salmonella* serotype Typhi, drug-resistant *Shigella*, methicillin-resistant *S. aureus*, drug-resistant *S. pneumoniae*, and drug-resistant *Tuberculosis* as serious threats to health care [6]. As can be noted, the current review strengthens the need to approach pathogens as a major issue problem related to resistance against antimicrobial agents.

Antibiotics with “high resistance potential,” even with limited use, have been associated with the emergence of MDR Gram-negative bacteria, e.g., imipenem, ceftazidime, gentamicin/tobramycin, and ciprofloxacin [89]. ASP is known to result in decreased ABC and ABR [90]. Due to a strong association between ABC and the development of antibiotic resistance [83], reducing the need for and inappropriate consumption of antibiotics through the implementation of appropriate ASPs can help delay the emergence and spread of ABR [90, 91]. Prudent use of

antibiotics has to be a pillar in the fight against ABR [82]. This requires aligning practice with evidence which requires changes in prescribing behavior based on the implementation of effective strategies to modify prescribing practices by aligning them with evidence-based recommendations for diagnosis and management [92]. Thus, the initial step in fight against ABR in healthcare institutions has to be to measure the situation of antimicrobial use and resistance in their setting to raise awareness on areas of improvement of local prescribing behaviors [82]. The current review will help to understand the relationship between ABC and resistance and justify the need for universal funding and urgency for implementation of ASPs taking into account the local context for sustainable behavioral change in physicians' antibiotic prescribing practices.

The review will serve as an important basis to better understand the issue and will inform policies, regulations, and interventions to optimize antibiotic use while reducing ABR. However, it has to be noted that the review does have limitations. The review includes literature in the English language and was not evaluated by independent evaluators. Because of the multiple numbers of antibiotics and microorganisms tested, risk assessment for bias and quality was not considered. Since most of the studies were done retrospectively, they may not necessarily show the true relationship between ABC and the rate of resistance. There are no data on the relationship between the consumption of antibiotics and the respective resistance rates in all parts of the world.

In conclusion, there was a strong relationship between antibiotic consumption and antibiotic resistance. The review also revealed a significant cross-resistance among different antibiotics. Most correlations were positively related, but a minority was negatively correlated, indicating the protective nature of antibiotic consumption for the development of resistance. There was a very strong correlation between fluoroquinolones, carbapenems, aminoglycosides, and penicillin consumption and respective resistance rates, but colistin, imipenem/cilastatin, and fluoroquinolones consumption was strongly correlated with the resistance rate of *K. pneumoniae*. Carbapenems were the most commonly used and strongly correlated with the rate of resistance for *A. baumannii*. Strict use of antibiotics is thus crucial to minimize the risk of emerging resistant organisms. ASP will help to optimize antibiotic therapy while reducing the amount of ABC to prevent the development and rate of ABR. Systems to assess institutional antibiotic utilization and the relationship between the trend of antibiotic use and rates of antibiotic resistance are strongly needed in health facilities to reduce resistance. Furthermore, special emphasis should be paid to antibiotics in the Watch and Reserve category of the WHO AWaRe classifications such as carbapenems, fluoroquinolones, macrolides, glycopeptides, and second-fourth generation cephalosporins.

Data Availability

Since all data are included in the review, no additional data is required to support the findings of this study.

Ethical Approval

Ethical clearance is not required for the review article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

AAA was involved in the conception, study design, execution, and acquisition of data, analysis and interpretation, and writing and review of manuscript. TGF was involved in the conception, study design, manuscript writing, and review. GY was involved in the writing and review of the manuscript.

Supplementary Materials

Annex 1: summary of relationship between antibiotic consumption and antibiotic resistance, 2016-2022, (N=58). (*Supplementary Materials*)

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Research Article

A Six Years' Trend Analysis of Antimicrobial Resistance Among Bacterial Isolates at Public Health Institute in Amhara Region, Ethiopia

Asrat Agalu Abejew ^{1,2}, Teferi Gedif Fenta ¹ and Gizachew Yismaw Wubetu³

¹Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

²Department of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia

³Amhara Public Health Institute, Bahir Dar, Ethiopia

Correspondence should be addressed to Teferi Gedif Fenta; teferi.gedif@aaau.edu.et

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Background: Antimicrobial resistance (AMR) is one of the top global threats to public health. This study determined trends in AMR from 2016 to 2021 in a regional research laboratory in Northwest Ethiopia.

Methods: Data from 2016 to 2021 was extracted from a database. Bacterial identification and resistance tests were made using the standard microbiologic procedures. The results were described, trends in AMR were determined using polynomial regressions, and binary logistic regression at p value < 0.05 was used.

Results: From 2016 to 2021, 25,143 specimens were sent for culture and susceptibility testing, among which 16,825 (66.9%) bacteria were isolated. About 12,528 (74.5%) isolates were gram-negative, and 4297 (25.5%) were gram-positive. *Klebsiella pneumoniae* (3783, 30.2%) and *Escherichia coli* (3199, 25.5%) were the most common gram-negative bacteria, whereas coagulase-negative *Staphylococcus* spp. (CoNS) (1765, 40.1%) and *Staphylococcus aureus* (1293, 30.1%) were the most common gram-positive bacteria. The overall prevalence of AMR was 2738 (59.9%), of which about 1807 (66.0%) accounted for gram-negative and 931 (34.0%) for gram-positive bacteria. *K. pneumoniae* (743, 80.2%), *Enterobacter cloacae* (196, 74.8%), and *Acinetobacter baumannii* (213, 66.6%) were the most common resistant isolates among gram-negative bacteria, while CoNS (406, 58%), *Streptococcus* species (34, 50%), and *S. aureus* (196, 37%) were from gram-positive bacteria. About 571 (20.9%) of bacteria were resistant to 2–10 drugs. The overall trend of AMR has been rising from year to year, reaching a peak in 2019 which was approximately 66% and then after has been predicted to decline.

Conclusion: AMR in the regional laboratory is prevalent and has been increasing although the quadratic equation has revealed downward-opening parabola over time. A growing number of multidrug-resistant bacteria are an alarm to awaken policymakers and those concerned to intervene before it is too late. This calls for a periodic, integrated, and continuing system to monitor AMR for commonly used antibiotics.

Keywords: antibiotic resistance; antibiotics; multidrug resistance; trend

1. Introduction

During the pre-antibiotic era, infectious diseases were the primary causes of morbidity and mortality [1]. Antibiotic therapy, one of the most significant achievements of humankind in the 20th century, has had a tremendous impact on prolonging life [2]. However, with the increasing rates of

antimicrobial resistance (AMR), treatment options are diminishing, and patients are left without viable options if the bacteria become resistant and the available antibiotics no longer work [3]. Although access to antibiotics remains a major issue in many parts of the world, the continued use, overuse, and misuse of antibiotics have accelerated the emergence and spread of resistant bacteria [4]. Furthermore,

the number of new classes of antimicrobials entering the market has been drastically decreasing over time. AMR, along with the lack of access to quality antimicrobials, further complicates healthcare [1].

Globally, there are still a substantial number of hospitalizations due to severe bacterial infections [5, 6], resulting in about 7 million deaths in 2019 and accounting for approximately 12% of all global deaths [7]. These deaths were associated with 33 bacterial pathogens, both resistant and susceptible to antimicrobials [8]. AMR has posed a major challenge [9], leading to an estimated 4.95 million deaths associated with bacterial AMR globally in 2019 [10], including 1.05 million deaths in Africa [11]. Additionally, the decrease in new antibiotics entering the market, along with limited access to quality antimicrobials, further complicates healthcare amidst the challenge of AMR [1]. To address the global crisis of AMR, the World Health Organization (WHO) [12] and the US Centers for Disease Control and Prevention (CDC) [13] identified a critical list of AMR “priority pathogens” based on health “threats.”

The COVID-19 pandemic has intensified and complicated AMR [14]. The pandemic has heightened the urgency and risk of AMR due to the overuse of antimicrobials, decreases in routine vaccinations, and disruptions to preventive health services, leading to a rise in untreatable drug-resistant infections and diseases that could potentially trigger another public health emergency [5, 12]. Although it is challenging to estimate the full impact of AMR in low- and middle-income countries (LMICs) [15], AMR poses a particularly severe challenge in these regions, resulting in high mortality and morbidity due to inadequate regulation, limited access to diagnostics, and antimicrobial overprescription [15, 16]. Only 46 (84%) of high-income countries and 58 (61%) of LMICs have developed national AMR action plans (NAPs) [17]. While most African countries have adopted the global action plan as a framework to prevent and combat AMR, fewer countries are able to fully implement country-specific action plans, and numerous challenges persist in many settings [9]. Therefore, despite the significant burden of AMR, substantial gaps remain in the fight against AMR in Africa [9, 11].

In sub-Saharan Africa, several challenges hinder the effective implementation of NAPs [9, 17, 18]. Similarly, in Ethiopia, although the country has committed to partnering globally in the detection and prevention of AMR [9], AMR for many antibiotics and multidrug-resistant (MDR) bacterial strains is becoming increasingly challenging [19, 20]. Furthermore, only a limited number of studies have documented trends in the prevalence of AMR and the antibiotic resistance profiles of bacterial isolates [19, 21]. Thus, this study is aimed at determining AMR trends at the Amhara Public Health Institute (APHI) in Northwest Ethiopia.

2. Methods

2.1. Study Area, Setting, and Period. Retrospective data was collected based on antimicrobial sensitivity tests conducted from 2016 to 2021 at the APHI Bahir Dar branch. APHI is an autonomous regional public health institute located in

Bahir Dar City, one of Ethiopia’s top tourist destinations, approximately 578 km from Addis Ababa, the nation’s capital. APHI aims to improve health services by generating and delivering scientific evidence, strengthening public health emergency management, and providing quality laboratory services to support effective public health interventions. Overall, the institute serves over 10 million people in Northwest Ethiopia.

2.2. Data Collection. Data, including sociodemographic characteristics of patients, isolated bacteria, and antibiotic susceptibility test results, were extracted from a database maintained in the microbiology laboratory unit. Antibiotic susceptibility test results were disaggregated by study year, and trend analysis was conducted based on polynomial equations. In this study, we used the term “MDR” to mean resistance to any drug in any class of at least two antibiotics. Thus, in this study, “MDR” refers to bacterial resistance to more than two antibiotics from any class. Similarly, in this study, “antibiotics” refers to all drugs targeting bacterial pathogens. The antibiotic categories used at APHI include aminoglycosides (AMG), macrolides (Macr), penicillins (Peni), carbapenems (Carb), beta-lactam/beta-lactamase inhibitors (BLIs), cephalosporins (CEF), tetracyclines (TTC), fluoroquinolones (FQs), lincosamides (Linco), sulfamethoxazole-trimethoprim (SXT), nitrofurantoin (NIT), chloramphenicol (CAF), and glycopeptides (Glyc).

2.3. Laboratory Diagnostic Methods. The APHI provides laboratory services to the community, including drug susceptibility testing. This study uses data collected from patients seeking culture and sensitivity tests for routine clinical care purposes. Various microbiological specimens—such as blood, urine, stool, swabs, discharges, and body effusions—were used for culture and susceptibility testing. Aseptic techniques were maintained during sample collection, handling, and specimen transport. Standard microbiological procedures were followed for bacterial identification and resistance testing. VITEK 2 methods were primarily used for bacterial isolation, identification, and susceptibility testing, supplemented by manual bacterial culture on different agars and disc diffusion testing with standard antibiotic discs for determining resistance. To verify VITEK 2 results, *Enterococcus casseliflavus* (ATCC 700327), *Kocuria rosea* (ATCC 186), *Staphylococcus aureus* (ATCC 29213), *Staphylococcus lugdunensis* (ATCC 700328), *Staphylococcus sciuri* (ATCC 29061), *Streptococcus pneumoniae* (ATCC 6301), and *Streptococcus uberis* (ATCC 9927) were used for bacterial identification. To ensure the accuracy and reliability of AMR testing, the reference strains *S. aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853) were used as internal quality controls.

2.4. Statistical Analysis. Data were checked for completeness, manually cleaned, entered, and analyzed using SPSS Version 20 statistical software. Descriptive statistics and trend analysis were performed using second-degree polynomial equations. Additionally, binary logistic regression was used to assess associations between sex, age, and type of health

facility. A p value of <0.05 was considered statistically significant for determining associations.

2.5. Ethics Consideration. Ethical approval was obtained from Addis Ababa University, the College of Health Sciences (protocol code: 106/22/SoP), and the School of Pharmacy (protocol code: ERB/SOP/472/14/2022). The deidentification of records was used to protect patient privacy. All data obtained were kept confidential and used only for this study.

3. Results

During the 6 years, 25,143 susceptibility tests were done to determine AMR. The majority of samples were collected from males (13,376, 53.2%) and pediatric patients who were <15 years old (11,985, 47.6%). The ages of 606 (2.4%) patients were not found to be recorded (Table 1).

3.1. Specimen Sources. The common specimens sent to the APHI for culture and susceptibility testing were blood (11,785, 46.87%), urine (6354, 25.27%), swabs (1993, 7.9%), stool (1620, 6.4%), discharges (436, 1.7%), body effusions (401, 1.6%), and sputum (200, 0.8%). But for 2516 (10%) of the samples, the source was not recorded. The majority of the samples were collected in 2019, 2020, and 2021, with respective values of 8480 (33.7%), 6469 (25.7%), and 7508 (29.9%) (Figure 1).

3.2. Bacterial Isolates. The growth of bacteria was evident in 16,825 (66.9%) of the tests, but in 7346 (29.2%), the status of the growth was not recorded, and in 994 (3.9%) of the tests, there was no bacterial growth. The most commonly isolated bacteria were gram-negative bacteria (GNB) (12,528, 74.5%), where *Klebsiella pneumoniae* (3783, 30.2%), *E. coli* (3199, 25.5%), and *Acinetobacter baumannii* (1444, 11.5%) were the most common. On the other hand, gram-positive bacteria (GPB) isolates accounted for 4297 (25.5%), where coagulase-negative *Staphylococcus* spp. (CoNS) (1765, 40.1%), *S. aureus* (1293, 30.1%), and *Enterococcus* spp. (870, 18.9%) were the commonly isolated bacteria (Table 2).

3.3. Prevalence of AMR. The overall prevalence of AMR was 2738 (59.9%), where about 1807 (66.0%) and 931 (34.0%) of AMR were accounted for GNB and GPB, respectively. *K. pneumoniae* (743, 80.24%), *Enterobacter cloacae* (196, 74.81%), and *A. baumannii* (213, 66.6%) were the most common resistant GNB, whereas CoNS (406, 57.8%), *Streptococcus viridans* (27, 57.8%), and *S. aureus* (196, 36.9%) were the top three resistant GPB. Overall, *Klebsiella* spp. (789, 78.5%), *Serratia marcescens* (22, 75.9%), and *Enterobacter* spp. (257, 73.2%) were highly resistant groups of bacteria (Figure 2).

3.4. Antibiotic Resistance Trends. The AMR trend in a quadratic model exhibits downward-opening parabola with vertex of approximately at (4.4, 66.9) as a function of $y = -5.3247x^2 + 46.768x - 36.069$ ($R^2 = 0.9351$). AMR increased from zero among 81 tested in 2016 to 6579 (64.8%) in 2019, but in 2021, it slightly declined to 2339 (56.9%). In 2017, 2018, and 2020, the AMR was 1512 (46.15%), 3683 (54.6%), and 6356 (58.8%), respectively. Overall, about 93.5%

TABLE 1: Distribution of samples by different variables (2016–2021), at APHI, Northwest Ethiopia ($N = 25,143$).

Variables	Frequency (%)
Sex	
Male	13,376 (53.2)
Female	11,767 (46.8)
Age	
<15 years	11,985 (47.6)
15–64 years	11,205 (44.6)
≥ 65 years	1347 (5.4)
Not recorded	606 (2.4)
Facility	
Public facility	19,194 (76.3)
Private facility	4867 (19.4)
Not known	1083 (4.3)
Total	25,143 (100)
Residence	
Bahir Dar City	23,719 (98.6)
Awı Zone	176 (0.7)
South Gondar Zone	111 (0.5)
West Gojjam Zone	50 (0.2)
Gondar City	4 (0.02)
Not specified	1083 (4.3)
Total	25,143 (100)

of the variability in the AMR in years can be explained by a second-order polynomial equation (Figure 3).

3.5. Antibiotic Resistance Pattern. *A. baumannii* was resistant to ceftriaxone (31, 100%), ciprofloxacin (30, 90.9%), SXT (37, 97.4%), TTC (18, 94.7%), and tobramycin (25, 96.7%). *Enterobacter* spp., *E. coli*, and *K. pneumoniae* were 90%–100% resistant to tobramycin. Although CAF, ceftriaxone, ciprofloxacin, erythromycin, and SXT were the most resistant antibiotics for most bacteria, amikacin, ampicillin/sulbactam, cefepime, cefazolin, and cefoperazone were sensitive to all bacteria (except for *Citrobacter* species (Table 3). Most antibiotics have shown the same trend in resistance from year to year. Ampicillin-resistant *E. coli*, Augmentin-resistant *Acinetobacter*, ceftazidime-resistant *E. coli*, ceftriaxone-resistant *Klebsiella*, and ciprofloxacin-resistant *Klebsiella* increased linearly. The peak resistance was recorded in 2019, and then, it was constant, declining, or rising for most antibiotics (Table 4).

3.6. Risk Factors for Resistance. Multivariate binary logistic regression analysis based on variables showed that the age of patients (p value = 0.004), gender (p value = 0.002), and type of facility (p value <0.01) were strongly associated with the rate of antibiotic resistance. Although the year of the test was strongly associated (p value <0.01), it was found to be confounding when treated with other variables (p value = 0.982).

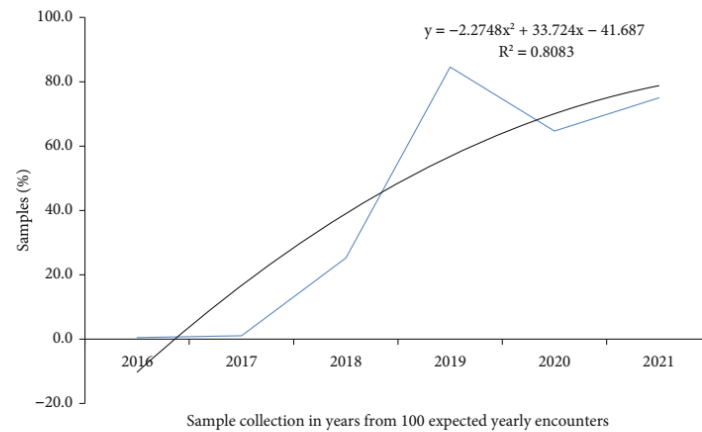


FIGURE 1: Trends in sample collection (2016–2021), at APHI, Northwest Ethiopia.

TABLE 2: Distribution of commonly isolated bacteria (2016–2021), at APHI, Northwest Ethiopia (N = 16,825).

Type of bacteria	Isolated specific bacteria	Frequency (%)
Gram-negative bacteria	<i>Klebsiella pneumoniae</i>	3783 (30.2)
	<i>Escherichia coli</i>	3199 (25.5)
	<i>Acinetobacter baumannii</i>	1444 (11.5)
	<i>Enterobacter</i> species	1330 (10.6)
	<i>Pseudomonas aeruginosa</i>	891 (7.1)
	<i>Klebsiella</i> species	615 (4.9)
	<i>Citrobacter</i> species	470 (3.8)
	<i>Proteus</i> species	216 (1.7)
	<i>Serratia marcescens</i>	135 (1.1)
	<i>Providencia</i> species	135 (1.1)
	<i>Shigella</i> species	102 (0.8)
	<i>Acinetobacter</i> species	77 (0.6)
	Unspecified	131 (1.1)
	Total gram-negative	12,528 (74.5)
Gram-positive bacteria	CoNS	1765 (40.1)
	<i>Staphylococcus aureus</i>	1293 (30.1)
	<i>Enterococcus</i> species	870 (18.9)
	<i>Streptococcus viridans</i>	213 (5.0)
	<i>Streptococcus</i> species	73 (1.7)
	<i>Staphylococcus</i> species	48 (1.1)
	Unspecified	35 (0.8)
	Total gram-positive bacteria	4297 (25.5)
Total isolates		16,825 (100)

3.7. MDR Bacteria. Of 2738 resistant bacteria, 571 (20.9%) were MDR, while 265 (46.2%), 253 (44.2%), and 56 (9.7%) of them were resistant to groups of 2–4, 5–7, and ≥ 8

antibiotics, respectively. The MDR GNB were 378 (18.1%), of which 166 (43.9%), 155 (41.5%), and 55 (14.6%) were resistant to 2–4, 5–7, and ≥ 8 antibiotics, respectively. The most commonly involved GNB in MDR were *K. pneumoniae* (133, 35.2%), *E. coli* (86, 22.8%), *A. baumannii* (39, 10.3%), and *E. cloacae* (37, 9.8%). The MDR among GPB was 193 (20.9%), of which 99 (50.8%), 96 (49.2%), and 1 (0.5%) were resistant to 2–4, 5–7, and ≥ 8 antibiotics, respectively, and CoNS (98, 50%), *S. aureus* (46, 23.6%), and *Enterococcus* spp. (27, 14.2%) were the most common MDR GPB. The group of MDR bacteria with multiple and specific bacteria with resistant antibiotics is presented in Supporting Information 4: Table S1, Supporting Information 5: Table S2, Supporting Information 6: Table S3, and Supporting Information 7: Table S4.

4. Discussion

In the past years, infections caused by MDR bacteria have dramatically increased in all parts of the world [22], and among them, resistant *Enterococcus* spp., *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp. (ESKAPE) have been increasingly involved in infectious diseases in humans, and antibiotic-resistant ESKAPE bacteria have significantly increased the risk for mortality and healthcare costs in developing countries [9, 11]. Providing evidence-based data on antibiotic resistance, including in livestock and food, and highlighting the need for coordination between animal and human surveillance systems are essential to strengthening infection control measures to reduce the spread of antibiotic-resistant bacteria [12]. Thus, determining the overall and specific trends of AMR has paramount importance.

In this study, the overall prevalence of AMR was 59.9%. It was similar when compared with a systematic review in Ethiopia, which showed an overall prevalence of 59.7% MDR bacteria [19], and in Sierra Leone, among patients with suspected urinary tract infections, the AMR prevalence was 45% [23]. The AMR in the current study was still too

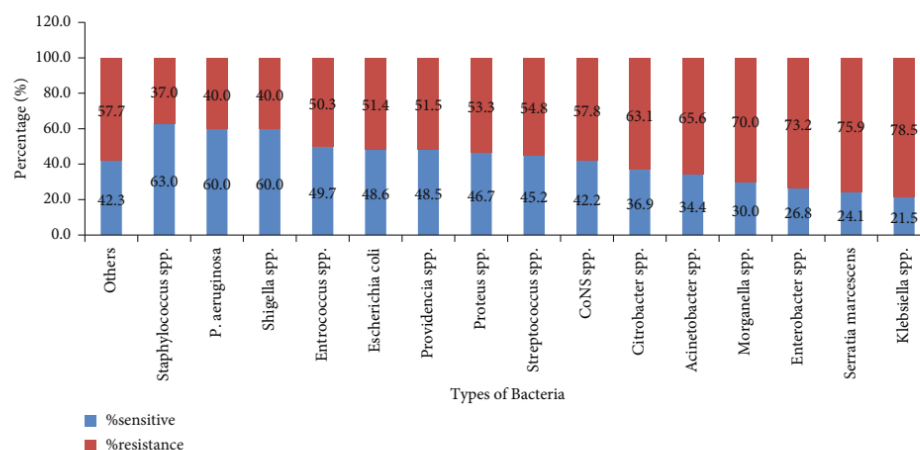


FIGURE 2: Prevalence of AMR (2016–2021), at APHI, Northwest Ethiopia. Others: *Salmonella choleraesuis*, *Bacillus*, *Moraxella catarrhalis*, and unidentified.

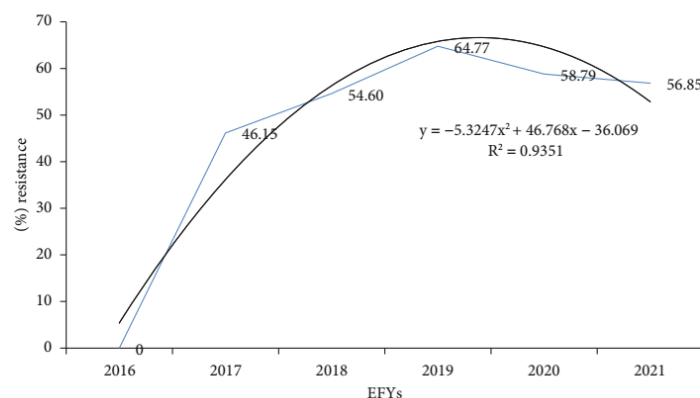


FIGURE 3: Trends in AMR (2016–2021), at APHI, Northwest Ethiopia.

high compared with the 29% pooled prevalence of AMR among food handlers [24]. In the current study, the prevalence of AMR GNB was 1807 (66.0%), which was lower compared with the 85.8% MDR GNB referral hospital in Northwest Ethiopia [21]. The difference might be due to differences in geographic and sample types, data collection methods, and the duration of the study, which might account for the variations in resistance patterns across studies.

In this study, the overall trend of antibiotic resistance was linearly increasing over time which had the tendency to decrease during the last two years. It is a fact that AMR is increasing from time to time and poses significant risks to both patients and public health [1]. However, different bacteria were found to have varying rates of resistance to different antibiotics, which may be different from region to

region [9]. AMR is a global burden leading to death worldwide, with the highest burdens in low-resource settings [10]; AMR data is unavailable or fragmented in many countries in Africa [11]. Globalization and increased mobility have aided in the spread [25] and increase in AMR worldwide [26]. Although COVID-19 fuels AMR because of increased antibiotic consumption, either by self-medication or by antibiotics prescribed by general practitioners, and reduced antimicrobial stewardship program (ASP) activities [27], the current study showed a decreased trend since COVID-19 which could be justified by a decrease in AMR testing due to shift of attention to contain the pandemic. Understanding the burden of AMR and the leading pathogen–drug combinations contributing to AMR is crucial to making informed and location-specific policy decisions,

TABLE 3: Antibiotic resistance pattern (2016–2021), at APHI, Northwest Ethiopia.

[illegible]

Abbreviation: SXT: sulfamethoxazole/trimethoprim.

Salmonella choleraesuis and unspecified gram-positive and gram-negative bacteria.

³Meropenem, norfloxacin, piperacillin-tazobactam, and vancomycin.

TABLE 4: Trends in antibiotic-resistant bacteria (2016–2021), at APHI, Northwest Ethiopia.

Antibiotic-resistant bacteria	2017 R (%)	2018 R (%)	Years		2021 R (%)	Total R (%)
			2019 R (%)	2020 R (%)		
Amoxicillin-resistant <i>Enterococcus</i>			1 (100)	0/1		1 (50)
Amoxicillin-resistant <i>S. aureus</i>	1 (100)					1 (100)
Ampicillin-resistant <i>Acinetobacter</i>			1 (100)		6 (85.7)	7 (87.5)
Ampicillin-resistant <i>E. coli</i>			3 (75)	7 (87.5)	19 (95)	29 (90.6)
Ampicillin-resistant <i>Enterobacter</i>			4 (100)	3 (75)	7 (100)	14 (93.3)
Ampicillin-resistant <i>Enterococcus</i>			4 (100)	0/3	14 (66.7)	18 (62.1)
Ampicillin-resistant <i>Klebsiella</i>			21 (100)	10 (100)	13 (92.9)	44 (97.8)
Ampicillin-resistant <i>Morganella</i>			1 (100)			1 (100)
Ampicillin-resistant <i>Proteus</i>				2 (66.7)	1 (100)	3 (75)
Ampicillin-resistant <i>Providencia</i>					1 (100)	1 (100)
Ampicillin-resistant <i>S. aureus</i>			1 (100)			1 (100)
Ampicillin-resistant <i>Streptococcus</i>						0/1
Ampicillin-resistant <i>Serratia</i>					1 (100)	1 (100)
Augmentin-resistant <i>Acinetobacter</i>			3 (75%)	3 (100)	9 (81.8)	15 (83.3)
Augmentin-resistant <i>E. coli</i>		1 (50)	8 (72.7)	31 (79.5)	19 (57.6)	59 (78.7)
Augmentin-resistant <i>Enterobacter</i>			10 (100)	4 (80)	19 (95)	33 (94.3)
Augmentin-resistant <i>Klebsiella</i>			34 (91.9)	27 (93.1)	22 (73.3)	83 (86.5)
Augmentin-resistant <i>Morganella</i>			0/1	1 (100)		1 (50)
Augmentin-resistant <i>Proteus</i>				1 (33.3)	3 (100)	4 (66.7)
Augmentin-resistant <i>Providencia</i>				1 (100)	1 (50)	2 (66.7)
Augmentin-resistant <i>Serratia</i>				1 (100)	0/1	1 (50)
Azithromycin-resistant CoNS				3 (75)		3 (75)
Azithromycin-resistant <i>Enterococcus</i>			0/1	1 (100)		0/1
Azithromycin-resistant <i>S. aureus</i>				1 (100)	0/1	1 (25)
Cefotaxime-resistant <i>Salmonella</i>				0/1		0/1
Cefoxitin-resistant CoNS					7 (87.5)	7 (87.5)
Cefoxitin-resistant <i>E. coli</i>			1 (100)	0/3		1 (25)
Cefoxitin-resistant <i>Enterobacter</i>					2 (100)	2 (100)
Cefoxitin-resistant <i>Klebsiella</i>			0/2		2 (100)	2 (50)
Cefoxitin-resistant <i>Proteus</i>					1 (100)	1 (100)
Cefoxitin-resistant <i>S. aureus</i>					3 (33.3)	3 (33.3)
Ceftazidime-resistant <i>Acinetobacter</i>			7 (77.8)	8 (88)	12 (75)	27 (79.4)
Ceftazidime-resistant <i>E. coli</i>			3 (30)	9 (69.2)	8 (72.7)	20 (58.8)
Ceftazidime-resistant <i>Enterobacter</i>			3 (100)	2 (50)	1 (25)	6 (54.5)
Ceftazidime-resistant <i>Klebsiella</i>			17 (85)	21 (100)	5 (100)	43 (93.4)
Ceftazidime-resistant <i>Morganella</i>				0/1		0/2
Ceftazidime-resistant <i>Proteus</i>				1 (100)	2 (100)	3 (100)
Ceftazidime-resistant <i>Pseudomonas</i>			4 (44.4)	2 (0.4)	7 (58.3)	13 (50)
Ceftazidime-resistant <i>Serratia</i>				1 (100)		1 (100)
Ceftriaxone-resistant <i>Acinetobacter</i>			10 (83.3)	11 (91.7)	18 (78.3)	39 (83)
Ceftriaxone-resistant <i>E. coli</i>	1 (100)		2 (22.2)	17 (58.6)	19 (61.3)	39 (55.7)
Ceftriaxone-resistant <i>Enterobacter</i>			9 (90)	6 (75)	15 (71.4)	30 (76.9)
Ceftriaxone-resistant <i>Klebsiella</i>			43 (95.6)	39 (97.5)	29 (100)	111 (97.4)
Ceftriaxone-resistant <i>Morganella</i>			1 (100)	4 (80)		1 (50)
Ceftriaxone-resistant <i>Proteus</i>				2 (50)	3 (100)	5 (71.4)
Ceftriaxone-resistant <i>Providencia</i>				1 (100)	1 (100)	2 (100)
Ceftriaxone-resistant <i>Pseudomonas</i>				1 (100)		1 (100)

TABLE 4: Continued.

Antibiotic-resistant bacteria	2017 R (%)	2018 R (%)	Years		2021 R (%)	Total R (%)
			2019 R (%)	2020 R (%)		
Ceftriaxone-resistant <i>Salmonella</i>				0/1		0/1
Ceftriaxone-resistant <i>Serratia</i>				1 (100)	1 (100)	2 (100)
Cefuroxime-resistant <i>S. aureus</i>	1 (100)					1 (100)
Cefuroxime-resistant <i>Salmonella</i>				1 (100)		1 (100)
Chloramphenicol-resistant <i>Acinetobacter</i>				2 (100)	0/4	2 (33.3)
Chloramphenicol-resistant CoNS			7 (38.9)	9 (32.1)	6 (20.7)	22 (29.3)
Chloramphenicol-resistant <i>E. coli</i>			2 (100)	1 (33.3)	0/2	3 (42.9)
Chloramphenicol-resistant <i>Enterobacter</i>			1 (100)	3 (75)	3 (60)	7 (70)
Chloramphenicol-resistant <i>Enterococcus</i>			3 (60)	5 (38.5)	1 (5.6)	9 (25)
Chloramphenicol-resistant <i>Klebsiella</i>			3 (75)	5 (83.3)	2 (28.6)	10 (58.8)
Chloramphenicol-resistant <i>Proteus</i>				1 (50)	1 (100)	2 (66.7)
Chloramphenicol-resistant <i>Providencia</i>				1 (100)		1 (100)
Chloramphenicol-resistant <i>S. aureus</i>			2 (11.1)	2 (10.5)	2 (11.8)	6 (11.1)
Chloramphenicol-resistant <i>Streptococcus</i>			8 (57.1)	1 (100)	0/2	9 (52.9)
Ciprofloxacin-resistant <i>Acinetobacter</i>			12 (54.5)	12 (75)	15 (50)	39 (57.4)
Ciprofloxacin-resistant CoNS		0/3	11 (47.8)	16 (64)	31 (64.6)	58 (58.6)
Ciprofloxacin-resistant <i>E. coli</i>		0/1	20 (54.1)	26 (72)	18 (56.3)	64 (60.4)
Ciprofloxacin-resistant <i>Enterobacter</i>			14 (73.7)	4 (50)	11 (52.4)	29 (60.4)
Ciprofloxacin-resistant <i>Enterococcus</i>			4 (66.7)	1 (25)	0/2	5 (41.7)
Ciprofloxacin-resistant <i>Klebsiella</i>			51 (60.7)	28 (65.1)	21 (65.6)	100 (62.9)
Ciprofloxacin-resistant <i>Morganella</i>			1 (100)	1 (100)		2 (100)
Ciprofloxacin-resistant <i>Proteus</i>				3 (60)	0/3	3 (37.5)
Ciprofloxacin-resistant <i>Providencia</i>			0/2	0/1	0/2	0/5
Ciprofloxacin-resistant <i>Pseudomonas</i>			5 (45.5)	3 (50)	7 (43.8)	15 (45.5)
Ciprofloxacin-resistant <i>S. aureus</i>	0/1		11 (50)	11 (44)	11 (40.7)	33 (44.6)
Ciprofloxacin-resistant <i>Salmonella</i>				1 (100)		1 (100)
Ciprofloxacin-resistant <i>Shigella</i>			2 (66.7)	0/1		2 (50)
Ciprofloxacin-resistant <i>Serratia</i>			3 (100)	1 (100)	1 (100)	5 (100)
Clindamycin-resistant CoNS		0/3	6 (25)	10 (35.7)	14 (27.5)	30 (28.3)
Clindamycin-resistant <i>Enterococcus</i>			1 (100)			1 (100)
Clindamycin-resistant <i>S. aureus</i>			4 (18.2)	3 (12)	2 (8)	9 (12.5)
Clindamycin-resistant <i>Salmonella</i>				0/1		0/1
Clindamycin-resistant <i>Streptococcus</i>			4 (28.6)	1 (100)	0/2	5 (29.4)
Erythromycin-resistant CoNS		2 (66.7)	22 (88)	25 (86.2)	35 (81.4)	84 (84)
Erythromycin-resistant <i>Enterococcus</i>			7 (77.8)	12 (100)	14 (82.4)	33 (86.8)
Erythromycin-resistant <i>S. aureus</i>	1 (100)		15 (65.2)	12 (48)	15 (62.5)	43 (58.9)
Erythromycin-resistant <i>Streptococcus</i>			14 (93.3)	1 (100)	1 (50)	16 (88.9)
Gentamicin-resistant <i>Acinetobacter</i>			11 (55)	9 (75)	16 (53.3)	36 (58.1)
Gentamicin-resistant CoNS			4 (21.1)	12 (54.5)	18 (41.9)	34 (40.5)
Gentamicin-resistant <i>E. coli</i>	0/1	1 (50)	10 (27.8)	9 (26.5)	9 (27.3)	29 (27.4)
Gentamicin-resistant <i>Enterobacter</i>			18 (100)	5 (62.5)	13 (61.9)	36 (76.6)
Gentamicin-resistant <i>Enterococcus</i>			0/1		0/1	0/2
Gentamicin-resistant <i>Klebsiella</i>			69 (81.2)	38 (92.7)	23 (71.9)	130 (82.3)
Gentamicin-resistant <i>Morganella</i>			1 (100)	1 (100)		2 (100)
Gentamicin-resistant <i>Proteus</i>				0/5	1 (33.3)	1 (12.5)
Gentamicin-resistant <i>Providencia</i>			0/2	0/1	1 (50)	1 (20)
Gentamicin-resistant <i>Pseudomonas</i>			4 (36.4)	1 (20)	4 (26.7)	9 (29)

TABLE 4: Continued.

Antibiotic-resistant bacteria	Years					Total R (%)
	2017 R (%)	2018 R (%)	2019 R (%)	2020 R (%)	2021 R (%)	
Gentamicin-resistant <i>S. aureus</i>			5 (26.3)	6 (15)	9 (34.6)	20 (30.3)
Gentamicin-resistant <i>Serratia</i>			3 (100)	0/1	0	3 (60)
Imipenem-resistant <i>Acinetobacter</i>			5 (55.6)	3 (37.5)	3 (30)	11 (40.7)
Imipenem-resistant <i>E. coli</i>			0/5	0/12	0/4	0/21
Imipenem-resistant <i>Enterobacter</i>			6 (50)	0/3	3 (50)	9 (42.9)
Imipenem-resistant <i>Klebsiella</i>			3 (7)	6 (40)	1 (25)	10 (16.1)
Imipenem-resistant <i>Morganella</i>				0/1		0/1
Imipenem-resistant <i>Pseudomonas</i>			2 (66.7)	0/1	1 (25)	3 (37.5)
Imipenem-resistant <i>Serratia</i>						0/2
Meropenem-resistant <i>Klebsiella</i>					0/1	0/1
Meropenem-resistant <i>Acinetobacter</i>					2 (66.7)	2 (66.7)
Meropenem-resistant <i>E. coli</i>				1 (33.3)		1 (33.3)
Meropenem-resistant <i>Providencia</i>					0/1	0/1
Nitrofurantoin-resistant <i>Acinetobacter</i>			3 (100)	3 (100)	2 (40)	8 (72.7)
Nitrofurantoin-resistant CoNS		0/3	0/1			0/4
Nitrofurantoin-resistant <i>E. coli</i>	0/1	1 (33.3)	5 (18.5)	3 (12)	2 (8.3)	11 (13.8)
Nitrofurantoin-resistant <i>Enterobacter</i>			1 (33.3)	2 (100)	1 (20)	4 (40)
Nitrofurantoin-resistant <i>Enterococcus</i>			0/1	1 (25)	0/2	1 (14.3)
Nitrofurantoin-resistant <i>Klebsiella</i>			3 (75)	2 (40)	1 (20)	6 (42.9)
Nitrofurantoin-resistant <i>Morganella</i>			0/1			0/1
Nitrofurantoin-resistant <i>Proteus</i>				2 (100)	1 (50)	3 (75)
Nitrofurantoin-resistant <i>Providencia</i>			2 (100)		0/1	2 (66.7)
Nitrofurantoin-resistant <i>Pseudomonas</i>			1 (50)	1 (100)		2 (66.7)
Nitrofurantoin-resistant <i>S. aureus</i>	0/1		0/3	0/4	0/2	0/10
Nitrofurantoin-resistant <i>Serratia</i>			1 (100)	1 (100)		2 (100)
Norfloxacin-resistant <i>E. coli</i>	1 (100)	1 (100)				2 (100)
Oxacillin-resistant CoNS			3 (75)	10 (55.6)	11 (68.8)	24 (63.2)
Oxacillin-resistant <i>Enterococcus</i>			0/1			0/1
Oxacillin-resistant <i>S. aureus</i>			4 (36.4)	6 (3)	1 (14.3)	11 (28.9)
Penicillin-resistant CoNS			1 (100)			1 (100)
Penicillin-resistant <i>Enterococcus</i>					15 (57.7)	15 (48.4)
Penicillin-resistant <i>S. aureus</i>			1 (100)			1 (50)
Penicillin-resistant <i>Salmonella</i>						0/1
Penicillin-resistant <i>Streptococcus</i>			1 (100)			1 (100)
Piperacillin-tazobactam-resistant <i>Acinetobacter</i>					3 (50)	3 (50)
Piperacillin-tazobactam-resistant <i>Pseudomonas</i>			0/2		4 (44.4)	4 (36.4)
Sulfamethoxazole-resistant <i>Acinetobacter</i>			14 (66.7)	15 (100)	18 (69.2)	47 (75.8)
Sulfamethoxazole-resistant CoNS		0/3	21 (87.5)	25 (89.3)	42 (80.8)	88 (82.2)
Sulfamethoxazole-resistant <i>E. coli</i>	1 (100)	1 (50)	23 (63.9)	30 (88.2)	24 (60.6)	79 (73.1)
Sulfamethoxazole-resistant <i>Enterobacter</i>			18 (94.7)	7 (87.5)	15 (75)	40 (85.1)
Sulfamethoxazole-resistant <i>Enterococcus</i>			1 (100)			1 (100)
Sulfamethoxazole-resistant <i>Klebsiella</i>			77 (91.7)	41 (95.3)	27 (84.4)	145 (91.2)
Sulfamethoxazole-resistant <i>Moraxella</i>			1 (100)			1 (100)
Sulfamethoxazole-resistant <i>Morganella</i>			1 (100)	1 (100)		2 (100)
Sulfamethoxazole-resistant <i>Proteus</i>				3 (0.6)	1 (33.3)	4 (50)
Sulfamethoxazole-resistant <i>Providencia</i>			2 (100)	1 (100)	2 (100)	5 (100)
Sulfamethoxazole-resistant <i>Pseudomonas</i>			0/1	3 (100)		3 (75)

TABLE 4: Continued.

Antibiotic-resistant bacteria	Years					Total R (%)
	2017 R (%)	2018 R (%)	2019 R (%)	2020 R (%)	2021 R (%)	
Sulfamethoxazole-resistant <i>S. aureus</i>			13 (54.2)	15 (53.6)	14 (48.3)	42 (51.8)
Sulfamethoxazole-resistant <i>Shigella</i>			1 (100)			1 (50)
Sulfamethoxazole-resistant <i>Streptococcus</i>					1 (100)	1 (100)
Sulfamethoxazole-resistant <i>Serratia</i>			2 (66.7)	1 (100)	1 (100)	4 (80)
Tetracycline-resistant <i>Acinetobacter</i>			4 (100)	10 (90.9)	14 (70)	28 (80)
Tetracycline-resistant CoNS			3 (100)	13 (76.5)	34 (77.3)	50 (78.1)
Tetracycline-resistant <i>E. coli</i>		1	5 (100)	17 (73.9)	18 (81.8)	41 (80.4)
Tetracycline-resistant <i>Enterobacter</i>			6 (100)	1 (25)	9 (64.3)	16 (66.7)
Tetracycline-resistant <i>Enterococcus</i>			5 (100)	3 (75)	1 (100)	9 (90)
Tetracycline-resistant <i>Klebsiella</i>			10 (90.1)	30 (83.3)	22 (81.5)	62 (83.8)
Tetracycline-resistant <i>Morganella</i>			1 (100)	1 (100)		2 (100)
Tetracycline-resistant <i>Proteus</i>				2 (100)	1 (50)	3 (75)
Tetracycline-resistant <i>Providencia</i>				1 (100)	1 (50)	2 (66.7)
Tetracycline-resistant <i>Pseudomonas</i>				1 (100)		1 (100)
Tetracycline-resistant <i>S. aureus</i>	0/1		6 (66.7)	14 (58.3)	10 (47.6)	30 (54.5)
Tetracycline-resistant <i>Salmonella</i>						0/1
Tetracycline-resistant <i>Streptococcus</i>					1 (100)	1 (100)
Tetracycline-resistant <i>Serratia</i>				1 (100)		1 (100)
Tobramycin-resistant <i>Acinetobacter</i>			10 (58.8)	8 (57.1)	13 (59.1)	31 (58.5)
Tobramycin-resistant <i>E. coli</i>			4 (17.4)	19 (54.3)	10 (50)	33 (42.3)
Tobramycin-resistant <i>Enterobacter</i>			10 (71.4)	6 (75)	6 (66.7)	22 (71)
Tobramycin-resistant <i>Klebsiella</i>			49 (80.3)	32 (91.4)	11 (73.3)	92 (82.9)
Tobramycin-resistant <i>Morganella</i>				1 (100)		1 (100)
Tobramycin-resistant <i>Proteus</i>					0/1	0/0
Tobramycin-resistant <i>Providencia</i>			0/2		1 (100)	1 (25)
Tobramycin-resistant <i>Pseudomonas</i>			4 (44.4)		1 (11.1)	5 (22.7)
Tobramycin-resistant <i>Serratia</i>			2 (100)			2 (66.6)
Vancomycin-resistant <i>Enterococcus</i>				2 (100)	4 (22.2)	6(30)
Vancomycin-resistant <i>Streptococcus</i>					0/2	0/2
Total	6 (54.5)	8 (29.6)	885 (62.7)	834 (63)	928 (57.4)	2661 (60.6)

particularly about infection prevention and control programs, access to essential antibiotics, and the research and development of new vaccines and antibiotics [10].

In this study, *K. pneumoniae* (743, 80.2%), *E. cloacae* (196, 74.8%), and *A. baumannii* (213, 66.6%) were common AMR GNB, whereas CoNS (406, 57.8%), *S. viridans* (27, 57.8%), and *S. aureus* (196, 36.9%) were common GPB with a high AMR rate. This was different from a systematic review in Ethiopia, which reported *E. coli*, *P. aeruginosa*, and *K. pneumoniae* as the most common isolates with high AMR rates [28]. In Indonesia, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *S. aureus*, and *A. baumannii* were the most common bacteria due to AMR [29]. The common MDR among food handlers, foods, animals, and the environment in Ethiopia were *Staphylococcus* spp. (96%), *Salmonella* spp. (81%), and *E. coli* (77%) [24]. In 2019 alone, resistant *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *A. baumannii*, and *P. aeruginosa* were responsible for 3.57 million deaths [10].

Thus, the increasing trend of resistance, geographic differences, and differences in sample types might account for the variations in the resistance patterns across studies.

Resistance to *A. baumannii*, and more importantly, Carb resistance, is one of the top priorities listed as critical by the WHO [13], and it was highly increased (70.3%) during the COVID-19 pandemic [26]. Accordingly, in the present study, imipenem-resistant *A. baumannii* accounts for 33.3%. A systematic review in Indonesia reported 70.7% Carb-resistant *A. baumannii* [29], which is very high. In this study, *A. baumannii* was resistant to ceftazidime (31, 100%), SXT (37, 97.4%), tobramycin (25, 96.2%), TTC (18, 94.8%), ciprofloxacin (30, 90.9%), gentamicin (28, 82.4%), and ceftazidime (23, 62.3%). Except for the comparable report for ceftazidime (65%), there is high *Acinetobacter* resistance compared with ceftazidime (73%), SXT (67%), ciprofloxacin (61%), gentamicin (61%), and TTC (56%) [28]. It is also different from a report in Indonesia on *A. baumannii*

resistance against gentamicin (67.9%), amikacin (31.0%), tigecycline (30.4%), and colistin (47.5%) [29]. If there is no intervention to tackle the silent tsunami of AMR, *A. baumannii*, which was responsible for more than 250,000 deaths globally in 2019 alone [10], will be one of the future tragedies in the healthcare system of the country. The emergence and spread of *Acinetobacter* species, which are resistant to most available antibiotics, are areas of great concern.

Similarly, in this study, *K. pneumoniae* was resistant to ampicillin (38, 100%), amoxicillin/clavulanic acid (73, 92.4%), ceftriaxone (95, 100%), ciprofloxacin (91, 100%), SXT (10, 100%), gentamicin (115, 95%), TTC (53, 96.4%), tobramycin (82, 91.1%), and ceftazidime (36, 43.4%). Although there are other highly resistant antibiotics, except for ceftazidime (57%), resistance to SXT (66%), amoxicillin/clavulanic acid (61%), tobramycin (60%), TTC (59%), ceftriaxone (56%), gentamicin (47%), and ciprofloxacin (37%) was high in the current study compared with a report in Ethiopia [28]. In Indonesia, low levels of *K. pneumoniae* resistance to 3GC (74.4%), gentamicin (57.3%), SXT (57.3%), and FQs (53.1%) were reported although resistance to colistin (88.5%), ceftazidime (68.9%), and fosfomycin (47.4%) [29] was different from the report in this study. It is a known fact that antibiotic resistance varies by location and is driven by several factors, such as antibiotic use and infection control practices in healthcare facilities, the underlying health and age of the patient population, and regional spread from nearby locations.

Antibiotic-resistant *P. aeruginosa* is the WHO's top priority [13]. In this study, *P. aeruginosa* showed resistance to ceftazidime (13, 72.2%), ciprofloxacin (15, 75%), gentamicin (9, 100%), and tobramycin (5, 83.3%). This was different from a report in Ethiopia on *P. aeruginosa* resistance to TTC (46%–100%), ampicillin (86%–100%), amoxicillin (77%–100%), and SXT (19%–100%) in the environment [24]. It was also low compared with another review in Ethiopia, which reported *P. aeruginosa* resistance to ceftazidime (34%), ciprofloxacin (20%), gentamicin (27%), and tobramycin (5, 83.3%) [28]. This study also revealed a 100% sensitivity of *P. aeruginosa* to ceftazidime and piperacillin-tazobactam (3, 100%). A 2021 review in Ethiopia reported high *P. aeruginosa* resistance to ceftazidime (56%) and piperacillin-tazobactam (33%) [28], which was more resistant than that in the current study. In Qatar, high resistance rates of *P. aeruginosa* to ceftazidime (96.6%), piperacillin/tazobactam (90.7%), and ciprofloxacin (91.2%) were reported, but low resistance rates to gentamicin (73.2%) and tobramycin (54.6%) were reported [22]. The difference might be attributed to differences in the availability and prior consumption of antibiotics [30].

The current study showed 931 (54%) of resistance among GPB, whereas resistant CoNS is 406 (57.8%), *S. viridans* is 27 (57.8%), and *S. aureus* is 196 (36.9%). *S. aureus*, *S. pneumoniae*, and *Streptococcus pyogenes* were the commonly isolated GPB in Ethiopia [26], and in Indonesia, *S. aureus* and *S. pneumoniae* [29] were the commonly isolated GPB. *S. aureus* and *S. pneumoniae* were among the five leading pathogens, leading to 54.9% of global deaths [8]; methicillin-resistant *Staphylococcus aureus* (MRSA) led to 23% deaths in the WHO African region [11]. In this study, *S. aureus* was resistant to SXT (39, 100%),

erythromycin (41, 100%), gentamicin (20, 100%), TTC (29, 93.5%), oxacillin (10, 100%), and clindamycin (9, 100%). Although the overall prevalence of resistance to *S. aureus* is slightly higher than 26.2% in a review in Ethiopia [19], it was lower than the report from Sierra Leone (44%) [23]; resistance to specific antibiotics was different—ceftriaxone (35.3%), ciprofloxacin (20.5%), and norfloxacin (43.5%) in 2019 [19]. It was highly resistant to SXT (44%), erythromycin (45%), gentamicin (29%), TTC (53%), and oxacillin (10, 100%) and clindamycin, compared with a review in Ethiopia [28]. It was high compared with *S. aureus* resistance to erythromycin (28.6%), methicillin (22.2%), and clindamycin (22.0%), except for vancomycin (5.0%) in Indonesia [29]. CoNS were 100% resistant to erythromycin, imipenem, oxacillin, and TTC and 89.1% to ciprofloxacin. This was high compared to CoNS resistance to erythromycin (39%), oxacillin (35%), TTC (47%), and ciprofloxacin (21%) in Ethiopia [28].

In this study, overall 571 (20.9%) cases of MDR were reported, which is comparable with 26.8% in Nepal [6], but it was low compared with the pooled prevalence of MDR from a systematic review in Ethiopia, which documented 59.7% in 2019 [18] and 70.5% in 2021 [20]. The current study also revealed 378 (18.1%) of MDR among GNB, which is lower compared with 85.8% in one of the hospitals in the study area [21] and 74% of MDR among food handlers, in foods, in animals, and in the environment in Ethiopia [24]. The high number of MDR among food handlers, foods, animals, and the environment [24] confirmed the complexity of socioecologic systems that drive the emergence and spread of AMR [30]. The potential crisis caused by MDR and the limited treatment options could be solved by integrating the pharmaceutical industry, research institutions, and other stakeholders [31]. There should be efforts at the health facility level to improve antibiotic prescribing, and isolated pathogen management will play a major role in controlling the spread of organisms [32]. This calls for effective policy and intervention measures to address AMR through the One Health approach.

Overall, resistant *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *A. baumannii*, and *P. aeruginosa* were the leading causes of death [10]. AMR, a multifaceted problem that affects almost all communities [1], is a complex process involving multiple factors beyond antibiotics [33, 34]. It requires coordinated strategies and actions from various stakeholders to curtail the emergence and spread of AMR [1]. Continuous monitoring, molecular detection of the gene responsible for AMR, and the implementation of recommended ASPs are important to reduce the emergence and spread of drug-resistant pathogens [2, 21]. While antibiograms are helpful, they cannot be relied upon as the sole resource for guiding empirical antimicrobial therapy since the patient's microbiological history and prior antibiotic use may provide more helpful information during therapy selection [35]. Thus, implementing context-specific and locally tailored ASPs in healthcare facilities is highly recommended to reduce inappropriate antibiotic use and resistance [2, 35].

The current study will serve an alarm to awaken health professionals during disease management and monitoring

of treatment. It will also help in addressing AMR to safeguard public health and inform effective interventions. However, the current study uses data which was not systematically collected from the population; it will not show an accurate picture of AMR in the area. However, it gives us a clue on the past trend among those routinely tested to predict the likelihood of an AMR occurrence in the future. Another limitation is that it may not include all antibiotics currently in use. A significant number of the tests were incomplete, which may understate the real picture of all tests done in the laboratory.

In conclusion, AMR is prevalent in the Amhara public health research laboratory. It has been increasing, reaching a peak in 2019, and started to decline in 2020 and will possibly decline over time. The vast majority of antibiotic-resistant and MDR bacteria were GNB. The decline trend in AMR and sample collection in the laboratory clearly indicated the impact of COVID-19 on the AMR surveillance. This calls for sustainable programs for surveillance and monitoring of AMR in the region. Overall, implementation of context-specific ASPs will be a cost-effective strategy to contain and delay the spread of the AMR tsunami.

Data Availability Statement

All data are included in the manuscript. If additional data are required, we will provide them upon request.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

A.A.A. is involved in the conception, study design, execution, acquisition of data, analysis and interpretation, and manuscript writing and review. T.G.F. is involved in the conception, study design, and manuscript writing and review. G.Y.W. is involved in the conception, study design, and manuscript writing and review.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information 1. Table S1: Distribution of MDR gram-positive bacteria (2016–2021), APHI, Amhara Region, Ethiopia (N = 195).

Supporting Information 2. Table S2: Distribution of MDR gram-negative bacteria (2016–2021), APHI, Amhara Region, Ethiopia (N = 378).

Supporting Information 3. Table S3: Distribution of MDR gram-negative bacteria (2016–2021), APHI, Amhara Region.

Supporting Information 4. Table S4: Distribution of MDR gram-positive bacteria in APHI during the last 6 years, 2016–2021 (N = 195).

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Original Paper

Antibiotic Prescribing Behavior of Physicians in Outpatient Departments in Hospitals in Northwest Ethiopia: Structural Equation Modeling Approach

Asrat Agalu Abejew^{1,2*}, BPharm, MSc; Gizachew Yismaw Wubetu^{3*}, BSc, MSc, PhD; Teferi Gedif Fenta^{1*}, BPharm, MPH, PhD

¹Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

²Department of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia

³Amhara Public Health Institute, Bahir Dar, Ethiopia

*all authors contributed equally

Corresponding Author:

Asrat Agalu Abejew, BPharm, MSc
Department of Pharmaceutics and Social Pharmacy, School of Pharmacy
College of Health Sciences
Addis Ababa University
Addis Ababa
Addis Ababa, +251
Ethiopia
Phone: 251 0917156682
Email: asruphar@gmail.com

Abstract

Background: Antibiotic resistance, fueled by irrational prescribing, is a global threat associated with health, social, and economic consequences. Understanding antibiotic prescribing behavior and associated factors is important to promote good prescribing practice.

Objective: This study aimed to determine the factors affecting antibiotic prescribing behaviors of physicians based on the theory of planned behavior in hospitals in northwest Ethiopia in 2022.

Methods: A cross-sectional study was conducted from September 2022 to October 2022. A total of 185 health professionals were included, and a self-administered questionnaire was used to collect data. A structural equation model based on the modified theory of planned behavior was used to determine factors affecting antibiotic prescribing behavior. The percentages of physicians' estimated prescriptions for patients with upper respiratory tract infections (URTIs) and during weekly outpatient visits were used to predict antibiotic prescribing behavior and finally linked with behavioral constructs. A *P* value <.05 was considered significant.

Results: Physicians estimated that they prescribed antibiotics for 54.8% (9896/18,049) of weekly outpatient encounters, and 178 (96.2%) of the 185 physicians estimated they prescribed antibiotics for patients who presented with symptoms of a URTI. Physicians aged ≤30 years were less likely to prescribe antibiotics (48/100, 48%) for patients who presented with a URTI than physicians older than 30 years (51/100, 51%; *P*=.004), and general practitioners were less likely to prescribe antibiotics (47/100, 47%) for patients who presented with a URTI than residents (51/100, 51%; *P*=.03). Similarly, during outpatient visits, physicians ≤30 years old were less likely to prescribe antibiotics (54/100, 54%) than physicians older than 30 years (57/100, 57%; *P*<.001), male physicians were less likely to prescribe antibiotics (53/100, 53%) than female physicians (64/100, 64%; *P*=.03), and general practitioners were less likely to prescribe antibiotics (53/100, 53%) than residents (57/100, 57%; *P*=.02). Physicians with good knowledge were less affected by perceived social pressure (mean 4.4, SD 0.6) than those with poor knowledge (mean 4.0, SD 0.9; *P*<.001) and felt it was easy to make rational decisions (mean 4.1, SD 1.1) compared with those with poor knowledge (mean 3.8, SD 1; *P*<.001). However, intentions to reduce and prescribe antibiotics were not affected by attitudes, subjective norms, or perceived behavioral control, and perceived antibiotic prescribing behavior was not related to intentions to reduce or prescribe antibiotics.

Conclusions: Antibiotic prescribing behavior was not under the volitional control of physicians. This calls for a systematic approach to change antibiotic prescribing practices in hospital.

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KEYWORDS

antibiotic prescribing behavior; Ethiopia; outpatient departments; physicians; SEM; TPB

Introduction

Antimicrobial resistance (AMR) is a natural phenomenon [1], to which overuse and misuse of antibiotics contribute and augment [1-4]. Globally, antibiotic consumption has increased (eg, by 65% from 2000 to 2015), and 30% to 50% of antibiotic prescriptions were used either inappropriately or unnecessarily [2], further resulting in increased inappropriate use [3,4] and the development of selective pressure on antibiotics [5-7]. Inappropriate prescribing is a key contributing factor to the emergence of AMR [1,8,9] and varies from 62.8% for respiratory tract infections to 78.5% in patients with skin and soft tissue infections [4]. This would strengthen the belief that antibiotics ought to be prescribed and are effective in circumstances when they are not [10]. Physicians' prescribing behaviors impact not only patient health but also medical expenses and health resources [11]. It is recommended to monitor antibiotic prescribing in hospitals to improve the quality of antibiotic prescribing through education and practice changes [12]. Identifying key behaviors and drivers for the behaviors that may be amenable to change and improve prescribing decisions is an important component of interventions in health care practice to mitigate the burden of AMR [1,10,11]. Antibiotic stewardship programs (ASPs), which are among the most common interventions in health facilities to optimize antibiotic use, are effective, low-cost methods to change behaviors that drive excessive prescribing of antibiotics in health facilities [1].

Human behavior is guided by beliefs about the likely consequence of the behavior (behavioral beliefs), beliefs about the normative expectations of others (normative beliefs), beliefs about the presence of factors that may facilitate or impede the performance of the behavior (control beliefs), shaping attitudes, subjective norms (SNs), and perceived behavioral control (PBC) [13]. It is reported that these behavioral beliefs (attitudes, PBC, and SN) of physicians are predictors of indiscriminate antibiotic prescribing behaviors in hospitals [9,14]; thus, campaigns that address both health service personnel and the general population should take this into account [8]. A high level of knowledge is known to be associated with a more positive attitude and behavioral intention for reducing antibiotic prescriptions and was linked with less complacency, less fear, and less ignorance, although it had indirect effects on intentions to prescribe antibiotics through the attitude of ignorance [14]. On the other hand, perceived higher patient pressure negatively affects attitudes toward the rational use of antibiotics and promotes higher use of antibiotics [15]. Thus, characterizing and designing behavior change interventions based on the behavior change wheel model and theory of planned behavior (TPB) serve as a framework for modeling the antibiotic prescribing behaviors of physicians [13,16,17]. Optimizing antibiotic consumption and reducing the rate of AMR are currently global issues [1,18]. In low- and middle-income countries, the prescribing of antibiotics

is highly influenced by inadequate diagnostic facilities, lack of guidelines, difficulty monitoring patient progress, poor intensive care facilities, patient demand for quick relief, perceived patient expectations from past prescriptions, and fear of losing patients to competition [19,20]. This results in high mortality and morbidity due to inadequate regulation, limited access to diagnostic facilities, and antimicrobial over-prescription [21,22]. Based on the behavior change wheel, once a problem is identified and context is considered, functions and policies may be implemented as interventions to understand and change prescribing behavior and improve antibiotic consumption [13,17]. This requires the design and implementation of sustained awareness campaigns to change behaviors and improve health outcomes [9].

In sub-Saharan Africa, physicians still prescribe antibiotics based only on a simple assessment of patients' symptoms, just as they used to when antibiotics first became commonly used in the 1950s [9], due to a lack of diagnostic and antibiotic susceptibility tests, resulting in up to 95% of antibiotic prescriptions as unnecessary [23]. Prescribing antibiotics requires balancing physician, patient, and facility-related factors [24]. In Ethiopia, antibiotic prescribing in hospitals may account for 52.39% of all prescriptions [25], and one-half of prescribed antibiotics might not be needed [26]. Although behavior change campaigns can be very cost-effective for changing antibiotic prescribing practices, based on identified gaps [9], in Ethiopia, to our knowledge, there have been no studies to model the antibiotic prescribing behavior of physicians other than determining the perceptions of health professionals on AMR and antibiotic use [27,28]. Modeling behavior is needed to help clinical leaders drive ASP and design educational programs to help standardize and improve antibiotic prescribing behaviors in health facilities [29]. Thus, this study assessed the determinants of antibiotic prescribing behavior among physicians serving in outpatient departments (OPDs) in hospitals in northwest Ethiopia using a structural equation modeling (SEM) approach.

Methods**Study Area and Period**

A cross-sectional study was conducted from September 2022 to October 2022 in 4 hospitals: Felege Hiwot Comprehensive Specialized Hospital, Tibebe Ghion Specialized Hospital, Debre Markos Comprehensive Specialized Hospital, and Injibara General Hospital. Except for attempts to implement ASPs in inpatient wards in some of the hospitals, there is currently no system to monitor antibiotic prescribing or enabling factors for prescribing antibiotics in OPDs. This survey assessed the knowledge, attitudes, SN, and PBC of physicians and their intention to prescribe antibiotics as possible factors for antibiotic prescribing behaviors to provide insights into the driving forces of antibiotic prescribing as a complementary factor for antibiotic

consumption, which together constitute baseline information to design effective ASPs to tackle AMR.

Study Participants, Sample Size Determination, and Sampling Procedures

Physicians (general practitioners and residents) working in OPDs of internal medicine, pediatrics, gynecology and obstetrics, and surgical departments were included in the study. The sample size for health professionals was determined based on the following formula for a finite population:

$$n = \chi^2 NP (1-P) / (d^2 (N-1) + \chi^2 P (1-P))$$

where n is the sample size and χ^2 is the table value of the chi square for 1 degree of freedom at the desired confidence level ($1.96 \times 1.96 = 3.84$), N is the total population, P is the population proportion (27%), and d is the degree of accuracy expressed as a proportion (0.05). According to Gebretekla et al [27], physicians estimate that they prescribe antibiotics to about 27% of their patients. Thus, a prevalence of 27% was used to calculate the sample size in this study. Accordingly, n was calculated as follows:

$$n = (1.96 \times 1.96) \times 487 \times 0.27(1-0.27) / ((0.05 \times 0.05) \times (487-1) + (1.96 \times 1.96) \times 0.27(1-0.27))$$

$$n = 181.26 \text{ or } \sim 182$$

To account for the nonresponse rate, 10% was added; thus, the total sample size was 200.

Data Collection Instruments and Processes

Data collection was based on the study by Liu et al [14,15] and customized to local scenarios in Ethiopian hospital settings. Questionnaires consisted of 4 behavioral aspects leading to antibiotic prescribing based on the TPB, namely attitudes (the degree to which a prescriber is in favor of the use of antibiotics), SN (perceived social pressure to which a prescriber is subject to prescribe antibiotics), PBC (the ease or difficulty of making a rational decision on antibiotic prescriptions), and intentions (the degree to which a prescriber is willing to prescribe or reduce antibiotics). The questionnaire for professionals was designed on a Likert scale with a 5-point response format, ranging from 1 (strongly disagree) to 5 (strongly agree) for attitudes about and intention to prescribe antibiotics, and a 5-point response

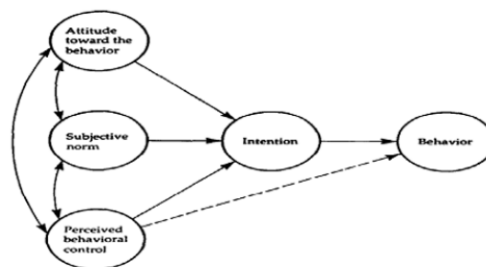
format (from always to never) for SN and PBC. In addition, physicians were asked to estimate the number of patients who receive antibiotics from their weekly encounters that involve prescriptions and the number of patients for whom they prescribe antibiotics from 10 encounters with patients with symptoms of upper respiratory tract infections (URTIs) to assess their antibiotic prescribing behavior or practices. To assess physicians' knowledge, 11 questions were used, attitude was assessed using 7 questions, SN was assessed using 8 questions, PBC was assessed using 5 questions, and there were 3 questions each to measure intentions to reduce and prescribe antibiotics.

Physicians (general practitioners and residents) working in internal medicine, pediatrics, gynecology and obstetrics, and surgical OPDs in the hospital were approached to participate in the study. The questionnaire was distributed while they were on duty. The completeness of the data was monitored on a daily basis. Finally, the data were compiled, and the behavioral constructs were linked with the percentages of physicians' perceived antibiotic prescribing behaviors and practices using SEM based on modified TPB (MTPB).

The Theoretical Framework for Structural Equation Modeling

Attitude, SN, and PBC were shown to be related to appropriate sets of salient behavioral, normative, and control beliefs about a behavior. PBC, together with behavioral intention, can be used directly to predict behavioral achievement. Attitude is defined as the degree to which a prescriber is in favor of the use of antibiotics in outpatient encounters, whereas SN and PBC measure the perceived social pressure to which a prescriber is subject to prescribe antibiotics and the perceived ease or difficulty of making a rational decision during antibiotic prescriptions, respectively. A behavioral intention that is intermediate measures the degree to which a prescriber is willing to prescribe antibiotics [13]. Thus, the theoretical framework was adopted from the TPB model (Figure 1), and links between knowledge and attitude, SN, and PBC were explored. However, since the comparative fit indexes (CFIs) were low, knowledge was linked to SN and PBC in relation to antibiotic use, and attitude, SN, and PBC were linked to intentions to prescribe antibiotics and finally to behaviors influencing antibiotic prescribing.

Figure 1. Theory of planned behavior [13].



Statistical Analysis

Data were coded, entered, cleaned, and transferred to STATA version 14.0 (Stata Corp) for SEM analyses, but descriptive statistics were analyzed using SPSS version 23 (IBM Corp). ANOVA and chi-squared tests were performed to determine the difference in the mean measuring knowledge, attitudes, SN, PBC, and behavioral intentions of the participants according to age, gender, city, professional status, workplace, and duration of clinical practice. For knowledge, the percentage of respondents who answered correctly and the total number of correct answers per respondent were calculated. In addition, correct answers were coded as 1, and incorrect answers were coded as 0 for the SEM. Each attitude item was coded using a 5-point Likert scale (1=strongly agree, 5=strongly disagree), then recoded (-2=strongly disagree, 2=strongly agree), with a negative score indicating disagreements and a positive score indicating agreement with the average scores (ranging from -2 to 2). Intentions to reduce and prescribe antibiotics were coded similarly as the attitude measurements, with a negative score indicating refusal and a positive score indicating support for reducing antibiotic prescriptions (from -2 to 2). SN and PBC were measured from 1 to 5, with 1 indicating always and 5 indicating never, then recoded from 0 to 4, where 0 denotes never and 4 represents always. Behaviors around antibiotic prescriptions were measured using the percentage of antibiotic prescriptions for URTIs, per every 10 patients, and the percentage of antibiotic prescriptions among the estimated weekly visits.

Each variable was modeled separately to exclude factor loadings <0.3. Finally, SEM was applied to establish the associations between knowledge, attitudes, and practices. Standardized path coefficients with statistical significance ($P < .05$) were used. The maximum likelihood method was used to estimate the parameters. The fitness of the data in the SEM model was assessed using model fitness indexes based on recommended level acceptances such as $P > \chi^2$ ($P > .05$), standardized root mean squared residual <0.09, and root mean squared error of approximation <0.08; Tucker-Lewis index >0.90; CFI >0.90; and coefficient of determination ≥ 0.7 . In addition, descriptive analysis was used.

Operational Definitions

We considered attitude to be the degree to which a participant had a positive or negative evaluation of indiscriminate antibiotic use. SNs were participants' beliefs about whether significant

others would approve or disapprove of indiscriminate antibiotic use (ie, the perceived social pressure to which a prescriber is subject to prescribe antibiotics). PBC was the participant's beliefs regarding the ease or difficulty of making a rational decision about antibiotic prescriptions. Knowledge was considered participants' understanding and awareness regarding indiscriminate antibiotic use and AMR. The level of knowledge was determined based on the average score for all the questions (ie, physicians who answered at least or above the average score were considered to have good knowledge). Behavioral intentions around antibiotic prescriptions were the degree to which a prescriber was willing to prescribe antibiotics. Behaviors were documented as physicians' self-reported antibiotic prescribing behaviors.

Ethical Considerations

Ethical approval was obtained from the College of Health Sciences (protocol code: 106/22/SoP) and the School of Pharmacy (protocol code: ERB/SOP/472/14/2022) of Addis Ababa University. A support letter to the hospitals was obtained from the Amhara Public Health Institute. During data collection, physicians' names were deidentified. All participants provided informed consent prior to participating in this study. The information obtained was kept confidential and used only for research purposes. Ethical issues like privacy and confidentiality were considered during data collection in order not to disclose information about people outside the research.

Results

Among 200 planned respondents, 185 completed the questionnaires. Thus, the overall response rate was 92.5%.

General Characteristics of Study Participants

The majority of physicians (153/185, 82.7%) were men, and their average age was 30.3 (3.9) years. Overall, physicians had been in their current roles an average of 3.0 (2.2) years and had worked at their current hospital for an average of 2.0 (1.8) years. The majority of physicians (149/185, 80.5%) had worked in their current roles for <5 years; 87 (87/185, 47%) and 55 (55/185, 29.9%) were from Tibebe Ghion Specialized Hospital and the gynecology and obstetrics department, respectively. Of the patients who visited the OPDs, the physicians estimated that 9896 (9896/18,049 54.8%) had received at least one antibiotic (Table 1).

Table 1. Characteristics of the 185 physician respondents in hospital outpatient departments in 2022.

Variables	Results
Sex, n (%)	
Male	153 (82.7)
Female	32 (17.3)
Age (years), n (%)	
≤30	116 (62.7)
>30	69 (37.3)
Professional title, n (%)	
GP ^a	93 (50.2)
Residents	92 (49.8)
Facility, n (%)	
FHCSH ^b	43 (23.2)
TGSH ^c	87 (47)
DMCSH ^d	31(16.8)
IGH ^e	24 (13)
Department, n (%)	
Medical	36 (19.5)
Surgery	40 (21.6)
Pediatrics	48 (25.9)
Gyne/obs ^f	55 (29.9)
Others	6 (3.2)
Length of employment in the current hospital (years), n (%)	
<5	172 (93)
≥5	13 (7)
Overall length of employment in the current role (years), n (%)	
<5	149 (80.5)
≥5	36 (19.5)
Training on antibiotic use	
No	159 (85.9)
Yes	26 (14.1)
Patients seen per week, n	18,049
Patients seen per week, mean (SD)	97.5 (79.7)
Patients estimated to receive antibiotics per week, n	9896
Patients estimated to receive antibiotics per week, mean (SD)	60.1 (53.5)

^aGP: general practitioner.^bFHCSH: Felege Hiwot Comprehensive Specialized Hospital.^cTGSH: Tibebe Ghion Specialized Hospital.^dDMCSH: Debre Markos Comprehensive Specialized Hospital.^eIGH: Injibara General Hospital.^fGyne/obs: gynecology and obstetrics.

Knowledge of Physicians About Antibiotic Prescription

The majority of physicians agreed that amoxicillin is safe for pregnant patients (169/185, 91.4%), metronidazole has the best activity against anaerobes (166/185, 89.7%), and antibiotics should not be prescribed for nonfebrile diarrhea (151/185, 81.6%). However, none of the physicians answered,

“Aminoglycosides are very active if they are administered parenterally once daily.” Physicians answered 5 of 11 (46%) questions correctly. Based on this, 121 (65.4%) of the 185 physicians had good knowledge, based on the cutoff of a mean ≥ 5 ; however, for 64 (34%) of the 185 physicians, knowledge was poor (Table 2).

Table 2. Knowledge about antibiotic prescriptions of 185 physicians in hospital outpatient departments in 2022.

Code	Items to assess knowledge levels	Response		Factor loading	<i>P</i> value
	Correct, n (%)	Incorrect, n (%)			
q35	Antibiotic treatment is not needed for non-febrile diarrhea.	151 (81.6)	34 (19.4)	0.43	<.001
q36	Antibiotics are not prescribed for upper respiratory tract infections.	19 (10.3)	166 (89.7)	−0.14	.11
q37	Dosage reduction for ceftriaxone and clindamycin is needed for renal failure.	37 (20)	148 (80)	−0.11	.22
q38	Amoxicillin is a safe antibiotic product for pregnant patients.	169 (91.4)	16 (9.9)	0.55	<.001
q39	Metronidazole has the best activity against anaerobes.	166 (89.7)	19 (10.3)	0.82	<.001
q40	Methicillin-resistant <i>staphylococcus aureus</i> is resistant to beta-lactam antibiotics.	108 (58.4)	77 (39.4)	0.42	<.001
q41	Ceftriaxone most effectively crosses the blood-brain barrier.	85 (45.9)	100 (54.1)	0.37	<.001
q42	Aminoglycosides are very active if they are administered parenterally once daily.	0	185 (100)	0	.99
q43	Bacterial pneumonia (with symptoms of fast breathing, chest in-drawing, or stridor) requires antibiotic treatment.	90 (48.6)	95 (48.6)	0.14	.15
q44	Antibiotics do not reduce the duration and the occurrence of complications of upper respiratory tract infections.	37 (20)	148 (80)	0.17	.07
q45	The average number of patients taking antibiotics should be below 30% in a primary care facility.	36 (19.5)	149 (80.5)	0.063	.47

Attitudes and Intentions of Physicians Toward Antibiotic Prescriptions

The mean response for attitude questions was 2.5 (0.4). Of the 185 physicians, 88 (47.6%) perceived that microbiology results are important for treating infectious diseases, 95 (51.4%) believed that over-prescribing of antibiotics contributes to the generation of antibiotic resistance, and 89 (48.1%) believed that over-prescription of antibiotics leads to the development of resistance. Regarding intention to prescribe antibiotics, the mean

score for intention to reduce antibiotics was 2.4 (0.9), whereas the mean score for intention to prescribe antibiotics 2.5 (0.8). Of the 185 physicians, 133 (71.9%) wanted to reduce antibiotic consumption, 132 (71.4%) expected to reduce antibiotic consumption, and 117 (63.2%) planned to reduce antibiotic consumption for outpatients; however, 107 (57.8%) wanted to prescribe antibiotics, 103 (55.6%) expected to prescribe antibiotics, and 102 (55.1%) planned to prescribe antibiotics to their patients (Table 3).

Table 3. Physicians' (n=185) responses to individual items about attitudes and behavioral intentions about antibiotic prescribing in hospital outpatient departments in 2022.

Measurement and items	Code	Response score, mean (SD)	Responses, n (%)					Factor loading	P value	
			Strongly agree (1)	Agree (2)	Neutral (3)	Disagree (4)	Strongly disagree (5)			
Attitude ^a										
In primary care, microbiology results are useful when treating infectious diseases.	Q1	1.8 (1)	88 (47.6)	73 (39.5)	8 (4.3)	11 (5.9)	5 (2.7)	0.34	<.001	
The prescription of an antibiotic to a patient does not influence the development of resistance.	Q2	4.2 (0.9)	0	16 (8.6)	12 (6.5)	68 (36.8)	89 (48.1)	−0.09	.30	
Overuse of antibiotics contributes to the generation of antibiotic resistance.	Q3	1.7 (1)	107 (57.8)	57 (30.8)	7 (3.8)	7 (3.8)	7 (3.8)	0.56	<.001	
Prescribing antibiotics to patients does not cause damage even if they are not indicated.	Q4	4.2 (0.9)	1 (0.01)	13 (7.0)	10 (5.4)	77 (41.6)	84 (45.4)	−0.03	.73	
Over-prescribing antibiotics contributes to the generation of antibiotic resistance	Q5	1.7 (0.9)	95 (51.4)	64 (34.6)	13 (7)	10 (5.4)	3 (1.6)	0.80	<.001	
Irrational use of broad-spectrum antibiotics contributes to generation of AMR ^b	Q6	1.7 (0.9)	88 (47.6)	81 (43.8)	7 (3.8)	5 (2.7)	4 (2.2)	0.62	<.001	
Not selecting antibiotics to be prescribed based on the infected bacteria contributes to the generation of antibiotic resistance.	Q7	2.2 (1.1)	56 (30.3)	82 (44.3)	16 (8.6)	22 (11.9)	9 (4.9)	0.27	.009	
Intention to reduce antibiotics ^c										
I want to reduce antibiotic consumption for outpatients.	Q29	2.5 (1.7)	20 (10.8)	113 (61.1)	27 (14.6)	18 (9.7)	7 (3.8)	0.40	<.001	
I expect to reduce antibiotic consumption for outpatients.	Q30	2.3 (0.8)	21 (11.4)	111 (60)	33 (17.8)	18 (9.7)	2 (1.1)	0.82	.001	
I plan to reduce antibiotic consumption for outpatients.	Q31	2.4 (0.8)	15 (8.1)	102 (55.1)	48 (25.9)	18 (9.7)	2 (1.1)	0.57	<.001	
Intention to prescribe antibiotics ^d										
I want to prescribe antibiotics to outpatients	Q32	2.5 (0.9)	23 (12.4)	84 (45.4)	55 (29.7)	17 (9.2)	6 (3.2)	0.74	<.001	
I expect to prescribe antibiotics to outpatients.	Q33	2.5 (0.9)	16 (8.6)	87 (47)	61 (33)	17 (9.2)	4 (2.2)	0.87	<.001	
I plan to prescribe antibiotics to outpatients.	Q34	2.5 (0.9)	15 (8.1)	87 (47)	57 (30.1)	21 (11.4)	5 (2.7)	0.80	<.001	

^aOverall score: mean 2.5 (SD 0.4).^bAMR: antimicrobial resistance.^cOverall score: mean 2.4 (SD 0.9).^dOverall score: mean 2.5 (SD 0.8).

Subjective Norms and Perceived Behavioral Control of Physicians

The mean scores for SNs and PBC were 4.3 (0.8) and 4.0 (1.1), respectively. Of the 185 physicians, 133 (71.9%), 128 (69.2%), 126 (68.1%), and 125 (67.6%) never prescribed antibiotics based on patients' expectations, based on patient pressure, based on

patients' requests for antibiotics, and to make patients trust them, respectively. Similarly, 119 (64.3%) of the 185 physicians never prescribed antibiotics to avoid being perceived as doing nothing for patients. Only a limited number of physicians agreed that they prescribed antibiotics based on patients' expectations or pressure (Table 4).

Table 4. Physicians' (n=185) responses to individual items about subjective norms and perceived behavioral control for intention to prescribe antibiotics in hospital outpatient departments in 2022.

Measurement and items	Codes	Response score, mean (SD)	Responses, n (%)					Factor loading	P value
			Always (1)	Often (2)	Sometimes (3)	Rarely (4)	Never (5)		
Subjective norm ^a									
I prescribe antibiotics since patients expect it.	Q15	3.9 (1.2)	6 (3.2)	21 (11.4)	38 (20.5)	48 (25.9)	72 (38.9)	0.54	<.001
I prescribe antibiotics since patients require and insist on it.	Q16	3.9 (1.1)	7 (3.8)	16 (8.6)	33 (17.8)	55 (29.7)	74 (40)	0.64	<.001
I prescribe antibiotics to satisfy patients.	Q17	4.1 (1.2)	10 (5.7)	12 (6.5)	24 (13.0)	46 (24.9)	93 (50.3)	0.55	<.001
I prescribe antibiotics so patients continue to trust me.	Q18	4.4 (1.0)	5 (2.7)	11 (5.9)	12 (6.5)	32 (17.3)	125 (67.6)	0.68	<.001
Even when I know that they are not indicated, I prescribe antibiotics since patients expect it.	Q19	4.5 (0.9)	3 (1.6)	4 (2.2)	19 (10.3)	26 (14.1)	133 (71.9)	0.84	<.001
Even when I know that they are not indicated, I prescribe antibiotics since patients ask for it.	Q20	4.5 (0.8)	1 (0.1)	7 (3.8)	13 (7)	38 (20.5)	126 (68.1)	0.86	<.001
Even when I know that they are not indicated, I prescribe antibiotics since patients press me to prescribe it.	Q21	4.5 (0.9)	3 (1.6)	3 (1.6)	19 (10.3)	32 (17.3)	128 (69.2)	0.87	<.001
Even when I know that they are not indicated, I prescribe antibiotics since I do not have time to explain to the patient the reason why they are not called for.	Q22	4.3 (1.1)	4 (2.2)	16 (8.6)	10 (5.4)	40 (21.6)	115 (62.2)	0.70	<.001
Perceived behavioral control ^b									
I prescribe antibiotics because I fear patient deterioration.	Q23	3.9 (3.2)	5 (2.7)	25 (13.5)	50 (27)	43 (23.2)	62 (33.5)	0.28	<.001
I prescribe antibiotics since it is impossible to track the patient accurately.	Q24	3.7 (1.1)	4 (2.2)	24 (13)	47 (25.4)	55 (29.7)	55 (29.7)	0.63	<.001
I prescribe antibiotics to avoid possible patient complaints or medico-legal problems.	Q25	4.1 (1.1)	8 (4.3)	10 (5.4)	31 (16.8)	44 (23.8)	92 (49.7)	0.85	<.001
I prescribe antibiotics to avoid being perceived as doing nothing for patients.	Q26	4.3 (1.1)	6 (3.2)	10 (5.4)	18 (9.7)	32 (17.3)	119 (64.3)	0.73	<.001
I prescribe antibiotics to avoid losing patients.	Q27	3.9 (1.3)	9 (4.9)	25 (13.5)	23 (12.4)	32 (17.3)	96 (51.9)	0.61	<.001

^aOverall score: mean 4.3 (SD 0.8).^bOverall score: mean 4.0 (SD 1.1).**Antibiotic Prescribing Practices of Physicians**

Of the 18,049 patients seen in the OPDs, 9896 (54.8%), or an average of 60.1 (53.5%) patients per week, were estimated to receive at least one antibiotic. Using an estimate of 10 patients for each of the 185 physicians, for a total of 1850 patients with URIs, about 916 (49.5%) were estimated to be prescribed at least one antibiotic. Accordingly, 178 (96.2%) of the 185 physicians estimated that they prescribed antibiotics for at least

one patient out of every 10 patients who presented with symptoms of a URI, with a mean score of 5.9 (SD 2.2); 142 (142/185, 76.8%) physicians believed they would prescribe antibiotics for >3 patients; and 43 (43/185, 23.3%) physicians estimated they would prescribe antibiotics for 0 to 3 patients. The majority of physicians (56/185, 30.3%) said they would prescribe antibiotics to 5 patients out of 10 encounters with patients with URIs in the OPDs (Table 5).

Table 5. Estimated prescriptions of antibiotics for upper respiratory tract infections (URTIs) out of every 10 patients by 185 physicians in hospital outpatient departments.

Number of patients prescribed antibiotics per every 10 patients	Physicians who estimated they would prescribe antibiotics, n (%)
0	7 (3.8)
1	4 (2.2)
2	9 (4.9)
3	23 (12.4)
Total for ≤3 encounters (30% of patients) with a URTI	43 (23.3)
4	31 (16.8)
5	56 (30.3)
6	20 (10.8)
7	10 (5.4)
8	12 (6.5)
9	2 (1.1)
10	11 (5.9)
Total for >3 encounters with a URTI	142 (76.8)

Structural Equation Modeling

The SEM using MTPB confirmed the theoretical framework for the antibiotic prescribing behaviors of physicians with some modifications. Based on the coefficient of determination (R^2), 94.6% of the variation in antibiotic prescribing behavior could be explained by all the exogenous variables. Data in the MTPB model had good fit, with $P > \chi^2$ ($P > 0.0001$), a root mean squared error of approximation of 0.049, a standardized root mean squared residual of 0.071, a CFI of 0.91, and a Tucker-Lewis index of 0.901 (Table 6).

The MTPB model indicated that only physician knowledge was associated with PBC and SN. There was covariance between SNs and PBC ($P < .001$). Attitudes, SNs, and PBC were not associated with intentions to prescribe or reduce use of antibiotics. Similarly, intentions to prescribe or reduce use of antibiotics was not associated with the estimated number of antibiotic prescriptions for URTIs or during weekly visits (Figure 2). Physician age ($P = .004$) and professional level ($P < .02$) were predictors of the number of estimated prescriptions for URTIs, and physician age ($P = .001$), sex ($P = .03$), and professional level ($P = .02$) were predictors of the estimated number of prescriptions during weekly OPD visits. Knowledge

was a direct predictor of SNs ($P < .001$) and PBC ($P < .001$). There was no indirect relationship between prescriber behaviors and knowledge, attitude, SN, and PBC (Table 7).

Based on the information in Table 7, for the 49.5% of the 1850 patients with URTIs who were estimated to be prescribed at least one antibiotic, physicians older than 30 years were more likely to prescribe antibiotics (51/100, 51%) than those ≤30 years old (48/100, 48%). Based on professional level, residents (51/100, 51%) were more likely to prescribe antibiotics than general practitioners (47/100, 47%). Similarly, for the estimated 54.8% (9896/18,049) of weekly OPD visits that had an antibiotic prescription, physicians older than 30 years were more likely to prescribe antibiotics (57/100, 57%) than those ≤30 years old (54/100, 54%). Women (63/100, 63%) and residents (57/100, 57%) were also more likely to prescribe antibiotics than men (53/100, 53%) and general practitioners (53/100, 53%), respectively. Good knowledge was a direct predictor of SNs (mean 4.4, SD 0.6) and PBC (mean 4.1, SD 1.1), both of which are in contrast for those with poor knowledge (mean 4.0, SD 0.9) and (mean 3.8, SD 1), respectively. However, intentions to reduce and prescribe antibiotics were not affected by attitudes, SNs, nor PBC, and perceived antibiotic prescribing behavior was not related to intentions to reduce or prescribe antibiotics.

Table 6. The model goodness of fit indexes for antibiotic prescribing behaviors of 185 physicians in hospital outpatient departments.

Fit statistics	Value	Description	Standard
Likelihood ratio			
χ^2_{ms} (314)	451.292	Model versus saturated	___ ^a
$P>\chi^2$	0.0001	—	—
χ^2_{bs} (348)	1878.872	Baseline versus saturated	—
$P>\chi^2$	0.0001	—	—
Information criteria			
Akaike information criterion (AIC)	14073.713	—	
Bayesian information criterion (BIC)	14337.782	—	
Population error			
Root mean squared error of approximation (RMSEA)	0.049	—	0.08
90% CI	0.038-0.058	—	—
Pclose	0.581	Probability of RMSEA ≤ 0.05	—
Size of residuals			
Standardized root mean squared residual (SRMR)	0.071	—	<0.09
Coefficient of determination (CD)	0.946	—	—
Baseline comparison			
Comparative fit index (CFI)	0.910	—	≥ 0.90
Tucker-Lewis index (TLI)	0.901	—	≥ 0.90

^aNot applicable.

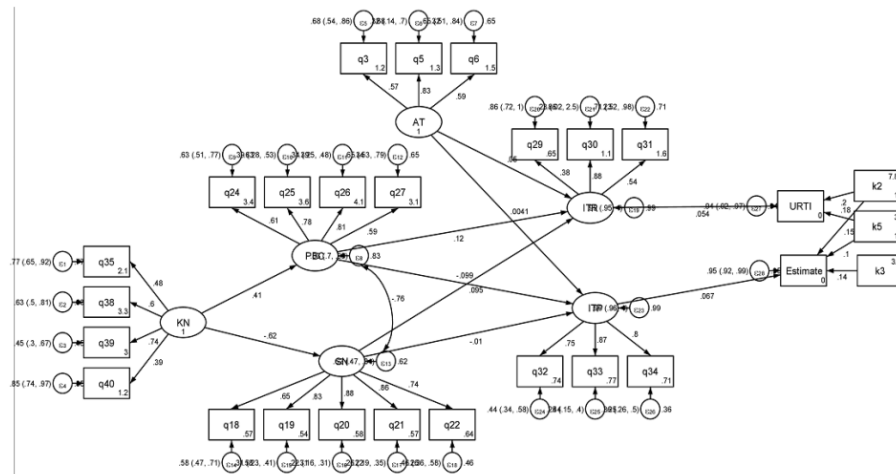
Figure 2. SEM of Antibiotic Prescribing Behavior in hospital outpatient departments using standardized coefficients in 2022.

Table 7. Effects of direct and indirect variables on the intention to prescribe antibiotics by 185 physicians in hospital outpatient departments in 2022.

Factor	Effects of covariates on each other		
	B	SE	P value
Subjective norms			
Knowledge	0.41	0.49	<.001
Perceived behavioral control			
Knowledge	−0.62	0.43	<.001
Intention to reduce antibiotic prescriptions			
Attitude	0.16	0.20	.42
Subjective norms	0.15	0.20	.45
Perceived behavioral control	0.13	0.21	.53
Intention to prescribe antibiotics			
Attitude	0.10	0.89	.91
Subjective norms	0.20	0.93	.83
Perceived behavioral control	−0.26	0.89	.79
Proportion of patients from 10 who were estimated to be prescribed antibiotics for a URTI^a			
Facility	3.09	1.84	.09
Age	1.05	0.37	.004
Sex	5.19	4.09	.20
Work area	0.17	1.56	.91
Professional level	6.96	3.24	.03
Length of employment in the current hospital	0.36	1.64	.83
Overall length of employment in the current position	−0.31	1.31	.81
Training	3.68	4.28	.39
ITRABx ^b	1.66	2.69	.54
ITPABx ^c	Constrained	Constrained	Constrained
Proportion of weekly visits during which physicians estimated they would prescribe antibiotics			
Facility	1.19	2.31	.61
Age	1.53	0.46	.001
Sex	11.15	5.16	.03
Work area	−2.83	1.97	.15
Professional level	9.69	4.08	.02
Length of employment in the current hospital	1.97	2.07	.34
Overall length of employment in the current position	−1.03	1.65	.53
Training	−8.13	5.39	.13
ITRABx	2.88	3.38	.39
ITPABx	0.65	0.78	.41

^aURTI: upper respiratory tract infection.^bITRABx: intention to reduce antibiotics.^cITPABx: intention to prescribe antibiotics.

Discussion

AMR is a global crisis [27,29-32], calling for urgent action to resolve it. One of the important strategies for combating AMR

is improving antibiotic prescribing practices by determining factors that affect physicians' prescribing behaviors [10,11,14]. Physicians' antibiotic prescribing practices are influenced by physician-related factors (knowledge, expertise, specific

prescription patterns, time constraints, and communication with patients), patient-related factors (preferences, expectations, knowledge, culture, economic status, and previous experience), and health system-related factors (guidelines, policies, regulations, and financial incentives) [24]. Thus, the TPB in its original or modified (MTPB) form provides a theoretical framework to identify the determinants of physicians' antibiotic prescribing behaviors [14,15,33]. This study, using SEM, confirmed the theoretical framework for physicians' antibiotic prescribing behaviors with some modifications. The MTPB model revealed that physician knowledge was associated with PBC and SN ($P < .001$). However, attitudes, SNs, and PBC did not influence intentions around prescriptions and perceived prescribing behaviors of physicians. Overall, the study revealed that physicians' perceived antibiotic prescribing behaviors were not affected by intentions to reduce and prescribe antibiotics.

A qualitative study in Ethiopia uncovered that "junior physicians (interns and residents) are more likely to prescribe broad-spectrum antibiotics, and they further speculate these practices are driven by poor knowledge" [27]. In this, 121 (65.4%) of the 185 physicians had good knowledge (answered 5 questions out of 11), although the respondents answered only 44.13% of the total questions about antibiotic prescriptions correctly. This was relatively low compared with the 55% to 86% for physicians in hospitals in China [14,15], Lao People's Democratic Republic, Democratic Republic of Congo, and Peru [34-36]. In this study, MTPB knowledge was directly linked with the PBC and SNs of physicians ($P < .05$). This was different than the findings of a study in China that reported a link between high knowledge and positive attitudes toward the rational use of antibiotics [14,15] but similar to a study that reported a link between high knowledge and decreased SNs to prescribe antibiotics [14]. This study revealed a lack of indirect links between knowledge and antibiotic prescribing behavior, which was similar to a study in China that reported a lack of a link between knowledge and antibiotic prescribing practices [14,15]. Knowledge helps physicians weigh the treatment options and increases the accuracy of risk perception; thus, physicians with different professional titles (such as resident physicians and general practitioners) and length of practice may have different attitudes toward antibiotics, based on findings in previous studies [37,38]. Although training can contribute to knowledge acquisition, this study revealed a lack of difference in knowledge between those who completed training on antibiotic prescribing and AMR and those who did not.

This study also revealed a lack of a link between attitudes, SNs, and PBC to prescribe antibiotics. This was different from a report in China that confirmed that "intentions to prescribe antibiotics are predicted by the attitudes, subjective norms, and sense of behavioral control of the prescribers" [33], although another study reported a lack of relationship with intentions to prescribe antibiotics [14,15]. It was reported that attitudes, SNs, and PBC were predictors of antibiotic prescribing behaviors [11,39]. However, this study did not show indirect relationships between attitudes, SNs, and PBC and prescribers' perceived antibiotic prescribing behaviors.

Of the patients seen in the OPDs weekly, 54.8% were estimated to receive at least one antibiotic, and of the 1850 estimated

patients who presented with a URTI, 916 (49.5%) were estimated to be prescribed at least one antibiotic. In Ethiopia, antibiotic prescribing ranges from 56.0% in primary health care facilities [40] to 73.7% in inpatient wards in the national referral hospital [41]. The majority of the prescriptions (32.9%-39.3%) were for respiratory tract infections, although about 54.2% of all antibiotic prescriptions might not be needed [27]. This could explain the high rates of perceived antibiotic prescriptions for outpatient visits and patients with URTIs in this study. In ambulatory care facilities in Tanzania, 95% to 96.3% of presenting cases were receiving at least one antibiotic [42], which is higher than the estimated prescriptions among weekly visits and patients with URTIs in this study. Another study in the same hospital reported 66.9% of patients were treated with or prescribed at least one antibiotic among weekly visits [28], which was higher than the perceived weekly prescriptions and prescriptions for URTIs in this study. A study in China reported that physicians prescribed antibiotics to an estimated 40% of patients with URTIs [14], and actual antibiotic prescribing behavior was 44.3% [33], both of which are lower than the rates in this study.

In this study, intention to reduce antibiotic use and intention to prescribe antibiotics were not linked with perceived antibiotic prescribing behaviors. Similar findings from China supported the limited role of intentions on antibiotic prescribing behavior [33]. Intraprescription variability is affected by the availability of clinical guidelines, experience, peer prescribing practices, pharmaceutical pressure, time pressure, financial considerations, individual practice patterns, practice volume, and relationships with patients [24]. Differences in these factors might explain the discrepancy in the findings from this study and those from a study in China [33], which reported that a positive attitude toward antibiotics resulted in a higher intention to prescribe antibiotics. The difference might be due to differences in the type of patients, clinical practice, and availability of structural and process controls in antibiotic prescribing. Two studies, one in Eritrea and one in Ethiopia, confirmed this by reporting that patient age (<18 years), gender (male), and the number of drugs in a prescription (≥ 2) were associated with the prescription of antibiotics [43,44]. Thus, physicians in different health systems may be subjected to different working environments and social pressures, which could affect their overall intention to prescribe and prescribing behavior.

In general, this study uncovered a lack of volitional control among physicians when prescribing antibiotics. This indicates the complex nature of antibiotic prescribing practices, which are influenced by various factors [24]. Thus, a campaign is needed to reduce over-prescriptions of antibiotics using a systems approach to addressing gaps in the knowledge and attitudes of prescribers [33]. Introducing educational programs and training on antibiotic prescribing practices and antibiotic resistance, preparing targeted guidelines to address gaps in antibiotic prescriptions for URTIs, and involving specialists will help address the gaps in antibiotic prescribing [24,33,45]. Providing antibiotics as a universal therapy due to gaps in knowledge and skills and financial or reputational incentives on the one hand and a lack of antibiotic and poor facility

regulations, the absence of a regulatory framework, and poor implementation of existing policies on the other hand might be drivers of inappropriate antibiotic prescriptions [46]. Thus, disease-specific prescribing guidelines like those for URTIs can facilitate the translation of intentions into practices, since the inability to make a clear diagnosis and over-prescription of antibiotics may be linked with physicians' clinical capacity rather than behavioral control intentions [24]. Despite this, self-regulation, outcome expectation, and anticipation of possible barriers may still have a considerable effect on prescribing behaviors and will help reduce inappropriate antibiotic use, since inappropriate prescribing of antibiotics in ambulatory care is known to be linked to current knowledge on antibiotics, ASPs, and AMR among prescribers [42].

Therefore, ASPs must have fiduciary responsibility for all health care institutions across the continuum of care [47]. A comprehensive approach through a hospital policy on the rational use of antibiotics is essential to developing and implementing an evidence-based antibiotic use policy and standard treatment guidelines for common infectious diseases, improving antimicrobial prescribing through educational and administrative means, and monitoring and providing feedback regarding antibiotic resistance, all of which are strategic approaches [48]. Knowledge of determinants that influence antibiotic prescription behavior is essential for the successful implementation of antimicrobial stewardship interventions [49]. In Ethiopia, at present, there are limited or no national or coordinated legislative or regulatory mandates designed to optimize the use of antimicrobial therapy through ASPs [6,26]. This research on behavioral determinants may have a substantial impact on designing policies on antibiotic prescribing behaviors and implementing effective, efficient, and evidence-based interventions. It urges strengthening efforts to improve prevention and control efforts for infectious diseases, including the adoption of ASPs in all health care facilities. Research is also needed to define the optimal elements and goals of ASPs in different health care settings; expand educational efforts on ASP; devise novel mechanisms to prevent the over-prescription of antibiotics; and implement rapid, point-of-care diagnostic tests that would enable appropriate prescription and care.

Overall, this study will help understand prescribing behaviors by applying the TPB model and will be helpful for regulating prescribing behaviors, improving clinical management, promoting physician-patient communication, and establishing a harmonious physician-patient relationship to improve rational prescribing behaviors in delivering high-quality medical services. Policymakers should also consider multiple scenarios rather than merely concentrating on creating awareness. The model can hopefully be incorporated as part of multilevel interventions designed to decrease irrational prescriptions for actual patients. Furthermore, it might help initiate a nationwide survey on factors affecting antibiotic prescribing behaviors, and more research is needed to explore the views of other stakeholders on antibiotic use. Although this study presents opportunities for future studies in the country, it does have its limitations. The sample size was relatively small, and self-administered questionnaires may not provide the possibility for respondents to verify their answers, resulting in socially desirable answers. Due to a lack of records for antibiotic prescriptions, it was not possible to determine the actual antibiotic prescribing behaviors of physicians. Another limitation might be that it did not include all comprehensive physician-related factors (expertise, knowledge, specific prescription patterns, time constraints, and communication with patients), patient-related factors (knowledge, preferences, expectations, culture, economic status, and previous experience), and health system-related factors (financial incentives, guidelines, policies, and regulations) that influence antibiotic prescribing practices. Thus, further studies using TPB with a large number of physicians are warranted.

In conclusion, there was a high level of estimated antibiotic prescriptions for URTIs and weekly outpatient visits. However, the perceived behaviors around antibiotic prescription were not affected by the intention to prescribe antibiotics or the intention to reduce antibiotic use. Although the physicians had a good level of knowledge about antibiotics, antibiotic resistance, and prescriptions, which were linked with the attitudes and SNs of physicians, intentions to reduce use and prescribe antibiotics were not significantly associated with attitudes, SNs, or PBC. This may show the complex nature of antibiotic prescriptions, which cannot be justified simply by intentions and behaviors of physicians, as determined based on TPB.

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Authors' Contributions

AAA was involved in study conception, study design, study execution, acquisition of data, data analysis and interpretation, manuscript writing, and manuscript review. TGF was involved in study conception, study design, supervision, manuscript writing, and manuscript review. GYW was involved in supervision, manuscript writing, and manuscript review.

Conflicts of Interest

None declared.

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Abbreviations

AMR: antimicrobial resistance
ASP: antibiotic stewardship program
CFI: comparative fit index
MTPB: modified theory of planned behavior
OPD: outpatient department
PBC: perceived behavioral control
SEM: structural equation modeling
SN: subjective norm
TPB: theory of planned behavior
URTI: upper respiratory tract infection

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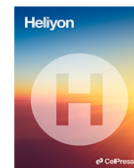
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Research article

Assessment of challenges and opportunities in antibiotic stewardship program implementation in Northwest Ethiopia

Asrat Agalu Abejew^{a,b,*}, Gizachew Yismaw Wubetu^c, Teferi Gedif Fenta^a^a Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia^b Department of Pharmacy, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia^c Amhara Public Health Institute, Bahir Dar, Ethiopia

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ABSTRACT

Background: Indiscriminate use of antibiotics leads to antibiotic resistance (AMR) and results in mortality, morbidity, and financial burden. Antibiotic stewardship programs (ASPs) with education can resolve a number of barriers recognized in the implementation of successful ASPs. The aim of this study was to assess health professionals' perceptions and status of ASPs in hospitals in 2022.

Methods: A cross-sectional study was conducted from September 1, 2022 to October 30, 2022. A total of 181 health professionals were included, and a self-administered questionnaire was used to collect data. The status of hospitals was assessed using a checklist. The data were analyzed using SPSS version 23, and descriptive statistics and Chi-square tests (χ^2) at a P-value of <0.05 were used.

Results: Of the 181 respondents, 163 (90.1 %), and 161 (89.0 %) believed that AMR is a significant problem in Ethiopia and globally, respectively. Easy access to antibiotics 155 (85.6 %), and inappropriate use 137 (75.7 %) were perceived as key contributors to AMR. Antibiotics were believed to be prescribed/dispensed without laboratory results 86 (47.5 %), and antibiotic susceptibility patterns were not considered to guide empiric therapy 81 (44.8 %). ASP was believed to reduce the duration of hospital stays and associated costs 137 (75.7 %), and improve the quality of patient care 133 (73.5 %), whereas 151 (83.4 %), 143 (79 %), and 142 (78.5 %) suggested education, institutional guidelines, and prospective audits with feedback interventions to combat AMR in their hospitals, respectively. There were significant differences in perception among professionals based on professional category and attempts by hospitals to implement ASPs. Although ASPs were not functioning according to standard, there have been attempts to implement it in three hospitals. The issue of ASP had never been heard in general hospitals. Currently, it is feasible to implement ASPs in four hospitals.

Conclusion: The status of ASP in hospitals was very poor. Despite a lack of prior knowledge on ASPs, most respondents do have a positive perception of AMR and the implementation of ASPs. Pharmacist-led prospective audits and feedback with education and institutional guidelines for empiric antibiotic use can be better implemented in hospitals. Involvement of representatives

* Corresponding author. Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

E-mail address: asruphar@gmail.com (A.A. Abejew).

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from infection prevention and control, and collaboration among hospitals in ASP implementation will help establish a strong ASP in the area.

1. Introduction

Antibiotics have saved millions of lives and transformed modern medicine [1,2]. Although the leading cause of death from infectious diseases was drastically reduced [1–4], about 30–50 % of antibiotic prescriptions in hospitals were used either unnecessarily or inappropriately. It was indicated that global antibiotic consumption was drastically increasing from time to time due to increased consumption of antibiotics in low- and middle-income countries (LMICs) [5]. The increased consumption of antibiotics toppled by inappropriate consumption has resulted in the ineffectiveness of antibiotics due to the development of AMR [2,6–15]. These could have resulted in treatment failure and an increased risk of adverse patient outcomes, such as *Clostridium difficile* infections and other adverse events [1,4,16]. AMR is a global public health treat resulting in morbidity and mortality [1,2,17–19]. The LMICs are disproportionately affected by AMR, which is a serious problem for the poorest countries due to different reasons [17,20–25]. Despite the high level of AMR and attempts to implement ASPs, in LMICs, evidence on effective and feasible stewardship interventions is still limited, and challenges for the implementation of interventions are numerous [26–29].

These call for locally contextualized strategies while identifying targeted and sustainable indicators to track antibiotic use, AMR, infection prevention and control, and improving access to antibiotics and reducing inappropriate use [30–34]. In hospital settings, inappropriate antibiotic prescribing is a key contributor to the emergence of AMR, which itself is often driven by patient demand for antibiotics, misaligned economic incentives, a lack of knowledge of appropriate antibiotic prescribing, and/or a lack of and delayed laboratory results to assist antibiotic prescribing [35,36], affecting the antibiotic prescribing behaviors of physicians [37,38]. Prescribing behavior is affected by social and cultural norms and attitudes toward prescribing, resulting in irrational prescribing of antibiotics and increased consumption of reserve antibiotics, such as carbapenems [5,39,40]. High antibiotic prescriptions may be related to poor knowledge, a lack of awareness of AMR, and limited motivation to change [38,41].

In most sub-Saharan African countries, AMR has not been a priority, even for those whose customized national AMR action plans (NAP) are developed based on global AMR action plans (GAP), the implementation is still inadequate [29,30,42], despite the high burden of AMR [17,31]. Although ASPs are recognized as formal strategies for curbing increased trends in AMR [43], ASP preparedness in Sub-Saharan Africa was reported to be very poor and varies greatly from country to country, ranging from the inability to determine the building blocks to support ASPs to those that have systems that allow ASP integration into clinical practices [28]. ASP strategies are not uniformly implemented across health facilities in those countries that have implemented ASP [44,45], indicating that the LMICs, including Africa, are facing multiple challenges and barriers to implementing ASP [43–50]. As a requirement for ASP implementation, determining the challenges and understanding the situation of health facilities is essential [4,43,44,51]. Since physicians and pharmacists are essential components of ASP teams for the successful implementation of ASPs, examining their perspectives about the dynamics within their team and contextual factors that facilitate the success programs is also a component and first step for ASP implementation [51]. This helps create awareness about AMR, develop and maintain guidelines for antibiotic use, monitor antibiotic use, ensuring the quality of low-cost generic medicines, and improve laboratory services for the successful implementation of ASP in hospitals [33].

In Ethiopia, AMR was taken as a priority [52], although ASP was not officially implemented yet [53], despite preparing ASP implementation guidelines [3]. Currently, there are only individual attempts to implement ASP [10,44] and pilot quality improvement interventions to optimize the use of antimicrobials for surgical prophylaxis in some hospitals [54]. Thus, this study is aimed at determining the gaps and readiness of hospitals for ASP implementation and the perception of health professionals about antibiotic resistance and ASPs in the inpatient wards of hospitals in Northwest Ethiopia.

2. Methods and materials

2.1. Study design, study setting and period

A cross-sectional study was conducted from September 2022 to October 2022 in five hospitals. The hospitals are Felege Hiwot Comprehensive Specialized Hospital (FHCSH), Tibebe Ghion Specialized Hospital (TGSH), Debre Markos Comprehensive Specialized Hospital (DMCSH), Finote Selam General Hospital (FSGH), and Injibara General Hospital (IGH). These hospitals are among the 81 hospitals in the Amhara National Regional State. The clinical service for infectious diseases in all health facilities in the region is mostly carried out based on clinical diagnosis and complete blood count (CBC) results. There are no rapid diagnostic techniques for the identification of bacterial infections in hospitals. The hospitals provide integrated services to patients in their outpatient departments, emergency triage assessment and treatment departments, inpatient departments, and neonatal intensive care units. Except for the attempts to assign patient-oriented pharmacists in some hospitals, there are no ASPs and clinical pharmacy services integrated into the hospital's patient care systems. This readiness assessment of hospitals to determine gaps for implementation of ASPs and a survey of health professionals to determine perceptions on AMR, antibiotic prescribing and use, ASPs, and possible solutions was part of broader data collection for gap analysis and baseline data collection, including trends in infectious diseases and antibiotic consumption and use in the pre-implementation phase of ASPs.

2.2. Study participants

About 200 health professionals were included in the study. Physicians working in the medical ward, pediatric ward, gynecology/obstetrics ward, and surgical ward were included in the study. In addition, pharmacy professionals who engaged in the dispensing of antibiotics in hospitals were also included in the study. Data on the readiness of hospitals was collected from those who do have full information about the situation of hospitals, such as medical directors, human resource personnel, laboratory personnel, and leaders of ASPs, using checklists.

2.3. Sample size and sampling procedures

The sample size for health professionals was determined based on the following formula for finite population:

$$n = \frac{X^2 NP (1-P)}{d^2 (N-1) + X^2 P (1-P)}$$

Where n is the sample size and X^2 is the table value of the chi-square for 1 degree of freedom at the desired confidence level ($1.96 \times 1.96 = 3.841$); N is the total population; P is the population proportion (27 %) and d is the degree of accuracy expressed as a proportion (0.05). Gebretekle et al. [44] reported a prevalence that ranges from 27 % for perceived antibiotic prescription or dispensing to 90 % for AMR. Thus, a prevalence of 27 % was used to provide the maximum sample size in this study.

Accordingly, $n, \frac{X^2 NP (1-P)}{d^2 (N-1) + X^2 P (1-P)}$ was calculated as follows:

$$= \frac{(1.96 \times 1.96) \times 487 \times 0.27(1-0.27)}{((0.05 \times 0.05) \times (487-1) + (1.96 \times 1.96) \times 0.27(1-0.27))}$$

$$= 181.26 \sim 182$$

To account for the nonresponse rate, 10 % was added, and thus, 200 health professionals were included in the study and allocated to hospitals proportionally based on the estimated number of physicians and pharmacy professionals in each hospital.

2.4. Data collection instruments and processes

A data collection tool used by Gebretekle et al. [44] to explore healthcare providers' knowledge and perceptions on AMR, barriers, and facilitators to successful implementation of a pharmacist-led ASP intervention in a referral hospital in Ethiopia was used. In addition, the capacity and readiness of health facilities were assessed based on the core elements of hospital ASPs [55]. The questionnaire was designed on a Likert scale with a 6-point response format, which ranges from 1 (strongly disagree) to 5 (strongly agree) and 6 (not applicable). The questionnaire consists of experiences with antibiotic use, perceptions about the scope of antibiotic resistance, the causes of antibiotic resistance, and the possible barriers to compliance with infection control precautions; strategies for antibiotic resistance prevention; and sources for information about antibiotic use. All physicians from the inpatient wards of internal medicine, surgery, pediatrics and gynecology/obstetrics, and pharmacy professionals working in the hospital were approached to participate in the study. The questionnaire was distributed in morning sessions, grand rounds, and/or while at work for physicians, and pharmacists were approached at their worksite during working hours. The completeness of the data was monitored on a daily basis.

2.5. Data analysis

Before the analysis of the quantitative data, the outcome metrics were first determined, and the data was coded, entered into SPSS version 21, and finally cleared and analyzed. Descriptive statistics were used to characterize the variables of interest. The degree of agreement with the statements was reclassified into "agree" (strongly agree/agree), "disagree" (strongly disagree/disagree), and "neutral" (neutral/NA). The χ^2 tests with a significance level of $p < 0.05$ were employed to explore differences in proportions of agreement between physicians and pharmacists and among health professionals from hospitals that attempted to implement ASPs and those that didn't. The results were finally presented in tables based on the nature of the results.

2.6. Ethical consideration

Ethical approval was obtained from Addis Ababa University, the College of Health Sciences (protocol code: 106/22/SoP), and the School of Pharmacy (protocol code: ERB/SOP/472/14/2022). A support letter to the hospitals was obtained from the Amhara Public Health Institute. All participants provided informed consent prior to participating in this study. The information obtained was kept confidential and used only for research purposes. Ethical issues were considered during data collection in order not to disclose information to people outside the research.

3. Results

Five hospitals were included in the assessment of the current situation, and a total of 181 (90.5 %) of the respondents returned the questionnaire among the 200 distributed. Those who didn't complete the questionnaires on time and returned them were considered non-responders. The results for the perception of health professionals on AMR, antibiotic use, and ASP, as well as the current situation

and status of ASP in hospitals, including the core elements of ASP, were described.

A. Perceptions of health professionals on AMR, antibiotic use, and ASP

3.1. Socio-demographic characteristics of respondents

The majority of health professional participants, 122 (75.8 %), were greater than 29 years old with a mean age of 32 ± 4.3 (range 23–45 years old), and 124 (77 %) were male. The respondents reported that they had treated or dispensed on average to 254 patients per week, among whom 69.7 % believed to prescribe or dispense antibiotics, during a one-week period (Table 1).

3.2. Believe of health professionals on the scope of AMR

From 181 health professionals, 163 (90.1 %), and 161 (89.0 %) agreed on the statements that AMR is a significant problem in Ethiopia and worldwide, respectively. But only 53 (29.3 %), and 52 (28.7 %) agreed with statements that a very high proportion (>30 %) of MRSA and a very high proportion (>30 %) of gram-negative infections are highly drug-resistant in this hospital, respectively. Pharmacy professionals believe more in a statement that a high proportion of gram-negative infections are highly drug-resistant to all cephalosporins, and some are even resistant to carbapenems (P-value = 0.035), and a very high proportion of staphylococcal infections are resistant to methicillin (MRSA) in their hospitals (P-value = 0.0001) (Table 2). The overall response of health professionals' beliefs on AMR, antibiotic use, ASP, and potential solutions is presented in Supplementary Table 1.

3.3. Beliefs of health professional on factors contributing to AMR

The majority, 155 (85.6 %) and 137 (75.7 %) of professionals, agreed that easy access to antibiotics and inappropriate use were key contributors to AMR, respectively. But only 19 (10.5 %) and 22 (12.2 %) of health professionals perceive that the staff education on antibiotic consumption and drug-resistant organisms and the performance of adequate surveillance for drug-resistant organisms are adequate, respectively. There was a significant difference between physicians and pharmacists on the prescription of broad-spectrum antibiotics, which is directly linked to AMR (P-value = 0.045), patient demands and expectations contribute to the overuse of antibiotics (P-value = 0.003), and poor infection control practices by health professionals significantly contribute to the spread of AMR (P-value = 0.022), all of which were more prevalent in pharmacists (Table 3).

Table 1
Socio-demographic characteristics of health professionals in the Hospitals, in 2022, (N = 181).

Variables		Frequency (%)
Age in years	18–29	46 (25.4)
	30–64	135 (74.6)
	Total	181 (100)
Sex	Male	138 (76.2)
	Female	43 (23.8)
	Total	181 (100)
Facility	FHRH	46 (25.4)
	TGSH	68 (37.6)
	DMCSH	31 (17.1)
	IGH	16 (8.8)
	FSGH	20 (11)
	Total	181 (100)
Work area	Medicine	29 (16)
	Surgery	29 (16)
	Pediatrics	28 (15.5)
	Gyne/obs	20 (11)
	Pharmacy	75 (41.4)
	Total	181 (100)
Position/profession	Physician	106 (58.6)
	Pharmacy	75 (41.4)
	Total	181 (100)
Work experience in the current hospital	Overall	3.7 ± 2.3
	<5 years	137 (75.7)
	≥5 years	44 (24.3)
	Total	181 (100)
Work experience in the current position	Overall	4.5 ± 4.1
	<5 years	123 (68)
	≥5 years	58 (32)
	Total	181 (100)
Average number patients treated/dispensed per week	34997	254 ± 198
Average number patients treated or dispensed with at least one antibiotic per week among visits	23415 (66.9 %)	204 ± 135

Table 2

Perception of health professionals on scope of antibiotic resistance in the hospitals, in 2022, (N = 181).

Items and Level of agreement on each statement		Category of Profession			P-value
		Physician (%)	Pharmacy (%)	Total (%)	
Antibiotic resistance is a significant problem worldwide	Disagree	7(0.5)	7 (0.5)	14 (7.7)	0.712
	Neutral	3(0.5)	3(0.5)	6 (3.3)	
	Agree	96 (59.6)	65(40.4)	161 (89.0)	
Antibiotic resistance is a significant problem in my country	Disagree	5 (45.5)	6(54.5)	11 (6.1)	0.532
	Neutral	5(71.4)	2(28.6)	7 (3.9)	
	Agree	96(58.9)	67(41.1)	163 (90.1)	
Antibiotic resistance is a significant problem in my hospital	Disagree	4 (40)	6(60)	10 (5.5)	0.23
	Neutral	29(67.4)	14(32.6)	43 (23.8)	
	Agree	73(57.0)	55(43.0)	128 (70.7)	
Antibiotic resistance is a problem in my daily practice	Disagree	10(52.6)	9(47.3)	19 (10.5)	0.84
	Neutral	32(60.4)	21(39.6)	53 (29.3)	
	Agree	64(58.7)	45(41.2)	109 (60.2)	
A patient is likely to develop drug-resistant infection during their hospital stay at this hospital	Disagree	19(63.3)	11(36.7)	30 (16.6)	0.842
	Neutral	25(58.1)	18(41.9)	43 (23.8)	
	Agree	62(57.4)	46(42.6)	108 (59.7)	
I think a very high proportion (>30 %) of gram-negative infections are highly drug- resistant in this hospital (resistant to all cephalosporins, and some are even resistant to carbapenems)	Disagree	19(70.3)	8(29.7)	27 (14.9)	0.035 ^a
	Neutral	64(62.7)	38(36.3)	102 (56.4)	
	Agree	23(44.2)	29(55.8)	52 (28.7)	
I think a very high proportion (>30 %) of Staphylococcal infections are resistant to methicillin (MRSA) in this hospital	Disagree	24(72.7)	9(27.3)	33 (18.2)	0.001 ^a
	Neutral	62(65.3)	33(34.7)	95 (52.5)	
	Agree	20(37.7)	33(62.3)	53 (29.3)	

*Physicians more agreed.

^a Pharmacy professionals agreed.

3.4. Belief of health professionals on antibiotics use

The majority of health professionals 104 (57.5 %) and 101 (55.8 %) had agreed only on two statements: I routinely try to step down intravenous antibiotics to an oral alternative antibiotic after about three days, and I routinely prescribe or dispensing very broad-spectrum antibiotics empirically because microbiology lab results are not available in a timely fashion, respectively. But 86 (47.5 %), 84 (46.4 %), and 81 (44.8 %) disagreed about routinely checking microbiology laboratory results to guide antibiotic choice, timely communication of microbiology lab results, and using evidence-based empiric antibiotic prescribing practices, respectively. There were differences between physicians and pharmacists on cost considerations (P-value = 0.03) and routinely stepping down intravenous antibiotics to an oral alternative antibiotic (P-value = 0.021), which was more favored by physicians, but recommending very broad-spectrum antibiotics empirically because microbiology lab results are not available in a timely fashion (P-value = 0.04) by pharmacy professionals (Table 4).

3.5. Perception of health professionals on implementation of ASP

The majority of health professionals, 151 (83.4 %), 137 (75.7 %), and 133 (73.5 %) believe that education on antibiotic therapy for physicians and pharmacy staffs, ASP reduces the duration of hospital stays and associated costs, and ASP improves the quality of patient care, respectively. Only 29 (16.0 %), and 39 (2.2 %) of professionals agreed that ASPs can be an obstacle to good patient care, and prescribing physicians are the only professionals who need to understand ASPs, respectively. Pharmacists believe that investing more in ASP reduces overall antibiotic consumption and can result in cost savings (P-value = 0.049), but they insist that they do not have enough time to invest in ASP (P-value = 0.03) (Table 5).

Table 3

Beliefs on possible factors contributing to antibiotic resistance in the hospitals, in 2022 (N = 181).

Items and Level of agreement on each statement, frequency (%)		Category of Profession			P-value
		Physician (%)	Pharmacy (%)	Total (%)	
Inappropriate consumption of antibiotics is a major cause of antibiotic resistance in this hospital	Disagree	9(64.3)	5(35.7)	14 (7.7)	0.31
	Neutral	21(70.0)	9(30.0)	30 (16.6)	
	Agree	76(55.5)	61(44.5)	137 (75.7)	
The easy access to antibiotics without a prescription in Ethiopia contributes to antibiotic resistance	Disagree	8(53.3)	7(42.7)	15 (8.3)	0.259
	Neutral	9(81.8)	2(19.2)	11 (6.1)	
	Agree	89(57.4)	66(42.6)	155 (85.6)	
The prescription of broad-spectrum antibiotics is directly linked to antibiotic resistance in this hospital	Disagree	20(69.0)	9(31.0)	29 (16)	0.045 ^a
	Neutral	34(70.8)	14(29.2)	48 (26.6)	
	Agree	52(50.0)	52(50.0)	104 (57.5)	
This hospital performs adequate surveillance for drug-resistant organisms	Disagree	80(63.0)	47(37.0)	127 (70.2)	0.144
	Neutral	18(51.4)	17(47.6)	35 (19.3)	
	Agree	8(42.1)	11(57.9)	19 (10.5)	
The lack of adequate diagnostic tests in this hospital leads to overuse of antibiotics contributing to AMR	Disagree	22(68.8)	10(31.2)	32 (17.7)	0.117
	Neutral	13(43.3)	17(56.7)	30 (16.6)	
	Agree	71(59.7)	48(40.3)	119 (65.7)	
This hospital provides adequate staff education regarding antibiotic consumption and resistance	Disagree	79(63.7)	45(36.3)	124 (68.5)	0.048 ^a
	Neutral	19(54.3)	16(45.7)	35 (19.3)	
	Agree	8(36.4)	14(63.6)	22 (12.2)	
I suspect that antibiotics available in my hospital are of poor quality and contribute to AMR	Disagree	56(55.4)	45(44.6)	101 (55.8)	0.547
	Neutral	32(60.4)	21(39.6)	53 (29.3)	
	Agree	18(66.7)	9(33.3)	27 (14.9)	
	Neutral	18(52.9)	16(47.1)	34 (18.8)	
	Agree	69(62.2)	42(37.8)	111 (61.3)	
The sporadic supply of antibiotics in my hospital leads to interruptions of therapy contributing to antibiotic resistance	Disagree	24(60.0)	16(40.0)	40 (22.1)	0.534
	Neutral	26(52.0)	24(48.0)	50 (27.6)	
	Agree	56(61.5)	35(38.5)	91 (50.3)	
The lack of close clinical follow-up during antibiotic consumption in my hospital contributes to antibiotic resistance	Disagree	25(73.5)	9(26.5)	34 (18.8)	0.182
	Neutral	24(58.5)	17(41.5)	41 (22.6)	
	Agree	57(53.8)	49(46.2)	106 (58.6)	
Patient demands and expectations contribute to overuse of antibiotics contributing to AMR in this hospital	Disagree	36(67.9)	17(32.1)	53 (29.3)	0.003 ^a
	Neutral	42(70.0)	18(30.0)	60 (33.2)	
	Agree	28(41.2)	40(58.8)	68 (37.6)	
	Neutral	14(53.8)	12(46.2)	26 (14.4)	
	Agree	81(64.3)	45(35.7)	126 (69.6)	
Poor infection control practices by health professionals significantly contributes to the spread of antibiotic resistance in this hospital	Disagree	19(52.8)	17(47.2)	36 (19.9)	0.022 ^a

(continued on next page)

Table 3 (continued)

Items and Level of agreement on each statement, frequency (%)	Category of Profession			P-value
	Physician (%)	Pharmacy (%)	Total (%)	
Adherence to hand-hygiene protocols is acceptable at this hospital	Neutral	31(77.5)	9(22.5)	0.044 ^a
	Agree	56(53.3)	49(46.7)	
	Disagree	48(69.6)	21(29.4)	
	Neutral	27(56.3)	21(43.7)	
	Agree	31(48.4)	33(51.6)	
Patient rooms and equipment are cleaned appropriately as per hospital cleaning protocol once a patient carrying a drug-resistant organism (DRO) has been discharged from this hospital	Disagree	60(66.7)	30(33.3)	0.007 ^a
	Neutral	32(60.4)	21(39.6)	
	Agree	14(36.8)	24(64.2)	

*Physicians more agreed.

^a Pharmacy professionals agreed.

3.6. Belief on potential interventions to combat AMR

Among 181 professionals, 151 (83.4 %), 143 (79 %), 142 (78.5 %), and 137 (75.7 %) believe that education on antibiotic therapy to medical and pharmacy staff, developing new institutional guidelines for empiric antibiotic use, implementation of prospective audit and feedback, and active involvement of the hospital infection prevention and control (IPC) team are effective potential interventions to combat AMR (Table 6).

3.7. Difference in level of agreement of health professionals in hospitals attempted ASP

There is difference in the level of agreement among professionals working in hospitals who attempted to implement ASP and those which didn't on the items antibiotic resistance is a significant problem worldwide (P-value = 0.013), inappropriate consumption of antibiotics is a major cause of antibiotic resistance in this hospital (P-value = 0.034) and the easy access to antibiotics without a prescription in Ethiopia contributes to antibiotic resistance (P-value = 0.003) all of which were better agreed by professionals in hospitals which attempted ASP implementation. The lack of adequate diagnostic tests in this hospital leads to overuse of antibiotics (P-value = 0.035) and my choice of antibiotics is often influenced by the availability of the antibiotics (P-value = 0.012) were better agreed by health professionals in hospitals which didn't attempted ASP implementation (Table 7).

B. Situational analysis of hospitals for implementation of ASP

Status and the current situation of ASPs in five hospitals were assessed using checklists to catch up on the availability and functionality status of ASPs, current practice in the management of infections, and the availability of resources for the implementation of ASPs. In the hospitals, there were 1718 beds, and the average bed occupancy rate was 94.5 %. On average, patients stay about five days in the hospital. There are about 18 clinical pharmacists and/or MSc holders and 9 microbiologists in the hospitals (Table 8).

Although it is not functioning according to standard requirements for ASP, out of five hospitals, only three have tried ASP implementation, among which FHCSH and TGSH have an active formal ASP committee during data collection time. In DMCSH, there was a temptation to establish the committee, but currently it is not functional, and the issue of ASP has never been heard in IGH or FSGH.

In all hospitals, there was no formal procedure for all clinicians to review the appropriateness of all antibiotics within 48–72 h of initial orders (e.g., antibiotic time out), except in the form of routine morning sessions and daily rounds. There were antibiograms in FHCSH and DMCSH, although there was no formal procedure to monitor trends in AMR. The antibiograms in FHCSH were updated in a quarterly manner, but they have never been reviewed and clinically interpreted. Although there have been recent attempts to start culture and sensitivity tests in TGSH, due to a lack of supplies, there have been no antibiograms. In general hospitals, there is no laboratory facility to conduct culture and sensitivity tests. Likewise, except for attempts to evaluate vancomycin use (DMCSH and FHCSH), ceftriaxone use (FHCSH and TGSH), and customizing AwaRe classification (DMCSH and FHCSH), there was no system in place to track antibiotic use and AMR trends in all hospitals.

The ASP team in the FHCSH is represented by physician, pharmacist, infection prevention focal person, quality assurance focal person, microbiologist, nurse, and information technology professional. The same is true in TGSH, except for the inclusion of an epidemiologist than information technology professional in the team. In both cases, the team is led by internists, and the secretaries are clinical pharmacists. In FHCSH, there is an infectious disease physician, but there is none in TGSH. Out of the five hospitals, four have agreed to strengthen and/or start ASP in their hospitals. The FHCSH is ready to implement ASP in the internal medicine ward, ICU,

Table 4
Belief of health professionals on antibiotics prescription/dispensing practices in the hospitals, in 2022 (N = 181).

Items and Level of agreement on each statement, frequency (%)		Category of profession			P-value
		Physician (%)	Pharmacy (%)	Total (%)	
Microbiology lab results are timely communicated to the health professionals in this hospital	Disagree	53(63.1)	31(36.9)	84 (46.4)	0.043 ^b
	Neutral	36(64.3)	20(35.7)	56 (30.9)	
	Agree	17(41.5)	24(58.5)	41 (22.7)	
My choice of antibiotics is often influenced by the availability of the antibiotics rather than by the local antibiogram or by the etiologic cause of disease (availability of laboratory results)	Disagree	19(52.8)	17(47.2)	36 (19.9)	0.465
	Neutral	18(52.9)	16(47.1)	34 (18.8)	
	Agree	69(62.2)	42(37.8)	111 (61.3)	
Cost considerations for the patient affects my choice of antibiotics	Disagree	11(37.9)	18(62.1)	29 (16)	0.03 ^a
	Neutral	14(53.8)	12(46.2)	26 (14.4)	
	Agree	81(64.3)	45(35.7)	126 (69.6)	
I regularly refer to/consider the antibiotic susceptibility patterns at this hospital (institutional antibiogram) when empirically prescribing or recommending antibiotics	Disagree	51(63.0)	30(37.0)	81 (44.8)	0.007 ^b
	Neutral	38(67.9)	18(32.1)	56 (30.9)	
	Agree	17(38.6)	27(61.4)	44 (24.3)	
If medically appropriate, I routinely try to step down intravenous antibiotics to an oral alternative antibiotic after about three days	Disagree	16(41.0)	23(59.0)	39 (21.5)	0.021 ^a
	Neutral	21(55.3)	17(44.7)	38 (21)	
	Agree	69(66.3)	35(33.7)	104 (57.5)	
If medically appropriate, I routinely try to step down broad-spectrum antibiotics to a narrow-spectrum antibiotic after about three days	Disagree	36(58.1)	26(41.9)	62 (34.3)	0.995
	Neutral	30(58.8)	21(41.2)	51 (28.2)	
	Agree	40(58.8)	28(41.2)	68 (37.6)	
Restrictions on antibiotics could impair my ability to provide good patient care	Disagree	43(67.2)	21(32.8)	64 (35.4)	0.08
	Neutral	24(63.2)	14(36.8)	38 (21)	
	Agree	39(49.4)	40(50.6)	79 (43.6)	
I routinely prescribe/recommend very broad-spectrum antibiotics empirically because I believe most patients are infected with a drug-resistant organism	Disagree	55(71.4)	22(28.6)	77 (42.5)	0.004 ^b
	Neutral	27(56.3)	21(43.7)	48 (26.5)	
	Agree	24(42.9)	32(57.1)	56 (30.9)	
I routinely prescribe/recommend very broad-spectrum antibiotics empirically because microbiology lab results are not available in a timely fashion	Disagree	40(71.4)	16(28.6)	56 (30.9)	0.029 ^b
	Neutral	10(41.7)	14(58.3)	24 (13.3)	
	Agree	56(55.4)	45(44.6)	101 (55.8)	
I routinely check microbiology laboratory results to guide my choice of antibiotics	Disagree	56(62.9)	30(37.1)	86 (47.5)	0.155
	Neutral	26(57.8)	19(42.2)	45 (24.9)	
	Agree	24(48.0)	26(52.0)	50 (27.6)	
In the past seven days, I have prescribed broad spectrum antibiotics for longer than 3 days for fewer than 10 % of my patients;	Disagree	42(60.0)	28(40.0)	70 (38.7)	0.013 ^a
	Neutral	27(45.0)	33(55.0)	60 (33.1)	
	Agree	37(72.5)	14(27.5)	51 (28.2)	
In the past seven days, I have prescribed broad spectrum antibiotics for longer than 3 days for 10–50 % of my patients	Disagree	46(66.7)	23(33.3)	69 (38.1)	0.201

(continued on next page)

Table 4 (continued)

Items and Level of agreement on each statement, frequency (%)	Category of profession			P-value
	Physician (%)	Pharmacy (%)	Total (%)	
In the past seven days, I have prescribed/recommended broad spectrum antibiotics for longer than 3 days for more than 50 % of my patients	Neutral	31(51.7)	29(48.3)	0.003 ^b
			60 (33.1)	
	Agree	29(55.8)	23(44.2)	
			52 (28.7)	
	Disagree	54(74.0)	19(26.0)	
			73 (40.3)	
	Neutral	27(48.2)	29(51.8)	
			56 (30.9)	
	Agree	25(48.1)	27(51.9)	
			52 (28.7)	

^a Physicians more agreed.

^b Pharmacy professionals agreed.

recovery rooms, NICU, pediatrics, and OR since, according to them, these are the common sites where reserve antibiotics are commonly prescribed. Despite the lack of laboratory facilities, IGH has shown interest in implementing ASP in collaboration with Injibara University. IGH suggested internal medicine wards, pediatric wards, AICU, NICU, and surgical wards for the implementation of ASP.

C. Core Elements of ASP in Hospitals

The core elements of ASP implementation in FHRH and TGSF were reported. Only in accountability and expertise were they at least partially fulfilled. In the areas of leadership support and commitment, and action taken to implement ASP to improve antibiotic consumption, the implementation is very poor. In general, out of the seven core elements, the two hospitals nearly fulfill two components of accountability and representation of drug experts in the ASP team. But for leadership, it was 4 out of 16; action on implementing ASP and improve antibiotic consumption (8 out of 22), tracking (8 out of 18), reporting (2 out of 6), and education (1 out of 6). There was a formal, written to ASPs team members and attempts to evaluate some antibiotics, but there is no formal prospective audit or feedback for specific disease syndromes and/or antibiotics, and there is no system to improve antibiotic consumption or track antibiotic use and resistance (Table 9, Supplementary Table 2).

4. Discussion

AMR is a public health problem globally [1,35,56–59] and in Ethiopia [13,60–63]. Implementation of agreed-upon ASPs, which do have beneficial clinical and economic impacts, following identified gaps is a key to tackle AMR [64,65]. Identifying perceptions, enablers, and barriers to ASP implementation is a critical step for the successful implementation of ASPs in hospitals [44,66–70]. Determining the knowledge, perceptions and attitudes of hospital-based clinicians toward antimicrobial prescription, AMR, and ASP, including the types of activities implemented in hospital-based ASPs, the methods used to measure the impact of ASP, and factors influencing the antimicrobial prescribing behavior of physicians, are necessary components to initiating ASP [71]. Thus, this study assessed the readiness of hospitals for implementation of ASP, explored physicians' and pharmacists' perceptions about AMR, antibiotic prescribing or prescribing practices, ASP, and suggested potential interventions to combat AMR in the hospitals. The key findings will be discussed hereafter.

In the current study, 163 (90.1 %), 161 (89.0 %) and 128 (70.7 %) of the health professionals believed that AMR was a significant problem both in Ethiopia, worldwide, and in their hospitals respectively. Although there was a slight difference on magnitude, the report was almost similar to a report on health professionals' beliefs at Black Lion Hospital, which showed that antibiotic resistance is a significant problem worldwide (94.6 %), in Ethiopia (91.7 %) and in their hospital (84.5 %) [44], 93 % of physicians in Cameroon perceive that AMR is a nationwide problem [72], physicians in Nigeria recognize AMR as a global (95.4 %) and local problem (81.1 %) [73], and in another study in Nigeria among health professionals, 96.0 % of whom believed that antibiotic resistance was a problem in Nigeria, 84.0 % agreed that AMR was a problem for their practice [46] but in Ghana very few physicians perceived antibiotic resistance as global problem (30.1 %), national problem (18.5 %), and problem in their hospital (8.1 %) [74]. In South Africa, 78.5 % of pharmacists perceived that AMR was a problem in their hospitals [75], and in Zambia, 95 % of health professionals perceived AMR as a current problem in their practice [76]. The current study also revealed a difference in level of agreement among physicians and pharmacy professionals in believing that a very high proportion (>30 %) of gram-negative infections are highly drug-resistant (resistant to all cephalosporins and some are even resistant to carbapenems) and that a very high proportion (>30 %) of staphylococcal infections are resistant to methicillin, which was more among pharmacy professionals, which was different from a report which didn't show any significant difference between physicians and pharmacy professionals [44]. The difference in reported magnitude might be attributed to differences in services and experience with AMR in hospitals in different countries and experiences in ASP implementation.

In the current study, health professionals believed that easy access to antibiotics without a prescription 155 (85.6 %), inappropriate

Table 5
Perception of health professionals on implementation of ASP in the hospitals, in 2022 (N = 181).

Items and Level of agreement on each statement		Category of Profession			P-value
		Physician (%)	Pharmacy (%)	Total (%)	
ASPs (ASP) improve quality of patient care	Disagree	5(55.6)	4(44.4)	9 (5)	0.929
	Neutral	22(56.4)	17(43.6)	39 (21.5)	
	Agree	79(59.4)	54(41.6)	133 (73.5)	
ASP reduces overall antibiotic consumption and can result in cost savings	Disagree	5(33.3)	10(66.7)	15 (8.3)	0.049 ^a
	Neutral	26 (70.3)	11(29.7)	37 (20.4)	
	Agree	75(58.1)	54(41.9)	129 (71.3)	
ASP reduces duration of hospital stay and associated costs	Disagree	11(55.0)	9(45.0)	20 (11)	0.94
	Neutral	14(58.3)	10(42.7)	24 (13.3)	
	Agree	81(59.1)	56(41.9)	137 (75.7)	
ASP reduce the problem of antibiotic resistance	Disagree	11(55.0)	9(45.0)	20 (11)	0.934
	Neutral	21(60.0)	14(40.0)	35 (19.3)	
	Agree	74(58.7)	52(41.3)	126 (69.6)	
ASP has impact on an institution's nosocomial infection rates	Disagree	9 (60.0)	6 (40.0)	15 (8.3)	0.369
	Neutral	24 (50.0)	24 (50.0)	48 (26.5)	
	Agree	73 (61.9)	45 (39.1)	118 (65.2)	
This hospital has the capacity to establish and implement an effective ASP	Disagree	23 (65.7)	12 (34.3)	35 (19.3)	0.149
	Neutral	35 (66.0)	18 (34.0)	53 (29.3)	
	Agree	48 (51.6)	45(48.4)	93 (51.4)	
My individual efforts in antibiotic stewardship can significantly impact this hospital's antibiotic resistance problem	Disagree	15 (57.7)	11(42.3)	26 (14.4)	0.844
	Neutral	31 (62.0)	19 (38.0)	50 (27.6)	
	Agree	60(57.1)	45(42.9)	105 (58.0)	
I would like to receive more feedback on my antibiotic selections	Disagree	12(50)	12(50)	24 (13.3)	0.141
	Neutral	17(41.2)	19(58.6)	36 (19.9)	
	Agree	77(63.6)	44(36.4)	121 (66.9)	
ASPs can be an obstacle to good patient care	Disagree	66(59.5)	45(40.5)	111 (61.3)	0.428
	Neutral	26(63.4)	15(36.6)	41 (22.7)	
	Agree	14(48.3)	15(51.7)	29 (16)	
ASPs override prescribers' decision autonomy	Disagree	50(60.2)	33(39.8)	83 (45.9)	0.086
	Neutral	40(65.6)	21(34.4)	61 (33.7)	
	Agree	16(43.2)	21(56.8)	37 (20.4)	
I do not have enough time to further invest into ASP	Disagree	53(55.8)	42(44.2)	95 (52.5)	0.03 ^a
	Neutral	40(71.4)	16(28.6)	56 (30.9)	
	Agree	13(43.3)	17(56.7)	30 (16.6)	
Infectious diseases experts that can provide guidance in antibiotic selection and prescription are available in this hospital	Disagree	59(65.6)	31(34.4)	90 (49.7)	0.002 ^a
	Neutral	29(67.4)	14(33.6)	43 (23.8)	

(continued on next page)

Table 5 (continued)

Items and Level of agreement on each statement		Category of Profession			P-value
		Physician (%)	Pharmacy (%)	Total (%)	
Additional staff education on antibiotic prescribing and use is needed in this hospital	Agree	18(37.5)	30(62.5)	48 (26.5)	0.118
	Disagree	13(41.9)	18(58.1)	31 (17.1)	
	Neutral	17(63.0)	10(37)	27 (14.9)	
Prescribing physicians are the only professionals who need to understand antibiotic stewardship	Agree	76(61.8)	47(38.2)	123 (67.9)	0.384
	Disagree	78 (61.9)	48(38.1)	126 (69.6)	
	Neutral	8(50.0)	8(50.0)	16 (8.9)	
Pharmacists with sufficient training to provide guidance on antibiotics (ex. Antibiotic switches, IV to PO step-down, renal dose adjustments) are available in this hospital	Agree	20(51.3)	19(48.7)	39 (2.2)	0.003 ^a
	Disagree	52(60.5)	34(39.5)	86 (47.5)	
	Neutral	32(76.2)	10(23.8)	42 (23.2)	
Implementation of electronic medical recording (e.g., receiving results electronically) can improve effect of ASP	Agree	22(41.5)	31(58.5)	53 (29.3)	0.757
	Disagree	9(64.3)	5(35.7)	14 (7.7)	
	Neutral	29(61.7)	18(38.3)	47 (26.0)	
	Agree	68(56.7)	52(43.3)	120 (66.3)	

*Physicians more agreed.

^a Pharmacy professionals agreed.

consumption of antibiotics 137 (75.7 %), lack of adequate surveillance for drug-resistant organisms 127 (70.2 %) and adequate staff education regarding antibiotic consumption and resistance 124 (68.5 %), and overuse of antibiotics due to a lack of diagnostic tests 119(65.7 %) were perceived as key contributors to AMR in hospitals. This was similar to the study in Black Lion Hospital, which reported 84.3 % agreement with easy access to antibiotics, 82.0 % inappropriate consumption, and 64.4 % lack of adequate diagnostic tests as the main perceived causes of AMR [44] and in Ghana overuse of antibiotics in hospitals (67.5 %), uncompleted antibiotic therapy were common causes for AMR (50.31 %) and poor quality of antibiotics (37.7 %) [74]. In Uganda, antimicrobial overuse at hospitals (91 %), poor infection control practices by health professionals (79 %), and prescribing broad-spectrum antimicrobials when equally effective narrower-spectrum antimicrobials are available (73 %), were perceived causes for AMR [70], and in Cameroon, physicians perceived that inappropriate use of antibiotics (94 %), overuse of antibiotics (87 %), and indiscriminate use of broad-spectrum antibiotics (71 %), were possible causes for AMR [72]. The current study also revealed perceived difference between pharmacy professionals and physicians on the causes of AMR. This was similar to a study at Black Lion hospital [44]. Overall, the perceived causes assures the general agreement that inappropriate prescribing is a key contributory factor to AMR [35,36] which occur in up to 50 % of in hospital prescriptions [41]. This supports the fact that AMR is a major global public health concern, with serious consequences in LMICs which is due to widespread and inappropriate use of antibiotics in along with inadequate management of pharmaceutical wastes [20].

In this study, health professionals uncovered their intention to prescribe/dispense antibiotics to 86 (47.5 %) without checking microbiology laboratory results to guide their choice of antibiotics, lab results were not communicated timely if available to 84 (46.4 %) and antibiotic susceptibility patterns were not considered when prescribing antibiotics empirically in 81 (44.8 %). This was similar to health professionals belief that microbiology laboratory were not communicated in a timely manner (85 %), and prescribing/dispensing antibiotics without checking laboratory results to guide the choice of therapy (65 %) in Black Lion Hospital [44], and perceived factors of lack of laboratory tests (93.9 %), availability of antibiotics (80.6 %), and cost of antibiotics (80.6 %) influencing empiric therapy in Nigeria [77], although there are differences in magnitude which were lower in the current study (cost antibiotics 126 (69.6 %), availability of antibiotics 111 (61.3 %) and a lack of diagnostic tests 119 (65.7 %)). The findings confirmed the claim that antibiotic prescribing in Africa is highly prevalent, ranging from 38 % to 80 % (average 50 %), and intravenous to oral switch and documentation of start and stop dates for antibiotics were the least reported [64]. The current study also revealed the difference in perception between physicians and pharmacists in prescribing/dispensing of antibiotics, which is similar to reports at Black Lion Hospital in Ethiopia [44].

In the current study, health professionals believed that ASP reduces the duration of hospital stays and associated costs 137 (75.7 %), improves the quality of patient care 133(73.5 %), reduces overall antibiotic consumption and can result in cost savings 129(71.3 %), and reduces the problem of AMR 126(69.6 %). Almost similar results were reported from Black Lion Hospital with a slightly higher magnitude, where 82.4 % believed that ASP improves the quality of patient care, ASP reduces overall antibiotic consumption and can result in cost savings (76.9 %), ASP reduces the duration of hospital stay and associated costs (73.5 %), and ASP reduces the problem of AMR (82.9 %) [44]. In Libya, pharmacy professionals believed that ASP reduces the rate of AMR (70.2 %), reduces inappropriate use of

Table 6
Belief of health professionals on potential intervention to combat AMR in the hospitals, 2022 (N = 181).

Item and level of agreement		Category of Profession			P-value
		Physician (%)	Pharmacy (%)	Total (%)	
Education on antibiotic therapy to medical and pharmacy staff	Not useful	5 (41.7 %)	7 (58.3)	12 (6.6)	0.466
	Unsure	11(61.1)	7(29.9)	18 (9.9)	
	Effective	90(59.6)	61(39.4)	151 (83.4)	
Develop new institutional guidelines for empiric antibiotic use	Not useful	6(37.5)	10(63.5)	16 (8.8)	0.192
	Unsure	14(63.6)	8(36.4)	22 (12.2)	
	Effective	86(60.1)	57(39.9)	143 (79.0)	
Access to institution-specific antibiogram to treating teams	Not useful	3(21.4)	11(79.6)	14 (7.7)	0.013 ^a
	Unsure	18(60.0)	12(40.0)	30 (16.6)	
	Effective	85(62.0)	52(38.0)	137 (75.5)	
Implementation of prospective audit and feedback (multidisciplinary rounds on appropriate prescribing and use of antibiotics)	Not useful	4(40.0)	6(60)	10 (5.5)	0.468
	Unsure	17(58.7)	12(41.3)	29 (16)	
	Effective	85(59.9)	57(60.1)	142 (78.5)	
Active involvement of hospital infection prevention and control team	Not useful	5(38.5)	8(61.5)	13 (7.2)	0.301
	Unsure	18(58.1)	13(41.9)	31 (17.1)	
	Effective	83(60.1)	54(39.9)	137 (75.7)	
Antibiotic cycling intervention (e.g., scheduled rotation of 3rd or 4th generation cephalosporins with carbapenems and piperacillin-tazobactam for pre-determined time periods)	Not useful	8(80.0)	2(20.0)	10 (5.5)	0.047 ^b
	Unsure	43(67.2)	21(32.8)	64 (35.4)	
	Effective	55(51.4)	52(49.6)	107 (59.2)	
Antibiotic restriction intervention (certain antibiotics cannot be prescribed without infectious disease specialist approval for restricted antibiotics)	Not useful	16(51.6)	15(48.4)	31 (17.1)	0.143
	Unsure	30(71.4)	12(28.6)	42 (23.2)	
	Effective	60(55.6)	48(44.4)	108 (59.7)	

^a Physicians deemed as effective strategy.

^b Pharmacy professionals deemed as effective.

antibiotics in the community (68.4 %), participation in ASP activities will boost public confidence in community pharmacy services (79 %), community pharmacists' participation in the ASP will promote (73.7 %) and ASP activities are important in the hospital setting but are not important in the community setting (16.7 %) [78]. This assures that reducing AMR is a public health priority [58], and the implementation of ASP reduces inappropriate antibiotic use and AMR in hospital settings, in the community and private health facilities as well [4,51,78–80].

The current study identified a lack of funding, infectious diseases physicians and trained pharmacists on ASPs, inadequate information technology resources, a lack of incentives and support for committees, a lack of documentation and reporting mechanisms, inadequate initiatives for antimicrobial control and management, and a lack of microbiology laboratories and reagents in most of the hospitals. In Sri Lanka, Kenya, and Tanzania, the barriers to implementing ASP were expensive antimicrobials, limited antimicrobial availability, resistance to changing current practices regarding antimicrobial prescribing, and limited diagnostic capabilities [68], whereas in Nigeria there was a lack of funding, poor awareness about ASP, prescribers' opposition, a lack of IT facilities, the unavailability of an ASP committee, a lack of trained staff, a lack of leadership support and administration not being aware of ASPs [81]. The challenges for ASP implementation in a resource-limited setting are lack of financing, access to technologies, and capacity building [82]. Access to formalized infectious diseases or clinical microbiology support, lack of access to education and training, and lack of internal expertise within healthcare facilities, especially pharmacists with ASP skills, are also common barriers to the implementation of ASP in hospitals [83]. Thus, the successful implementation of ASPs needs targeted diagnosis and treatment, developing and updating antibiograms to direct empiric antimicrobial use, and increasing the use of microbiologic tests [1,84].

The current study uncovered the status of ASPs in hospitals and gaps in implementation of the CDC's Core Elements of ASP in hospitals, which attempted to implement ASP, which is known to ensure appropriate use of antibiotics [1]. The hospitals didn't

Table 7

Difference in level of agreement by attempts to implement ASP in the hospitals, in 2022 (N = 181).

Items and level of agreement for each items		Hospitals attempted ASP			P-value
		No (%)	Yes (%)	Total (%)	
Antibiotic resistance is a significant problem worldwide	Disagree	7(50.0)	7(50.0)	14(7.7)	0.013 ^a
	Neutral	1(16.7)	5(83.3)	6(3.3)	
	Agree	28(17.4)	133(82.6)	161(82.6)	
Inappropriate consumption of antibiotics is a major cause of antibiotic resistance in this hospital	Disagree	6(42.9)	8(57.1)	14(7.7)	0.034 ^a
	Neutral	8(26.7)	22(73.3)	3(16.6)	
	Agree	22(16.1)	115(83.9)	137(75.7)	
The easy access to antibiotics without a prescription in Ethiopia contributes to antibiotic resistance	Disagree	8(53.3)	7(46.7)	15(8.3)	0.003 ^a
	Neutral	2(18.2)	9(81.8)	11(6.1)	
	Agree	26(16.8)	129(83.2)	155(85.6)	
The lack of adequate diagnostic tests in this hospital leads to overuse of antibiotics	Disagree	6(18.8)	26(81.2)	32(17.7)	0.035 ^b
	Neutral	1(3.3)	29(96.7)	30(16.6)	
	Agree	29(24.4)	90(75.6)	119(65.7)	
My choice of antibiotics is often influenced by the availability of the antibiotics	Disagree	11(30.6)	25(69.4)	36(20.0)	0.012 ^b
	Neutral	1(2.9)	33(97.1)	34(18.8)	
	Agree	24(21.6)	87(78.4)	111(61.3)	
I regularly consider susceptibility patterns at this hospital when empirically prescribing or recommending antibiotics	Disagree	24(29.6)	57(70.4)	81(44.8)	0.009 ^a
	Neutral	5(8.9)	51(91.1)	56(30.9)	
	Agree	7(15.9)	37(84.1)	44(24.3)	
I routinely try to step down broad-spectrum antibiotics to a narrow-spectrum antibiotic after about three days	Disagree	8(12.9)	54(87.1)	62(34.3)	0.016 ^a
	Neutral	17(33.3)	34(66.7)	51(28.2)	
	Agree	11(16.2)	57(83.8)	68(37.6)	
I routinely prescribe/recommend very broad-spectrum antibiotics empirically because I believe most patients are infected with a drug-resistant organism	Disagree	22(28.6)	55(71.4)	77(42.5)	0.032 ^a
	Neutral	8(16.7)	40(83.3)	48(26.5)	
	Agree	6(10.7)	50(89.3)	56(30.9)	
I routinely check microbiology laboratory results to guide my choice of antibiotics	Disagree	27(31.4)	59(68.6)	86(47.5)	0.002 ^a
	Neutral	6(13.6)	38(86.4)	44(24.3)	
	Agree	3(6.0)	48(94.0)	51(88.1)	
In the past seven days, I have prescribed broad spectrum antibiotics for longer than 3 days for more than 50 % of my patients	Disagree	8(11.0)	65(89.0)	73(40.3)	0.001 ^b
	Neutral	9(16.1)	47(83.9)	56(30.9)	
	Agree	19(36.5)	33(63.5)	52(28.7)	
ASP has impact on an institution's nosocomial infection rates	Disagree	1(6.7)	14(99.3)	15(8.3)	0.013 ^a
	Neutral	4(8.3)	44(91.7)	48(26.5)	
	Agree	31(26.3)	87(73.7)	118(65.2)	
Total for all items		36(19.9)	145(80.1)	181(100.0)	

^a Hospitals attempted to implement ASP have better agreement.^b Hospitals which didn't attempted ASP do have better agreement.

Table 8
Distribution of health professionals in the hospitals, in 2022.

Variables		Hospitals					
		FHCSH	TGSH	DMCSH	IGH	FSGH	Total
Physicians	Internists	6	27	4	2	2	41
	Other specialization	45	101	16	7	5	174
	General Practitioners	118	100	43	33	32	326
Pharmacy professionals	Clinical pharmacist/MSc	7	1	4	2	3	18
	Pharmacist	37	36	19	7	7	105
	Other pharmacy professionals	7	20	25	7	15	74
Medical laboratory professionals	Microbiologists	2	1	4	0	2	9
	BSc+	40	42	26	9	7	124
	Others laboratory professionals	28	16	8	11	8	71
Other professionals*		459	459	415	286	192	1552
Total number of beds		800	467	216	140	95	1718
Average bed occupancy rate (%)		88	100	95.5	90	99	94.5
Average patient stays		5	7	4	5	4.7	5.14

Other professionals*: nurse, public health, environmental health, midwifery, anesthesia, HIT, optometry nurse; **Abbreviations:** FHCSH-Felege Hiwot Comprehensive Specialized Hospital; TGSH-Tibebe Ghion Specialized Hospital; DMCSH-Debre Markos Comprehensive Specialized Hospital; IGH- Injibera General Hospital; FSGH- Finote Selam General Hospital.

implement any specific ASP strategy or set metrics to evaluate the ASPs, except for attempts to evaluate vancomycin use, ceftriaxone use, and customizing the WHO AWaRe classification for antibiotics. This supports the lack of budget lines for AMS activities in 23 (74.2 %) countries in the WHO African region, where only 25.8 % of the countries had developed a national ASP implementation policy incorporating defined goals, targets, and operational plans [85]. Similar study in Nigeria reported lack of ASPs in a substantive proportion of hospitals, and suboptimal functioning in those who attempted to implement ASPs [86]. Successful ASP implementation relies on a strong commitment from senior hospital leadership, accountability, and responsibilities, among other core elements [87], but leadership commitment, action on implementing ASP and improving antibiotic consumption, tracking and reporting, and education were very poor in the current study. The presence of formal multidisciplinary organizational team structures responsible for ASP is one opportunity to strengthen the existing ASPs, as evidenced by the 79 % increase and improvements pertained to the core ASP checklist element on the multidisciplinary organizational structures responsible for ASP in Tanzania, Zambia, Uganda, and Ghana after ASP implementation [69]. Different strategies, such as prescriber education, formulary restriction, prior approval, streamlining, antibiotic cycling, and computer-assisted programs, have been proposed to improve antibiotic use [4,88]. Attempts for the WHO AWaRe categorization of antibiotics, which is an initiative to facilitate ASP, taking into consideration the potential of different antibiotic classes to cause resistance when used for the treatment of clinical infections [85] and evaluation of Watch antibiotics (vancomycin and ceftriaxone) as an early detection for inappropriate antibiotic use and signals the need for intervention [2,3,85] is an opportunity to further strengthen the ASP in the hospitals.

In resource-limited settings, a lack of clear political commitment, overcrowded healthcare systems, inadequate funding, lax legal and regulatory frameworks, the absence of electronic health record systems, non-uniform access to diagnostics, issues with access to quality-assured medicines, limited knowledge and awareness, and a shortage of trained manpower are challenges for the successful implementation of the core elements of ASP [88]. There are marked gaps and variability in the implementation and maturity of NAPs to facilitate sustainable delivery and operationalization at country and regional levels and to identify AMR-related priorities that are relevant to infrastructure needs and contexts [30]. Thus, the design and implementation of ASP interventions should foster data management and sharing tools between physicians, pharmacists, and microbiology laboratories using antibiotic prescribing guidelines based on hospital epidemiology data and easily accessible antibiograms [89,90]. Of course, political will from governments is critical in establishing, implementing, and sustaining ASPs [91].

In many LMICs, including Sub-Saharan Africa, pharmacist-led antimicrobial stewardship program interventions were shown to improve adherence to guidelines, reduce inappropriate prescribing, and improve compliance with process measures [10,92,93]. In this hospital, the availability of specialized physicians and laboratory technologists is an additional opportunity to start and strengthen ASP in hospitals. Although the role of the ASP pharmacist in the preservation of antibiotics through the monitoring, evaluation, and guidance of appropriate antibiotic use is vast [94], cooperation between physicians and pharmacists is essential to ensure high-quality treatment and improve patient outcomes [95]. Due to the complexity and challenges of implementing various ASP strategies in LIMCs, it is advised to rely on the plan-do-check-act (PDCA) model to improve efficiency and the likelihood of success of the programs through faster troubleshooting and continuous maintenance in the system [90]. The positive perception of health professionals towards hospital-based ASPs and potential interventions will help ensure the successful implementation of quality improvement ASPs in hospitals. Since the success of ASPs will be hampered by a lack of laboratory and technological support, limited stewardship time, poor documentation, and a lack of guidelines and policies [92], to achieve better outcomes from the interventions (antibiotic use, patient outcomes, and economic outcomes) [65], examining use practices, documenting antibiotic use data, and serving as an educational resource for clients, as well as strengthening and establishing diagnostic labs to provide antibiograms, is critical [1].

It was believed that education on antibiotic therapy for medical and pharmacy staff 151(83.4 %), developing new institutional guidelines for empiric antibiotic use 143(79.0 %), implementation of prospective audits and feedback 142(78.5 %), active involvement of hospital infection prevention and control teams 137(75.7 %) and access to institution-specific antibiograms to treating teams 137

Table 9
Core elements of hospital antibiotic stewardship programs in hospitals, 2022.

Category	Questions	Responses			
		FHCSH		TGSB	
		Yes	No	Yes	No
Leadership support and commitment	1. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (ASP)?	✓		✓	
	2. Does facility leadership provide stewardship program leader(s) dedicated time to manage the program and conduct daily stewardship interventions?		✓	✓	
	3. Does facility leadership provide stewardship program leader(s) any budgeted financial support including for resources (e.g., IT support, training) to effectively operate the program?		✓		✓
	4. Does your facility demonstrate leadership support for antibiotic stewardship?		✓		✓
	5. Does your ASP have a senior executive that serves as a point of contact or “champion” to help ensure the program has resources and support to accomplish its mission?	✓			✓
	6. Do stewardship program leader(s) have regularly scheduled meetings with facility leadership and/or the hospital board to report and discuss stewardship activities, resources and outcomes?		✓		✓
	7. Does your facility leadership ensure that staff from key support departments and groups has sufficient time to contribute to stewardship activities?		✓		✓
	8. Does facility leadership ensure that ASP activities are integrated into other quality improvement and patient safety efforts, such as sepsis management and diagnostic stewardship?		✓		✓
Accountability	9. Does your facility have a leader or co-leaders responsible for program management and outcomes of stewardship activities?	✓		✓	
	10. Is there a pharmacist or microbiologist or infectious disease specialist, leader responsible for working to improve antibiotic consumption for working to improve antibiotic use at your facility?	✓		✓	
	11. Does your facility have a pharmacist member/leader responsible for program outcomes of stewardship activities at your facility?	✓		✓	
Drug Expertise	13. Does your facility have a pharmacist(s) responsible for leading implementation efforts to improve antibiotic use?	✓		✓	
	14. Do your pharmacist(s) leading implementation efforts have specific training and/or experience in ASP?	✓		✓	
Action: Implement ASP And improve antibiotic consumption	15. Does your facility have access to individual(s) with ASP expertise?		✓		✓
	16. Does your facility perform prospective audit and feedback for specific antibiotic agents?		✓		✓
	17. Does your facility perform preauthorization for specific antibiotic agents?	✓			✓
	18. Does your facility have facility-specific treatment recommendations, based on national guidelines and local pathogen susceptibilities, to assist with antibiotic selection for common clinical conditions?		✓	✓	
	19. Does your facility have specific interventions to ensure optimal use of antibiotics for treating the most common infections in most hospitals?		✓	✓	
	20. Does your facility have specific interventions in place to ensure optimal use of antibiotics in specific infection/disease situations?		✓	✓	
	21. Does your facility have a policy that requires prescribers to document in the medical record or during order entry a dose, duration and indication for all antibiotic prescriptions?	✓		✓	
	22. Does your facility have a formal procedure for all prescribers to conduct daily reviews of antibiotic selection until a definitive diagnosis and treatment duration are established?		✓		✓
	23. Does your ASP assess how often patients are discharged on the correct antibiotics for the recommended duration?		✓		✓
	24. Does your ASP track antibiotic resistance?		✓		✓
Action: Tracking	25. Does your facility have policies to improve antibiotic prescribing/use?		✓		✓
	26. Does your facility implemented practices to improve antibiotic consumption?		✓		✓
	27. Does your ASP track antibiotic use?	✓		✓	
	28. Does your ASP monitor prospective audit and feedback interventions by tracking the types of interventions and acceptance of recommendations?		✓	✓	
	29. Does your ASP monitor preauthorization interventions by tracking which agents are being requested for which conditions?	✓			✓
	30. Does your ASP monitor adherence to facility specific treatment recommendations?		✓		✓
	31. Does your ASP monitor adherence to a documentation policy (dose, duration and indication)?		✓	✓	
	32. Does your ASP monitor the performance of antibiotic timeouts to see how often these are being done and if opportunities to improve use are being acted on during timeouts?		✓		✓
	33. Does your ASP routinely perform medication use evaluations to assess courses of therapy for select antibiotics and/or infections to identify opportunities to improve use?	✓		✓	

(continued on next page)

Table 9 (continued)

Category	Questions	Responses			
		FHCSH		TGSH	
		Yes	No	Yes	No
Reporting	34. Does your ASP routinely perform medication use evaluations to assess courses of therapy for select antibiotics and/or infections to identify opportunities to improve use?	✓		✓	
	35. Does your ASP assess how often patients are discharged on the correct antibiotics for the recommended duration?		✓		✓
	36. Does pharmacist/s support ASP activities?	✓		✓	
	37. Does your facility monitor one or more measures of antibiotic consumption?	✓		✓	
	38. Does your facility monitor one or more outcomes of antibiotic consumption?		✓		✓
	39. Does your ASP share facility and/or individual prescriber-specific reports on antibiotic use with prescribers?		✓		✓
	40. Does your ASP report adherence to treatment recommendations to prescribers?	✓		✓	
Education	41. Has your facility distributed a current antibiogram to prescribers within 18–24 months?		✓		✓
	42. Does your ASP provide education to prescribers and other relevant staff on optimal prescribing, adverse reactions from antibiotics, and antibiotic resistance?		✓		✓
	43. Does your ASP provide education to prescribers as part of the prospective audit and feedback process?		✓		✓
	44. Does your ASP provide educational resources/materials on antibiotic resistance and opportunity to improve antibiotic consumption?		✓	✓	
Additional Questions on ASP Challenges	45. Are there areas of antibiotic misuse in your facility?	✓		✓	
	46. Are there barriers to starting the ASP?		✓		✓

Abbreviations: FHCSH-Felege Hiwot Comprehensive Specialized Hospital; TGSH-Tibebe Ghion Specialized Hospital.

(75.5 %) were believed to be effective interventions. This was similar to the report at Black Lion Hospital, which ranges from 92.9 % for education to 83.2 % each for active involvement of hospital infection prevention and control teams and access to institution-specific antibiogram to treating teams [44]. These strategies were included in the national ASP guideline for Ethiopia [3]. Together with other strategies, education is a key component of every coordinated ASP effort to optimize hospital antimicrobial use due to its direct impact on healthcare professionals' knowledge, attitude, and practice [80]. As has been evidenced, even attempts to implement ASPs do have a positive impact on the perception of professionals to contain AMR and implement ASP.

The major findings from this study were most respondents do have positive perception towards implementation of ASP where pharmacists had more positive concerns towards AMR, causes for AMR and implementation of ASP in the hospitals. It also documents availability of ASP teams in some of the hospitals and attempts to document WHO AWaRe categorization and evaluations of most commonly consumed of Watch antibiotics in the hospitals. Some limitations in this study must be noted. The study didn't collect qualitative data based on key informant interviews and focus group discussions but simply collected quantitative data and assessed the status of hospitals based on checklists. The sampling was not done systematically but rather collected data from available staff during the data collection period. Since questionnaires were distributed and collected back, a potential bias would have been introduced if the participants had discussed them with their colleagues while filling them out. The hospitals that didn't attempt ASP were not included in the core elements analysis but rather were included in the readiness assessment. We didn't validate the core elements of ASPs filled by medical directors or leaders of ASPs. Since the findings were based on five hospitals, they may not be generalizable to other hospitals.

In conclusion, the status of ASP in hospitals is very poor. Although it is not of concern in general hospitals, the issue of ASP is, in principle, accepted in comprehensive specialized hospitals and referral hospitals. AMR was perceived as a problem in at the global level and in Ethiopia, where easy access to antibiotics without a prescription, inappropriate consumption of antibiotics, and overuse of antibiotics were perceived as key contributors to AMR in hospitals. Antibiotics were believed to be prescribed/dispensed without laboratory results, and antibiotic susceptibility patterns were not considered to prescribing antibiotics empirically. To tackle the problems, pharmacist-led prospective audits and feedback with education and institutional guidelines for empiric antibiotic use can be better implemented in the hospitals. Involvement of hospital infection prevention and control teams and collaboration between hospitals in ASP implementation help establish a strong ASP in the area.

Data availability

The data associated with this study is not deposited into a publicly available repository but all data are included in the manuscript. We will avail additional data if any when requested.

CRedit authorship contribution statement

Asrat Agalu Abejew: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Gizachew Yismaw Wubetu:** Writing – review & editing, Supervision, Conceptualization. **Teferi Gedif Fenta:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Asrat Agalu reports financial support provided by Addis Ababa University College of Health Sciences. Other authors, has declared that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e32663>.

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Annexes

Annex I: Consent Forms

1. For patients to get access to their card/if unconscious/children to care givers or attendants caring them

Dear participants, I'm PhD student in Addis Ababa University, college of health sciences, School of pharmacy in Social and administrative pharmacy program. I am conducting my dissertation on a title, **“ANTIBIOTICS STEWARDSHIP PROGRAMS IN AMHARA REGION, NORTHWEST ETHIOPIA, 2025”**. The study will be conducted by reviewing patient cards, HIMS records, drug acquisition and distribution sheets and models, purchasing vouchers, computerized physician order entry's (if any), culture and sensitivity tests; from health professionals (discussion and questionnaire based); from health sector managers, etc. If you are voluntary and you have the right not to give your card in the study or to take your card at any time you feel uncomfortable. The information obtained and accessed is used only for the purpose of research. The output of this research will be greatly helpful to the Hospitals, patient, community and health professionals by creating awareness and recommending possible solutions. The information obtained will be kept confidential by avoiding using names and securing from access to others other than research teams. After the research is over, the information obtained will be discarded. Thank you in advance for your cooperation.

Shall I proceed?

Yes-----

No -----

Annex II: Situational analysis of Hospital's readiness for AMS implementation

Section 1: General information of hospitals

1. Name of hospital: _____

2. Position/responsibility of respondent _____
3. Number of beds in the hospital: _____
4. Average bed occupancy rate: _____ Length of stay: _____
5. Number of health professionals in the hospitals: _____
 - a. Physicians: _____
 - i. Internists (sub-specialty on Infectious disease if any): _____
 - ii. Other specialists: _____
 - iii. GPs: _____
 - Currently working at Outpatient departments
 - b. Pharmacists: _____
 - i. Clinical pharmacists: _____
 - c. Laboratory technologists
 - I. Microbiologists: _____
 - d. Nurses: _____
 - e. Others health professionals: _____
6. How many full-time infection prevention staffs are employed at your facility? _____
7. If no to Q6, who is providing Infection prevention services including training? _____

8. Which professions are represented in the infection prevention practice

- Physicians	- Microbiologist
- Pharmacists	- Others: _____
9. Top ten infectious diseases that caused admission to the hospital:

A. _____	F. _____
B. _____	G. _____
C. _____	H. _____
D. _____	I. _____
E. _____	J. _____
10. Top ten infectious diseases that caused death in the hospital (if any):

A. _____	C. _____
B. _____	D. _____

E. _____

H. _____

F. _____

I. _____

G. _____

J. _____

11. Is there a formal procedure for all clinicians to review the appropriateness of all antibiotics within 48–72 hours of initial orders (e.g., antibiotic time out)

☐ No

☐ Yes

If yes, list the specific wards, if any:

12. Does your facility have a system for review courses of therapy for specified antibiotic/s?

☐ Yes

☐ No

13. If yes to question number 11 above, which staff member is responsible for the review and treatment change of specified antibiotic agents? (List all that applies)

☐ Physician

☐ Both

☐ Pharmacist

☐ Other (specify): _____

14. Is there a system for intravenous to the oral conversion of antibiotics by the pharmacists?

☐ No

☐ Yes

15. Is there an antibiogram in your hospital? ____ Yes, _____No:

If yes, how often do you update it? _____

16. Who manages your antibiogram review process, if any? _____

17. Does your hospital have a system in place to track antibiotic use trends?

☐ Yes

☐ No

18. Does your hospital have a system in place to track resistance trends?

☐ Yes

☐ No

19. If yes to Q16 and Q17, who is following trends in antibiotic use and resistance?

20. If yes to Q16 and Q17 Does your facility tracks antibiotic consumption on paper or electronically?

☐ Yes (☐ Paper

☐ Electronically)

☐ No

21. Does your facility have order sets for any of the following indications?

- | | |
|--|---|
| ☐ Urinary tract infection | ☐ Skin and soft tissue infection |
| ☐ Community-acquired pneumonia | ☐ Sepsis |
| ☐ Hospital-acquired pneumonia | ☐ Surgical prophylaxis |
| ☐ Ventilator-associated pneumonia | ☐ Neutropenic fever |
| ☐ Intra-abdominal infections | ☐ Other _____ |

22. Does your facility currently implement any antibiotic stewardship activities?

- ☐ Yes ☐ No

If yes, is there antibiotic stewardship team established in the hospitals?

- ☐ Yes ☐ No

23. If yes to Q 22, what are the strategies used for ASP (Preauthorization, prospective audit with feedback, IV to oral conversion, Any other):

24. Who is member of the antibiotic stewardship team? (Please encircle your answer of choice)

- | | |
|-------------------------|---------------------------|
| A. Physicians | G. Nursing |
| B. Pharmacist | H. Information Technology |
| C. Infection Prevention | I. Others _____ |
| D. Epidemiologist | _____ |
| E. Quality assurance | _____ |
| F. Microbiologist | |

25. Does your facility have an infectious disease physician available for 24/7?

- ☐ Yes ☐ No

26. Does your stewardship program monitor adherence to a documentation policy?

- ☐ Yes ☐ No ☐ Unknown

27. Is there formal discussion on effectiveness of the program among infection control staffs, pharmacists, physicians, and microbiology? _____yes _____ No

If yes, how often do infection control, pharmacy, and microbiology meet to discuss the effectiveness of the program?

- ☐ Monthly
 ☐ Quarterly
☐ Semiannually
 ☐ Annually
☐ Never
 ☐ Other (please specify): _____

28. Is there system for tracking antibiotic resistance pattern for common infections?

- ☐ Yes
 ☐ No

29. What are the common target microorganisms and antibiotics for test? (List common ones)

- | | |
|----------|----------|
| a) _____ | g) _____ |
| b) _____ | h) _____ |
| c) _____ | i) _____ |
| d) _____ | j) _____ |
| e) _____ | k) _____ |
| f) _____ | |

30. Is your hospital currently ready to implement Antibiotic stewardship? If not yet started

- ☐ Yes
 ☐ No

If yes, in which ward (wards) _____

28. Why do you select the wards(s)?

29. Which type and strategies of ASP do you recommend in your hospital? In which specific ward? Why?

Section 2: Core Elements of Hospital Antibiotic Stewardship Programs

Name of Facility: _____

Name of person filled the form: _____ position _____ date completed _____

Category	Questions	Yes	No	NA
Leadership support and commitment	1. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (antibiotic stewardship)?			
	2. Does facility leadership provide stewardship program leader(s) dedicated time to manage the program and conduct daily stewardship interventions?			
	3. Does facility leadership provide stewardship program leader(s) any budgeted financial support including for resources (e.g., IT support, training) to effectively operate the program?			
	4. Does your facility demonstrate leadership support for antibiotic stewardship? If yes, indicate which of the following are in place (select all that apply)			
	- Antibiotic stewardship duties are included in medical director, nursing and or pharmacy job description			
	- Leadership monitors adherence to antibiotic stewardship policies			
	- Antibiotic consumption and resistance data are reported in the quality assessment and assurance (QAA) meetings			
	5. Does your antibiotic stewardship program have a senior executive that serves as a point of contact or “champion” to help ensure the program has resources and support to accomplish its mission?			
	6. Do stewardship program leader(s) have regularly scheduled meetings with facility leadership and/or the hospital board to report and discuss stewardship activities, resources and outcomes?			
	7. Does your facility leadership ensure that staff from key support departments and groups has sufficient time to contribute to stewardship activities? (Refer to Core Elements for key support staff)			
	8. Does facility leadership ensure that antibiotic stewardship activities are integrated into other quality improvement and patient safety efforts, such as sepsis management and diagnostic stewardship?			
Accountability	9. Does your facility have a leader or co-leaders responsible for program management and outcomes of stewardship activities?			
	10. Is there a pharmacist or microbiologist or infectious disease specialist, leader responsible for working to improve antibiotic consumption for working to improve antibiotic use at your facility?			
	- If a non-physician is the leader of the program, does the facility have a designated physician who can serve as a point of contact and support for the non-physician leader?			
	11. Does your facility have a pharmacist member/leader responsible for program outcomes of stewardship activities at your facility?			
	12. Others			

Drug Expertise	13. Does your facility have a pharmacist(s) responsible for leading implementation efforts to improve antibiotic use?			
	14. Do your pharmacist(s) leading implementation efforts have specific training and/or experience in antibiotic stewardship?			
	15. Does your facility have access to individual(s) with antibiotic stewardship expertise? If yes, indicate who serves as your antibiotic stewardship expert (select all that apply)			
	- Other staffs work with the stewardship teams to improve antibiotic use (Check all that applies) A. Infection Prevention and Healthcare Epidemiology B. Quality assurance C. Microbiology (Laboratory) D. Nursing E. Information Technology (IT) F. Other (please specify): _____			
Action: Implement Interventions to Improve Antibiotic Use	16. Does your facility perform prospective audit and feedback for specific antibiotic agents?			
	17. Does your facility perform preauthorization for specific antibiotic agents?			
	18. Does your facility have facility-specific treatment recommendations, based on national guidelines and local pathogen susceptibilities, to assist with antibiotic selection for common clinical conditions?			
	19. Does your facility have specific interventions (e.g., ensuring correct discharge duration of therapy) to ensure optimal use of antibiotics for treating the most common infections in most hospitals?			
	If yes please list:			
	20. Does your facility have specific interventions in place to ensure optimal use of antibiotics in specific infection/ disease situations?			
	If yes please list:			
	21. Does your facility have a policy that requires prescribers to document in the medical record or during order entry a dose, duration and indication for all antibiotic prescriptions?			
	22. Does your facility have a formal procedure for all prescribers to conduct daily reviews of antibiotic selection until a definitive diagnosis and treatment duration are established (i.e., time out)?			
Action: Improve Antibiotic consumption	23. Does your antibiotic stewardship program assess how often patients are discharged on the correct antibiotics for the recommended duration?			
	24. Does your antibiotic stewardship program track antibiotic resistance?			
	25. Does your facility have policies to improve antibiotic prescribing/use? If yes, indicate which policy is			

	currently active (select all that apply)			
	- All antibiotic orders must have dose, frequency, duration, and indication			
	- Use of facility-specific algorithms to assess residents for suspected infections			
	- Use of facility-specific algorithms to request diagnostic tests for specific infections			
	- Use of facility-specific treatment recommendations for infections			
	- Antibiotics are reviewed before being added to the medication formulary, if one exists			
	- Other (please specify): _____			
	26. Does your facility implemented practices to improve antibiotic consumption? If yes, indicate which practices are currently in place (select all that apply)			
	- Situation-Background-Assessment-Recommendation (SBAR) are used when patients are suspected having infection			
	- Antibiotic consumption information is communicated/received when patients are transferred to/from other healthcare facilities			
	- Reports summarizing antibiotic susceptibility patterns (e.g., antibiogram) are available and updated periodically			
	- Antibiotic reviews/time-outs are performed for antibiotic orders			
	- At least one infection-specific intervention to improve antibiotic consumption has been successfully implemented. If yes, indicate for which infection(s):			
Action: Tracking Antibiotic Use and Outcomes	27. Does your antibiotic stewardship program track antibiotic use?			
	28. Does your antibiotic stewardship program monitor prospective audit and feedback interventions by tracking the types of interventions and acceptance of recommendations?			
	29. Does your antibiotic stewardship program monitor preauthorization interventions by tracking which agents are being requested for which conditions?			
	30. Does your stewardship program monitor adherence to facility specific treatment recommendations?			
	31. Does your stewardship program monitor adherence to a documentation policy (dose, duration and indication)?			
	32. Does your antibiotic stewardship program monitor the performance of antibiotic timeouts to see how often these are being done and if opportunities to improve use are being acted on during timeouts?			
	33. Does your antibiotic stewardship program routinely perform medication use evaluations to assess courses of therapy for select antibiotics and/or infections to identify opportunities to improve use?			
	34. Does your antibiotic stewardship program routinely perform medication use evaluations to assess courses of therapy for select antibiotics and/or infections to identify opportunities to improve			

	use?			
	35. Does your antibiotic stewardship program assess how often patients are discharged on the correct antibiotics for the recommended duration?			
	36. Does pharmacist/s support antibiotic stewardship activities? If yes, indicate activities performed by the pharmacist (select all that apply)			
	- Review's antibiotic appropriateness based on agent selected, dosing regimen, duration of therapy and indication			
	- Establishes standards for clinical/laboratory monitoring for antibiotic-associated adverse drug events			
	- Review's microbiology culture data to assess and guide antibiotic selection			
	37. Does your facility monitor one or more measures of antibiotic consumption? If yes, indicate which of the following are being tracked (select all that apply)			
	- Adherence to clinical assessment documentation (including signs/symptoms, vital signs, physical exam findings)			
	- Adherence to include dose, frequency, duration and indication for antibiotic orders			
	- Adherence to facility-specific treatment recommendations for infections			
	- Point prevalence of antibiotic consumption (e.g., proportion of residents on antibiotic over a given time period)			
	- Other (please specify):			
	38. Does your facility monitor one or more outcomes of antibiotic consumption? If yes, indicate which of the following are being tracked (select all that apply)			
	- Rates of antibiotic-resistant micro-organisms			
	- Rates of antibiotic-associated adverse drug events			
	- Other (please specify):			
Reporting Antibiotic Use and Outcomes	39. Does your antibiotic stewardship program share facility and/or individual prescriber-specific reports on antibiotic use with prescribers? If yes, indicate which of the following are being shared (select all that apply)			
	- Measures of antibiotic consumption at the facility			
	- Personalized feedback on antibiotic prescribing practices (shared only with individual clinical providers)			
	Other (please specify):			
	40. Does your antibiotic stewardship program report adherence to treatment recommendations to prescribers (e.g., results from medication use evaluations, etc.)?			
	41. Has your facility distributed a current antibiogram to prescribers within 18-24 months?			

Education	42. Does your stewardship program provide education to prescribers and other relevant staff on optimal prescribing, adverse reactions from antibiotics, and antibiotic resistance?			
	43. Does your stewardship program provide education to prescribers as part of the prospective audit and feedback process (sometimes called “handshake stewardship”)?			
	44. Does your stewardship program provide educational resources/materials on antibiotic resistance and opportunity to improve antibiotic consumption? If yes, indicate which of the following group is provided these educational resources/materials (select all that apply)			
	Physicians			
	Pharmacists			
	Nursing staff			
	Other (please specify):			
Additional Questions on Antibiotic Stewardship Challenges	a. What is the scope and scope of education on ASP? (Observe and record the scope of training)			
	45. Are there areas of antibiotic misuse in your facility? If yes, answer one of the following questions			
	- ASP can help address misuse (If stewardship program has not been established)			
	- More ASP efforts are needed to address misuse (If stewardship program has been established)			
	46. Are there barriers to starting the ASP? If yes, list the top three barriers hindering initiation or improvement of the ASP			
Which type and strategies of ASP do you recommend in your hospital? In which specific wards? Why?				

Annex III. Knowledge and attitude survey

1. Healthcare professional's pre-intervention perception survey in the hospitals

This survey is designed to be administered pre- and post-intervention to health professionals and managers. It asks for your perceptions about antibiotic resistance (AMR) and ASPs. The findings of this survey will be used as input for developing an effective ASP in the hospital. It will take you about 10 to 15 minutes to complete. Your honest response is essential. If you do not wish to answer a question, or if a question does not apply to you, you may answer n/a. Please indicate your level of agreement with the statements about your institution on the questions indicated in the table.

A. ANTIBIOTIC RESISTANCE: SCOPE OF THE PROBLEM AND KEY CONTRIBUTORS							
Please indicate your agreement or disagreement with the following statements by encircling ONE number on the provided scales: 1= Strongly Disagree; 2= disagree; 3=Neutral; 4= Agree; 5= Strongly Agree . If you don't feel that you have the knowledge to rate the item, please tick mark (✓) on the "n/a" column.							
Items		Your Level of Agreement					
101.	Antibiotic resistance is a significant problem worldwide	1	2	3	4	5	n/a
102.	Antibiotic resistance is a significant problem in my country	1	2	3	4	5	
103.	Antibiotic resistance is a significant problem in my hospital	1	2	3	4	5	
104.	Antibiotic resistance is a problem in my daily practice	1	2	3	4	5	
105.	Inappropriate consumption of antibiotics is a major cause of antibiotic resistance in this hospital	1	2	3	4	5	
106.	The easy access to antibiotics without a prescription in Ethiopia contributes to antibiotic resistance	1	2	3	4	5	
107.	The prescription of broad-spectrum antibiotics is directly linked to antibiotic resistance in this hospital	1	2	3	4	5	
108.	This hospital performs adequate surveillance for drug-resistant organisms	1	2	3	4	5	
109.	The lack of adequate diagnostic tests in this hospital leads to overuse of antibiotics	1	2	3	4	5	
110.	This hospital provides adequate staff education regarding antibiotic consumption and resistance	1	2	3	4	5	
111.	A patient is likely to develop drug-resistant infection during their hospital stay at this hospital	1	2	3	4	5	
112.	I suspect that antibiotics available in my hospital are of poor quality and might not be effective	1	2	3	4	5	
113.	My choice of antibiotics is often influenced by the availability of the antibiotics rather than by the local antibiogram or by the etiologic cause of disease (availability of laboratory results)	1	2	3	4	5	
114.	The sporadic supply of antibiotics in my hospital leads to interruptions of therapy thereby contributing to antibiotic resistance	1	2	3	4	5	

115.	The lack of close clinical follow-up during antibiotic consumption in my hospital contributes to antibiotic resistance	1	2	3	4	5	
116.	Patient demands and expectations contribute to overuse of antibiotics in this hospital	1	2	3	4	5	
117.	Cost considerations for the patient affects my choice of antibiotics	1	2	3	4	5	
118.	Poor infection control practices by health professionals significantly contributes to the spread of antibiotic resistance in this hospital	1	2	3	4	5	
119.	Adherence to hand-hygiene protocols is acceptable at this hospital	1	2	3	4	5	
120.	Patient rooms and equipment are cleaned appropriately as per hospital cleaning protocol once a patient carrying a drug-resistant organism (DRO) has been discharged from this hospital	1	2	3	4	5	
121.	I think a very high proportion (>30%) of gram-negative infections are highly drug-resistant in this hospital (resistant to all cephalosporins, and some are even resistant to carbapenems)	1	2	3	4	5	
122.	I think a very high proportion (>30%) of Staphylococcal infections are resistant to methicillin (MRSA) in this hospital	1	2	3	4	5	

B. ANTIBIOTIC PRESCRIBING/DISPENSING PRACTICES

123.	Microbiology lab results are timely communicated to the health professionals in this hospital	1	2	3	4	5	n/a
124.	I regularly refer to/consider the antibiotic susceptibility patterns at this hospital (institutional antibiogram) when empirically prescribing or recommending antibiotics	1	2	3	4	5	
125.	If medically appropriate, I routinely try to step down intravenous antibiotics to an oral alternative antibiotic after about three days	1	2	3	4	5	
126.	If medically appropriate, I routinely try to step down broad-spectrum antibiotics to a narrow-spectrum antibiotic after about three days	1	2	3	4	5	
127.	Restrictions on antibiotics could impair my ability to provide good patient care	1	2	3	4	5	
128.	I routinely prescribe/recommend very broad-spectrum antibiotics empirically because I believe most patients are infected with a drug-resistant organism	1	2	3	4	5	
129.	I routinely prescribe/recommend very broad-spectrum antibiotics empirically because microbiology lab results are not available in a timely fashion	1	2	3	4	5	
130.	I routinely check microbiology laboratory results to guide my choice of antibiotics	1	2	3	4	5	
131.	In the past seven days, I have prescribed broad spectrum antibiotics for longer than 3 days for fewer than 10% of my patients;	1	2	3	4	5	
132.	In the past seven days, I have prescribed broad spectrum antibiotics for longer than 3 days for 10-50% of my patients	1	2	3	4	5	
133.	In the past seven days, I have prescribed broad spectrum antibiotics for longer than 3 days for more than 50% of my patients	1	2	3	4	5	

C. ASPS (ASP)

(A formal multidisciplinary program that monitors and manages the appropriate use of antibiotics)

134.	ASPs (ASP) improve quality of patient care	1	2	3	4	5	n/a
135.	ASP reduces overall antibiotic consumption and can result in cost savings	1	2	3	4	5	
136.	ASP reduces duration of hospital stay and associated costs	1	2	3	4	5	
137.	ASP reduce the problem of antibiotic resistance	1	2	3	4	5	
138.	ASP has impact on an institution's nosocomial infection rates	1	2	3	4	5	
139.	This hospital has the capacity to establish and implement an effective ASP	1	2	3	4	5	
140.	My individual efforts in antibiotic stewardship can significantly impact this hospital's antibiotic resistance problem	1	2	3	4	5	
141.	I would like to receive more feedback on my antibiotic selections	1	2	3	4	5	
142.	ASPs can be an obstacle to good patient care	1	2	3	4	5	
143.	ASPs override prescribers' decision autonomy	1	2	3	4	5	
144.	I do not have enough time to further invest into ASP	1	2	3	4	5	
145.	Infectious diseases experts that can provide guidance in antibiotic selection and prescription are available in this hospital	1	2	3	4	5	
146.	Additional staff education on antibiotic prescribing and use is needed in this hospital	1	2	3	4	5	
147.	Prescribing physicians are the only professionals who need to understand antibiotic stewardship	1	2	3	4	5	
148.	Pharmacists with sufficient training to provide guidance on antibiotics (ex. <i>Antibiotic switches, IV to PO step-down</i> , renal dose adjustments) are available in this hospital	1	2	3	4	5	
149.	Implementation of electronic medical recording (e.g., receiving results electronically) can improve effect of ASP	1	2	3	4	5	

D. Beliefs on Suggested Potential Solutions for Preventing Antibiotic Resistance

Please indicate your perception of the potential of suggested solution to reduce AMR by encircling ONLY ONE number on the provided scale: 1= Probably or definitively ineffective (Not useful); 2= Unsure; 3= Probably or definitively effective							
Suggested Solutions to Reduce Antibiotic Resistance						Agreement	
301.	Education on antibiotic therapy to medical and pharmacy staff					1	2 3
302.	Develop new institutional guidelines for empiric antibiotic use					1	2 3
303.	Access to institution-specific antibiogram to treating teams					1	2 3
304.	Implementation of prospective audit and feedback (multidisciplinary rounds on appropriate prescribing and use of antibiotics)					1	2 3
305.	Active involvement of hospital infection prevention and control team					1	2 3
306.	Antibiotic cycling intervention (e.g., scheduled rotation of 3rd or 4th generation cephalosporins with carbapenems and piperacillin-tazobactam for pre-determined time periods)					1	2 3
307.	Antibiotic restriction intervention (certain antibiotics cannot be prescribed without infectious disease specialist approval for restricted antibiotics)					1	2 3

E. Background Information of Respondents

Socio-demographic Questions		Response
401.	Age in years	_____ years
402.	Gender	☐ Male ☐ Female
403.	What is your primary work area or unit in this hospital? (Please check ONE answer)	☐ Medicine (non-surgical) ☐ Surgery ☐ Pediatrics ☐ Gynecology/Obstetrics ☐ Rotation (among wards) ☐ Emergency (ED) ☐ Pharmacy ☐ Other (please specify): _____
404.	What is your staff position in this hospital?	☐ Consultant physician or attending staff ☐ Fellow (postgraduate) physician ☐ Medical student ☐ Resident physician/Intern ☐ Pharmacist ☐ Other (please specify): _____
405.	How long have you worked in this hospital?	_____ years; _____ months
406.	How long have you worked in your current specialty or profession?	_____ years; _____ months
407.	How many patients do you treat on average, per week (provide your best estimate)	_____ patients/week
408.	How many of your patients do get antibiotic prescription, per week (provide your best estimate)	_____ patients/week

Is there anything you would like share with us? Please write it in the space provided.

2. Survey of GPs' and residents' knowledge, attitudes and behaviors on antibiotic prescribing in the Hospitals

This survey is designed to be administered GPs working in the OPDs of in the hospitals. It asks for your perceptions about antibiotic prescribing and antibiotic resistance (AMR). The findings of this survey will be used as input for developing an effective antibiotic stewardship in the hospital. It will take you about 15 minutes to complete. Your honest response is essential. Please indicate your level of agreement with the statements about your institution on the questions indicated in the table. Your personal information would be confidential and the responses were only used for academic research purpose only. Please feel free and provide us genuine information. Thanks very much for your participation.

Name of institution _____

Part 1: Attitudes

Please note that this part of the questions **does not have the correct answer**; please fill in them according to your personal opinion situation.

	To what extent you agree with the following statements	Very agree	Agree	Neutral	Disagree	Very Disagree
1.	In OPDs, microbiology results are useful when treating infectious diseases					
2.	Prescription of antibiotic to a patient does not influence the development of resistance					
3.	Overuse of antibiotics contributes to generation of antibiotic resistance					
4.	Prescribing antibiotics to patients does not cause damage even they are not indicated					
5.	Over-prescribing of antibiotics contributes to generation of antibiotic resistance					
6.	Irrational use of broad-spectrum antibiotic contributes to generation of antibiotic resistance					
7.	Antibiotics prescribed which are not selected based on the specific bacteria contributes to generation of antibiotic resistance					
8.	In OPDs, diagnosis is mainly based on symptoms since bacterial laboratory and antibiotic susceptibility test were inaccessible					
9.	I need rapid and effective diagnostic techniques for diagnosis of infectious diseases					

10.	One of main causes for emergence of antibiotic resistance is patients' misuse of antibiotics					
11.	Dispensing antibiotics without a prescription should be more closely controlled					
12.	Patients were satisfactory with my treatment, so I do not need to change my antibiotic prescribing pattern					
13.	My patients and colleagues do not think I that I am over-prescribing antibiotics, so I do not need to change my antibiotic prescribing pattern					
14.	My antibiotic prescription is rational so I do not need to change my antibiotic prescribing pattern					
Please tick the appropriate option in the blank space below		Always	Often	Sometimes	Rarely	Never
15.	I ____ prescribe antibiotic since patients expect it					
16.	I ____ prescribe antibiotic since patients require and insist on it					
17.	I ____ prescribe antibiotic to satisfy patients					
18.	I ____ prescribe antibiotic to make patients continue to trust me					
19.	Even when I know that they are not indicated, I ____ prescribe antibiotic since patients expect it					
20.	Even when I know that they are not indicated, I ____ prescribe antibiotic since patients ask for it					
21.	Even when I know that they are not indicated, I ____ prescribe antibiotic since patients enforce me to prescribe it					
22.	Even when I know that they are not indicated, I _____ prescribe antibiotics since I do not have time to explain the reason to the patient why they are not indicated					
23.	I ____ prescribe antibiotic since I fear patient deterioration					
24.	I ____ prescribe antibiotic since it is impossible to track the patient accurately					
25.	I ____ prescribe antibiotic to avoid possible patient complaints or medico-legal problems					
26.	I ____ prescribe antibiotics to avoid being perceived as doing nothing for patients					
27.	I ____ prescribe antibiotic to avoid losing patients					

Part 2: Behaviors

Please note that this part of the questions **does not have the correct answer**; please fill in them according to your personal situation / attitude.

28.	Given 10 patients with URTIs, how many patients of them would you prescribe antibiotics to?	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10									
	➔ To what extent you agree with the following statements	Very agree	Agree	Neutral	Disagree	Very Disagree					
29.	I want to reduce antibiotic consumption in										

	outpatients					
30.	I expect to reduce antibiotic consumption for in outpatients					
31.	I plan to reduce antibiotic consumption in outpatients					
32.	I want to prescribe antibiotics to outpatients					
33.	I expect to prescribe antibiotics to outpatients					
34.	I plan to prescribe antibiotics to outpatients					

Part 3: Knowledge

Please note that this part of the questions **only has one correct answer**

35. A 4-year-old girl has diarrhea for 4 days (3 stools/day). She has no fever at examination nor during the last few days. Which treatment do you propose?

- a. Amoxicillin p.o.
- b. TMP/SMX p.o.
- c. Amoxicillin-clavulanic acid p.o.
- d. No antibiotic treatment, only oral rehydration;
- e. I don't know

36. A 6-year-old child has a fever of 38°C, purulent rhinitis and angina for two days. At inspection, the throat is reddish. Which treatment do you recommend?

- a. TMP/SMX p.o.
- b. Amoxicillin p.o.
- c. Amoxicillin-clavulanic acid p.o.
- d. No antibiotic
- e. I don't know

37. During your ward round, you see two patients with severe renal failure. Patient A is a 68-year-old man suffering from serious cellulitis at the leg, he is treated with clindamycin. Patient B is a 64-year-old diabetic woman which is blindly (empirically) treated for septicemia with ceftriaxone. Dosage reduction is needed for:

- a. Patient A
- b. Patient B
- c. Both patients
- d. In neither patient A nor patient B
- e. I don't know

38. Which one of the following antibiotics is safe during pregnancy?

- a. Amoxicillin
- b. Ciprofloxacin
- c. Gentamicin
- d. I don't know

39. Which one of the following antibiotics has the best activity against anaerobes?

- a. Ciprofloxacin
- b. Metronidazole
- c. Cotrimoxazole
- d. I don't know

40. Methicillin resistant - *Staphylococcus aureus* is susceptible to:
- a. Amoxicillin-clavulanic acid
 - b. Cefotaxime
 - c. Ceftriaxone
 - d. None of those antibiotics
 - e. I don't know
41. Which one of the following antibiotics most effectively crosses the blood-brain barrier?
- a. Clindamycin
 - b. Ceftriaxone
 - c. Vancomycin
 - d. I don't know
42. Aminoglycosides such as gentamicin are very active if they are administered as follows:
- a. Orally three times daily
 - b. Parenteral once daily
 - c. Parenteral three times daily
 - d. I don't know
43. In case of having respiratory infectious symptoms, when does the child need antibiotic?
- a. Cough, stuffy nose or runny nose without fever
 - b. Cough, stuffy nose or runny nose with fever
 - c. Including one of the following symptoms: fast breathing, chest in-drawing or stridor
 - d. Both b) and c)
 - e. I don't know
44. Which of the following statements is correct?
- a. Antibiotics are helpful in treating URTIs
 - b. Antibiotics reduce the duration of URTIs
 - c. Antibiotics can reduce the occurrence of complications of URTIs
 - d. None of the above
 - e. I don't know
45. According to international recommendations, the average number of prescriptions containing antibiotics per 100 should be _____ in a primary care facility (one prescription per patient)?
- a. Below 30
 - b. 30 – 50
 - c. 50 – 70
 - d. Above 70
 - e. I don't know

Part 4: Background Information of Respondents

Socio-demographic Questions		Response
40	Age in years	_____ years
40	Gender	☐ Male ☐ Female
40	What is your primary work area or unit in this hospital? (Please check ONE answer)	☐ Medicine (non-surgical) ☐ Surgery ☐ Pediatrics ☐ Gynecology/Obstetrics ☐ Rotation (among wards) ☐ Emergency (ED) ☐ Other (please specify): _____
40	What is your staff position in this hospital?	☐ Consultant physician or attending staff ☐ Fellow (postgraduate) physician ☐ Medical student ☐ Resident physician/Intern ☐ Other (please specify): _____
40	How long have you worked in this hospital?	_____ years; _____ months
40	How long have you worked in your current profession?	_____ years; _____ months
40	How many patients do you treat on average, per week (provide your best estimate)	_____ patients/week
40	How many of your patients do get antibiotic prescription, per week (provide your best estimate)	_____ patients/week
40	Additional Education/training if any	
41	Whether received training on antibiotics use and resistance in the last year	☐ Yes ☐ No/I don't know

Is there anything you would like share with us? Please write it in the space provided.
